The 5-Minute Neurology Consult

2ND EDITION

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–D.J.L.

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–H.B.N.

To my family, colleagues, and particularly to my patients, with gratitude.

–A.D.R-G.

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PREFACE

We are pleased to bring a second edition of the Neurology volume to the 5-Minute Consult series. This book is intended to present current clinical information to several groups:

- Busy clinical practitioners in neurology general practice, emergency rooms, and non-neurologic specialties who need a reference source where they can quickly refresh their knowledge about the basics of a neurologic condition
- Residents and students seeking rapid access to basic data about diagnosis and treatment for various neurologic conditions
- Patients and families who want quick information about their diagnoses and referrals to patient information sources and support organizations

Neurology is an area of medicine that incites anxiety and discomfort for many students, nurses, and physicians who have not trained in the specialty. Effective therapeutic interventions continue to expand and flourish; every practitioner must understand the diagnosis and treatment of basic neurologic conditions. Information is provided in a structured format that allows easy access and rapid assimilation. We have attempted to offer relevant and current references. We hope that this rapid information source will help all to approach patients suffering from neurologic disorders with more confidence.

It has been a great honor and pleasure to work with the many chapter authors who have shared their expertise in and enthusiasm for clinical neurology. Some are young stars while others are accomplished masters in neurology, but all have attempted to provide the best distillation of relevant information for each condition. The staff at Lippincott Williams & Wilkins, including Louise Bierig and Tom Gibbons, kept us on track in this effort with advice, encouragement, and humor.

Practice is science touched with emotion.

—Stephen Paget, *Confessio Medici*, 1909

D.J.L.
H.B.N.
A.D.R-G.

CONTENTS

Section I

Neurological Symptoms and Signs

APHASIA

Andrew Kirk, MD, FRCPC

BASICS

DESCRIPTION

Aphasia is an acquired impairment of language characterized by word-finding difficulty and paraphasias with a variable disturbance of comprehension. In right-handed persons and most left-handers, aphasia results from a lesion in the left cerebral hemisphere. Occasionally a right-hander is seen with aphasia due to a right hemisphere lesion, a phenomenon known as "crossed aphasia." The term "aphasia" refers to spoken language, but aphasics almost always have impaired reading (alexia) and writing (agraphia).

DEFINITIONS

- *Paraphasias* are errors in word production. They may be *phonemic*, with substitution of a wrong sound ("bup" for "cup"); *semantic*, with substitution of a wrong word that is often related in meaning ("dinner" for "cup"); or *neologisms*, with production of a meaningless non-word ("bitko" for "cup").
- *Fluency* refers to the flow of speech and may be thought of as number of words per unit time or length of longest utterance. Nonfluent speech is halting, with long pauses and phrases shorter than 4 words. Fluent speech retains long phrases with a normal number of words per unit time.
- Nonfluent aphasics can often make themselves understood in a few words produced effortfully, while fluent aphasics often make very little sense despite lengthy output.

CLINICAL CHARACTERISTICS

- Aphasia is usually readily apparent during history-taking. The patient exhibits word-finding difficulty, resulting in paraphasias, circumlocutory descriptions ("that thing you write with" for "pen"), or obvious searching for words with pauses and filler phrases ("oh, um, you know"). Aphasia, a disorder of language, must be distinguished from other disorders of speech. *Dysarthria* is a disturbance of articulation due to lesions lower in the nervous system. Although aphasia and dysarthria may coexist, a patient with only dysarthria should be able to read and write normally. *Dysphonia*, a disturbance of voice, may be due to problems with the larynx or its innervation.
- Aphasia must also be distinguished from more diffuse disturbances of cerebral function, such as delirium, where attention and other cognitive abilities are also affected.

PATHOPHYSIOLOGY

- Language centers surround the left Sylvian fissure within territory supplied by the middle cerebral artery (MCA). Figure 1, "Lichtheim's house," presents a schematic of language processing based on the work of Lichtheim. While obviously a gross oversimplification of a complex process, it nonetheless serves as a useful tool for bedside assessment of aphasia. Auditory input (I) is presented to Wernicke's area (W) in the posterior third of the superior temporal gyrus where sounds heard are linked to representations of words that Lichtheim called "auditory word engrams." Broca's area (B) in the inferior frontal gyrus programs lower centers to articulate a word, producing speech output (O) and may be thought of as containing Lichtheim's "motor word engrams." Broca's area is also important in producing correct word order so that sentences make grammatical sense. Wernicke's and Broca's areas are connected by white-matter tracts such as the arcuate fasciculus (line W–B). Lichtheim visualized an extra-Sylvian area of concepts (C) where engrams were linked to actual meanings of words and, while there is no one brain area corresponding with this, C may be thought of as the rest of the cerebrum, beyond left MCA territory.
- Lesions disrupting the line C–B–O impair fluency. Lesions along I–W–C impair comprehension. Repetition is affected by lesions along I–W–B–O.

DIAGNOSIS

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

Initial approach

- Imaging studies
- CT or MRI scanning is useful to confirm the location and nature of the causative lesion.

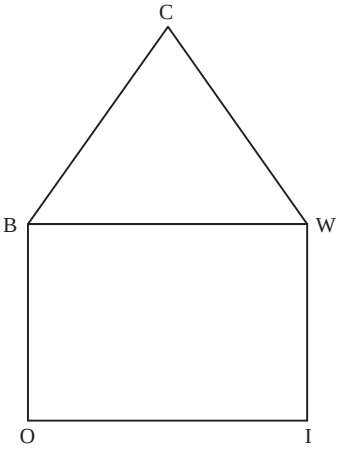

Figure 1. Lichtheim's house.

- Bedside examination is generally sufficient to determine aphasia type and severity, but numerous standardized aphasia test batteries provide more detailed assessment. These range from 3- to 10-minute screening tests, such as the Frenchay Aphasia Screening Test, to the Boston Diagnostic Aphasia Examination which can take several hours. In 45 minutes, the Western Aphasia Battery determines the type and severity of aphasia.

DIFFERENTIAL DIAGNOSIS

Aphasia is most often due to ischemic or hemorrhagic stroke within or adjacent to the territory of the left MCA but may result from trauma, tumor, infection, or other lesions in this location. Aphasia is uncommon with external compressive lesions such as subdural hematoma. A hemiparetic patient with aphasia is thus likely to have an intraparenchymal rather than an extraparenchymal lesion. Language disturbance is often present in dementias such as Alzheimer's disease and is often prominent in frontotemporal dementia, types of which are often termed "primary progressive aphasia." Progressive nonfluent aphasia presents with impaired fluency and usually agrammatisms, phonemic paraphasias, and anomia. In semantic dementia, speech is fluent but meaning is lost with impaired naming and comprehension. Paraphasias are generally semantic. Although deficits in primary progressive aphasia may be confined to language for quite some time with relatively preserved day-to-day functioning, later in the illness, frontal and temporal degeneration take their toll in the form of further behavioral disturbances. Although usually sporadic, frontotemporal dementia can also be inherited.

SIGNS AND SYMPTOMS

- Patients' spontaneous speech reveals paraphasias and word-finding difficulty and is also used to judge whether they are fluent or nonfluent. Naming is tested by showing patients objects. Patients with mild aphasia may name common items well but have more difficulty producing less common words such as parts of objects. Thus, aphasics tend to have more difficulty naming a watch strap than a watch. Comprehension is tested by asking the patient to carry out commands of varying levels of difficulty. One can begin with a simple one-step command and progress to complex three-stage commands. Repetition is tested beginning with single words and progressing to complex phrases such as "no ifs, ands, or buts."

- Peri-sylvian aphasias (Broca's, Wernicke's, conduction, and global) are typically due to infarcts in left MCA territory and since all disrupt I–W–B–O, they have in common a disturbance of repetition.
- Broca's aphasia
  - A lesion in Broca's area (B) causes nonfluent speech with poor repetition but relatively preserved comprehension, particularly for nouns and verbs. Since Broca's area is adjacent to the precentral gyrus, this is usually accompanied by right hemiparesis.
- Wernicke's aphasia
  - A lesion in Wernicke's area (W) results in fluent speech with impaired comprehension and repetition. Although it may be accompanied by a right superior homonymous quadrantanopia due to involvement of temporal fibers of the optic radiations (Meyer's loop), Wernicke's aphasia is not typically accompanied by hemiparesis. Due to the paucity of other findings on examination, it is not unusual to see a patient referred with "confusion" who actually has Wernicke's aphasia.
- Conduction aphasia
  - A lesion between Wernicke's and Broca's areas in the arcuate fasciculus/insular area (W–B) results in fluent speech with good comprehension but poor repetition.
- Global aphasia
  - A large MCA infarct causes nonfluent speech with poor comprehension and repetition and is typically accompanied by severe hemiparesis. Global aphasia unaccompanied by hemiparesis suggests multiple lesions sparing motor cortex, often of cardioembolic or metastatic origin.
- Transcortical aphasias
  - These result from lesions in the watersheds between middle, anterior, and posterior cerebral arteries (ACA and PCA) or within ACA or PCA territory, disconnecting peri-Sylvian language centers from the rest of the cerebrum. Watershed infarcts may result from hypotension, a shower of small emboli, or carotid occlusion. During cardiac surgery, either of the first two of these conditions may occur, and this is a typical clinical setting for transcortical aphasia. Because peri-Sylvian language areas are spared, repetition is intact.
- Transcortical motor aphasia
  - A frontal lesion outside Broca's area (C–B) results in a language deficit similar to Broca's aphasia except that repetition is intact.
- Transcortical sensory aphasia
  - Temporo-parieto-occipital junction lesions (W–C) may result in an aphasia similar to Wernicke's except that repetition is preserved.
- Mixed transcortical aphasia
  - An aphasia similar to global aphasia but with preserved repetition may result from a large MCA/PCA/ACA watershed infarct (C–B and W–C).
- Anomic aphasia
  - Impairment of naming with good comprehension, repetition, and fluency is a common but poorly localizing aphasia type. Lesions in many left cerebral areas my cause this mild aphasia.
- Subcortical aphasia
  - Lesions in left thalamus or subcortical white matter may cause aphasia syndromes rather similar to the cortical aphasia types described above. Associated deficits may be atypical (e.g., Wernicke's like aphasia with dense hemiparesis). These patients are often quite dysarthric, and repetition is often relatively preserved. Particularly with thalamic lesions, patients may fluctuate dramatically between near-normal output and mumbled jargon.

TREATMENT

MEDICATION

First Line

- Drug(s) of choice
- Although some reports have suggested improved speech output with bromocriptine or stimulants, specific pharmacotherapy of aphasia has been disappointing and is not generally used.

ADDITIONAL TREATMENT

General Measures

The underlying lesion type determines overall management. Acute aphasia due to ischemia may be amenable to thrombolytic therapy. Time is thus of the essence in evaluation.

SURGERY/OTHER PROCEDURES

- Determined by the underlying lesion.
  - Symptomatic treatment
    - Determined by underlying lesion. Patients with poor comprehension often benefit from being told information repeatedly and in different words.
  - Adjunctive treatment
    - Large trials suggest that speech therapy by speech pathologists improves recovery.

IN-PATIENT CONSIDERATIONS

Discharge Criteria

Usually determined by the underlying lesion.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Usually determined by the underlying lesion.

Patient Monitoring

Usually determined by the underlying lesion.

PATIENT EDUCATION

Family members benefit from an explanation of language impairment. They often do not understand that patients' answers may not reflect true understanding of questions asked. National Aphasia Association. Website: www.aphasia.org

PROGNOSIS

Aphasia following stroke generally improves the most in the first 3 months but may continue getting better at a slower rate for 1–2 years. Global aphasia often evolves into Broca's, while Wernicke's may become conduction or anomic during recovery.

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebrovascular disease

CODES

ICD9

784.3 Aphasia

CLINICAL PEARLS

- Some confused patients actually have a Wernicke's aphasia.
- Spared repetition indicates transcortical aphasia.

ATAXIA

Magali Fernandez, MD

BASICS

DESCRIPTION

Ataxia is defined as incoordination of movements, especially voluntary movements. Gait, limb movements, balance, speech, eye movements, and tone can be involved. Ataxia may be of sudden or insidious onset. Irregular movements are especially prominent with directed movements of the limbs and become more pronounced closer to the target (hypermetria, intention tremor). Gait is wide based and unsteady. Speech may be hesitant or explosive. Nystagmus and irregular eye movements may be seen.

EPIDEMIOLOGY

Incidence

No reports available.

Prevalence

- The National Ataxia Foundation estimates that there are 150,000 individuals affected by either a hereditary or sporadic ataxia in the US.
  - Prevalence of the autosomal dominant cerebellar ataxias (ADCAs) in Europe is estimated to be between 1 and 3 per 100,000 Europeans (1).

RISK FACTORS

- Acquired ataxias:
  - Excessive alcohol consumption, drug or toxin exposure, nutritional deficiencies.

Genetics

- The hereditary ataxias progress slowly and can be classified by type of inheritance.
  - In autosomal-dominant ataxias, risk to offspring (of being affected) is 50%.
  - In autosomal-recessive forms, risk to siblings is a 25% chance of being affected, 50% of being an unaffected carrier, and 25% chance of being unaffected and not a carrier. Offspring of an affected individual are obligate carriers.
  - In X-linked recessive inheritance, all daughters of an affected male are carriers; sons are not affected. For siblings, if the mother of the affected individual is a carrier, brothers are at 50% risk of being affected; sisters have a 50% chance to be carriers and unaffected.
  - Mitochondrial disorders are transmitted by maternal inheritance. Males do not transmit mitochondrial DNA mutations. A female with a mitochondrial (mt) DNA mutation may transmit a variable amount of mutant mtDNA to her offsprings, which results in clinical variability among siblings in the same family.

GENERAL PREVENTION

- There are no specific treatments, prophylaxis, or vaccines available for sporadic or hereditary ataxia, with the exception of:
  - Vitamin E therapy for ataxia with vitamin E deficiency (AVED).

PATHOPHYSIOLOGY

Varies depending on the specific cause of ataxia. Ataxia is most commonly related to disruption of cerebellar pathways. However, coordinated movements require synchronization of multiple sensory and motor pathways, and injury to the spinal cord, brainstem, cortex or peripheral nervous system can also cause ataxia.

ETIOLOGY

- Cerebellar ataxia may be acquired or genetic.
  - The acquired ataxias include Toxic, vascular, infectious, imflammatory/demyelinating, endocrine, neoplastic/paraneoplastic, metabolic/nutritional, degenerative causes.
  - The hereditary spinocerebellar ataxias (SCAs): Most are caused by trinucleotide repeat expansions.

COMMONLY ASSOCIATED CONDITIONS

- Mitochondrial disorders are frequently associated with other manifestations: Seizures, diabetes mellitus, cardiomyopathy, short stature, retinopathy, and deafness.
- Ataxia telangiectasia is associated with recurrent infections and susceptibility to malignancies.

DIAGNOSIS

HISTORY

Age of onset, family history, and drug, alcohol, or toxin exposure should be elicited. Determine if the ataxia is static or progressive and if the symptoms are intermittent or permanent. Association with acute headache, nausea, vomiting, and/or diplopia may be a sign of acute cerebellar infarct or hemorrhage and should be treated as potentially life threatening. In older males with recent onset ataxia and tremor inquire about grandchildren with mental retardation to assess for the fragile X-associated tremor/ataxia syndrome.

PHYSICAL EXAM

Ataxia may be cerebellar or sensory in origin or both. The brainstem, basal ganglia, spinal cord, retina, or peripheral nervous system are often involved. There is great overlap in the phenotype of the hereditary SCAs. There are a few distinguishing features for some types. Molecular diagnosis is needed for definitive classification.

- Distinguishing features of some autosomal-dominant hereditary ataxias:
  - SCA2: Slow saccadic eye movements, hyporeflexia, or areflexia
  - SCA4: Sensory axonal neuropathy
  - SCA6: Sometimes episodic ataxia is present
  - SCA7: Visual loss with retinopathy
  - SCA10: May be associated with seizures
  - SCA12: Early tremor, late dementia
  - SCA13: Mild mental retardation and short stature
  - SCA14: Early axial myoclonus
  - SCA16: Head and hand tremor
  - DRPLA: Chorea, seizures, and myoclonus
  - EA1: Episodic ataxia lasting seconds/minutes, myokymia
  - EA2: Episodic ataxia lasting minutes to hours, nystagmus (2,3)
- Distinguishing features of the autosomal-recessive disorders:
  - Friedreich ataxia (FA): Hyporeflexia or areflexia, extensor plantars, depressed vibratory/proprioceptive sense, and cardiac involvement
  - AVED: Similar to FA, plus head titubation and dystonia
  - Ataxia telangiectasia: Telangiectasia, immunodeficiency, cancer and endocrine abnormalities
  - Ataxia with oculomotor apraxia: Oculomotor apraxia, choreoathetosis, and mental retardation
  - Spastic ataxia autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS): Pyramidal signs, peripheral neuropathy, and retinal striations
- X-linked disorder:
  - Fragile X-associated tremor/ataxia syndrome

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum levels of vitamin B_{12}, thyroid-stimulating hormone (TSH), and vitamin E should be checked. Heavy metal screening in cases of suspected exposure should be performed. Plasma amino acids and urine organic acids are helpful when an inherited metabolic cause is suspected. If the Miller-Fisher variant of Guillain–Barré syndrome is suspected (ataxia with areflexia and ophthalmoplegia), lumbar puncture for cell count and protein level and nerve conduction studies should be considered.
- Molecular genetic testing for patients with a family history.

Follow-up & special considerations

- DNA testing is commercially available for SCA1, 2, 3, 5–8, 10–15, 17–18, 23, 27, 28, DRPLA, EA1, 2, 5, and 6, FA, ataxia-telangiectasia, and other autosomal recessive ataxias (3). These tests are expensive. Genetic counseling prior to testing is advised.
- A premutation (an increased number of CGG repeats under the full mutation range) in the fragile X (FMR1) gene on the X chromosome may result in fragile X-associated tremor/ataxia syndrome. Specific tests for this are available.

Imaging

Initial approach

Cranial MRI may identify structural abnormalities including infarcts, hemorrhage, tumors, and demyelination. Atrophy of involved structures in the brain or spinal cord can be found in some neurodegenerative disorders.

Follow-up & special considerations

MRI may be repeated in patients with no initial findings.

Diagnostic Procedures/Other
Antigliadin antibodies and glutamic acid decarboxylase antibodies (GAD-Abs) should be searched in all patients with cerebellar ataxia of unknown etiology. Paraneoplastic cerebellar syndrome is associated with anti-Yo, -Hu -Ri, -Ta, -Ma, or -CV2. Paraneoplastic symptoms may be the first sign of an occult cancer. In ataxia-telangiectasia, serum electrophoresis shows decreased concentrations of immunoglobulin A (IgA) and immunoglobulin G (IgG), while serum α-fetoprotein levels are elevated. Cultured cells show cytogenetic abnormalities and increased sensitivity to ionizing radiation. The percentage of sporadic ataxia patients with no apparent acquired cause who test positive for a genetic test is about 13% (4C).

Pathological Findings
Muscle biopsy may confirm a mitochondrial disorder.

DIFFERENTIAL DIAGNOSIS
- Vascular: Infarcts, hemorrhage, vasculitis
- Structural: Tumors, abscess, arteriovenous malformations, Chiari malformations
- Multiple sclerosis
- Infectious: Postinfectious cerebellitis, Gerstmann–Sträussler syndrome, Creutzfeldt–Jakob disease (CJD)
- Toxins: Alcohol, anticonvulsants, heavy metals, toluene, cytarabine (ara-C), cyclosporine
- Endocrine: Hypothyroidism
- Nutritional: Vitamin E deficiency, vitamin B_{12} deficiency, Wernicke–Korsakoff disease
- Immune: Gluten sensitivity and glutamic acid decarboxylase antibodies, Miller-Fisher variant of Guillain–Barré syndrome
- Paraneoplastic cerebellar degeneration
- Sporadic neurodegenerative diseases: Cerebellar cortical atrophy, multiple system atrophy
- Hereditary:
  - Autosomal dominant: SCA 1-31 and 36, DRPLA, episodic ataxia types 1–6. Autosomal dominant spastic ataxia.
  - Autosomal recessive: FA, ataxia telangiectasia, AVED, infantile-onset spinocerebellar ataxia, ataxia with oculomotor apraxia, Marinesco–Sjögren, spastic ataxia (ARSACS), myoclonus-ataxia syndromes, ataxia with hypogonadism
  - X-linked: X-linked ataxia with spasticity, X-linked ataxia with sideroblastic anemia, X-linked ataxia with deafness and blindness and fragile X-associated tremor/ataxia syndrome
  - Mitochondrial: Neuropathy, ataxia, and retinitis pigmentosa (NARP), myoclonic epilepsy and ragged-red fiber disease (MERRF)
  - Metabolic: Abetalipoproteinemia, hexosaminidase deficiency, Refsum disease

TREATMENT

MEDICATION
First Line
- In most cases, no effective medications are available.
- Adults with vitamin E deficiency: Replace with 60–75 IU PO or IM. Adjust dosage to normal plasma levels.
- Thiamine deficiency in chronic alcoholics and malnourished patients: Thiamine 50 mg PO daily. In Wernicke encephalopathy, thiamine 50–100 mg IV and IM immediately, 50 mg/day IM for 3 days, and then 50 mg PO daily. Higher dosages may be necessary at times.
- Vitamin B_{12} deficiency: Cyanocobalamin 1,000 μg IM daily for 5–7 days, then weekly for a month and then monthly for life.
- For episodic ataxia: Acetazolamide (3).

Second Line
Stroke prevention, multiple sclerosis, or cancer treatment as indicated.

ADDITIONAL TREATMENT
General Measures
Protect from fall risks; acute-onset ataxia needs to be treated as a possible neurosurgical emergency. Cerebellar hemorrhages and large infarcts are associated with a high risk of swelling and may compromise brainstem respiratory centers leading to death—rapid imaging needed.

Issues for Referral
Patient and families with a diagnosed hereditary ataxia should receive genetic counseling.

Additional Therapies
Physical, occupational, and speech therapy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Antiemetics for nausea and vomiting; eye patching for diplopia.
- Antispastic medications for those with spasticity.
- Patients with GAD-Abs and the Miller-Fisher variant of Guillain–Barré syndrome may respond to IV immunoglobulin.

SURGERY/OTHER PROCEDURES
Decompression of hematomas or infarcts associated with edema compressing the cerebellum, brainstem, and fourth ventricle, surgical removal of tumors.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Assess patient condition and look for signs of increased intracranial pressure and brainstem compromise.

Admission Criteria
Acute ataxia associated with inability to walk generally requires admission and evaluation.

IV Fluids
Avoid hypotonic fluids.

Nursing
Protect from fall risks.

Discharge Criteria
Discharge criteria include assurance of safety from falls.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
In ataxia secondary to acute cerebellar stroke or hemorrhage, patients are followed closely (often in the ICU for cerebral edema and brainstem compromise).

DIET
- Gluten-free diet may benefit patients with antigliadin antibodies.

PATIENT EDUCATION
- National Ataxia Foundation
- International Network of Ataxia Friends

PROGNOSIS
Prognosis depends on the underlying etiology.

COMPLICATIONS
Acute cerebellar conditions may present with increased intracranial pressure such as in vascular events and structural lesions.

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See Also (Topic, Algorithm, Electronic Media Element)
- Cerebellar ataxia
- Spinocerebellar ataxia
- Friedreich's ataxia

CODES

ICD9
- 334.0 Friedreich's ataxia
- 334.3 Other cerebellar ataxia
- 781.3 Lack of coordination

CLINICAL PEARLS

Ataxia may be acquired or genetic: Percentage of sporadic ataxia patients with a positive genetic test is about 13%.

BACK PAIN

R. Douglas Orr, MD

BASICS

DESCRIPTION

Back pain is a symptom and not a diagnosis. It is the final common pathway through which numerous pathologies can express themselves. Different pathologies can cause different patterns of pain and have different prognosis and treatment. The vast majority of back pain is benign and self limiting, but in some cases it may represent significant pathology or become chronic. Recently, numerous review and clinical practice guidelines have been published, which have greatly helped clarify diagnosis and treatment recommendations (Dagenais et al., 2010).

EPIDEMIOLOGY

Incidence

Axial back pain is very common. Approximately 80% of the population suffers at least 1 significant episode of back pain defined as back pain lasting more than a day that limits activities. In any given year, 38% of the population reports an episode of back pain (Hoy et al., 2010).

Prevalence

At any given time, 18% of the population is estimated to have back pain (Hoy et al., 2010)

RISK FACTORS

Although many different risk factors have been identified, recent reviews show that there are a few risk factors for onset of back pain. Genetics, smoking, and low-frequency vibration probably have the strongest associations with back pain. Although occupational exposures are widely accepted as causes of back pain, objective studies are inconsistent in the relationship between work-related factors and episodes of back pain (Hartvigsen et al., 2003)

Genetics

As noted above. No specific genetic markers.

GENERAL PREVENTION

Evidence is limited on the benefit of special training or equipment to avoid back injury. Maintaining good physical fitness and weight reduction may be beneficial in prevention.

PATHOPHYSIOLOGY

Most acute episodes of lumbar back pain are felt to be due to muscular injury or strain. The underlying findings of disk degeneration are weakly correlated with the acute episodes of back pain. The process of disk degeneration is ubiquitous. In asymptomatic individuals, the incidence of disk degeneration on MRI is essentially equal to age in years. Acute disk herniation is correlated with acute radiculopathies. Spinal stenosis is correlated with claudicant pattern leg pain.

DIAGNOSIS

HISTORY

Elucidating the pattern of pain is often the first step in establishing a diagnosis. Acute injuries occurring with lifting or other work-related activities usually indicate a lumbar strain. Pain of more insidious onset is more typical of disk degeneration. Associated symptoms are important in establishing more ominous diagnoses.

Definitions

- Axial back pain: Pain located in the midline or paraspinal area of the back. It may be central or located more to 1 side.
- Mechanical back pain: Pain that occurs with mechanical strains on the back such as sitting, standing, or changes in position. Typically this pain is relieved by lying supine.
- Myofascial pain: Pain thought to arise from muscle or fascial tissue that often crosses dermatomes and may be associated with trigger points; may not be relieved by rest.
- Radicular pain: Pain radiating in the distribution of a nerve root.
- Sciatica Pain: Pain in the distribution of the sciatic nerve.
- Dermatomal pain: Pain in the cutaneous distribution of the nerve root.
- Myotomal pain: Pain in the muscular distribution of the nerve root.

Lumbar strain is the most common cause of episodes of acute low back pain. They are often associated with lifting, bending, or twisting injuries. Pain may begin immediately or after a delay of 24–48 hours.

Acute disk herniation will often present with axial back pain before the onset of radiculopathy, and this is thought to be due to an annular tear. Associated radicular pain will follow the distribution of the affected nerve.

- L2/3 Upper thigh
- L3/4 Anterior thigh to knee and sometime anterior shin
- L4/5 Posterior thigh and calf to dorsal surface of the foot
- L5/S1 Posterior thigh to lateral margin of the foot

Facet pain is axial back pain with activity such as standing or walking relieved by flexion or sitting and is often thought to be due to facet degeneration. The hallmark of this pain pattern is lack of symptoms when sitting; much more common in 7th and 8th decade.

Spondylolisthesis can lead to back pain and radicular symptoms. In younger patients, the isthmic form is more common and is typical at L5/S1. It may be associated with repetitive hyper extension. Sports such as gymnastics, figure skating, and football lead to increased incidence though there is a genetic component. In older patients, the degenerative form is more common and typical at L4/5.

Tumors and infections are much less common causes of axial back pain. They typically are associated with other symptoms and should be suspected in any patient with a previous history of malignancy or with recent systemic infections. Night pain in the absence of mechanical stresses is sometimes indicative of these diagnoses.

Fractures in older patients or patients on long-term corticosteroid therapy: Sudden onset back pain may indicate the presence of an osteoporotic vertebral compression fracture even in the absence of trauma. This pain generally worsens with changes in position and is often felt a higher in the spine such as the thoracolumbar junction.

Visceral diseases: Back pain may also be a symptom of visceral disease. Retroperitoneal pathology such as renal disease or vascular diseases may present with back pain. Pelvic pathologies such as rectal cancers and gynecologic malignancies may also present with back pain. Pain tends to be more constant and not as affected by activity.

PHYSICAL EXAM

The main goal of the physical exam is to rule out more significant causes of pain. The exam in an acute episodic low back pain tends to be benign. There may be some paraspinal tenderness or spasm noted. A detailed neurological exam should be performed to look for neurological signs or symptoms. Nerve root tension signs such as straight leg raise or femoral stretch may indicate the presence of an acute disk herniation.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

There are no lab tests that are indicated in a routine investigation of back pain. In patients with suspected malignancy or infection, these may be part of the workup. ESR and C-reactive protein are the best tests in the presence of a suspected infection. Serum protein electrophoresis (SPEP) is indicated in the workup of suspected multiple myeloma or plasmocytoma. HLA B 27 can indicate the diagnosis of ankylosing spondylitis, but it is important to remember that there will be many more false positives than true positives.

Imaging

Initial approach

In the majority of cases of acute episodic low back pain, there is no indication for imaging. The Quebec Task Force on low back pain identified a series of 'red flags' that are indications for imaging at first presentation of acute low back pain. These red flags are:

- Age <15 or >50 at first onset of pain
- Any history of malignancy
- Recent history of significant trauma
- Constitutional symptoms such as fevers, chills, unexplained weight loss
- Duration of pain exceeding 6 weeks
- Progressive neurological deficit

Standing AP and lateral radiographs with a spot view of L5-S1 are the first screening test. They show abnormalities of alignment, disk degeneration, and any fractures. Very little is added by getting flexion extension films or oblique films.

MRI is the most sensitive test to look for lumbar pathology. Its drawback is relatively low specificity. Screening studies in asymptomatic individuals show high rates of MRI abnormalities. There is no role for routine use of gadolinium unless malignancy is suspected.

CT scan is excellent for assessing bony abnormalities. It can be used to assess the stenosis. When combined with myelography, it is a good substitute for MRI in patients for whom MRI cannot be obtained.

Bone scan does not have a lot of use in the diagnoses of acute low back pain. It may be used in assessing the acuity of compression fractures in patients unable to have MRI.

Diagnostic Procedures/Other

Although commonly used, there is really no indication for EMG testing in the workup of low back pain. It may have use in radicular syndromes or to differentiate peripheral from central causes of neurogenic symptoms.

TREATMENT

MEDICATION

Most back pain is self limiting in nature, and the goal of treatment is symptom control and maintenance of function. Bed rest is to be avoided. Chronic back pain is more complex and difficult to treat.

Nonsteroidal anti-inflammatories are effective in the early stages. They have both analgesic and anti-inflammatory effects. Numerous options exist and patient response may be idiosyncratic; so it is reasonable to try multiple options prior to moving on to other options.

- Naproxen 250–500 mg q12h
- Ibuprofen 400–800 mg q8h
- Oxaprozin 600 mg q12h

Pulsed corticosteroids are sometimes used although definitive studies of their effectiveness are lacking.

Antidepressants have multiple effects and may be very beneficial as a component of polypharmacy in chronic pain:

- Amitriptyline 10–100 mg q.h.s.
- Fluoxetine 10–80 mg daily
- Paroxetine 10–40 mg daily

Membrane stabilizers such as gabapentin or pregabalin may be useful for the treatment of radicular syndromes but in general have little use in axial back pain. They have been shown effective in treatment of spinal stenosis:

- Gabapentin 100–300 mg t.i.d.
- Pregabalin 50–150 mg q8–12h

Narcotic analgesics have been extensively used and misused. They should be used judiciously and ideally for only short periods of time. They may be valuable in allowing a quicker return to function, but the risks of dependency and tolerance are not insignificant. Long-term use of narcotics for uncomplicated back pain is controversial (Altman and Smith, 2010).

- For short term moderate pain:
  - Hydrocone/acetaminophen 5/500 1–2 q6h
  - Codeine 30–60 mg q4–6h
- For short term severe pain:
  - Oxycodone 5–10 mg q4–6h
- Long-term narcotic:

Should be done under strict supervision and a narcotic contract. Use long acting medications with short acting for breakthrough

- Oxycodone-sustained release 20–80 mg q8–12h
- Morphine-sustained release 20–80 q12h
- Methadone 5–30 mg q12h

A physical therapy program based on active exercise is the mainstay of acute treatment and long-term prevention of relapse or chronicity. If the patients have a directionality to their pain pattern, then it is recommended that the dominant exercise should be opposite the painful direction (i.e. those who have pain worsening with extension should exercise in flexion) Passive modalities such as heat, cold, ultrasound and transcutaneous electrical nerve stimulation have the primary goal of reducing symptoms to allow an active exercise program to be done. They are not in and of themselves sufficient treatment.

ADDITIONAL TREATMENT

Multiple injection therapies have been advocated. These include facet blocks, facet rhizotomies, epidural injections, selective nerve root blocks and trigger point injections. Although epidural injections and nerve blocks may be beneficial in the treatment of radicular syndromes, there is little evidence for their efficacy in the treatment of axial back pain. The effectiveness of facet blocks and facet rhizotomies in the treatment of chronic axial back pain has not been clearly established, but there is reasonable evidence for its use (Chou et al., 2009b)

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Manipulation has been shown in some studies to be effective in the treatment of acute episodic low back pain irrespective of whether it is delivered by chiropractors, physical therapists, or osteopaths. It has not been shown to be effective for the prevention of recurrences or for chronic pain (Bishop et al., 2010)

SURGERY/OTHER PROCEDURES

Surgery is rarely indicated for the treatment of axial back pain. In the presence of documented instabilities or deformities or as an adjunct to decompressive surgery for radicular syndromes, it is well accepted. In the rare case of a patient with a relatively focal disease, who has not responded to other conservative therapies, fusion has been shown to be effective. Surgery for axial back pain in the absence of radicular syndromes really should not be considered until a minimum of 6 and more likely 12 months of conservative care has been tried. Results of psychometric testing have been shown to correlate highly with outcome from surgery. Patients who score high on measures of anxiety, depression, and hypochondriasis have poor outcomes and should not be considered candidates for surgery (Chou et al., 2009a)

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ADDITIONAL READING

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CODES

ICD9

- 724.2 Lumbago
- 724.4 Thoracic or lumbosacral neuritis or radiculitis, unspecified
- 724.5 Backache, unspecified

And for multiple others see specific etiology.

CLINICAL PEARLS

Acute back pain is very common and early mobilization with judicious nonsteroidal anti-inflammatory treatment is appropriate in most cases.

BENIGN PAROXYSMAL POSITIONAL VERTIGO

Judith A. White, MD, PhD

BASICS

DESCRIPTION

- Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of vertigo bringing patients to medical attention. Vertigo lasting for seconds to minutes is repeatedly provoked by changes in head position relative to gravity, such as lying back or rolling over in bed.

EPIDEMIOLOGY

Incidence

- One-year incidence 0.6%
- Between 17 and 42% of patients with vertigo are diagnosed with BPPV.
- Occurs across the lifespan, with increasing risk of 38% with each decade of life.

Prevalence

- Estimated lifetime prevalence of 2.4% in the general population.

Cost

- Of patients, 86% have interruption of their daily activities, and on average over 2,000 dollars per patient is spent in diagnostic studies.
- BPPV increases fall risk, with concomitant significant morbidity and societal cost from falls.

RISK FACTORS

- Head injury, recent ear surgery or vestibular insult such as vestibular neuritis, repetitive work while looking up (such as ceiling painting or under-car repair), high-impact exercise, inverted positioning during yoga, possibly migraine.

Genetics

- There is no known genetic association with BPPV.

PATHOPHYSIOLOGY

- Otoconia in the inner ear detach from the utricle and move into the semicircular canals, where they render the canals gravitationally sensitive by floating and acting as a plunger on the endolymph during changes in head position. Posterior semicircular canal involvement is the most common (94%), although lateral semicircular canals can also be involved (5–15%) and some anterior canal cases may be seen.

DIAGNOSIS

HISTORY

- Patients often report the onset of vertigo when rolling over in bed, lying down, arising from bed, bending over or looking up. Sometimes, symptoms occur in the dentist chair or beauty parlor during shampoo. Vertigo usually lasts for minutes, and is reproducible in the provoking position. Especially in older patients, equilibrium may be decreased and fall risk is increased. Episodes usually last for weeks, but in 31% of untreated patients episodes may persist more than 1 year.

PHYSICAL EXAM

- Otoscopic visualization of the tympanic membranes is necessary to rule out other structural ear disease, such as cholesteatoma.
- Positioning maneuvers are important in establishing the diagnosis of BPPV. The Dix–Hallpike maneuver, developed in 1952, is performed with the patient seated on an exam table. The head is turned 45 degrees to the side, and the patient quickly lies back flat while holding the head turned to the side. The neck may be extended slightly but care should be taken to avoid neck strain. The characteristic nystagmus of BPPV is delayed by a few seconds, is briskly torsional and upbeat, and lessens after 10–30 seconds. If no nystagmus is seen after lying to the initial side, the patient returns to sitting and the opposite ear is similarly tested. The presence of the characteristic nystagmus is highly predictive of posterior semicircular canal BPPV.
- If posterior canal BPPV is not identified, testing of the lateral canals can be performed by laying the patient in the head-centered supine position, and turning the head to the right and the left while remaining supine. Lateral canal BPPV, first described in 1985, provokes brisk horizontal paroxysmal nystagmus that reverses direction when the head is turned to the contralateral side while supine.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Laboratory tests are of limited benefit in the diagnosis of BPPV.

Imaging

Initial approach

- Imaging is reserved for cases of atypical nystagmus, or persistent positional vertigo not responding to repositioning maneuvers.

Follow-up & special considerations

- CT scan is helpful to evaluate superior semicircular canal dehiscence in persistent cases of positional nystagmus. MRI with contrast brain is indicated in atypical or persistent positional vertigo failing repositioning maneuvers.

Diagnostic Procedures/Other

- Infrared video nystagmography or optical Frenzel lenses may be helpful in visualizing nystagmus, especially in atypical or persistent cases.
- Full vestibular testing, including ocular motor, caloric, and rotary chair testing, may be appropriate in atypical or persistent cases when a comprehensive evaluation of vestibular function is desired.

Pathological Findings

- Basophilic deposits have been seen adherent to the cupula of the posterior semicircular canal in temporal bone specimens, and free floating otoconia have been visualized during canal fenestration in patients undergoing canal occlusion surgery.

DIFFERENTIAL DIAGNOSIS

- The characteristics of the nystagmus are important in differentiating BPPV from other disorders. Nystagmus typical for posterior canal BPPV is paroxysmal, torsional and upbeat, and fatiguing during Dix–Hallpike. Lateral canal BPPV nystagmus is horizontal and reversing in direction during supine head turns.
- Nystagmus that is horizontal and beats in the same direction throughout multiple positions suggests acute vestibular syndrome (see Dizziness section). When acute vestibular syndrome is accompanied by marked postural dyscontrol, central acute pathology such as cerebellar infarction is a consideration.
- Vertical or disconjugate nystagmus suggests central pathology.

TREATMENT

MEDICATION

First Line

- Medication is of limited benefit in BPPV. Several controlled randomized trials have found no symptomatic or therapeutic benefit of vestibular suppressants.

ADDITIONAL TREATMENT

General Measures

- Fall prevention and prevention of dehydration.

Issues for Referral

- Persistent symptoms of paroxysmal positional vertigo despite repositioning maneuvers, atypical nystagmus, and vertigo not explained by BPPV.

Additional Therapies

- The canalith repositioning maneuver is highly effective in treating posterior semicircular canal BPPV (single treatment efficacy 78%, multiple treatment efficacy over 90%). The maneuver is initiated when the characteristic nystagmus is seen during Dix-Hallpike testing. Without returning to sit, the patient slowly rolls onto the unaffected side until the nose is pointed toward the floor. Then they are slowly returned to sit with chin tucked and head still turned to the unaffected shoulder. The maneuver may be repeated, starting with the Dix-Hallpike position on the affected side.
- Lateral canal BPPV may be initially treated with 360 degree roll maneuvers while supine. If symptoms persist, examination of nystagmus direction and amplitude help to establish the affected ear and appropriate maneuver.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Vestibular physical therapy is very effective in treating BPPV. Trained vestibular physical therapists are familiar with BPPV nystagmus and perform repositioning maneuvers routinely. They also can assess and remediate fall risk.

SURGERY/OTHER PROCEDURES

- In less than 1% of cases, surgical canal occlusion is necessary due to persistent of frequently recurrent posterior canal BPPV. Once the canal is occluded, the floating otoconial debris cannot cause endolymph movement

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Patients rarely need admission for BPPV unless it provokes nausea and vomiting unresponsive to anti-emetics and vestibular suppressants.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Following canalith repositioning for BPPV, many patients benefit from a follow-up visit to recheck their nystagmus, and receive information on performing self-repositioning maneuvers in the event of recurrence. Recurrence of BPPV is estimated at 15% per year.

PATIENT EDUCATION

- Patient education in identifying and self-treating recurrent BPPV is helpful. Generally, we advise patients to seek help if their own repeated attempts to reposition recurrent BPPV are not successful.

COMPLICATIONS

- BPPV and repositioning maneuvers may provoke nausea and vomiting in some patients.
- Care should be taken to avoid neck strain during positional and positioning test and maneuvers.

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CODES

ICD9

- 386.9 Unspecified vertiginous syndromes and labyrinthine disorders
- 386.11 Benign paroxysmal positional vertigo

CLINICAL PEARLS

- BPPV is easy to identify and treat with positioning testing and canalith repositioning maneuvers.
- Posterior canal BPPV is most common, followed by lateral canal. Both can be tested at the bedside.

BRAIN HERNIATION SYNDROMES AND MANAGEMENT

Christopher R. Newey, DO
Joao Gomes

BASICS

DESCRIPTION

- The cranial vault is a fixed area composed of parenchyma (~1,200 cc or 80%), CSF (~150 cc or 10%) and blood (~150 cc or 10%). The Monroe–Kelli doctrine states that an increase in one of these constituents must be balanced by a decrease in another constituent. Herniation is the shift of brain tissue from its proper location to a new location. The cerebral hemispheres can absorb some degree of distortion from mass effect and increases in intracranial pressure (ICP) as long as blood and CSF can be displaced extracranially. ICP can be reflected as changes in compliance. Compliance is defined as the change in volume divided by the change in pressure. This is not a linear relationship. When compensatory mechanisms are exhausted, brain tissue may herniate to an area of lower pressure/volume. The location of the herniated tissue determines the type of clinical syndrome. Several herniation syndromes have been described:
  - Subfalcine herniation: Lateral supratentorial lesions herniating the cingulate gyrus under the falx cerebri. This may compromise blood flow to the anterior cerebral artery resulting in leg weakness and or mutism due to anterior cerebral artery infarction.
  - Uncal (also known as lateral) herniation: Mesial temporal lobe lesions herniating medially displacing the midbrain resulting in pupillary dilation from compression of the third nerve and contralateral hemiparesis from ipsilateral cerebral peduncle. Ipsilateral hemiparesis may result if contralateral cerebral peduncle is compressed (i.e., Kernohan's phenomenon).
  - Central transtentorial herniation: Supratenorial mass causing downward pressure on midbrain and diencephalon resulting in altered level of consciousness, posturing, and respiratory compromise.
  - Cerebellar (tonsillar) herniation: Mesial aspect of cerebellum (tonsils) into the foramen magnum resulting in alterations in respiration, autonomic functions, vertigo, skew deviation, vomiting, and coma/death.
  - Upward transtentorial herniation: Upward herniation of infratentorial compartment (cerebellum/brainstem) through tentorium resulting in pupillary dysfunction, vertical gaze paresis, decerebrate posturing, respiratory changes, and coma.
  - Transcalvarial herniation: Herniation of cortex through skull defect.

PATHOPHYSIOLOGY

- Brain herniation can cause injury in several ways.
  - When there is little compensatory room for brain tissue to continue herniating, the diencephalon and midbrain can be affected—either laterally, rotationally, or downward. The degree of displacement corresponds to the level of impaired consciousness.
  - Compression of arterial supply (e.g., posterior cerebral artery (PCA) at the edge of the tentorium or anterior cerebral artery at the edge of the falx cerebri) during herniation can cause infarction of the brain parenchyma.
  - Increasing intracranial CSF due to outflow blockage (obstructive hydrocephalus). For example, blockage of the aqueduct of Sylvius may occur with posterior fossa herniation syndromes.

RISK FACTORS/ETIOLOGY

- The etiology of brain herniations can be grouped as follows:
  - Masses: Tumors, hematomas, abscess, air, foreign body
  - Vascular: Increased cerebral blood flow/cerebral blood volume (CBV) from exhausted autoregulation, cerebral venous thrombosis
  - Edema: Cytotoxic (ischemia, ATPase pump failure), vasogenic (vessel injury from tumor, abscess), hydrostatic (transmural pressure from hydrocephalus), hypo-osmolar (hyponatremia), hyper-ammonemia (liver failure)
  - CSF excess: Hydrocephalus (obstructive or nonobstructive), overproduction (papilloma)

DIAGNOSIS

HISTORY

- The key to diagnosis is recognizing that cerebral herniation is a possibility.
- The history should document time of onset, prior cancer, recent stroke, coagulopathy, infectious history, trauma, preceding headache, nausea/vomiting, and hiccuping.

PHYSICAL EXAM

First, assess the airway, breathing, and circulation. Identify the Cushing's response if present. This is an increase in blood pressure and fall in heart rate with respiratory abnormalities. Make note of the breathing patterns given the localizable information they provide (e.g., Cheyne–Stokes (cortex), hyperventilation (midbrain), apneustic (pons), cluster (pons), and ataxic (medulla). Perform a Glasgow Coma Scale. Decorticate posturing localizes from the cortex to the red nucleus. Decerebrate posturing localizes from the red nucleus to the vestibular nucleus. Pupils can be small and reactive (diencephalic), fixed and dilated (third nerve palsy from compression of the uncus of the temporal lobe or the PCA), midposition and fixed (midbrain), pinpoint and reactive (pons), large and fixed with hippus (tectal). Papilledema and absent venous pulsation may be found on fundoscopy examination. Weakness is typically contralateral but can be ipsilateral to the herniation if the contralateral cerebral peduncle is also involved (Kernohan's notch).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Complete blood count (CBC), complete metabolic panel (CMP), partial thromboplastin time (PTT), prothrombin time (PT)/international normalized ratio (INR), arterial blood gas (ABG), serum osmolality, type and cross

Follow-up & special considerations

Serial neurological examinations with a focus on level of consciousness and changes in neurological function are critical in monitoring for cerebral herniation.

Imaging

Initial approach

CT head without contrast is necessary to rapidly identify type and extent of herniation, treatable underlying causes of herniation (e.g., bleeds or large infarcts), and secondary pathologies. Look for midline shift, degree of pineal shift, mass effect, effacement of basal cisterns and sulci, global or focal edema, and obstructive hydrocephalus. In traumatic brain literature, it is estimated that 10% of patients with increased ICP will have normal head CT.

Follow-up & special considerations

Serial neuroimaging (either MRI or CT) can be useful in confirming herniation as well as further identifying the underlying etiology.

Diagnostic Procedures/Other

- Measurement of ICP can be accomplished via several anatomic spaces including:
  - Intraventricular (gold standard, but with highest risk of hemorrhage and/or infection)
  - Intraparenchymal (lower rates of hemorrhage and infection, but inability to drain CSF as a therapeutic intervention)
  - Subdural
  - Subarachnoid
  - Epidural (typically used in patients with liver failure)

These locations are in reference to the foramen of Monro which is estimated by the external auditory meatus. Normal ICP is typically defined as <15–20 mm Hg. ICP waveforms have three components. P1 is the arterial wave, P2 is the rebound wave, and P3 is the venous outflow. An elevated P2 waveform indicates poor compliance.

Pathological Findings

- The emergence of elevated ICP (20–100 mm Hg) for several minutes to hours is called a plateau wave (Lundberg A wave). Lundberg B waves are an elevation of ICP (10–20 mm Hg) that lasts a few minutes and are thought to be related to respiratory fluctuations in $PaCO_2$. Lundberg C waves are rapid sinusoidal fluctuations corresponding to arterial pressure.

DIFFERENTIAL DIAGNOSIS

Cerebral herniation can result from any intracranial process causing mass effect. Diffuse processes are less likely to cause cerebral herniation.

- Seizure
- Metabolic coma with altered mental status
- Mydriasis with normal examination such as from beta agonists or anticholinergic medications or physiological anisocoria
- Meningeal irritation
- Migraine

TREATMENT

MEDICATION

- Osmotic agents:
  - Mannitol 20%: Typically loaded at 1–1.5 g/kg followed by maintenance of 0.5 g/kg every 4–6 h if needed. The goal is titrate to serum osmolarity of 300–320 mOsm. The half life is 0.16 h but is efficacious up to 1.5 to 6 h. Use in caution in patients with renal disease or patients who are volume depleted and/or hypernatremic.
  - Hypertonic saline (23%): Typically given at as a 30 cc bolus over 10–15 minutes via central access followed by 3% hypertonic saline infusion at 0.5–1 mL/kg/h with goal Na of 155–160. Be careful to not infuse 23% too rapidly as pulmonary edema and hypotension can occur.
  - Mannitol has a reflection coefficient of 0.9 compared to hypertonic saline of 1. Thus, mannitol is more likely to cross blood brain barrier resulting in gradient degradation.

ADDITIONAL TREATMENT

General Measures

- Optimize cerebral perfusion pressure (CPP = MAP-ICP) to >60–65 mm Hg
- Head of bed 30–45 degrees
- Neutral neck angle. Lateral rotation may collapse venous outflow and increase ICP.
- Treat agitation and pain
- Treat fever with acetaminophen and/or cooling devices (either surface or invravascular)
- Normocarbia
- Avoid hyper- or hypo-glycemia
- Minimize shivering
- Prompt nutritional support
- Prophylactically treat for seizures

Additional Therapies

- Hyperventilation to $PaCO_2$ of 25–30 mm Hg can reduce CBV and ICP. If actively herniating and on mechanical ventilation, disconnect patient from ventilation and manually bag. Transient benefit only from hyperventilation.
- Barbiturates: Pentobarbital at 10–20 mg/kg bolus followed by 1–4 mg/kg/h titration can reduce metabolic demand and thus decrease ICP.
- Induced hypothermia to 32–34°C can reduce cerebral oxygen metabolism and reduce inflammation.
- Paralytics can reduce metabolic demand but carry risk of intensive care units (ICU) myopathy/neuropathy.
- Steroids have been shown effective in vasogenic cerebral edema but not in other forms of cerebral edema (e.g. cytotoxic).

SURGERY/OTHER PROCEDURES

Neurosurgical evaluation is imperative in management of cerebral herniation syndromes. Surgical decompression may be an option for malignant cerebral edema in selecting patients with large infarcts. Patients are selected based on age, timing of surgery, and neuroimaging findings. Additionally, debulking surgery may be an option for tumors. Lastly, placement of ventricular pressure monitoring devices or ventricular drainage devices should be considered.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with signs and symptoms of increased ICP and brain herniation should be admitted to the ICU of the hospital. Discharge will be based on stabilization of the underlying cause.

Nursing

- Serial neurological examinations are necessary. These should be performed every hour.
- Cardiac and respiratory monitoring
- Strict ins and outs must be maintained

Discharge Criteria

Discharge will be determined upon stabilization of the underlying cause of the cerebral herniation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients should have follow up after discharge with appropriate departments. For example, ischemic strokes will need to be seen in stroke clinics, tumors will need to be seen in neuron-oncology clinics.

DIET

Prompt nutritional support should occur with either nasogastric tube or percutaneous endoscopic gastrostomy (PEG) tube.

PATIENT EDUCATION

ICUs are necessary for monitoring patients with cerebral herniation. Aggressive cardiac, respiratory, and ICP monitoring along with serial neurological examinations are necessary.

PROGNOSIS

The prognosis of cerebral herniation depends on the course and extent of the herniation, secondary injuries, and the primary pathology underlying the cerebral herniation.

COMPLICATIONS

- Patients need to be monitored for complications of prolonged bedrest and malnutrition. Patients should have serial duplex scans for Deep-vein thrombosis (DVTs). Prophylaxis for DVTs should be initiated if not contraindicated. Serial chest x-rays need to occur to evaluate for pneumonia, particularly in those patients who are intubated. Nutritional markers will need monitoring to ensure adequate nutrition.
- Once patients are able, physical and occupational therapy evaluations are recommended.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebral herniation
- Increased ICP
- Hydrocephalus

CODES

ICD9

348.4 Compression of brain

CLINICAL PEARLS

The key is to recognize patients at risk of herniating and also recognizing the clinical syndromes that occur with herniation. Once recognized, prompt treatment should be initiated along with neurosurgical consultation.

CHOREOATHETOSIS

Alexander D. Rae-Grant, MD

ALERT
Choreoathetosis may result from a variety of medications and this should be considered early in the differential diagnosis.

Geriatric Considerations
Dopaminergic agents particularly levodopa/carbidopa are prescribed commonly in this population and may cause variable choreoathetosis. Senile chorea occurs in this population as well.

Pediatric Considerations
There are specific syndromes of choreoathetosis in childhood.

Pregnancy Considerations
Choreoathetosis may occur in pregnancy de novo (see below).

BASICS

DESCRIPTION
Choreoathetosis is a combination of the term *chorea* and the term *athetosis*. These are two abnormal types of movement that are often combined in the same disorder. Chorea refers to rapid, involuntary, brief, irregular, and unpredictable jerks of muscles and can occur in the limbs, face, or trunk muscles. Athetosis is characterized by slow, writhing, uncoordinated involuntary movements usually involving the limbs, though similar movements may affect the face and trunk muscles as well.

- Definitions
- *Chorea:* Rapid, involuntary, brief, irregular movements
- *Athetosis*: Writhing, involuntary, slow, uncoordinated movements
- *Parakinesia*: A choreic movement camouflaged by a superimposed purposeful act
- Clinical characteristics
- Choreoathetosis may occur acutely or on a chronic basis, be transient, or be a persistent, lifelong phenomenon. It may interfere with the ability to speak, use the limbs, walk, or stand still. The movements may be unilateral (hemichorea), and at times are flinging (merging into hemiballismus, a separate but related disorder). Tone is usually reduced, but strength is unaffected. Patients may be unable to sustain a tight hand grip (milkmaid's hand). The tongue may dart in and out irregularly while attempting to protrude it

EPIDEMIOLOGY
Incidence/Prevalence
There is limited data on the prevalence of choreoathetosis. Huntington's disease (HD) is estimated to affect 1 in 10,000 persons of European descent.

RISK FACTORS
Genetics
- HD: Autosomal dominant, onset in 20s and 30s, with a combination of progressive chorea, a personality disorder and dementia. HD gene *(IT15)* on short arm of chromosome 4 (4p16.3).
- Other rarer genetic syndromes which can cause choreoathetosis.

GENERAL PREVENTION
- Avoiding use of medications that cause chorea, or limiting duration of use.
- Prevention of rheumatic fever from *Streptococcus*.

PATHOPHYSIOLOGY
Choreoathetosis is caused by a degeneration or fixed injuries to the striatum (putamen, globus pallidus, caudate), or is due to a biochemical imbalance affecting these parts of the brain. The basal ganglia are critical in modulating motor activity from the corticospinal tract, and help maintain the posture, tone, and amplitude of motor activity both at rest and in action. In HD selective loss of "spiny" neuron gabaergic cells may disinhibit thalamic neurons leading to hyperkinesis.

ETIOLOGY
- There are a large number of possible causes of choreoathetosis (1) including inherited genetic disorders such as HD, choreoacanthocytosis, Wilson's disease, and rarer syndromes; focal striatal pathology (stroke, tumor, etc.); drug induced, chorea gravidarum; thyrotoxicosis; SLE/antiphospholipid antibody syndrome; Postinfectious (Sydenham's chorea, PANDAS, Herpes encephalitis); Polycythemia rubra vera: AIDS affecting the brain; variant Creutzfeldt–Jakob disease.
- Medications that are associated with drug-induced choreoathetosis include Amantadine, Amphetamines, Anticonvulsants including phenytoin, carbamazepine and valproic acid, carbon monoxide poisoning, Cocaine-induced chorea ("Crack dancing"), Anticholinergics, Antihistamines, Azithrimycin, Benzodiazepines, Bronchodilators, Levo-dopa and dopa agonists, Lithium, Oral contraceptives, Phenothiazines, Sildenifil in PD males, Tricyclic antidepressants.

COMMONLY ASSOCIATED CONDITIONS
The commonly associated conditions include HD.

DIAGNOSIS

HISTORY
In a patient presenting with choreoathetosis, symptoms suggesting cognitive dysfunction (memory loss, altered judgment, impulsivity, altered sexuality) may suggest HD. The clinical setting suggests Sydenham chorea, chorea gravidarum, and chorea related to systemic disease or medications. Choreoathetosis related to prenatal and perinatal insults is usually self-evident. Signs to seek include presence of associated neurologic findings (hyporeflexia, sensory loss suggesting neuropathy; cognitive dysfunction; presence of focal signs suggesting stroke).

PHYSICAL EXAM
Watch patient for choreoathetosis at rest, while walking, or while doing tasks (may be incorporated into tasks). Other signs include associated neurologic findings (hyporeflexia, sensory loss suggesting neuropathy; cognitive dysfunction; focal signs suggesting stroke).

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
Directed by clinical circumstances. In suspected cases of systemic causes of choreoathetosis, with blood smear (polycythemia vera, neuroacanthocytosis), glucose (hyperosmolar nonketotic hyperglycemia), thyroid indices (thyrotoxicosis), liver function studies (Wilson's disease, kernicterus), antiphospholipid antibodies (antiphospholipid antibody syndrome). Genetic testing is available in HD but should be linked with counseling.

Follow-up & special considerations
See individual disorders.

Imaging
Initial approach
CT scanning and MRI may both show focal basal ganglia lesions causing choreoathetosis. In situations such as acute chorea, imaging to assess for infarction, hemorrhage, tumor, or vascular malformation may be useful. Carbon monoxide poisoning may show hypodensities in the globus pallidus bilaterally. In HD, MRI later in disease may show atrophy of both caudate nuclei. PET scanning may show caudate hypermetabolism in choreoathetotic disorders.

Follow-up & special considerations
See individual disorders.

Diagnostic Procedures/Other
These will depend on the specific etiologies under consideration. For example, slit lamp examination for Kayser–Fleischer rings in Wilson's disease.

Pathological Findings
Pathological findings vary depending on etiology.

DIFFERENTIAL DIAGNOSIS

- *HD*: Autosomal dominant, onset in 20s and 30s, with a combination of progressive chorea, a personality disorder and dementia. HD gene *(IT15)* on short arm of chromosome 4 (4p16.3).
- *Sydenham chorea*: Rheumatic chorea in childhood and adolescence, often hemichorea, occurring after rheumatic fever, now rare. Self-limited disease.
- *Senile chorea*: Late onset, generalized chorea, no family history, no dementia. Mild, slowly progressive. Various causes.
- *Chorea gravidarum*: Chorea occurring with pregnancy. May also be seen with use of oral contraceptives.
- *Choreoathetosis with medications*: May occur with dopaminergic medications (L-dopa, bromocriptine, newer dopaminergic medications). Occasionally with famciclovir (in dialysis patients), digoxin, oral contraceptives, and gabapentin. Case reports with cocaine use.
- *Choreoathetosis with surgery*: Choreoathetosis has been described after cardiac transplantation or after open heart surgery, usually in children.
- *Choreoathetosis with systemic diseases*: May occur with lupus erythematosus, thyrotoxicosis, polycythemia vera, and hyperosmolar, nonketotic hyperglycemia, antiphospholipid antibody syndrome, Creutzfeldt–Jakob disease.
- *Neuroacanthocytosis*: Familial multisystem progressive disorder with chorea, cognitive impairment, neuropathy, reduced reflexes, abnormal red cells (acanthocytes).
- *Developmental disorders*: A variety of prenatal and perinatal insults including kernicterus may cause choreoathetosis, which is nonprogressive and present from infancy or early childhood.
- *Rarer associations with choreoathetosis*: Neuro-Behçet's disease, stroke, tumors, vascular malformations, moyamoya, tuberculous meningitis, multiple sclerosis, Wilson's disease.
- *Hereditary nonprogressive chorea*: Rare autosomal-dominant disorder, with chorea, no dementia or progression, no other neurologic signs.
- *Paroxysmal kinesigenic choreoathetosis*: Choreoathetotic movements brought on by volitional movements. May be familial.
- *Dentatorubral-pallidoluysian atrophy*: Rare autosomal-dominant disorder sometimes confused with HD. Patients show chorea, myoclonus, ataxia, seizures, and dementia.

TREATMENT

MEDICATION

First Line

Treatment is primarily symptomatic unless there are specific medications for the etiology. There is no standard practice for suppression of choreoathetosis. Removal or reduction of offending medications first line.

Second Line

- Atypical and typical antipsychotics are moderately effective for suppressing choreoathetosis due to their dopamine depleting action. Potential side effects include akathisia, sedation, and tardive dyskinesia.
- Other dopamine depleting agents such as reserpine and tetrabenazine.
- Gabaergics such as clonazepam, gapentin, valproic acid.
- Intravenous immunoglobulin or plasmapheresis may shorten course of Sydenham's chorea.
- Chorea after heart transplant may respond to steroids.

ADDITIONAL TREATMENT

General Measures

Treatment is directed at symptomatic management of the movements of chorea and athetosis, if necessary. If choreoathetosis is the result of a specific disease, that disease management should be used. For severe chorea attention to avoiding injury is paramount.

Issues for Referral

Patients with choreoathetosis not due to readily identifiable medications or causes should be referred to either adult or pediatric neurology for evaluation. Families considering genetic testing for HD especially in presymptomatic candidates should have formal genetic counseling prior to testing to review the issues related to such testing.

Additional Therapies

Minocycline and coenzyme Q10 have been tried in animal models of HD but there is limited data on human trials.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Coenzyme Q10 as noted. Otherwise there are no specific CAM recommendations.

SURGERY/OTHER PROCEDURES

No reports available.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

See IV fluids. Avoid self-harm due to flinging movements if needed. Assess suicidality in HD cases.

Admission Criteria

Patients with acute onset of chorea may require hospitalization for diagnosis and stabilization. Patients with HD may require admission if at risk of harming themselves or others based on their psychiatric state.

IV Fluids

Some patients with severe choreoathetosis (e.g., Hemiballismus) may suffer from dehydration due to exertion and may need IV fluid replacement.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Follow-up recommendations depend on causation and disease course.

Patient Monitoring

Patient monitoring depends on causation.

DIET

No special diet in most cases.

PATIENT EDUCATION

The movement should be named and described for the patient. The etiology and prognosis if known or the possibilities if not known should be reviewed. If medication is used to suppress the movements the dosing, side effects, and expected effect should be reviewed.

PROGNOSIS

Prognosis depends on etiology.

COMPLICATIONS

The complications vary depending on etiology and severity.

REFERENCE

1. Wild EJ, Tabrizi SJ. The differential diagnosis of chorea. *Pract Neurol* 2007;7:360–373.

ADDITIONAL READING

- Walker FO. Huntington's disease. *Lancet* 2007;369: 218–228.

See Also (Topic, Algorithm, Electronic Media Element)

http://www.movementdisorders.org/UserFiles/file/flow%20chart.pdf (Flow chart evaluation chorea)

CODES

ICD9

333.5 Other choreas

CLINICAL PEARLS

- Valproate-associated choreoathetosis
- Consider Wilson's disease in young adult with new onset chorea

COMA

Douglas W. Scharre, MD

BASICS

DESCRIPTION

- Coma is a state of unconsciousness with complete absence of awareness of the environment even when externally stimulated; the most severe form of unresponsiveness.
  - Patient unarousable to verbal or noxious stimuli; eyes closed
  - No spontaneous eye opening, facial movements, utterances or body movements
  - Painful stimuli may produce non-directed reflexive movements from spinal cord or brainstem pathways but do not result in any conscious responsiveness
- Results from severe diffuse bilateral cerebral dysfunction or significant brainstem impairment
- Structural, metabolic, hypoxic, and infectious causes are typical
- Clinical presentation, examination, and laboratory and neuroimaging evaluations determine the specific cause and guide treatment options

EPIDEMIOLOGY

No typical age or gender predilection due to multiple potential causes for coma.

Incidence

Incidence varies with the cause of coma. Overall coma occurs in 6/100,000 general population and 31/100,000 in children <16 years (1).

Prevalence

Prevalence varies with the cause of coma.

RISK FACTORS

The risk factors comprise any condition causing diffuse bilateral cerebral dysfunction or brainstem impairment.

Genetics

No reports available.

GENERAL PREVENTION

As there are multiple potential causes for coma there are no general prevention guidelines.

PATHOPHYSIOLOGY

- Conscious behavior requires both arousal and cognitive processing
  - The brainstem reticular activating system (RAS) extending from the midpons to the hypothalamus is responsible for arousal
  - The cerebral hemispheres are responsible for cognitive abilities and processing
- Coma results only from conditions disrupting both cerebral hemispheres diffusely or the brainstem ascending reticular activating system
- The locked-in syndrome is not coma; it results from lesions below the midpons that preserves the RAS for arousal and the brain for consciousness

ETIOLOGY

- Diffuse encephalopathies
  - Cerebral anoxia/ischemia
  - Encephalitis/Meningitis
  - Subarachnoid hemorrhage
  - Vasculitis
  - Cerebral shower of emboli
  - Hepatic/uremic encephalopathy
  - Metabolic encephalopathy (e.g., hyponatremia)
  - Diabetes (ketoacidosis, hypoglycemia, nonketotic hyperosmolar coma)
  - Nutritional deficiency (thiamine)
  - Alcohol/narcotic abuse
  - Drug overdose/intoxication
  - Hypothyroidism
  - Sepsis
  - Seizures (nonconvulsive status epilepticus)
  - Hypothermia/hyperthermia
  - Hypertensive encephalopathy
- Structural lesions
  - Brain herniation syndromes
  - Brain or brainstem tumor or abscess
  - Epidural/subdural hematoma or empyema
  - Intracerebral/brainstem/cerebellar infarction or hemorrhage
  - Basilar artery thrombosis
  - Head trauma (cerebral contusion)

COMMONLY ASSOCIATED CONDITIONS

Structural, metabolic, hypoxic, infectious, and drug toxicity are most commonly associated.

DIAGNOSIS

HISTORY

- Ask about onset and time course of the coma
  - Sudden onset with rapid progression suggests stroke or hemorrhage; subacute courses may indicate tumor or abscess
- Coma proceeded by acute confusion without focal deficits suggest diffuse encephalopathies
- Ask about recent head trauma, progressive neurologic deficits (brain tumor), fever, infection, severe headache, stroke risk factors, seizures, current medications, drug or alcohol abuse, nutritional deficiencies, depression, diabetes, and organ failure (heart, lung, liver, and kidney)

PHYSICAL EXAM

- Observe for signs of head trauma
- Evaluate for stiff neck (meningitis or subarachnoid hemorrhage)
- Check vital signs and temperature
  - Elevated blood pressure (hemorrhage, stroke, or hypertensive encephalopathy)
  - Hypothermia (drug intoxication, hepatic encephalopathy, hypothyroid, hypoglycemia)
  - Hyperthermia (anticholinergic intoxication, heat stroke, status, hypothalamic lesions)
- Fundi
  - Papilledema and retinal hemorrhages suggest increased intracranial pressure
- Pupils
  - Normal to smaller and reactive (diffuse encephalopathies or hypothalamic compression)
  - Bilateral dilated and fixed (midbrain lesion, anoxia, drug intoxication: Anticholinergic, sympathomimetic, barbiturates, glutethimide)
  - Unilateral dilated and fixed (third nerve palsy)
  - Pinpoint reactive (pontine lesion, narcotic intoxication, organophosphate poisoning, and miotic eye drops)
- Extraocular movements
  - Check primary gaze for skews or deviations, roving eye movements; test oculocephalic (doll's) and oculovestibular (calorics) reflexes
  - Normal primary gaze with intact doll's and calorics (diffuse encephalopathies)
  - Normal primary gaze with impaired doll's and calorics (some drug intoxications: Tricyclics, barbiturates, antibiotics, benzodiazepines, succinylcholine, phenytoin; or preexisting vestibular dysfunction)
  - Dysconjugate gaze (structural lesions)
  - Deviated eyes toward lesion with intact doll's and calorics (supratentorial structural lesion)
  - Single downward deviated eye at rest that fails to adduct with doll's or calorics (third nerve palsy)
  - Skewed, deviated at rest (away from lesion) or normal primary gaze with absent doll's and calorics (pontine lesion)
- Brainstem reflexes
  - Corneal reflexes: Normal responses, direct and consensual (intact midbrain and pons)
  - Gag responses: If present (intact medulla)
- Motor examination
  - Look for spontaneous movements, check posture (laterally rotated legs, facial droop), tone, reflexes, response to noxious stimuli to extremity or face to detect hemiparesis, facial weakness, or other focal deficits
  - Repetitive movements: Limb or face (seizures)
  - Tremors, myoclonus, or asterixis (diffuse encephalopathies)
  - Flaccid tone (diffuse encephalopathies, pontine or medulla lesions)
  - Decorticate posturing to noxious stimuli: Arm flexion, leg extension (supratentorial or thalamic lesions, diffuse encephalopathies)
  - Decerebrate posturing to noxious stimuli: Arm and leg extension (subtentorial or brainstem)
- Transtentorial brain herniation
  - Progressive downward pressure on thalamus and brainstem due to supratentorial structural lesions or edema
  - Pupils: Progressing from small to mid-sized and nonreactive
  - Extraocular movements: Doll's and calorics progressively impaired until absent
  - Motor examination: Progressing to decorticate, then decerebrate posturing and finally flaccid

- Uncal brain herniation
  - Progressive lateral pressure on thalamus and upper brainstem due to lateral masses
  - Pupils: Dilated and fixed ipsilateral to lesion
  - Extraocular movements: Eye ipsilateral to lesion deviated laterally and fails to adduct
  - Motor examination: Hemiplegia ipsilateral to lesion due to cerebral peduncle compressed on the incisura of the tentorium (Kernohan's notch)
- Respiratory breathing patterns
  - Cheyne–Stokes: Periodic episodes of apnea alternating with hyperpnea (diffuse encephalopathies or structural lesions)
  - Central neurogenic hyperventilation: Rapid, sustained hyperpnea (midbrain to upper pons damage, diffuse encephalopathies or structural lesions)
  - Apneustic: Pausing at full inspiration (pontine damage, anoxia, meningitis, hypoglycemia)
  - Ataxic: Irregular (medullary damage)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Lab tests: To identify specific causes of coma.

Initial lab tests

- Arterial blood gas, electrolytes, BUN, glucose, creatinine, calcium, magnesium, liver function tests, ammonia, CBC, PT, PTT, sedimentation rate, thyroid function tests, and toxicology screen
- Cervical spine films if trauma suspected
- Electrocardiogram to evaluate the heart
- Lumbar puncture for meningitis/encephalitis; avoid with mass lesions to prevent herniation
- Electroencephalogram if seizures suspected

Follow-up & special considerations

ICU required for monitoring and intubation.

Imaging

Initial approach

CT and MRI scans show structural lesions; MRI is better for visualizing the brainstem.

Follow-up & special considerations

Repeat scans as clinically indicated.

Diagnostic Procedures/Other

Evaluation for brain death: Apnea testing (no spontaneous respirations observed with PCO_2 >59 mm Hg) and if indicated, confirmatory testing (cerebral angiography, electroencephalogram, nuclear scan) consistent with brain death.

Pathological Findings

Pathological findings depend on etiology.

DIFFERENTIAL DIAGNOSIS

- Persistent vegetative state: Unresponsiveness despite wakefulness and return of sleep–wake cycles; usually emerges after 2 weeks of coma
- Stupor: Can be aroused with noxious stimuli
- Lethargy: Arousable with verbal stimuli
- Acute confusional state: Represents attentional deficits between full responsiveness and lethargy
- Locked-in state: Mute, quadriplegic, conscious and blinks or vertically moves eyes on command
- Brain death: Irreversible cessation of all brain and brainstem function from an explainable cause

TREATMENT

MEDICATION

First Line

Drug choices depend on causes of the coma.

ADDITIONAL TREATMENT

General Measures

Supportive care is critical.

Issues for Referral

Patients that survive often need rehabilitation or long-term care.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Complementary and alternative therapies depend on the specific etiology of coma.

SURGERY/OTHER PROCEDURES

Neurosurgical evaluation for neurosurgical causes of coma.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Airway, breathing, and circulation
- Check and stabilize cervical spine fractures
- Give every coma patient 100 mg thiamine IV, 50 mL of 50% dextrose IV, 0.4–1.2 mg naloxone IV to treat for possible Wernicke's encephalopathy, hypoglycemic coma, and opiate overdose
- Treat seizures
- Diagnostic studies for causation of coma
- Wean off any sedative medications
- Stabilize vital signs and treat fever
- Correct metabolic and other treatable causes
- Treat meningitis, encephalitis, and brain abscess with antibiotics
- Treat hepatic encephalopathy if present
- Treat cerebral edema
  - Ischemic stroke edema is not helped by osmotic diuretics or steroids
  - Elevate head
  - Intubate and hyperventilate to PCO_2 25 mm Hg
  - Administer mannitol 20% 1.5–2.0 g/kg IV over 30–60 minutes
  - Give normal saline two-thirds maintenance
  - For tumor, abscess, and maybe intracerebral hemorrhage, give dexamethasone 10 mg IV then 4 mg PO or IV every 6 hours with an H_2 blocker and monitor blood sugar

Admission Criteria

Admit to the intensive care unit for initial evaluation and treatment of coma.

IV Fluids

As needed depending on condition.

Nursing

- Adherence to medical orders
- Close monitoring to care for all basic activities of daily living and ensure patient comfort

Discharge Criteria

Discharge to rehabilitation or long-term care facilities once stabilized if recovery not complete.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Neurological checks required frequently for detecting changes in neurologic function.

DIET

Parenteral feeds initially, maximize nutrition.

PATIENT EDUCATION

Provide strategies to reduce reoccurrence of preventable, metabolic or other forms of coma.

PROGNOSIS

Mortality high in coma but depends on causation.

COMPLICATIONS

Complications will vary depending on the etiology of coma.

REFERENCE

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Brain herniation syndromes

CODES

ICD9

780.01 Coma

CLINICAL PEARLS

- Coma means unconsciousness with absence of awareness.
- Caused by diffuse cerebral dysfunction or brainstem reticular activating system impairment.
- Structural, metabolic, hypoxic, and infectious causes are typical.

DELIRIUM/ENCEPHALOPATHY

Alexander D. Rae-Grant, MD

BASICS

DESCRIPTION

Delirium describes a state where the patient is confused, with an agitated, inattentive behavior. Delirious patients frequently hallucinate or have delusional thoughts. This syndrome develops over a brief period of time, usually hours or days. Disorientation in time is characteristic. Patients may have autonomic symptoms such as sweating and tachycardia and often thrash around purposelessly. Encephalopathy is a more nonspecific term that describes a state of altered consciousness that is usually acute, caused by metabolic or systemic disorders, and often is reversible (see specific chapters on encephalopathies).

- Definitions
  - Delirium: Acute confusional state in patients with agitation and hallucinations.
  - Dementia: Chronic, progressive cognitive impairment in otherwise alert patients.
  - Encephalopathy: Nonspecific term for altered mental state, usually of acute onset.
- Clinical characteristics
  - Delirium and acute encephalopathy are common in the inpatient setting. The prevalence of delirium has been estimated at 11–42% of inpatient medical populations in a systematic review. Up to 50% of patients with hip fractures experience delirium at some time, and delirium is common in patients with severe burns. Clinical characteristics of delirium include an acute onset of mental status changes, usually over hours or a few days. The mental state is marked by inattention. Patients are either drowsy or hypervigilant (hypoactive or hyperactive form) and show an altered response to their environment. Patients have difficulty interacting for mental status testing and tend to either not interact appropriately with the examiner or make errors in orientation, repetition, and memory testing related to their inattention and clouded sensorium. Characteristic of delirium is agitation, frequently with hallucinations, which may be visual and at times formed (e.g., insects crawling). Patients may make perceptual errors, misidentifying objects in the room. Patients may also have signs of autonomic hyperactivity, including tachycardia, diaphoresis, flushed facies, and hyperventilation.

PATHOPHYSIOLOGY

Delirium is caused by a variety of toxic, metabolic, infectious, and medication-related disorders. Thus, the specific pathophysiology of neurological dysfunction depends on the etiology. Different delirious states have in common dysfunction of CNS neurons, due to reduced/altered substrates, acid–base disorders, hypoxemia, toxins or medications that affect neuronal function, secondary immunologic effects, or inflammatory activity in the CNS. Each of these causes an alteration of function of CNS neurons, leading to the clinical state. There may be a reduction of acetylcholinergic deficiency but data is limited on this concept.

RISK FACTORS

- Age, hospitalization, dementia, depression, pain, stroke, metabolic dysfunction, infection, perioperative, heart failure, alcohol abuse.
- Medications (anticholinergics, antiepileptics, antipsychotics, antiparkinsonian agents, barbiturates, benzodiazepines, corticosteroids, histamine H2-receptor blockers, NSAIDs, opioids, tricyclics. Consider alcohol, barbiturate, or benzodiazepine withdrawal.
- High rates with hip fracture, aortic and cardiac surgery.

DIAGNOSIS

Patients with delirium show inattention, with difficulty doing tasks such as counting backward by 7 from 100, listing the months backward, etc. They drift off in conversation and are unable to give a history. More complex tasks of mental status are clouded by inattention. Patients are often restless but usually show no focal neurological signs. Reflexes and cranial nerves are unaffected. The toes are usually down going unless there is neurological disease causing delirium. Patients may show signs of hallucinating. They may be drowsy or frankly stuporous. Patients may have asterixis, particularly with hepatic encephalopathy.

DIAGNOSTIC TESTS AND INTERPRETATION

Screening Tests: Clinical

variety of screening bedside tests, confusion assessment method (CAM), CAM-ICU, nursing delirium screening scale (Nu-DESC), and delirium detection score (DDS).

Lab

Depending on the history, laboratory studies may assist in diagnosis. CBC (for increased white blood cells); electrolytes (for hypo- or hypernatremia, low bicarbonate associated with metabolic acidosis); glucose (for hypo- or hyperglycemia); liver function tests; BUN and creatinine; drug screen; levels of therapeutic medications for intoxication; arterial blood gases. Consider vitamin B12, autoimmune studies, sedimentation rate in selected cases.

Imaging

Imaging of the brain may be important to exclude focal disorders causing encephalopathy. Depending on the clinical circumstance, CT scanning or MRI may be used.

Diagnostic Procedures/Other

Lumbar puncture should be used once an intracranial mass lesion is excluded in those patients considered to have an intracranial infection (encephalitis or meningitis). If CT scanning is negative and subarachnoid hemorrhage is suspected, lumbar puncture may be diagnostic. EEG may be useful in showing triphasic waves, characteristic of metabolic encephalopathy, as well as excluding nonconvulsive status epilepticus, which may present as an unexplained delirium.

DIFFERENTIAL DIAGNOSIS

A variety of disorders may cause delirium or encephalopathy during their course. Patients with underlying brain disorders are more likely to show delirium or encephalopathy as a result of disease. Patients with dementia who have new infections commonly become delirious. Patients who are either very old or very young are more at risk of responding to disease with delirium or encephalopathy. Other risk factors include a history of alcohol abuse, multiple medical problems, visual or hearing impairment, and sleep deprivation.

- Medical/surgical diseases: Sepsis, focal infections, postoperative states, endocrine disorders (e.g., thyrotoxicosis, Cushing's disease), metabolic disorders (e.g., hyponatremia, hyperglycemia, hypoglycemia, etc.), hepatic or renal failure, hypoxia, or hypercarbia.
- Neurological diseases: Meningitis, encephalitis, subarachnoid hemorrhage, traumatic brain injury, vascular, neoplastic, inflammatory, or other disorders. May occur after seizures.
- Drug or medication use or withdrawal states: Street drugs, alcohol withdrawal or intoxication, sedative/hypnotic agents, opiates, anticholinergics, atropine, amphetamines, drug overdoses, steroids.
- Toxins: Organophosphates, heavy metals, organic solvents, etc.

TREATMENT

MEDICATION

The primary treatment for delirium or encephalopathy is to treat the underlying disorder. At times, patients may require treatment to reduce their symptoms of agitation or restlessness. Care should be taken to avoid respiratory suppression by medications in such patients. Melatonin 0.5 mg at night significantly reduced the incidence of delirium in a randomized trial in patients admitted to a tertiary medical unit (1).

If necessary, medication such as haloperidol in low doses may be useful without significant risk of respiratory compromise.

Administer haloperidol 0.5–2 mg IM or IV repeated q4–6h as needed, depending on age, weight, degree of agitation. Switch to oral when possible. For alcohol withdrawal, use benzodiazepines.

- Contraindications: Avoid with significant hypotension or sensitivity to similar medications.
- Precautions: Watch for dystonic reactions and hypotension.
- Alternative drugs
  - Risperidone may be used.
  - Risk of increased mortality with use of antipsychotics needs to be weighted against benefit.
  - Single-dose olanzepine 10 mg reduced incidence of delirium at the time of joint surgery in a randomized trial (2).
  - Rivastigmine was not useful in preventing delirium.
  - Reduced sedation during surgery reduced the incidence of delirium.

ADDITIONAL TREATMENT

General Measures

Careful attention must be given to the maintenance or establishment or an airway, breathing, and circulation. Any evidence of cardiovascular instability must be treated immediately. Intravenous access is important to allow medication to be provided, as well as electrolyte solutions. Consider providing IV thiamine (patients suspected of having Wernicke's syndrome), glucose (suspected hypoglycemia), and naloxone (opioid intoxication). Measures should be taken to protect patients from harming themselves; a bed check may help prevent falls, or, if necessary, restraints or provision of 1:1 nursing may be helpful. Consider providing a secure environment if the patient is a potential threat to others. Reorientation is helpful. Having family at the bedside is also beneficial.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Once an etiology or delirium or encephalopathy is determined, treating the cause of this state is required. Treatment guidelines pertinent to the etiology should be followed.
- Adjunctive treatment
  - Ensure that all drugs or toxins that may be causing the delirium are withdrawn. Make sure that fluid requirements, particularly in patients with autonomic overactivity, are met.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with delirium or encephalopathy require admission for their diagnosis and safety. Such patients are at risk of falls and injuries in the home setting.

Discharge Criteria

Patients should be fully alert and oriented if possible before discharge. They should usually be discharged into the care of a responsible party if possible.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients with delirium or encephalopathy should be closely monitored until stabilization occurs.

PATIENT EDUCATION

Since this is a self-limited disorder, patient education is limited to reassurance, reorientation, and explanation of the clinical condition after the patient has returned to a more normal mental status.

PROGNOSIS

Delirium and encephalopathy are usually self-limited conditions that should resolve with the improvement of the medical condition. Recent case series have shown that some patients do not return to baseline status, particularly when there is an underlying dementia. The presence of delirium predicts a poor outcome after acute admissions with a higher post-discharge mortality.

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See Also (Topic, Algorithm, Electronic Media Element)

- Acute confusional state
- Dementia
- Encephalopathy, hepatic
- Encephalopathy, septic
- Encephalopathy, renal

CODES

ICD9

- 292.81 Drug-induced delirium
- 293.0 Delirium due to conditions classified elsewhere
- 348.9 Unspecified condition of brain

DIZZINESS

Judith White, MD, PhD

BASICS

DESCRIPTION

Dizziness is a common, nonspecific term used to describe a range of sensations including the illusion of movement of the visual surround (vertigo), lightheadedness, near-syncope, or postural instability. The etiology may be central or peripheral, with a broad differential, ranging from benign to life-threatening conditions. Vertigo is predictive of involvement of the vestibular system (peripheral or central). The historical characteristics and duration of symptoms, and any provoking or alleviating factors, are helpful in narrowing the diagnosis.

- Clinical characteristics
  - Dizziness can affect patients of all ages; however, it is more common in elderly patients. It is one of the most common diagnoses for which adults seek medical evaluation, affecting 15–30% of the population at some point during their lifetime. There is a slight female preponderance. All races are affected equally.
  - Risk factors for dizziness include older age, diabetes, infections, inner ear problems, vision problems, trauma, hypertension, dehydration, orthostatic hypotension, atherosclerotic vascular disease, anemia, menopause, and familial factors.

PATHOPHYSIOLOGY

- The vestibular labyrinth contains the semicircular canals and the otolithic organs (saccule and utricle). Neural discharge rates vary depending on linear and angular acceleration, and innervate the vestibular nuclei and central vestibulo-ocular and vestibulo-spinal pathways. Acute loss of unilateral vestibular function produces the acute vestibular syndrome, characterized by nausea and vomiting, vertigo, nystagmus, and postural instability. Symptoms usually persist for days and gradually subside over weeks.
- Acute vestibular syndrome is usually peripheral in origin, but central pathology such as infarction and hemorrhage of the inferior cerebellum may simulate peripheral symptoms in up to 25% of patients in emergency settings with central risk factors (age over 65, diabetes, hypertension, smoking, and heart or atherosclerotic disease). Some who present with isolated acute vestibular syndrome have infarction of the inferior cerebellum. Severe imbalance is a finding which predicts central pathology in this group.

DIAGNOSIS

The characteristics of the dizzy sensation (vertigo vs. pre-syncope, imbalance, or lightheadedness) are helpful to narrow diagnostic categories. In patients with vertigo, the duration is especially helpful in diagnosis. Vertigo lasting for seconds, occurring with position change, suggests benign paroxysmal positional vertigo. Vertigo lasting for hours associated with hearing change, tinnitus, and fullness suggests Meniere's syndrome. Acute onset of vertigo lasting for days to weeks suggests acute vestibular syndrome. Episodic vertigo in a patient without other features, with a history of migraine, is commonly migraine associated. Vertigo associated with loud sounds or pressure changes may be seen in dehiscence of the vertical semicircular canals. Imbalance without vertigo is seen in bilateral vestibular hypofunction.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Blood tests have a low yield in identifying a specific cause of dizziness.

Diagnostic Procedures/Other

Positioning testing including the Dix–Hallpike can be helpful to distinguish peripheral causes of dizziness, such as benign paroxysmal positional vertigo, and may be performed in the emergency department without special equipment. Examination with Frenzel lenses or eliminating visual fixation in low room light or placing a uniform blank surface in front of the patient's eyes can reveal nystagmus. Formal laboratory tests of audio-vestibular function may be of benefit in challenging cases, including audiometry, electronystagmography, and rotational testing.

Imaging

MRI, with and without contrast, is important to exclude structural lesions or malformations of the soft tissue, such as acoustic neuroma, infarction, or demyelinating disorders. CT scan of the temporal bones, without contrast, with fine cuts, and reconstruction in the plane of the semicircular canals, is helpful in identifying semicircular canal dehiscence. Imaging studies are strongly indicated for patients with focal neurological findings, marked imbalance, or persistent unexplained dizziness. MR and cerebral angiography are used to identify vertebrobasilar insufficiency or atherosclerosis.

DIFFERENTIAL DIAGNOSIS

- Benign paroxysmal positional vertigo
- Superior semicircular canal dehiscence
- Vestibular neuronitis
- Ramsay Hunt syndrome
- Meniere's syndrome
- Multiple sclerosis
- Migraine-associated dizziness
- Autonomic dysfunction
- Orthostatic hypotension
- Hypoglycemia
- Infections (otitis media, syphilis, meningitis, AIDS, viral encephalitis)
- CNS vasculitis
- Cerebellar lesion (infarct, vascular malformation, hemorrhage, neoplasm)
- Lateral medullary syndrome
- Pontine syndrome
- Posterior fossa neoplasm (e.g., acoustic neuroma, brainstem glioma)
- Neurofibromatosis type 2
- Paraneoplastic syndrome
- Posterior fossa structural lesion (e.g., Chiari malformation)
- Postconcussion syndrome
- Alcoholic cerebellar degeneration
- Vitamin E deficiency
- Vitamin B12 or folate deficiency

TREATMENT

MEDICATION

- Vestibular suppressants are useful for brief (3 days or less) control of symptoms associated with acute vestibular syndrome. They are not indicated for long-term management of dizziness, and have no proven effect in benign paroxysmal positional vertigo.
  - Antihistamines: Meclizine (Antivert 25–50 mg q6h PRN PO) is most commonly used; dimenhydrinate (Dramamine 50 mg q4–6h PO or IM) is also used as a vestibular sedative medication. Central anticholinergic activity may be the underlying mechanism.
  - Benzodiazepines: Diazepam (Valium 2.5–5 mg t.i.d. or PRN PO, IM, or IV) or clonazepam (Klonopin 0.5 mg t.i.d. PO) can be helpful in alleviating severe vertigo and anxiety. Care should be taken to avoid tolerance and habituation.
  - Anticholinergics: Scopolamine transdermal patch is effective for motion sickness and posttraumatic vertigo.

- Antiemetics
  - Promethazine (Phenergan, 25 mg q6h PRN by mouth, or via suppository) and prochlorperazine (Compazine 5–10 mg q6h PO or IM, or 25 mg q12h suppository) are useful in relieving the severe nausea associated with vertigo. Ondansetron (4 mg q8h PRN) and prochlorperazine are used for severe nausea from central vertigo.
  - For Meniere's disease, 1,500 mg/day low-sodium diet and diuretics (triamterene/hydrochlorothiazide 37.5/25 once a day by mouth) are helpful. Intratympanic steroids are useful if episodic vertigo persists. Rarely, chemical labyrinthectomy with intratympanic gentamicin is indicated.
  - For acute vestibular neuritis, prednisone 1 mg/kg/day for 10 days has been suggested to improve recovery.
- Contraindications: Prior history of hypersensitivity or allergic reaction. Transtympanic aminoglycoside treatment of Meniere's disease is associated with risk of profound hearing loss; bilateral involvement of Meniere's disease is a relative contraindication for ototoxic treatment.
- Precautions: Drowsiness is commonly associated with antihistamines and antiemetics. Steroid therapy for vestibular neuritis can be associated with hypertension, psychiatric symptoms, hyperglycemia, gastric ulcers, osteoporosis, hip necrosis, and cataract.

ADDITIONAL TREATMENT

General Measures

Specific therapies are directed to the underlying etiology of the dizziness. Canalith repositioning is highly effective in benign paroxysmal positional vertigo. Vestibular exercises and rehabilitation programs are designed to readjust perceptual, vestibulo-ocular, and vestibulo-spinal reflexes by fostering central compensation of vestibular tone imbalance, and minimizing fall risk.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Adjunctive treatments
  - In the acute phase, bed rest, adequate hydration, mental relaxation, and visual fixation are helpful. Vestibular habituation and balance retraining exercises are beneficial for chronic persistent dizziness secondary to multiple sensory deficits. Physical and occupational therapies involving eye, head, and body movements are also beneficial for dizziness due to upper cervical dysfunction and cerebrovascular accident, and should be begun as soon as the acute stage of nausea and vomiting has ended.

SURGERY/OTHER PROCEDURES

In patients with refractory Meniere's syndrome, surgical intervention such as endolymphatic shunt placement and selective vestibular nerve section can be performed, although intratympanic therapies are commonly attempted prior to invasive surgical therapies. Semicircular canal dehiscence may be treated with canal occlusion.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with profound disequilibrium or intractable vomiting may require imaging studies, hospitalization, and IV rehydration. The presence of focal neurological findings other than nystagmus warrants thorough evaluation of possible central pathology.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients are followed to monitor progression and recurrence of symptoms and efficacy of pharmacologic and rehabilitation therapy. This can be done with serial physical exams and specific outcome measures such as the Dizziness Handicap Inventory, Activities Specific Balance Confidence Scale, Computerized Dynamic Posturography, and gait measures.

PATIENT EDUCATION

- Vestibular Disorders Association, P.O. Box 4467, Portland, OR 97208-4467. Website: www.vestibular.org
- Balance and Dizziness Disorders Society in Canada, 5525 West Boulevard, #325, Vancouver, BC, Canada V6M 3W6. Website: www.BalanceAndDizziness.org
- Meniere's Society, 98 Maybury Rd., Working Surrey, GU21 5HX, UK

PROGNOSIS

Clinical course and prognosis varies with etiology. Most cases of dizziness are benign and self-limited, and recover spontaneously over several weeks to months. Symptomatic recovery is due to vestibular compensation (central reorganization of vestibular circuits). Prognosis is better if the symptoms are due to vestibular dysfunction. In dizziness of central origin or from systemic illness, success depends on treating the underlying disorder.

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See Also (Topic, Algorithm, Electronic Media Element)

- Vertigo, disequilibrium, pre-syncope
- Meniere's syndrome

CODES

ICD9

- 780.2
- 386.01 Active meniere's disease, cochleovestibular
- 386.10 Peripheral vertigo, unspecified

DYSARTHRIA

Alexander D. Rae-Grant, MD

BASICS

DESCRIPTION

Dysarthria is defined as a defect in the production of speech affecting the volume, rate, tone, or quality of spoken language. Dysarthria affects the intelligibility of speech. Abnormalities in a number of neurologic structures can lead to dysarthria by altering the function of the muscles of phonation and articulation. Dysarthria must be discriminated from aphasia, in which there is a disorder of the production of language with or without an articulation disorder.

- Definitions
  - Phonation: The production of vocal sounds.
  - Articulation: Contractions of the pharynx, palate, tongue, and lips that alter the vocal sound to form components of speech.
  - Anarthria: Inability to produce speech with sparing of comprehension of speech and ability to read and write.
- Clinical characteristics
  - The origin of dysarthria is neurologic, associated with damage to either the central or peripheral nervous system. It is a disorder of movement and abnormal speech execution, disrupting the range, timing, speed, or accuracy of the movement producing speech. It does not therefore disrupt the structure of speech, or its linguistic or cognitive components. Disorders affecting the physical structures of the speech apparatus, such as a cleft lip or palate, are not referred to as dysarthrias.
  - Dysarthria can be characterized by the major neurologic abnormality causing it. Each level of the neuraxis causes a different quality of dysarthric speech.
  - Lower motor neuron dysarthria (bulbar palsy): Speech slurred, nasal, drooling, raspy quality, monotonous, indistinct. Tongue atrophy, flaccid palate, reduced gag.
  - Spastic dysarthria (pseudobulbar palsy): Speech explosive, forced, effortful. No tongue atrophy, brisk jaw jerk, brisk gag. Slow tongue movements.
  - Extrapyramidal dysarthria: Rapid, slurred speech, low pitched, trailing off at the end of sentences. May be whispering. May have hesitant initiation.
  - Ataxic dysarthria: Arrhythmic, slurred, syllables of words broken up (scanning speech). Variable force, rate, rhythm of speech.
  - Choreiform dysarthria: Prolonged sentences interspersed with silences, improper stresses in words. Speech may come in outbursts.

PATHOPHYSIOLOGY

Speaking depends on the coordinated movement of the respiratory muscles, the pharynx and larynx, the lips, palate, tongue, and jaw. These structures are innervated by cranial nerve nuclei (facial, trigeminal, vagal, hypoglossal, and phrenic). They are controlled by corticobulbar connections and ultimately by the motor cortex. There are influences from cerebellar and extrapyramidal inputs, which modify the rate, range, volume, and force of speech. By varying the amount of expelled air, the physical qualities of the sound passage, and the tension of the vocal cords, various sounds and words can be developed. Thus, disorders at multiple levels of the nervous system may lead to dysarthria.

DIAGNOSIS

Ask about difficulty swallowing liquids and solids, other cranial nerve symptoms (diplopia, facial numbness, vertigo), parkinsonian symptoms, muscular weakness, toxin or chemical ingestion, medical problems. Evaluate oropharynx for mass lesions. Listen to the quality of speech and reading. Have patient repeat linguals (sounds l and t), labials (b, p), and gutturals (nk, ng). Have the patient hold a vowel to assess the stability of phonation.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Depends on underlying disorders.

Imaging

Depends on level of neuraxis affected.

Diagnostic Procedures/Other

Patients with unexplained dysarthria should be considered for a Tensilon test for myasthenia gravis and other neuromuscular disorders. EMG-NCS may be helpful in muscular disorders and neuromuscular disorders.

DIFFERENTIAL DIAGNOSIS

- Muscular disorders: Muscular dystrophies may occasionally cause slurred speech of the bulbar type.
- Neuromuscular disorders: Myasthenia gravis may cause bulbar muscle weakness; involvement with characteristics of a fluctuating, bulbar dysarthria.
- Cranial nerve diseases: Combinations of disorders of vagal, hypoglossal, and facial nerves may cause dysarthria, whose characteristics are those of the specific cranial nerve involvement. Chronic meningitis, leptomeningeal disorders, skull base tumors, inflammatory disorders.

- Brainstem diseases: Bulbar or pseudobulbar speech, depending on the level in the brainstem. Stroke, demyelination, tumor, vascular malformations, etc.
- Cerebellar and cerebellar connection disorders: Ataxic dysarthria associated with gait ataxia, nystagmus, and incoordination. Various causes.
- Extrapyramidal disorders: Parkinson's and related disorders, Huntington's and other choreoathetotic disorders. Consider Wilson's disease in a young patient.
- Corticobulbar disorders: Strokes, cerebral palsy, anoxic encephalopathy, etc. Motor neuron disease may give a mixture of upper and lower motor neuron signs, i.e., wasted tongue, brisk gag, pseudobulbar affect, etc.

TREATMENT

MEDICATION

This depends on the clinical basis of dysarthria. For example, for myasthenia gravis, use of pyridostigmine (Mestinon), steroids, or other immunomodulating therapy may improve speech. Treatment of Parkinson's disease with L-dopa or dopaminergic agents may modulate speech disorders. There are no specific medications for dysarthria itself.

ADDITIONAL TREATMENT

General Measures

Speech therapy to retrain speech precision, or if necessary training in alternative communication strategies may be useful. Various therapy strategies are employed to improve speech intelligibility. One example is alphabet clues with the speaker pointing to the first letter of a word while reading the word aloud. For severe dysarthria, alternative or augmentative communication strategies may be useful. These include communicators or computer systems that may incorporate computer-synthesized voice. Speech therapy should be aimed at the particular aspect of speech that is most affected to improve comprehensibility and speech output. Note that there is limited data in the literature about the efficacy of therapies for dysarthria.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  – Depends on specific diagnosis.
- Adjunctive treatment
  – Depends on specific diagnosis.

SURGERY/OTHER PROCEDURES

For patients with certain kinds of dysarthria, there may be surgical options. A pharyngeal flap may be considered for patients with hypernasal speech. Procedures aimed at improving vocal cord apposition may help speech in disorders of vocal cord paralysis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Dysarthria does not usually require hospital admission. But associated neurologic problems such as aspiration due to dysphagia, respiratory disorders, and weakness may require admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Depends on specific diagnosis.

PATIENT EDUCATION

Depends on specific diagnosis.

PROGNOSIS

Depends on specific diagnosis.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Myasthenia gravis
- Amyotrophic lateral sclerosis and other motor neuron diseases
- Parkinson's disease

CODES

ICD9

784.51 Dysarthria

FALLS

Richard Camicioli, MD

BASICS

DESCRIPTION

For research purposes, falls are defined as *coming unintentionally to the ground* or at some lower level other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis, or an epileptic seizure. Practically speaking clinicians need to consider causes of *syncope* or *seizures* when evaluating a patient who has fallen (1). Falls are common in older people and are particularly common among people with neurological conditions. Prior falls and balance or mobility impairment represent important risk factors. In addition to directly causing injury and death, falls can lead to restriction of activities leading to increased care needs. Falls are associated with *intrinsic* (patient-centered) or *extrinsic* (environmental/external to the patient) risk factors, which may interact. Falls are accidents and therefore can occur in the absence of internal or external risk.

EPIDEMIOLOGY

Incidence/Prevalence

Approximately 1/3 of people older than age 65 fall annually, with 10% of falls leading to serious injury such as significant head trauma or a fracture. The risk is even higher in hospitalized and institutionalized people. The risk of falls increases with increasing age, but people can fall at any age. While both men and women are at risk of falls, some studies suggest that women are at higher risk (2).

RISK FACTORS

Risk factors for falls include older age, previous falls, use of multiple (4+) medications, arthritis, depression, orthostatic blood pressure drop, cognitive impairment, visual impairment, weakness, gait impairment, and balance disorders (3). In a study by Tinetti, risk of falls was 8% in people with no risk factor but increased to 80% in people with 4 risk factors in a cohort study of older people. Substance abuse needs to be considered in all people who present with falls.

Genetics

Although specific genetic factors are not typically associated with falls, some populations may have altered risk. In typical populations, genetic factors are associated with balance and mobility and can be invoked for differences in drug metabolism that can predispose individuals to side effects of medications. The apolipoprotein E4 allele has been associated with an increased risk of hip factors independent of its impact on risk of dementia. Narcolepsy with cataplexy, where people can have spontaneous loss of tone is associated with falls and is also associated with the HLADQB1*0602 allele. Neurodegenerative disorders that predispose to falls, such as spinocerebellar ataxias, can be hereditary.

ETIOLOGY

Falls can be related to intrinsic factors, such as a drop in blood pressure upon standing, or extrinsic factors, such as use of multiple medications. These features overlap but can be identified by history or examination and potentially can be modified to prevent future falls. Falls can further be classified according to how and where they occur. Although most falls occur while standing and walking (bipedal stance) they can occur from a sitting or lying position (out of a chair or bed). They can occur on the basis of a trip or slip or external displacement (being pushed over, for instance). Some people fall with no obvious reason, and some falls cannot be readily classified. Drop attacks are a particular type of fall where people fall spontaneously with no obvious reason, commonly associated with neurocardiogenic syncope (4).

Pregnancy Considerations

Pregnant patients with a diagnosis of epilepsy may have changes in medication management or pharmacokinetics, which might increase their risk of seizures, and which can lead to falls. Clearly this is a difficult situation that requires discussion of the risks and benefits of treatments. Younger women are at risk for multiple sclerosis, which can also be associated with falls.

COMMONLY ASSOCIATED CONDITIONS

One-third of people with neurological disorders will have had a fall over a year (5). These include both central neurological disorders such as dementia, stroke, multiple sclerosis, Parkinson's disease, myelopathy, and motor neuron disease and peripheral disorders such as polyneuropathy. Syncope and seizures can also cause falls (6). Conditions such as diabetes may be associated with neuropathy or hypoglycemia which can precipitate falls.

DIAGNOSIS

PHYSICAL EXAM

- After obtaining a detailed history to establish the nature of the fall and determine if the fall occurred with or without loss of consciousness, a detailed medical history should be obtained. Risk factors for further falls should be identified. Medications require careful review, given their consistent association with falls. A history suggestive of vascular events or consistent with a neurodegenerative disorder or worsening systemic disorder is particular relevant. The examiner should measure postural blood pressure changes, visual acuity (bearing in mind that specific aspects of vision such as contrast sensitivity may be relevant), and vestibular function (head thrust and Hallpike maneuver if there is vertigo). A systemic examination should identify evidence for cardiac and pulmonary dysfunction. Evidence for musculoskeletal problems should be sought. Restriction in range of motion and pain on movement may affect mobility and arthritis may contribute to falls. A systemic examination might reveal evidence for underlying illness (i.e., abdominal mass) prior to laboratory investigations. A thorough neurological examination is important in order to identify disease and to stage severity of disease. Balance and gait should be examined.
- In addition to the standard neurological examination, balance and gait can be assessed semi-quantitatively using scales such as the Performance-Oriented Mobility Assessment (3) which helps quantify components of balance and mobility, or the get-up-and-go test or timed-up-and-go test. The latter requires the patient to get up from a chair, walk 3 meters, turn, and return to sit in the chair. The test is timed and abnormalities in mobility are noted (7). Impairment rating scales are validated in various neurological disorders.

DIFFERENTIAL DIAGNOSIS

- Most falls are multifactorial in that impaired judgment, mobility, and balance conspire in increase risk in the setting of environmental hazards. Interventions are aimed at impairments that increase risk as well as at environmental hazards.
- Early falls in the setting of a progressive disorder are *characteristic* of Dementia with Lewy bodies (defined by dementia and 2/3 features: Parkinsonism, hallucinations, and fluctuations) and other dementias (8), progressive supranuclear palsy (associated with supranuclear gaze palsy and marked balance impairment), and multiple system atrophy (associated with autonomic or cerebellar signs along with parkinsonism and often pyramidal signs). Vascular risk factors are associated with both cerebrovascular disease and cardiac disease both of which can lead to falls. Since ischemic strokes are often covert, brain imaging may be necessary to identify them in the setting of patients who fall and have neurological signs.
- In addition to bedside testing, formal testing of postural blood pressure change, testing in an autonomic laboratory for evidence for neurocardiogenic syncope and carotid sinus sensitivity, and other cardiac rhythm evaluations should be considered if falls remain unexplained.

TREATMENT

- Once hemodynamically stabilized, patients presenting with a fall need an initial assessment focused on identifying injuries (concussion, fractures). If neck injury may have occurred, a cervical fracture must be ruled out. Assessment of risk factors should be done. If these are identified they can be modified. This might require further follow-up (e.g., if medications are discontinued). Patients with multiple falls and falls with injury may benefit from a multifaceted falls intervention, which includes risk factor modification, mobility assessments, and home safety evaluation by an occupational therapist. A physiotherapist may assist the patient to gain mobility, especially if they develop "fear of falling." Assistive devices may be necessary for safe mobility.

- Fractures are important consequences of falls. Therefore, osteoporosis needs to be treated. Older people should be taking vitamin D and adequate calcium. Regular physical activity is important for falls prevention as well as general health maintenance. Specific activities that have been associated with falls prevention include Tai Chi.
- See chapters on epilepsy and syncope for further recommendations of testing for these conditions where indicated.

MEDICATION

First Line

In general, medications are not necessary in the treatment of falls unless a specific disorder is identified that requires treatment. If hypotension does not respond to conservative maneuvers, medications such as midodrine or fludrocortisone are considered. If seizures are considered, empiric therapy may also be considered. If they are present, treatment of seizures using medications that minimize side effects and drug interactions is necessary. Medications for prevention of osteoporosis (vitamin D, calcium, etc.) should be considered in at-risk patients.

Contraindications

Specific medications are risk factors for falls. For example, benzodiazepines need to be used with great caution in the elderly.

Precautions

Supine hypertension is a risk for medications that raise blood pressure in the setting of orthostatic hypotension.

ADDITIONAL TREATMENT

General Measures

Older people (aged 65 and older) and people with neurological disorders should be asked if they have experienced a fall in the last year. Walking and balance impairment should be assessed (9). The assessment should include use of a standardized gait and balance assessment tool. Specific instruments may be of in use specific neurological disorders (such as the Unified Parkinson's Disease Rating Scale in people with Parkinson's disease). People who have fallen only once and have no balance or gait difficulties do not need multifactorial risk assessment.

Additional Therapies

Symptomatic measures

(http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/2010/)

Patients who fall would generally benefit from assessment from a professional with expertise in falls prevention. Functional assessment should be done, including identification of the use of adaptive devices, such as mobility aids. If needed these patients should receive instruction from a therapist experienced in their use (kinesiotherapist or physiotherapist). Fear of falling and self-perceived functional ability should be identified. These may benefit from therapy. Lastly, a home safety assessment by a trained professional (usually an occupational therapist) should be performed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Exercise is an effective way to prevent falls (10). Strategies to get up after or a fall or get assistance for safety should be in place.

SURGERY/OTHER PROCEDURES

Surgery is targeted at identification management (including repair) of fractures. Myelopathy is an important risk factor for falls and anyone who has fallen and sustained a neck injury should have structural myelopathy ruled out acutely. Head injury after fall should be appropriately managed.

IN-PATIENT CONSIDERATIONS

Admission Criteria

People with falls may need to be admitted for injuries or for investigations. Patients with a medical condition that has increased falls risk (hematological conditions, metabolic derangements, infections) may need admission for treatment. This allows monitoring and observation of events. Most investigations in patients for falls can be accomplished in the outpatient setting.

ONGOING CARE

PATIENT MONITORING

Patient monitoring needs to be tailored to the individual patient needs. The neurologist needs to optimize management and ensure adjunctive measures are in place.

PROGNOSIS

People who have had more than one fall and other risk factors are at high risk for repeated falls; therefore, follow-up is needed to assure compliance with interventions and to determine if environmental factors have been optimized.

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See Also (Topic, Algorithm, Electronic Media Element)

- Gait chapter

CODES

ICD9

- 780.2 Syncope and collapse
- 780.39 Other convulsions
- 781.2 Abnormality of gait

CLINICAL PEARLS

Falls are multifactorial and are extremely common in the older population and in people with neurological disorders. The key is primary or secondary prevention, which currently should be based on existing guidelines.

GAIT DISORDERS

Richard Camicioli, MD

BASICS

Gait disorders are common with aging and in neurological diseases. The presence of a gait disorder increases the risk of dependency, falls, dementia, and death. Neurological disorders with gait impairment may be amenable to specific treatment, while gait impairment may be an indicator of an undiagnosed medical or neurological condition. While it is fairly straightforward to determine if a patient's gait is (ab)normal, a more refined approach to classify the nature of gait abnormalities is helpful and can help target diagnosis and therapy.

DESCRIPTION

Abnormal gait can be identified by virtue of changes in normal spatiotemporal characteristics of walking, which are assessed by examining a patient walk. The challenge is to determine if mobility change is clinically significant give age-relate slowing of gait. Functional impact and falls clearly indicate clinically significant gait impairment. In general, gait impairment can be divided into neurological and non-neurological gait patterns.

EPIDEMIOLOGY

Incidence/Prevalence

The prevalence of gait impairment increases with age. Up to age 60, 85% of people have a normal gait, but by age 85, up to 85% of people have an abnormal gait. Both men and women are at risk for developing gait impairment, but women may have greater slowing with age (1–3).

RISK FACTORS

Risk factors for gait impairment in the absence of specific neurological illness are predominantly risk factors for vascular disease, such as hypertension.

Genetics

Genetic factors are associated with white matter changes and might modulate the effects of risk factors such as hypertension. Specific disorders, such as spinocerebellar ataxias and hereditary spastic paraparesis may be associated with gait impairment as a presenting feature. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) leads to white matter disease. At the peripheral level, familial myopathies or neuropathies can sometimes present as a gait disorder.

ETIOLOGY

The pathophysiological basis for gait impairment is multifactorial in most cases; nevertheless, the causes of gait impairment can often be identified. General classifications can be grouped according to the level of the nervous system affected (4). *Lower level gait* disorders have impairments at a peripheral level and include sensory abnormalities in the visual, vestibular, and proprioceptive systems. Neuropathy, myopathy, and musculoskeletal problems are common causes of lower level disorders. *Middle level gait* disorders include paraplegia and hemiplegia, as well as cerebellar and parkinsonian gaits. Dystonic and choreic contributions to gait can be considered middle level gait disorders. *Higher level gait* disorders (frontal gait apraxia) are not accompanied by obvious abnormalities on the basic neurological examination. Specific features include impaired initiation, marked difficulties in maintaining balance, widened (or excessively narrow) base, and difficulty with propulsion (including inappropriate ability to move the legs appropriately).

COMMONLY ASSOCIATED CONDITIONS

Gait impairment is a hallmark of neurological disorders, but it is also common in dementias, particularly Parkinson's dementia and dementia with Lewy bodies and vascular dementia (5). In an older population, coexistent medical conditions can alter gait. For instance, cardiopulmonary disease such as congestive heart failure or COPD can lead to exercise intolerance and slowing of gait. Musculoskeletal conditions such as arthritis can also affect gait.

DIAGNOSIS

The diagnosis of gait impairment may be triggered by patient complaint or by assessment. It must be kept in mind that many causes of gait impairment can lead to similar changes. Slowing, decreased stride length, and increased base of support occurs from a range of etiologies including aging. Decreased cadence suggests a pathologically impaired gait (6).

PHYSICAL EXAM

- Characteristics of gait that merit evaluation include initiation, base–width, symmetry (stride and arm-swing) and stride length. Parameters are readily quantified by timing a subject walk a preset distance (3, 5, or 10 meters). The timed-up-and-go test incorporates assessment of a subject rising from a chair, walking 3 meters, turning and then returning to the chair. Steps taken to walk the distance counted can be used to indirectly measure stride length. Cadence (steps per second) is another measure, which can be calculated and is more related to rhythm of walking. Step-to-step variability (in timing or step length) is harder to quantify without more sophisticated apparatus, but this may be an important parameter in predicting falls and cognitive or motor decline. In addition to a direct walk, turns should be examined as they are frequently involved in falls.
- The actual assessment of gait may not be as useful in assigning etiology as the neurological examination, though specific findings like freezing of gait are always abnormal and are related to frontostriatal dysfunction.

DIFFERENTIAL DIAGNOSIS

In a series of patients referred for gait impairment to a specialized gait clinic, etiology included myelopathy (structural and nutritional), parkinsonian disorders, frontal gait disorders (vascular, normal pressure hydrocephalus), cerebellar degeneration, sensory loss, and encephalopathy (7). Miscellaneous causes include tumors, subdural hematomas, and depression. Over 85% of patients could have an etiology established. Covert cerebrovascular disease is particularly common, with undiagnosed strokes present in roughly 20% of the population: both white matter changes and lacunes contribute to gait abnormalities.

TREATMENT

MEDICATION

First Line

- There are no specific medications that are useful in improving gait in most situations. In patients with Parkinson's disease dopaminergic medications (levodopa and dopamine agonists) improve the bradykinetic aspects of gait (such as stride length). However, gait and balance impairment are considered relatively dopamine non-responsive features of Parkinson's disease. Other parkinsonian syndromes such as vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, and normal pressure hydrocephalus do not respond as well to dopaminergic agent. In patients with dementia or mild cognitive impairment the effects of cognitive enhancers on gait are not clear. Cognitive enhancers, including cholinesterase inhibitors, antidepressants and other channel inhibitors, and psychostimulants are under investigation for the treatment of gait disorders. A long acting form of 4-amino pyridine improves gait speed in patients with multiple sclerosis, and is FDA approved for this indication (dalfampridine) (8).

Contraindications

Drugs that block dopamine lead to parkinsonism with attendant gait impairment. Given their additional increase in vascular risk and limited data regarding efficacy these should be avoided without very clear specific indications.

Precautions
A key in pharmacologic management of older people is to eliminate unnecessary medications that might increase the risk of falls. While studies have more commonly addressed balance, effects on gait are likely present.

Second Line
Non-medications-related interventions are primary considerations in gait disorders.

ADDITIONAL TREATMENT
General Measures
General measures are critical in the treatment of gait disorders. In addition to quantifying impairment as described above and optimizing management of diagnosed medical conditions, safety, and prevention of fractures are paramount concerns. Management of bone health with medications and nutrition is critical. Exercise is also important and this can be in the context of a regular patient- or group-centered program.

Additional Therapies
Assessment by a physiotherapist or appropriate professional for training and optimization of assistive devices is important. Home assessment by and occupational therapist can be triggered by the recognition of gait impairment.

SURGERY/OTHER PROCEDURES
- Parkinson's disease can be treated with surgical lesions or deep brain stimulation. Standard targets such as the pallidum and subthalamic nucleus do not dramatically improve gait. Novel targets such as the pedunculopontine nucleus (side of a locomotor generator) are being explored, in particular with regards to improving freezing.
- Normal pressure hydrocephalus is an example of a surgically responsive gait disorder (9). This is identified by noting the clinical triad of progressive gait impairment, dementia, and urinary incontinence with evidence of hydrocephalus on imaging. Given the common co-morbidities of dementia and incontinence in an older patient this diagnosis can be challenging. A large volume (30–50 cc) lumbar puncture showing evidence of measurable gait improvement makes it more likely the patient will benefit from a ventricular shunt. This test is relatively insensitive, however, and a repeat CSF removal or a drain (with several days of diminished CSF pressure) increases the sensitivity of this approach to selecting candidates.

IN-PATIENT CONSIDERATIONS
Admission Criteria
In general, gait impairment is managed in the outpatient setting, though patients with severe gait disturbance and safety concerns with or without a history of falls may benefit for inpatient evaluation. Stroke, which is a common cause of mobility disturbance, requires urgent evaluation and functional intervention, often requiring admission.

ONGOING CARE
PATIENT MONITORING
If physical therapy or other interventions are implemented, improvements need to be monitored. A key is to ensure safety and function. This may require changes in living setting or assistive devices including the use of electric scooters in subjects who can mobilize independently.

PATIENT EDUCATION
Apart from education regarding the natural history of disease, which can help set realistic expectations, the specialist can direct patients, families, and primary care physicians to appropriate resources based on diagnosis.

PROGNOSIS
Prognosis depends on the specific cause of the gait disorder. For example, an acute stroke with hemiplegia can recover either completely or partially with time. A degenerative disorder such as progressive supranuclear palsy is inexorably progressive. Recognition of changing needs and direction provided to the patient and family and primary care physician is a role that the consultant can fill.

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ADDITIONAL READING
- Gait impairment, walking, mobility.

See Also (Topic, Algorithm, Electronic Media Element)
- Falls chapter

CODES
ICD9
781.2 Abnormality of gait

CLINICAL PEARLS
- Gait disorders may be multifactorial.
- Evaluation leads to specific diagnoses in most cases.

HEADACHE

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Headache is one of the most common medical complaints of modern society, affecting virtually every person during their lifetime. Each year, more than 5% of the US population seeks medical attention for headache. More than 1% of primary care and emergency room visits are due to headache. Most recurrent headaches are symptomatic of a chronic primary headache disorder.

- Primary headaches occur without an underlying cause and include migraine, tension type, cluster, and miscellaneous headaches (such as benign exertional headache).
- Secondary headaches always have a direct underlying cause [e.g., subarachnoid hemorrhage (SAH), brain tumor, meningitis, carotid dissection, sinusitis, medications], some of which can be life-threatening.
- Headache affects all races; tension headaches and migraines may be more common in Caucasians. The peak age for headaches in adults is between 30 and 40 years. Tension headaches and migraines are more common in women than men.

EPIDEMIOLOGY

Incidence

For tension headaches, the estimated incidence for ≥15 headache days per year was 14.2 per 1,000 person-years. For migraines, the estimated incidence was 8.1 cases per 1,000 person-years.

Prevalence

For tension headaches, the estimated 1-year prevalence was 38.3%. For migraines, the estimated prevalence was 12% in the general population.

RISK FACTORS

The risk factors for headaches vary, depending on the specific type. In general, the degree of life stress and fatigue may increase the likelihood of tension headaches and migraine.

Genetics

Genetic influences are strongly suspected for migraine and cluster headaches, although the specific genes and mechanisms remain unclear.

GENERAL PREVENTION

There are no general preventive measures for headache. Specific preventive strategies regarding lifestyle, diet, sleep, etc., will be variable between headache subtypes.

PATHOPHYSIOLOGY/ETIOLOGY

The pain of headache can be caused by several different mechanisms, including elevated intracranial pressure, inflammation or irritation of pain-sensitive intracranial structures (e.g., vessels, meninges), and inflammation or damage to structures in the head and neck region (e.g., muscles). Migraine pain is incompletely understood, but involves dysfunction of brainstem control over the trigeminovascular system, with dilation and inflammation of innervated vessels and release of vasoactive neuropeptides. Cluster headaches may involve abnormal interactions between the trigeminovascular system and the posterior hypothalamic circadian cycling mechanism. Tension headache involves inflammation and tenderness of the pericranial and upper cervical musculature. Central mechanisms may also be involved, including over-sensitization to peripheral activation of muscle nociceptive afferent input.

COMMONLY ASSOCIATED CONDITIONS

This will vary depending on the specific type of headache syndrome. For example, there is a frequent association between migraine and multiple sclerosis.

DIAGNOSIS

HISTORY

- The headache history is essential to establish the proper diagnosis. Several key issues should be discussed:
  - Age of onset: Migraines usually begin before the age of 40. Temporal arteritis typically begins after age 50.
  - Time to maximum intensity: Thunderclap headaches are severe, with maximum intensity within 1 minute, and can be caused by SAH, carotid artery dissection, and migraine. Severe headaches can also have a gradual onset, such as migraine or viral meningitis.
  - Frequency: Primary headaches are quite variable in frequency, ranging from a few migraines in a lifetime to cluster headaches occurring up to 8 times daily.
  - Time of day: Cluster headaches often occur during certain times of the day and may awaken the sufferer from sleep about the same time. Headaches that awaken from sleep are usually benign (e.g., migraine, cluster). However, they can also occur with brain tumors, meningitis, and SAH. Tension type headaches often occur in the afternoon.
  - Duration: Migraine typically lasts 4–72 hours without treatment. Cluster headaches typically last 15–180 minutes. Tension type headaches typically last 30 minutes to days.
  - Triggers: Most migraineurs have one or more triggers that can induce a headache. During periods of cluster headaches, alcohol can be a trigger. Tension type headaches can be triggered by stress.
- About 60% of migraineurs have a prodrome before the headache. Complaints may involve the mental state (irritability, depression, euphoria) and neurological function (decreased concentration; light, noise, and smell hypersensitivity), as well as more general function (diarrhea or constipation, thirst, sluggish feeling, food cravings, or neck stiffness). About 20% of migraines involve an aura, which generally develops over 5–20 minutes and lasts less than 60 minutes. The headache can begin before, during, or after the aura. The most common auras in descending frequency are visual, sensory, motor, and speech and language abnormalities. Prodromal low-grade fever and upper respiratory symptoms or diarrhea are frequently present in viral meningitis.
  - Migraine is accompanied by nausea in 90% of patients, vomiting in 30%, and light/noise sensitivity in 80%. These same symptoms are often present in headaches due to SAH or meningitis. Ipsilateral conjunctival injection, tearing, and nasal congestion or drainage typically occur during cluster headaches. Ipsilateral ptosis and miosis are present in 30% of cases.
  - Cluster headaches are always unilateral while about 40–60% of migraines are unilateral. Headaches from brain tumors or subdural hematomas can be bilateral or unilateral.
  - Quality of pain is another important aspect. In about 85% of cases, migraine pain is throbbing, pounding, or pulsatile. Tension type headaches are a pressure, aching, tight, or squeezing sensation. Cluster headaches are described as boring or burning. Headaches due to brain tumors can produce a variety of pains ranging from a dull steady ache to throbbing.
  - After the headache resolves, many migraineurs report feeling tired and drained with decreased mental acuity. Depression or euphoria is sometimes reported. In some systemic disorders, high fever and headache may then be followed by other symptoms or signs.

PHYSICAL EXAM

In the vast majority of patients with primary headache disorders, the neurological examination will be intact and non-focal. Some patients with complicated migraine may have mild focal findings. In general, the presence of focal neurological deficits dramatically increases the potential for a secondary headache disorder.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

ESR is necessary when temporal arteritis is under consideration. A vasculitis screen (e.g., ESR, ANA, rheumatoid factor, ENA) is helpful in patients with headache and arthralgias. Endocrine and metabolic testing may be necessary to rule out other systemic disorders that can cause secondary headache.

Follow-up & special considerations

Lumbar puncture, usually after CT/MRI, may be helpful to exclude SAH, infection (e.g., meningitis, encephalitis, HIV), or low or high CSF pressure.

Imaging

Initial approach

A CT scan of the head will detect most pathology able to cause headaches and is the preferred study for acute head trauma and SAH. MRI scan of the brain (with and without gadolinium) is more sensitive than CT and is superior for the evaluation of all other causes. Magnetic resonance angiography may detect intracranial aneurysms and carotid dissection. The yield of a CT or MRI scan in a patient with headache and a normal neurological examination is about 2%.

Pathological Findings

The pathological findings in most primary headache disorders are nonspecific; in many cases the brain may be unremarkable. For secondary headache disorders, the pathology will vary depending on the underlying cause.

DIFFERENTIAL DIAGNOSIS

In addition to the common primary headache syndromes (e.g., migraine, tension, cluster), other secondary headaches to consider include: Head and neck trauma, subdural or epidural hematoma; headaches during pregnancy and the postpartum period, consider pre-eclampsia and cortical vein thrombosis; in obese young women, consider pseudotumor cerebri; pheochromocytoma should be considered in patients with paroxysmal hypertension accompanied by headache; new onset headache in an HIV-positive patient could be due to mass lesion (e.g., lymphoma) or infection (e.g., meningitis); headaches in patients with a cancer diagnosis should be screened for brain metastasis; SAH should be considered in a patient with the acute onset of the worst headache of their life; frequent use of prescription and over-the-counter drugs (including analgesics) may lead to persistent rebound headaches; oral contraceptives can cause a vascular type headache in some women; headaches associated with fever, stiff neck, nausea and vomiting, and altered sensorium may be related to CNS infection.

TREATMENT

MEDICATION

First Line

For abortive treatment of migraine, the triptan medications are preferred. For prophylactic treatment, choices include beta-blockers, valproate, and amitriptyline. Cluster headaches respond best to oxygen and subcutaneous sumatriptan; corticosteroids may also be of benefit.

Second Line

Other drugs to consider for migraine or cluster headaches include ergot derivatives, serotonin antagonists, calcium channel blockers, gabapentin, nonsteroidal anti-inflammatory drugs, topiramate, and SSRIs.

ADDITIONAL TREATMENT

General Measures

Will vary depending on the specific form of primary or secondary headache disorder. Non-pharmacological methods of treatment may be helpful. Migraine headaches may resolve with sleep or improve with lying down in a dark, quiet room; the application of ice to the forehead may help. Tension type headaches may improve with relaxation techniques in some patients and an exercise regimen in others.

SURGERY/OTHER PROCEDURES

Surgery is not indicated for primary headache disorders, but may be appropriate for specific secondary headache disorders (e.g., brain tumor, SAH, abscess).

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission is not indicated for most patients with primary headache disorders, except for treatment of status migrainosus. Admission is often appropriate for work-up and treatment of patients with secondary headache syndromes (e.g., SAH, brain tumor, meningitis).

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients with primary and secondary headaches will need intermittent follow-up to assess response to treatment and, in some cases, to follow neurological status.

Patient Monitoring

Will be specific to the type of primary or secondary headache disorder.

DIET

Will be specific to the type of primary or secondary headache disorder.

PATIENT EDUCATION

Patients with primary headache disorders should be thoroughly educated about the specifics of their form of headache, and instructed about behavioral and lifestyle changes that might improve control (e.g., avoidance of triggers).

PROGNOSIS

The course and prognosis for most patients with primary headache disorders is good, with adequate control of headache pain after appropriate diagnosis and treatment. For secondary headache disorders, the course and prognosis is quite variable and depends on the specific cause.

COMPLICATIONS

On occasion, patients with complicated migraines can develop focal neurological deficits.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Migraine
- SAH
- Brain tumor
- Meningitis
- Encephalitis

CODES

ICD9

- 346.90 Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus
- 339.10 Tension type headache, unspecified
- 784.0 Headache

MUSCLE CRAMPS AND PAIN

Yuebing Li, MD, PhD

BASICS

DESCRIPTION

- Myalgia: Diffuse or focal pain perceived as originating from skeletal muscle. Generally occurs without muscle contraction.
- Muscle cramp: Involuntary and painful contractions of muscle or muscle groups.
- Both seen in a variety of conditions including healthy objects and patients with dreadful diseases such as amyotrophic lateral sclerosis.

EPIDEMIOLOGY

- Incidence
  - Myalgia is very common and its incidence is unknown. The incidence of muscle cramps increases with age. Studies suggested that nocturnal leg cramp does not occur until 8 years of age, has an incidence of 7.3% in children, and approaches 30% in patients ≥60 years.
- Prevalence
  - As many as 60% of adults have muscle pain. About 50–65% of outpatients report frequent cramps.

RISK FACTORS

- Older age, dehydration, vitamin deficiency, professions involving physical and repetitive work, trauma, infection, metabolic factors, medication usage, and many others.

Genetics

- Both can be seen in rare genetic disorders but, overall, the genetic influence is small.

GENERAL PREVENTION

- In some cases, myalgia can be prevented or reduced by regular light exercise, avoidance of infection (e.g., getting annual influenza vaccination), and treatment of underlying medical conditions.
- Exercise-induced or nocturnal muscle cramps can be prevented by regular stretching and keeping good hydration.

PATHOPHYSIOLOGY

- Myalgia: Excitation of muscle nociceptors by stimuli or a dysfunctional central pain processing (fibromyalgia)
- Muscle cramps: Spontaneous discharges of the motor nerves.

ETIOLOGY

- Myalgia
  - Viral myositis: Influenza, Coxsackie, HIV; usually generalized; accompanied by any combination of the following:
    - Fever, malaise, headache, nausea, vomiting, diarrhea, and upper respiratory symptoms
  - Other infectious myositis: Trichinosis, toxoplasmosis, and *Staphyloccus aureus*
  - Inflammatory myopathy: Polymyositis, dermatomyositis, and inclusion body myositis
  - Myalgia in collagen vascular disease: Rheumatoid arthritis, lupus, Sjogren's syndrome
  - Toxic, such as alcoholic myopathy
  - Medication: Statins, interferons, chloroquine, glucocorticoids, and zidovudine
  - Trauma: Direct, blunt, or minor but repetitive trauma occurring with occupational or recreational pursuit; generally focal, worsened by specific posture or exertion
  - Endocrine myopathy: Hypothyroidism, hyperthyroidism, diabetes mellitus, and adrenal insufficiency
  - Metabolic myopathy: Carnitine palmityltransferase deficiency, glycogen- or lipid-storage disorders, and mitochondrial myopathy
  - Vascular insufficiency: Intermittent and predictable after exercise when associated with arterial insufficiency; vague in onset and description when due to venous insufficiency
  - Muscular dystrophies
- Myalgia in neuropathy or motor neuron diseases
  - Fibromyalgia: More common in women than men (10:1); peak incidence at age 35; widespread pain for >3 months; presence of >10 of 18 tender points; coexistence of fatigue, stiffness, numbness, mood swings, and insomnia
  - Myofascial pain syndrome: Chronic regional muscle pain surrounding trigger points; commonly involve head, neck, shoulder, and lower back
  - Polymyalgia rheumatica: Pain and stiffness primarily in neck, shoulders, hips, and thighs; usually begins quickly over a few days; seen in patients >65 years old
  - Psychiatric or somatization disorder
- Muscle cramp:
  - Nocturnal leg cramps: Commonly seen in elderly, but may occur in any age group without associated conditions
  - Exercise-induced muscle cramp: When beginning a new exercise program or following intensive exercise of long duration
  - Pregnancy: Third trimester
  - Lower motor neuron disorders: Anterior horn cell disease, radiculopathy, and neuropathy
  - Parkinsonism and restless leg syndrome
  - Metabolic derangement: Hypothyroidism, adrenal insufficiency, uremia, cirrhosis, electrolyte disturbance, and volume depletion
  - Medications: Statins and diuretics
  - Hyperexcitable nerve disorders: Cramp-fasciculation syndrome and Isaac's syndrome

DIAGNOSIS

HISTORY

- Myalgia is usually described as a deep, aching sensation by most patients. Muscle cramp is recognized by the sudden uncomfortable muscle contraction, relieved by stretching, lasting seconds to minutes.
- Needs to document the following: Quality, duration, intensity, location, modifying factors (at rest or during exercise), associative symptoms, and disease course
- Inquiry about urine color post exercise

PHYSICAL EXAM

- Muscle cramp: During cramp, there is often a palpable hard knot. The involved area can be tender upon palpation for 2–3 days.
- Infectious myopathy may have fever.
- Traumatic myalgia is associated with focal muscle tenderness.
- Fibromyalgia and myofascial pain syndrome exhibit tender or trigger points.
- Myalgia associated with connective tissue disorders are accompanied by joint swelling, Raynaud's phenomenon, conjunctivitis, and uveitis.
- Myalgia due to vascular insufficiency may have decreased pulse or extremity edema.
- Inflammatory myopathy and muscular dystrophy are associated with fixed muscle weakness.
- Neuropathy and radiculopathy may present with reflex and sensory changes.
- Motor neuron disease is suspected in patients with diffuse fasciculations.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Complete blood count, serum electrolytes including sodium, potassium, calcium, and magnesium, renal and liver function, thyroid function, creatinine kinase, and aldolase

Follow-up & special considerations

- Sedimentation rate, antinuclear antibody, and rheumatoid factor if suspecting rheumatologic disorder
- Serum and urinary myoglobin if suspecting rhabdomyolysis
- Electromyography (EMG) if suspecting neuropathy, radiculopathy, motor neuron disease, inflammatory myopathy, or muscular dystrophy
- Cramps are characterized on EMG by repetitive firing of normal motor unit potentials at high frequencies. The number of activated motor units and their firing frequencies increase then decrease gradually.

Imaging

Initial approach

- Plain x-ray of joints or bones if injury is suspected
- Ultrasound and MRI scan of the muscle may show distinctive and diagnostically helpful abnormalities in many muscle diseases. May help to select appropriate sites for muscle biopsy.
- CT imaging or MRI of the spine may be necessary to rule out degenerative disc disease

Diagnostic Procedures/Other

- Ischemic forearm exercise test is indicated in patients with suspected metabolic myopathies. Normally both lactate and ammonia levels are elevated. In many subtypes of glycogen diseases, lactate level does not increase.
- Muscle biopsy: Indicated for patients with inflammatory myopathy, muscular dystrophy, metabolic myopathy, and sometimes infectious myopathy. Should not be performed for at least 6–8 weeks following an episode of rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS

- Myalgia:
  - Arthralgia: Presence of joint swelling, effusion, erythema, and warmth
  - Neuropathic pain: Electrical in quality, i.e., burning, shooting, stabbing, tingling. The involved area usually has abnormal sensation.
  - Bone pain: A breakthrough pain when moving in bed, sitting, or standing. Can be seen in patients with hyperparathyroidism, osteomalacia, fracture, or bone metastasis
- Muscle cramp
  - Dystonia: Sustained twisting motion or posture due to involuntary muscle contraction. Can be task-driven
  - Myotonia: Involuntary but painless muscle contractions. EMG very useful
  - Contracture: Involuntary and painful muscle contraction due to inability to relax after exercise, but generally of longer duration. Electrically silent on EMG. Commonly seen in metabolic myopathies
  - Tetany due to hypocalcemia or hypomagnesemia: Generally painless. Sensation of tingling and spasm around the mouth and peripheral extremity spreading proximally. Commonly affect laryngeal muscles

TREATMENT

MEDICATION

First Line

- Myalgia:
  - Acetaminophen and NSAIDs: Diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, nabumetone, and naproxen. Helpful in reducing pain and inflammation
  - Tricyclic antidepressants: Amitriptyline, desipramine, and nortriptyline. Cause drowsiness, which may help with sleep in cases of chronic pain
  - Selective serotonin reuptake inhibitors (SSRI): Duloxetine or milnacipran
  - Anticonvulsants: Gabapentin or pregabalin
- Muscle cramp:
  - Most subside spontaneously or by lengthening or stretching the cramping muscle. No medication is necessary.

Second Line

- Myalgia:
  - SSRIs: Bupropion, sertraline, and venlafaxine.
  - Tramadol or narcotics
- Muscle cramp:
  - Although effective (level A), quinine tablet is no longer available in the USA due to concern with regard to its side effects. For patients with nocturnal cramps, drinking tonic water at bedside could be an option
  - Muscle relaxants: Baclofen, cyclobenzaprine, methocarbamol, and tizanidine
  - Anticonvulsants: Clonazepam, carbamazepine, diazepam, and gabapentin
  - Others: Verapamil, chloroquine, or hydroxychloroquine
  - Vitamin B complex and Vitamin D supplement
  - Botulism toxin injection

ADDITIONAL TREATMENT

General Measures

- Gentle massage of the muscle; avoidance of causative drugs

Issues for Referral

- Rarely admitted due to diffuse myalgia or muscle cramps. Should follow up with a neurologist or rheumatologist in 3 months, then twice a year.

Additional Therapies

- Physical and occupational therapies helpful
- Swallowing therapy needed for patients with motor neuron disease, inflammatory myopathy, or muscular dystrophies

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Calcium and vitamins such as Vitamin B complex and Vitamin D have been used.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Fever relief. Monitoring of blood pressure due to volume depletion. Monitoring of heart rate due to painful stress and underlying cardiomyopathy

Admission Criteria

- Significant volume depletion with or without rhabdomyolysis; severe and generalized weakness; inability to swallow; severe pain that may need parenteral medication; and significant trauma that may require surgery

IV Fluids

- IV fluid therapy needed for patients with significant volume depletion or inability to swallow. Patients with severe pain may need parenteral medication.

Discharge Criteria

- Improvement in pain scale, normalized volume status, improvement or stabilization in strength, and stabilization in trauma status

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Adjustment of medications according to the response and tolerance
- Periodic blood tests (CBC, hepatic and kidney function) in patients taking anticonvulsants

Patient Monitoring

- Most patients can be admitted to floor.
- Monitor pain scale, strength, progression, and frequency of cramps

PATIENT EDUCATION

- Patient assurance. Educate patients about their condition and measures to avoid vigorous exercise that can trigger muscle pain

PROGNOSIS

- Varies according to etiology. Most conditions that cause muscle pain and cramps without weakness are benign and self-limited.

COMPLICATIONS

- Myalgia itself has no complications. Severe and persistent cramp can rarely cause muscle, bone, or blood vessel injuries. May impair sleep and life quality. Significant elevation of creatine phosphokinase may lead to rhabdomyolysis and renal failure.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Fibryomyalgia, polymyositis, and rhabdomyolysis

CODES

ICD9

- 729.1 Myalgia and myositis, unspecified
- 729.82 Cramp of limb

CLINICAL PEARLS

- Muscle pain without objective weakness, or changes in muscle bulk and reflexes are mostly benign.
- Cramps that occur only in the calf and foot muscles at night in an elderly patient are likely to represent benign nocturnal cramps.

SYNCOPE

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BASICS

DESCRIPTION

Syncope is a transient loss of consciousness (LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.

- Clinical characteristics:
  - The onset of syncope may either be abrupt or subacute with or without prodromal symptoms. The patient may only recall "passing out," while someone who observed the event may provide more detailed information. Thus, a thorough history involves both the patient and any observers the patient wishes to include in the interview.

PATHOPHYSIOLOGY

Neurally Mediated Syncope (NMS)

In neurocardiogenic syncope, which usually occurs with normal cardiac function, reflective changes in heart rate or BP fail to appropriately maintain cardiac output; this may include an abnormal fall in heart rate or BP or simply a failure to adequately augment these parameters. Vasodepressor syncope occurs with a situational stimulus (blood draw, unpleasant surprise) and likely has similar pathophysiology. These are the most common forms of syncope.

Arrhythmia

Arrhythmias induce hemodynamic impairment causing a critical decrease in cardiac output and cerebral blood flow. Syncope often has multiple contributory factors such as the heart rate, type of arrhythmia (supraventricular or ventricular), left ventricular function, and adequacy of vascular compensation. Bradyarrhythmias in particular should be considered in elderly patients with resting bradycardia or atrioventricular conduction disease. Atrial fibrillation can be an important cause. Several drugs can also cause brady- and tachyarrhythmia. Many antiarrhythmic drugs can cause bradycardia as a consequence of their specific effect on sinus node function or AV conduction. Syncope due to torsade de pointes is not uncommon, especially in women, and is caused by drugs prolonging the QT interval. It is particularly frequent in patients affected by the long QT syndrome. QT-prolonging drugs belong to different categories, i.e., antiarrhythmics, vasodilators, psychotropics, antimicrobials, non-sedating antihistamines, etc.

Structural Disease

Structural cardiovascular disease can cause syncope when circulatory demands overweigh the impaired ability of the heart to increase its output. In conditions with a fixed or a dynamic obstruction to the left ventricular outflow such as hypertrophic cardiomyopathy or severe aortic stenosis, syncope results from obstruction to cardiac output. Any mechanical obstruction to cerebral blood flow may produce syncope in a similar mechanism; less frequent causes include ascending aortic dissection flap or occlusion of the left ventricular outflow tract by a dislodged left atrial myxoma.

DIAGNOSIS

Initial evaluation consists of careful history, physical examination including orthostatic BP measurements and an ECG. Other less specific tests such as neurological evaluation or blood test are only indicated when there is a suspicion of non-syncopal transient LOC. The following questions should be answered: Was seizure activity present? Was somnolence present after syncope? Was the LOC transient with rapid onset and short duration? Was the recovery spontaneous, complete, and without sequel? And did the patient lose postural tone? Neurally mediated syncope is suspected in the absence of any heart disease; long history of recurrent syncope; prodrome of nausea and vomiting; occurrence after sudden, unexpected, or unpleasant sight, sound, smell, or pain and with head rotation or pressure on carotid sinus (as in tumors, shaving, and tight collars). Orthostatic hypotension is often considered a cause of syncope if it occurs after standing up; temporal relationship with start or changes of dosage of vasodepressive drugs leading to hypotension; standing after exertion and presence of autonomic neuropathy or Parkinsonism. Clinical features that suggest a diagnosis on initial evaluation are presence of definite structural heart disease, family history of unexplained sudden death or channelopathy, sudden onset of palpitation immediately followed by syncope and abnormal ECG findings (bifascicular block, Mobitz I second-degree AV block, sinus bradycardia, right bundle branch blocks (BBB) pattern, Q waves suggesting myocardial infarction, etc.).

DIAGNOSTIC TESTS AND INTERPRETATION

An array of diagnostic tests is available. Appropriate selection of any test should be guided by individual patient assessment, as typically the history provides sufficient information to obtain at least a tentative diagnosis in most cases.

Carotid Sinus Massage (CSM)

CSM is performed to evaluate patients with suspected carotid sinus hypersensitivity (CSH). This test may be performed at the bedside with patients in the supine or upright positions under continuous ECG and BP monitoring. CSH is diagnosed when CSM causes a >3 second pause, a >50 mm Hg fall in systolic BP or both, associated with presyncope and/or syncope. CSM should not be performed in patients with a history of recent transient ischemic attack or stroke or on a carotid artery that had a significant bruit or known stenosis.

Tilt Testing

Patients with a suspicion of orthostatic or vasodepressor syncope undergo this test. Patients are placed on a tilt table and then tilted upward at angles between 60 and 80 degrees for 30 to 40 minutes with regular monitoring of clinical response, BP and heart rates. This test promotes venous pooling in the lower extremities and provokes vasovagal response through the Bezold–Jarisch mechanism leading to bradycardia and hypotension. Pharmacologic provocation with sublingual nitroglycerine, Isuprel or adenosine triphosphate infusion is occasionally administered during this test. Symptomatic hypotension without bradycardia is indicative of orthostatic syncope.

Exercise Stress Test

Exercise stress testing in patients with syncope is performed to identify coronary artery disease and exercise-induced cardiac arrhythmias such as sinus node dysfunction, AV block, or tachycardia. This testing is particularly helpful in patients with syncope during activity or exercise.

ECG Monitoring

- ECG monitoring is indicated for diagnosing intermittent bradycardia and tachyarrhythmia. The gold standard for diagnosis of syncope is when a correlation between the symptoms and a documented arrhythmia is recorded. The choice of outpatient cardiac monitoring is based on the frequency of syncope. In patient monitoring (in bed or telemetry) is warranted only when the patient is at high risk for a life-threatening arrhythmia. ECG monitoring is helpful in almost all instances of syncope and particularly indicated in patients with palpitations.
- The Holter monitor is an external device that is used to monitor the ECG tracing continuously for a period of 24 hours or longer. It may be of value of the symptoms are very frequent and to differentiate patients with psychogenic pseudo-syncope. Holter monitoring may also reveal QT interval changes, T wave alternans or ST changes.
- Longer term monitoring such as with external loop or implantable devices should occur when there is a high suspicion of arrhythmia as a cause of syncope.

Echocardiogram

Structural heart diseases that predispose patients to syncope can be effectively evaluated by echocardiography. This test provides diagnostic and prognostic information with assessment of parameters such as cardiac size, left ventricular function, wall motion, and valvular heart disease. Transesophageal echocardiography, CT, and MRI may be performed in selected cases (e.g., aortic dissection and hematoma, pulmonary embolism, cardiac masses, pericardial and myocardial diseases, and congenital anomalies of coronary arteries).

Electrophysiology

The electrophysiologic study (EPS) is an invasive procedure that is recommended when cardiac arrhythmias are suspected to be the cause of syncope and noninvasive diagnostic studies are not conclusive. It is indicated in patients who have unexplained syncope in the presence of impaired left ventricular function or structural heart disease. The EPS involves placing catheters inside the heart with conduction system measurements and arrhythmia provocation. In patients with BBB, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC) and hypertrophic cardiomyopathy, EPS should be considered when noninvasive tests have failed to make the diagnosis.

DIFFERENTIAL DIAGNOSIS

Establishing that syncope occurred is usually straightforward, the patient will say, "I passed out." Distinguishing near-syncope from vertigo or non-specific neurologic syndromes may be more challenging. The history from the patient or an observer will allow the clinician to distinguish vestibular phenomena from true syncope. In eliciting a history of tonic–clonic movements or incontinence, keep in mind that seizure-like activity may ensue from syncope of any etiology, but focal neurologic signs should prompt consideration of a primary neurologic disorder. Identifying other autonomic disturbances raises the possibility of diseases such as Shy-Drager syndrome, Parkinson's disease, and diabetic neuropathy. Volume depletion due to any cause may predispose a susceptible patient to syncopal episodes. Neurological evaluation is indicated in patients in whom transient LOC is suspected to be epilepsy.

TREATMENT

The goals in treating patients with syncope should include: Limiting physical injuries, preventing recurrences, and prolonging survival.

NMS:

- Patient education is an important part of the treatment of NMS. Educating patients about mechanism and avoidance may reduce the incidence of such episodes. Medical treatment for NMS includes avoiding dehydration, physical counterpressure maneuvers (PCM) at the onset of prodrome (lying down with their feet popped up, squatting, isometric hand gripping, arm tensing, and leg crossing), increasing the intravascular volume by oral or intravenous fluids and dietary salt, wearing support hose, and physical tilt training. Some patients may require pharmacotherapy, such as volume expanders (fludrocortisones), beta blockers, and vasoconstrictors. Randomized controlled trials have demonstrated no clear clinical benefit of these agents, and the patient should be warned of possible side effects of hypertension (dietary salt, fludrocortisones, or urinary retention or urgency).
- Cardiac pacing is rarely considered in NMS unless symptoms are refractory.

Orthostatic Syncope

The treatment of orthostatic syncope consists of education regarding aggravating factors for orthostatic syncope, non-pharmacologic and pharmacologic corrections of hypovolemia, and autonomic imbalance. The non-pharmacologic approach focuses on making slow and careful changes in position, adequate hydration and salt intake, increasing intravascular volume, wearing support hose, and a routine exercise program. The patients may also benefit from PCM, tilt training, and sleeping with the head of the bed elevated to 20 to 25 cm to increase fluid volume. Pharmacotherapy with volume expanders or vasoconstrictors (Fludrocortisones and Midodrine) may be prescribed for severe symptoms of orthostasis.

Cardiac Arrhythmia-Related Syncope

- **Cardiac pacing:** Cardiac pacemaker therapy is indicated and has proved highly effective in patients with sinus node dysfunction when bradyarrhythmia has been demonstrated as cause for syncope (symptom—ECG correlation). Syncope and second degree Mobitz II, advanced or complete AV block, BBB and positive electrophysiological study are all indications for cardiac pacing.
- **Catheter ablation:** In patients with paroxysmal AV nodal reciprocating tachycardia, AV reciprocating tachycardia or typical atrial flutter associated with syncope, catheter ablation is first-choice treatment. However, patients with onset of rapid atrial fibrillation, the decision should be individualized. The role of drug therapy is limited.
- **Antiarrhythmic drug therapy:** Antiarrhythmic drug therapy including rate control drugs is indicated in patients with syncope due to onset of rapid atrial fibrillation.
- **Implantable cardioverter defibrillator:** ICD should be considered in patients with documented ventricular tachycardia, structural heart disease and inherited cardiomyopathies or channelopathies.

Unexplained Syncope in Patients with High Risk of Sudden Cardiac Death (SCD)

Unexplained syncope with a high risk of SCD is seen in the following groups: Hypertrophic cardiomyopathies, ARVC, inherited cardiac ion channel abnormalities, long QT syndromes, and Brugada syndrome. All should be evaluated by a cardiologist with expertise in these syndromes.

Driving

The American Heart Association established driving guidelines related to arrhythmias that may affect consciousness were later amended to include drivers with ICD insertion for primary prevention. Two groups of drivers are defined: Private and commercial. Drivers of taxicabs, small ambulances, and other vehicles form an intermediate category. Data suggest that the risk for a motor vehicle accident related to syncope is low. The efficacy of drug therapy for NMS remains inconclusive, and repeat tilt-table testing to assess therapy has no predictive value. There is no evidence that allowing three asymptomatic months to elapse provides assurance that syncope will not recur. Driving recommendations should be prescribed in conjunction with the collaborating physician or cardiologist.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Any episode of syncope resulting in significant harm to the patient mandates inpatient evaluation. Furthermore, patients with structural heart disease and syncope probably should be admitted to a telemetry ward given the risk of sudden death. On the other hand, a young person with a clearly identified reversible precipitant such as dehydration or presumed vasodepressor (neurocardiogenic) syncope could be managed as an outpatient in the absence of high-risk features.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patient monitoring is indicated particularly if an arrhythmic cause is suspected but a diagnosis has not been made.

PATIENT EDUCATION

Symptoms of noncardiac syncope are briefly outlined at this NIH website: http://www.ninds.nih.gov/health_and_medical/disorders/syncope_doc.htm

PROGNOSIS

Two important elements should be considered with the risk stratification of syncope: The risk of death and life-threatening events and the risk of recurrence and physical injury associated with syncope. Structural heart disease and primary electrical disease are associated with poor prognosis, conversely young patients affected by reflex syncope have excellent prognosis. The number of episodes of syncope during life is the strongest predictor of recurrence. Recurrent syncope may be associated with bone fractures and soft tissue injuries. Morbidity is particularly high in elderly and ranges from loss of confidence, depressive illness and fear of falling to fractures and subsequent institutionalization. Nonetheless recurrent syncope is comparable with chronic illnesses as it significantly impairs the quality of life.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Fainting, spells, LOC.
- Autonomic Reflex Testing
- Orthostatic Hypotenion
- Epilepsy

CODES

ICD9

- 458.0 Orthostatic hypotension
- 780.2 Syncope and collapse

TREMOR

Anwar Ahmed, MD

BASICS

DESCRIPTION

Tremor is the most common movement disorder. It is defined as a rhythmic, involuntary, oscillating movement of a body part occurring in isolation or as part of a clinical syndrome. In clinical practice, characterization of tremor is important for etiologic consideration and treatment.

- Terminology
  - Resting tremor occurs when a body part is at complete rest against gravity. Tremor amplitude decreases with voluntary activity.
  - Postural tremor occurs during maintenance of a position against gravity.
  - Action or kinetic tremor occurs during voluntary movement.
  - Task-specific tremor emerges during a specific activity.
  - Intention (or terminal) tremor manifests as a marked increase in tremor amplitude during a terminal portion of targeted movement.

EPIDEMIOLOGY

Prevalence

- Essential tremor (ET) prevalence rate 0.4–5.6%. Family history + in 60% of patients, autosomal dominant.
- Approximately 60% of patient experience tremor in Parkinson's disease (PD). PD prevalence 56–234 per 100,000.

RISK FACTORS

- Genetic and environmental factors
- The risk of ET in a first-degree relative is 5 times greater than the risk in control cases
- Exposure to certain drugs

Genetics

- The inheritance of ET is autosomal dominant, with incomplete penetrance.
- Specific genes for ET have been linked to chromosomes 2p, 3q, and 4p.
- In ET, onset younger with family history positive.

GENERAL PREVENTION

Drug-induced tremor may be prevented by avoiding certain drugs.

PATHOPHYSIOLOGY

Four basic mechanisms are linked to the production of tremor. It is likely that combinations of these mechanisms produce tremor in different diseases.

- Mechanical oscillations of the limb can occur at a particular joint; this mechanism applies in cases of physiologic tremor.
- Reflex oscillation is elicited by afferent muscle spindle pathways and is responsible for stronger tremors by synchronization. This mechanism is a possible cause of tremor in hyperthyroidism or other toxic states.
- Central oscillators are groups of cells in the CNS present in the thalamus, basal ganglia, and inferior olive. These cells have the capacity to fire repetitively and produce tremor. Parkinsonian tremor might originate in the basal ganglia, and ET might originate within the inferior olive and thalamus.
- Abnormal functioning of the cerebellum can produce tremor.

ETIOLOGY

Tremor can be classified on a clinical and etiologic basis. Signs and symptoms depend on tremor type and cause. Multiple etiologies have been identified including neurodegenerative diseases, brain ischemia or demyelination, metabolic derangements, drugs and toxic states.

COMMONLY ASSOCIATED CONDITIONS

- Physiologic tremor: Low-amplitude tremor (6–12 Hz); neurological examination normal.
- Drugs and toxins may induce an enhanced physiological tremor.
- ET frequency of 7–10 Hz; predominantly postural- or action-type tremor; drinking alcohol temporarily reduces the tremor. Other associated symptoms can include mild gait difficulty.
- PD tremor is a low-frequency 4–6 Hz rest tremor typically defined as a pill-rolling tremor. Some patients also have postural and action tremors.
- Cerebellar tremor is a low-frequency (<4 Hz) intention tremor often unilateral. Signs and symptoms of cerebellar dysfunction may be present, including ataxia, dysmetria, dysdiadochokinesia, and dysarthria.
- Dystonic tremor is predominantly postural in nature often irregular in rhythm.
- Holmes' tremor or rubral tremor is a combination of rest, postural, and action tremors due to midbrain lesions in the vicinity of the red nucleus. This type of tremor is irregular and low frequency (4.5 Hz).
- Common tremor-inducing drugs include neuroleptics, lithium, divalproex sodium (Depakote), amiodarone, metoclopramide, theophylline, and bronchodilators.
- Tremor can occur in diseases such as thyrotoxicosis and hepatic failure and in drug withdrawal.
- Psychogenic tremor can involve any part of the body, but it most commonly affects the extremities. Usually, tremor onset is sudden and begins with an unusual combination of postural, action, and resting tremors. Psychogenic tremor decreases with distraction and is associated with multiple other psychosomatic complaints.
- Orthostatic tremor occurs in the legs immediately on standing and is relieved by sitting down. Orthostatic tremor is usually high frequency (14–18 Hz), and no other clinical signs or symptoms are present.
- Essential palatal tremor is an uncommon disorder, characterized by rhythmic movements of the soft palate.

DIAGNOSIS

Diagnostic evaluation of the tremor should include a thorough clinical history, clinical examination (including tremor rating), and differential diagnosis

HISTORY

The clinical history must detail tremor onset, duration, severity, affected area, activating factors, relieving factors, effect of alcohol, family history, and associated symptoms

PHYSICAL EXAM

- The clinical examination should determine a tremor rating and tremor frequency.
- The patient should be examined during rest, when assuming various positions, and when moving.
- An examination of gait, muscle tone, facial expressions, and dexterity is also important, particularly in differentiating ET from PD.
- Tremor in each affected body part can be rated as resting, kinetic, or postural and with a scale developed by Kahn and colleagues as follows: (1) No tremor; (2) slight tremor; (3) moderate tremor (less than 2 cm excursion); (4) marked tremor (2–4 cm excursion); and (5) severe tremor (more than 4 cm excursion).

DIAGNOSTIC TESTS AND INTERPRETATION

A laboratory workup is not necessary for most tremor patients.

- Thyroid function test.
- In young patients with parkinsonism or tremor, serum copper, serum ceruloplasmin, 24-hour urinary copper, and slit-lamp examination (Wilson's disease).

- To rule out systemic causes of tremor, such as hypoglycemia, liver disease, electrolyte imbalance, or drug abuse, appropriate tests should be ordered.
- An MRI or computed tomography scan of the brain is needed in some patients if tremor onset is acute, progression is rapid, and cerebellar signs suggest stroke, demyelinating disease, or structural lesion.
- In difficult cases FDA-approved FP-CIT SPECT Scan (DaTscan) can differentiate Parkinsonism from ET.
- Tremor also can be analyzed and diagnosed with the help of accelerometers and surface electromyogram recordings (tremor analysis).

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of tremor include the following:

- Myoclonus is irregular or rhythmic brief muscle jerks that can mimic tremor.
- Clonus is a rhythmic movement around joints that is stimulated through stretch reflex.
- Asterixis is a type of myoclonus that can cause a flapping tremor of the extremities.
- Epilepsia partialis continua can cause rhythmic jerks in the extremities.

TREATMENT

Dependent on the type of tremor:

- Treatment of ET usually begins with primidone or propranolol monotherapy. The dosages are gradually increased to achieve optimal response. They may be combined.
  - Primidone can gradually be increased to a range of 150 mg/day to 250 mg/day and a maximum of 750 mg/day.
  - Propranolol can gradually be increased over several weeks to 240 mg/day or as high as 320 mg/day.
  - Relative contraindications to use propranolol include asthma, diabetes, congestive heart failure, and bradycardia.
  - Common side effects of primidone and propranolol include dizziness, tiredness, and depression.
  - Second-line medications: Topiramate, gabapentin, clonazepam can be used for ET after trial of propranolol and primidone.
- PD tremor usually improves with dopaminergic and anticholinergic medications (see Parkinson's disease).
- Orthostatic tremor may respond to clonazepam treatment.
- Psychogenic tremor requires early psychiatric intervention and psychotherapy.
- Drug-induced tremor improves after stopping the offending agent.
- Tremor caused by metabolic or toxic states responds to the treatment of underlying conditions.

SURGERY/OTHER PROCEDURES

- For patients with severe, disabling, medication-refractory ET and PD tremor, surgery is a reasonable treatment option.
  - Surgical management includes ablative therapy through stereotactic thalamotomy or chronic thalamic deep brain stimulation. The ventral intermediate nucleus of the thalamus is the best target for both ablative and deep brain stimulation surgeries for ET.
  - Similarly in PD, tremor improves significantly after subthalamic nucleus deep brain stimulation surgery. Although these surgical techniques are widely available, they should be used with caution and only after exhausting all possible pharmacologic treatment options.
  - Contraindications for surgical management of tremor include unstable medical illnesses, swallowing difficulty, and marked cognitive problems.

IN-PATIENT CONSIDERATIONS

N/A

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Periodic follow-up is helpful to check the medication response and progression of disease.

PATIENT EDUCATION

- Community support groups for ET, PD, and dystonia
- National organizations:
  - International Essential Tremor Foundation (IETF), 7046 West 105th Street, Overland Park, KS 66212-1803; Tel: 913-341-3880; website: www.essentialtremor.org
  - WE MOVE, 204 West 84th Street, New York, NY 10024; Tel: (US): 800-437-MOV2; (outside US): 212-875-8312, www.wemove.org

PROGNOSIS

- PD is a chronic progressive neurodegenerative disease that leads to worsening of cognitive and motor symptoms particularly gait and balance.
- ET course is benign and remains mild for years, but tremor worsens with age.

ADDITIONAL READING

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- Tremor: clinical features, pathophysiology, and treatment. *Elble RJ Neurol Clin* 2009;27(3): 679–695.

CODES

ICD9

- 332.0 Paralysis agitans
- 333.1 Essential and other specified forms of tremor
- 781.0 Abnormal involuntary movements

WEAKNESS

D. Joanne Lynn, MD

BASICS

DESCRIPTION

- Weakness can be defined as a deficit in the motor system, with decreased strength in one or more muscles or limbs, or generalized weakness. Patients may use the term weakness to refer to fatigue, muscle and joint pain, and incoordination. Therefore, it is important to explore exactly what is meant when the term weakness is used.
- Definitions: Upper motor neuron (UMN) deficit refers to weakness caused by an injury to the CNS (brain or spinal cord). A lower motor neuron (LMN) syndrome refers to weakness caused by injury to any of several levels of the peripheral nervous system (including anterior horn cell, nerve root, plexus, nerve, neuromuscular junction, and, for general purposes, muscle).

EPIDEMIOLOGY

Incidence

In developed countries, the most common causes of acute weakness are Guillain–Barré Syndrome (GBS), myasthenia gravis, drug effects, botulism, rhabdomyolysis, and hypokalemia.

RISK FACTORS

- In-hospital onset suggests hypermagnesemia, hypokalemia, myasthenia gravis, GBS, antibiotic-induced weakness, botulism, critical illness polyneuropathy, or myopathy.
- Travel history suggests fish poisoning, polio, diphtheria, botulism, tick paralysis, rabies, or snake or other envenomation.

Genetics

Family history of episodes of acute weakness may suggest porphyria, periodic paralysis, or rhabdomyolysis.

GENERAL PREVENTION

None

PATHOPHYSIOLOGY

Weakness of UMN etiology is caused by injury to the major descending motor pathway, the corticospinal tract. The corticospinal tract may be injured at multiple levels, including its cortical origin, through the cerebral white matter, internal capsule, caudal brainstem, or within the spinal cord. LMN weakness is caused by more diverse sites of injury, including the anterior horn cells of the spinal cord, roots, plexus, nerves, neuromuscular junction, and muscle.

ETIOLOGY

Many diverse causes

DIAGNOSIS

HISTORY

- The most important factors to ascertain the etiology include rapidity of onset and development of weakness, distribution of weakness, fluctuating versus fixed weakness, and associated findings such as abnormal reflexes, sensory loss, impaired bowel and bladder function, exposure to toxins, and family history of weakness.
- GI symptoms suggest porphyria, botulism, or organophosphate, thallium, or arsenic poisoning.

PHYSICAL EXAM

- UMN weakness is typically associated with hypertonia or spasticity, hyperreflexia, and extensor plantar responses. Myelopathy that develops slowly is generally associated with hyperactive reflexes and Babinski signs. Acute spinal cord injury may present with "spinal shock" and flaccid areflexic paralysis, which can be confused with LMN pathology. Differentiation from root, plexus, or peripheral nerve disease usually can be made based on determination of sensory level, urinary symptoms (urinary retention, urgency, frequency, and incontinence), frequent asymmetry of weakness, and eventual development of UMN signs.
- LMN weakness is typically associated with hypotonia or flaccidity if the weakness is severe, with hyporeflexia or areflexia and flexor or absent plantar responses. Fasciculations may be present if the anterior horn cell or motor nerve has been injured with resultant denervation of muscle.
- Patterns of weakness help to localize the site of pathology:
  - Hemiparesis that includes the face suggests cerebral or high brainstem lesions.
  - Hemiparesis without facial and other cranial nerve involvement suggests lower brainstem or spinal cord.
  - Myotomal level suggests spinal cord pathology.
  - Proximal weakness in all limbs suggests myopathy.
  - Distal weakness suggests peripheral neuropathy.
  - Weakness of eye movements suggests botulism, myasthenia gravis, diphtheria, hypermagnesemia, antibiotic-induced weakness, tick paralysis, and thallium intoxication.
  - Decreased or absent pupillary responses suggest a differential diagnosis of diphtheria, botulism, anticholinergic toxicity, antibiotic-induced weakness, snake venoms, and Lambert–Eaton syndrome.
- Various types of pain may suggest different causes of weakness.
  - Neck and back pain may herald weakness for GBS, porphyria, polio.
  - Tender muscles: Rhabdomyolysis
  - Proximal myalgias: Periodic paralysis, GBS
  - Distal dysesthesias: Toxic neuropathies
  - Respiratory failure disproportionate to limb weakness: Myasthenia gravis, botulism, antibiotic-induced weakness, hypermagnesemia, hypophosphatemia, rabies, amyotrophic lateral sclerosis, high cervical cord lesions, critical care polyneuropathy, rabies, snake envenomations

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Electrolytes
- Creatine kinase for question of muscle injury
- Anti-acetylcholine receptor antibodies for suspicion of myasthenia gravis
- CSF analysis for evaluation of GBS (elevation of protein with normal or near-normal cell count), carcinomatous meningitis (cytology, tumor markers), multiple sclerosis (IgG synthesis rate and index and oligoclonal bands), transverse myelitis
- Serum levels of organophosphates (TEPP, parathion)
- Urine studies for toxins such as arsenic
- Serum, feces, and gastric contents for botulinum toxin assay
- Hair and fingernail analysis for metals such as arsenic and thallium

Imaging

Initial approach

Imaging will depend on the level or system involved and will be directed at this level or system [i.e., imaging of the brain for a cortical disorder, imaging of lumbar spine for a radiculopathy, electromyography (EMG) for a muscle disorder, etc.]

Diagnostic Procedures/Other

- Nerve conduction velocity studies/EMG to investigate pattern and type of radiculopathy, plexopathy, neuropathy, or myopathy.
- Repetitive stimulation nerve study to explore neuromuscular junction function in suspected myasthenia gravis, myasthenic syndromes, or botulinum poisoning.
- Edrophonium (Tensilon) test for suspected myasthenia gravis

Pathological Findings

Dependent upon the cause of weakness

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of weakness is extremely broad and only a few major causes are listed here.
  - Cerebrum/brainstem:
    - Cerebrovascular accident
    - Multiple sclerosis
    - Mass lesions (tumors, abscess)
    - Trauma
  - Spinal cord:
    - Trauma
    - Compressive myelopathy (neoplastic, herniated disc, spondylotic)
    - Transverse myelitis
    - Anterior spinal artery syndrome
  - Motor neuron:
    - Amyotrophic lateral sclerosis
    - Acute anterior poliomyelitis

- Peripheral nerve:
  - GBS
  - Porphyria
  - Toxic neuropathies [heavy metals (e.g., arsenic, lead, thallium, gold), hexacarbons, nitrofurantoin, lithium, disulfiram]
  - Diphtheria
  - HIV-associated neuropathies
- Neuromuscular junction:
  - Myasthenia gravis and myasthenic syndromes
  - Organophosphate poisoning
  - Drug-induced neuromuscular blockade
  - Botulism
  - Animal venoms/poisons
  - Electrolyte derangements (hypermagnesemia, hypokalemia, hypophosphatemia)
- Muscle:
  - Muscular dystrophies
  - Inflammatory myopathies
  - Rhabdomyolysis
  - Periodic paralysis

TREATMENT

MEDICATION

First Line

- The choice of medications depends on the cause of weakness. Treatments for some of the commonly considered causes include:
  - Patients with weakness from acute cerebral infarction who present within 3 hours and meet inclusion/exclusion criteria should be considered for treatment with thrombolytic therapy.
  - Treatment with high-dose corticosteroids should be considered for weakness from acute exacerbations of multiple sclerosis, transverse myelitis, spinal cord compression, myasthenia gravis, inflammatory myopathies, and chronic inflammatory polyneuropathy (CIDP).
  - GBS, CIDP, myasthenia gravis, and inflammatory myopathies may respond to intravenous immunoglobulin therapy.
  - Porphyric neuropathy may respond to infusions of IV glucose 10–20 g/hour and hematin 4 mg/kg every 12 hours.
  - Atropine and pralidoxime (a cholinesterase reactivator) for organophosphate poisoning
  - Botulinum antitoxin for botulism
  - IV calcium gluconate for hypermagnesemia

ADDITIONAL TREATMENT

General Measures

The initial approach to weakness depends upon the etiology. Separate chapters on causes of weakness will go into greater detail. Patients with progressive generalized weakness with possibility of threatened respiratory insufficiency must be monitored closely for vital capacities and inspiratory pressures to determine the need for intubation and ventilation.

Additional Therapies

- Physical therapy
- Occupational therapy
- Speech therapy for dysarthria or dysphagia

SURGERY/OTHER PROCEDURES

- Potential surgical measures include:
  - Decompression/excision of cord lesions
  - Stabilization of vertebral fractures or spinal instability
  - Biopsy of cerebral/cord lesions
  - Release of nerve entrapments as in carpal tunnel syndrome

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Management of respiratory insufficiency and metabolic derangements; prevention of deep venous thrombosis (DVT)

Admission Criteria

- Admission criteria for this diverse group of causes of weakness vary but include:
  - Rapidly progressive course of generalized weakness
  - Impending respiratory failure or inability to protect the airway
  - Need for expedited workup
  - Inability to perform activities of daily living and transfers

IV Fluids

Fluid replacement may be required if patient is unable to swallow. Rhabdomyolysis requires aggressive hydration.

Nursing

- Range of motion and frequent turning
- Splinting to prevent contractures
- Measures to prevent DVT if patient is not ambulatory

Discharge Criteria

Variable but must have stable strength and respiratory function

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

After discharge to home or a rehabilitation facility, monitoring should continue to assess response to therapy, possibility of relapse.

DIET

Modified consistency for dysphagia

PATIENT EDUCATION

See separate chapters for sources of information on disorders causing weakness

PROGNOSIS

Expected course and prognosis depend on the underlying cause of the weakness.

COMPLICATIONS

- Paralysis is associated with complications of DVT, decubitus ulceration, aspiration pneumonia, and joint contractures.

ADDITIONAL READING

- Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. *Arch Neurol* 2010;67(9):1089–1094.
- Dhand UK. Clinical approach to the weak patient in the intensive care unit. *Respir Care* 2006;51(9): 1024–1040; discussion 1040–1041.
- Elegbe O, Wickremaratchi M, Hinchcliffe M. The patient with acute paraplegia: a problem-based review. *Acute Med* 2011;10(1):40–44.
- Saguil A. Evaluation of the patient with muscle weakness. *Am Fam Physician* 2005;71(7): 1327–1336.

See Also (Topic, Algorithm, Electronic Media Element)

- Neuropathy, peripheral
- Guillain–Barré syndrome
- Myasthenia gravis
- Lambert–Eaton syndrome
- Transverse myelitis
- Polymyositis
- Dermatomyositis

CODES

ICD9

- 357.0 Acute infective polyneuritis
- 728.87 Muscle weakness (generalized)
- 780.79 Other malaise and fatigue

CLINICAL PEARLS

- A careful history and physical examination are critical to determination of the cause of generalized weakness.
- Patients with severe generalized weakness require close attention to respiratory status and prevention of DVTs and decubitus ulcerations.

Section II

Neurological Diagnostic Tests

ANGIOGRAPHY

Shaye Moskowitz, MD, PhD

ALERT
Inquire about dye allergy in all patients undergoing angiography. Special caution in diabetic and renal patients.

BASICS

DESCRIPTION
- Angiography is the invasive x-ray imaging of the cerebral vasculature using catheters to directly inject contrast into cerebral arteries. Catheters are navigated through the vasculature, usually starting at the femoral or less commonly brachial artery, into the common carotid, internal carotid, and vertebral arteries for imaging of the cervical or cerebral vascular system. Both fluoroscopy and digital subtraction imaging are employed to perform this safely.
- This imaging modality utilizes an iodine-based contrast to image the vasculature as it passes through the arterial, capillary, and venous beds of the head and neck. The individual phases last several seconds each, and each "run" lasts from 5 to 20 seconds.

INDICATIONS
- Because of its invasive nature and potential risks, angiography should be considered in situations where cerebral vascular disease requires evaluation in greater detail than can be offered by non-invasive testing, including CT and MR angiography. Many situations exist which justify this, and include:
  - Suspicion of a cerebrovascular abnormality, including aneurysm, arteriovenous malformation (AVM), or fistula
  - Evaluation of a stroke or transient ischemic attack, with consideration of cervical or intracerebral atherosclerotic disease
  - Consideration of vasculitis, vasospasm, or venous occlusive disease
  - Evaluation of a subarachnoid or unexplained intraparenchymal hemorrhage
  - Evaluation of blunt or penetrating vascular injury
  - Functional testing for epilepsy surgery, including a Wada test
  - Evaluation of spinal vascular disease, including fistula or AVM
  - Identification of the spinal artery of Adamkiewicz prior to certain spinal surgeries

STRENGTHS
Relative to other angiographic modalities, catheter angiography provides greater temporal and spatial resolution than other imaging modalities. It is the most precise mode for imaging of smaller vessels in the head and neck, and allows for imaging of selective beds offering more dedicated imaging. Should an intervention be appropriate, this can be performed in the same setting as the diagnostic study, should that be indicated and appropriate for the disease being considered.

LIMITATIONS
- The images obtained are two-dimensional representations of a three-dimensional structure. Newer computer modes of this imaging can create rotational models of the arterial beds being imaged and as such may now offer true spatial resolution, formerly available with non-invasive modes.
- The study does carry some risk and may be time-consuming for the patient, which should be considered.
- Availability of the angiography equipment may limit the use of this test, as it is often expensive and not immediately available.

RISKS
- The incidence of vascular or neurologic injury during a catheter angiogram remains low, and is estimated to be below 0.5%. This may be lower in the hands of a skilled and dedicated neuro-angiographer or neuro-interventionalist. The risks may be slightly higher in patients with significant atherosclerotic disease of the aorta or craniocervical vasculature. The risks include injury, such as dissection, and thromboembolism, from either disturbed plaque or de novo thrombus formation of the catheter. While use of heparinization is not standard, prolonged procedures or manipulation may increase this risk.
- Vascular access complications include less serious groin ecchymosis to more serious hematomas or injury. Less commonly, this can be significant enough to justify transfusion or consultation with a vascular surgeon for management or repair.
- Rarer complications can occur and include contrast allergy, infection at the access site, retroperitoneal hematoma, or hemodynamic changes.

CONTRAINDICATIONS
There are no absolute contraindications, though renal dysfunction, pregnancy, coagulation disorders, and prior contrast allergies are relative contraindications. Catheter angiography in certain collagen disorders, such as Ehlers–Danlos Type 4, may carry increased risks of dissection or vascular injury.

PREPARATION/SPECIAL INSTRUCTIONS
- Patients should not eat or drink prior to the procedure. Prescribed medications may be continued. Patients with poor renal function should be hydrated prior to the procedure, and dialysis should be timed around the angiogram. Metformin should be held prior to and following the angiogram as there is increased risk of renal failure.
- Following the procedure, the patient is monitored for a short period for groin or systemic complications. The patient is usually kept flat with the hip held straight. Following discharge, routine behavior is acceptable though oral hydration is recommended, as is light function, including limitation of weight lifting and excessive joint movement. These limits are relative and usually applied for 2–5 days following the angiogram.

ADDITIONAL READING

- Kaufmann TJ, Huston J, Mandrekar JN, et al. Complications of diagnostic cerebral angiography: evaluation of 19 826 consecutive patients. *Radiology* 2007;243:812–819.
- Willinsky RA, Taylor SM, terBrugge K, et al. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. *Radiology* 2003;227:522–528.

CODES

ICD9
- 435.9 Unspecified transient cerebral ischemia
- 436 Acute, but ill-defined, cerebrovascular disease
- 437.9 Unspecified cerebrovascular disease

AUTONOMIC REFLEX TESTING (ART)

Angelique Petropouleas, BA
David S. Younger, MD

BASICS

DESCRIPTION
Noninvasive ART techniques are designed to detect and quantitate autonomic failure by evaluation of sudomotor, cardiovagal, and adrenergic autonomic function and the effectiveness of treatment thereof.

QUANTITATIVE SUDOMOTOR AXON REFLEX TEST (QSART)
Postganglionic sympathetic sudomotor axons innervate sweat glands of the epidermis with the neurotransmitter acetylcholine (ACh). Testing of sweat gland function commences with the application of a 10% saline AChR solution applied iontophoretically to the skin. An electrical impulse is generated antidromically to a branching point along the postganglionic sympathetic sudomotor axon from which it travels orthodromically to the nearest sweat gland. The activated sweat gland releases sweat that is quantified by a sudorometer, the commercially available FDA-approved model which is known as a Q-Sweat apparatus.

Recording Sites
Dorsum of the foot (sural nerve), distal leg (saphenous), proximal leg (peroneal), and medial forearm (ulnar)

Normal Response
Similar sweat volumes measured on all recording sites indicate normal responses. Men show greater sweating than women; however, both decline with age.

Abnormal Response
Reduced, excessive, or persistent sweating patterns

Silastic Imprints
The silastic imprint technique records directly from the sweat gland bypassing the nerve by the application of 1% pilocarpine or acetylcholine so that there is no dependence on an axon reflex.

SYMPATHETIC SKIN RESPONSES (SSR)
The sympathetic skin response evaluates sudomotor function by measuring changes in skin resistance following stimuli delivered at random intervals and with increasing intensity.

Recordings Sites
SSR measurements are made along the palms and soles via surface electrodes.

Normal Response
Readily elicitable, amplitude in hands > foot

Abnormal Response
A difference of 50% or more from side to side, or absent response; both are considered abnormal.

THERMOREGULATORY SWEAT TEST (TST)
The thermoregulatory sweat test examines efferent sympathetic cholinergic pathways. Alizarin red, cornstarch, and sodium carbonate in a ratio of 50:100:50 grams respectively is dusted over the body to identify sweat production signaled by a change in color from white to red, while in a temperature- and humidity-controlled chamber used to control core body temperature. Areas of hypo- or anhidrosis, or hyperhidrosis, are documented by anatomical drawings or photography.

Normal Response
Homogeneous sweating

Abnormal Response
Distal, segmental, regional, focal, mixed, and global sweat loss patterns

DEEP BREATHING TEST (DB)
The heart rate (HR) response to deep breathing (HRDB) is assessed by continuous ECG of a respiratory frequency of six cycles per minute.

Normal Response
- Age 20–39 (14–41 bpm), 40–59 (10–33 bpm), ≥60 (7–27 bpm)
- Acceleration of heart rate during inspiration and deceleration during expiration

Abnormal Response
Reduced HRDB is an early sign of autonomic dysfunction and potentially associated with increased cardiovascular risks.

VALSALVA MANEUVER (VM)
This maneuver consists of forced expiration for 15 seconds against a fixed resistance, maintaining an expiratory pressure of 40 mm Hg. The calculated Valsalva ratio (VR) is a measure of peripheral adrenergic function, based upon conduction through the baroreflex arc along sympathetic adrenergic and parasympathetic cardiovagal pathways. Patients are instructed to forcefully blow into a mouthpiece attached to a manometer maintaining an expiratory pressure of 40 mm Hg for 15 seconds. Four phases of the VM response are recognized. Beat-to-beat continuous BP is obtained using a Finometer-based servoplethysmograph that generates reliable waveforms for digital data acquisition and computerized waveform display. Four hemodynamic phases are produced for analysis. Phase I coincides with mechanical compression of the aorta leading to a brief decrease in HR and increase in BP. The early phase II (II_E) response coincides with the progressive fall of BP, venous return, and cardiac output compensated by baroreflex-mediated tachycardia. The late phase II (II_L) response coincides with the restoration of BP to resting levels due to increasing peripheral resistance. Phase III coincides with a decrease in BP and increase in HR. The phase IV response coincides with a BP overshoot as venous return and cardiac output return toward normal in spite of increased peripheral vasoconstriction and baroreflex-mediated bradycardia. The VR is an index of tachycardia during phase II and bradycardia during phase IV.

Abnormal Response
- Adrenergic overactivity: Reduced pulse pressure, increased phase IV
- Adrenergic failure: Increased fall of BP, reduced or absent late phase II, reduced phase IV
- Cholinergic failure: Flat HR response

HEAD-UP TILT (HUT)
BP and HR are recorded continuously before, during, and after 5–10 minutes of 70 degrees automated tilting before returning to the supine position.

Normal Response
HR increment >10 and <30 bpm, stable BP, and cerebral blood flow

Abnormal Response
- Orthostatic intolerance (OI): HR increment >30 bpm and <120 bpm, pulse pressure reduced <50% of baseline
- Postural tachycardia syndrome (POTS): Heart rate >120 bpm, pulse pressure falls >50% of baseline, >10% reduction of cerebral blood flow
- Syncope: Rapid fall of BP with brady- or tachycardia and cerebral hypoperfusion
- Orthostatic hypotension: Sustained fall of BP >30/10 mm Hg for 3 minutes with or without OI

Time-Frequency Analysis
Power spectrum of R-R intervals, beat-to-beat variation, etc., are sensitive methods for evaluation of HR variability.

Indications
- Loss of consciousness, dizziness, lightheadedness, orthostatic and postprandial intolerance
- Painful small fiber neuropathies, diabetic neuropathy, sweating disturbance
- CNS neurodegenerative conditions including Parkinson disease, multiple system atrophy

Strengths
Non-invasive and reproducible

Limitations
Interpretation may be limited in older people with anticholinergic, sympatholytic, and sympathomimetic medications. Withdrawal of these medications for 24 hours may be indicated. HR variation is reduced by aging, tachycardia, hypocapnia, and anticholinergic medications.

RISKS
HUT may induce orthostatic hypotension, syncope with tachy-, bradycardia, or rarely sinus arrest. Risks of stopping cardioactive medications such as beta-blockers.

Contraindications
Caution needed for tilt testing of older people with cardiac disease and pacemakers.

Preparation/Special Instructions for Patients
No caffeine or cigarettes for 8 hours and 1 hour after meal. No lotion. Patient should be well hydrated.

Miscellaneous
None

CODES

ICD9
337.9 Unspecified disorder of autonomic nervous system

BIOPSY, BRAIN

Herbert B. Newton, MD

BASICS

DESCRIPTION OF PROCEDURE

Brain biopsy can be obtained by open craniotomy or via computer-assisted stereotactic procedures (i.e., needle biopsies using a stereotactic frame, under local anesthesia). Several considerations are important in deciding between the two techniques and whether or not to pursue surgery. The most important issues related to the lesion or process in the brain are: Is it too deep or too small to be accessible? Is it located in an eloquent region of brain? Are the lesions solitary or multiple? Is the process too diffuse to define an adequate target? Other considerations focus on the patients, such as, are they too old or too ill to undergo biopsy? Do they have a specific preference? Lesions that are generally considered most appropriate for stereotactic biopsy include those that are small and deep, located in eloquent cortex, diffuse within deep portions of the brain, and multifocal. Biopsy by open craniotomy requires general anesthesia and is most appropriate for lesions of non-eloquent cortical and adjacent subcortical tissues, and the meninges. A wedge of tissue that includes the cortex, meninges, and underlying white matter is usually optimal.

Indications

Diseases that require biopsy may be infectious, neoplastic, degenerative, vascular, metabolic, or developmental. The differential diagnosis of diseases where biopsy may be helpful is broad and includes enhancing lesions (infarct, abscess, glioma, metastasis, and necrosis), tumors (primary versus metastasis), degenerative or dementing illnesses (prion diseases, Pick's disease, and Lewy body disease), skull and soft tissue disorders (histiocytosis X), inflammatory conditions (vasculitis, tumefactive multiple sclerosis, neurosarcoidosis), infectious processes (abscess, progressive multifocal leukoencephalopathy), and patients with AIDS (lymphoma, toxoplasmosis).

Strengths

Diagnostic accuracy based on neuroimaging criteria alone is limited. Clinically significant alterations of the preoperative diagnosis occur in 12 to 25% of cases after tissue is obtained and analyzed. In many patients, this allows for the administration of more specific and appropriate therapy.

Limitations

The major limitation of brain biopsy involves the decision of which region of the mass lesion or abnormal area of brain to access. If there is not a well-defined target, it is possible to miss the target and obtain normal or nondiagnostic tissue. This can also occur with a mass lesion, if the needle removes tissue only from the edge or transition zone. Biopsy of the center of a mass may also be nondiagnostic, by obtaining only necrotic tissue. There is an 8 to 9% failure rate associated with brain biopsy, in which the obtained tissue does not result in a definitive histologic or microbiologic diagnosis. The problem of sampling error is improved by taking multiple samples of the lesion, as well as samples of the region of interface between the lesion and the normal brain. Intraoperative pathologic assessment by frozen section is also useful to ensure diagnostic adequacy of samples.

RISKS

- The risks involved in brain biopsy include those to the patient, in the form of surgical complications during or after the brain biopsy, as well as potential risks to the surgical team and pathologist. In most series of brain biopsy, surgical mortality is less than 1%, while surgical morbidity ranges between 1 and 6%. The most significant risks during the procedure are intracranial hemorrhage, brain swelling and edema, and new focal neurologic deficits. Other potential risks include cerebral infarction, infection, and scarring with formation of an epileptic focus.
- The surgical team and pathology staff must handle specimens with care, since they may be at risk for infection from agents such as HIV, hepatitis, and Creutzfeldt–Jakob disease.

Contraindications

Include patients at high risk of hemorrhage due to excessive anticoagulation, specific drugs (e.g., bevacizumab) that increase the risk for bleeding, liver abnormalities, thrombocytopenia, and related conditions. Patients who are medically unstable or too ill may not be suitable for anesthesia and brain biopsy.

Preparation/Special Instructions for Patients

The pathologist should be aware of the differential diagnosis before surgery to ensure proper tissue handling and to improve diagnostic yield at the time of frozen section review. For a frozen section, biopsy tissue is snap frozen in liquid nitrogen and then prepped onto slides for microscopic interpretation. Based on this preliminary diagnosis (which takes 15 to 20 minutes), the pathologist advises the neurosurgeon about the need for further samples. The definitive diagnosis will be made after review of the permanent (i.e., paraffin embedded) tissue slides.

Miscellaneous

- Special stains may be helpful to improve diagnostic accuracy. Immunohistochemical analyses of specific protein antigens on the cell surface or in the nucleus are particularly useful for differentiating between categories of disease (e.g., lymphoma versus an inflammatory condition). Genetic studies may also be of benefit for diagnosis (e.g., immunoglobulin gene rearrangement studies of lymphoma) or prognosis (e.g., chromosome 1p and 19q deletion status of oligodendroglial neoplasms).
- A postoperative CT scan is necessary to screen for hemorrhage and to evaluate the accuracy of the biopsy in relation to the target lesion.

BIOPSY, MUSCLE

D. Joanne Lynn, MD

BASICS

DESCRIPTION

- Muscle may be biopsied using either a needle or an open surgical technique. Open muscle biopsy is generally preferred to needle biopsy in most cases because of the larger samples obtained. The muscles often biopsied are the biceps, quadriceps (usually vastus lateralis), and deltoid. It is usually best to biopsy a muscle with moderate weakness in a chronic situation, as a severely weak muscle may yield pathology of end-stage scarring and fibrosis that obscures the underlying disorder. It is best to avoid muscles that were the site of EMG investigation, injections, etc., because of traumatic pathologic changes. Sometimes, the peroneus brevis muscle is biopsied at the same time as the superficial peroneal nerve when vasculitis is suspected to increase diagnostic yield.
- A skin incision is made after local anesthesia. The muscle fascia is then anesthetized and opened. Sections of muscle are excised, and samples are sent for frozen section (for histochemistry and light microscopy), fixation in glutaraldehyde, embedding in plastic (for ultrastructural analysis), and embedding in paraffin (for examination for inflammation).
- Needle biopsy may be used for sampling of multiple sites and provides samples sufficient for biochemical and DNA studies. However, the samples obtained by needle biopsy are smaller and less satisfactory for electron microscopy.

Indications

- A muscle biopsy is indicated for investigation of etiology when a patient presents with clinical and laboratory evidence of myopathy such as weakness, myopathic EMG findings, elevated serum creatine kinase, and/or chronic or intermittent muscle pain. A muscle biopsy may also be useful for diagnosis of systemic conditions that may have relatively silent muscle manifestations such as vasculitis or sarcoidosis. Specific indications for muscle biopsy include suspected:
  - Inflammatory conditions of muscle, connective tissue or blood vessels
  - Infections of the muscle such as trichinosis
  - Metabolic defects of muscle
  - Muscular dystrophy or congenital myopathy

Strengths

Many muscle disorders such as dystrophies and inflammatory myopathies have distinct cytoarchitectural characteristics that readily allow diagnosis. Patterns and distribution of inflammatory cells may help distinguish polymyositis, dermatomyositis, vasculitis, fasciitis, and other inflammatory disorders. Special histochemical analysis may identify disorders such as lipid-storage myopathy, inclusion body myositis, or mitochondrial myopathies (ragged-red fibers). Immunochemistry for dystrophin may confirm Duchenne dystrophy when DNA studies are uninformative. Histologic features of individual muscle fibers may suggest a neuropathic cause (fiber type grouping, atrophic and angular fibers, and target fibers) but muscle biopsy is rarely diagnostic for neurogenic etiologies.

Limitations

Unfortunately, many types of muscle disease may share common pathologic features on biopsy, such as increased connective tissue, changes in fiber size and shape, and fiber necrosis. In recent years, expanding knowledge of the genetic defects that cause many myopathies has supplemented routine muscle histology to increase definitive diagnosis. Muscle biopsy cannot differentiate between various neuropathic causes for weakness. In addition, there is the risk of sampling error in multifocal disease such as polymyositis. Needle biopsies are even more prone to miss patchy (as in inflammatory myopathies) or endomysial pathology.

Risks

Risks include hemorrhage, hematoma, infection, and pain and rarely damage to other tissues in the area.

Contraindications

Contraindications include uncorrected coagulopathy and thrombocytopenia.

Preparation/Special Instructions for Patients

Patients should limit heavy use of the biopsied limb for several days after biopsy, and monitor for signs of infection such as excessive drainage, swelling, or erythema. No submersion in water for bathing or showering until the sutures have been removed. Sutures are generally removed in 7 to 10 days.

ADDITIONAL READING

- Dubowitz V, Sewry CA. *Muscle biopsy: A practical approach*, 3rd ed. Philadelphia, PA: Saunders Elsevier, 2007.
- Lacomis D. The utility of muscle biopsy. *Curr Neurol Neurosci Rep* 2004;4(1):81–86.
- O'Ferrall EK, Sinnreich M. The role of muscle biopsy in the age of genetic testing. *Curr Opin Neurol* 2009;22(5):543–553.
- Younger DS, Gordon PH. Diagnosis in neuromuscular diseases. *Neurol Clin* 1996;14(1): 135–168.Website of the Neuromuscular Disease Center at Washington University has detailed information about muscle biopsy including indications, procedure, interpretation: http://neuromuscular.wustl.edu/lab/mbiopsy.htm (accessed July 1, 2011).

BIOPSY, NERVE

D. Joanne Lynn, MD

BASICS

DESCRIPTION

Nerve biopsy for diagnosis of the cause of peripheral neuropathy is most commonly performed not only on the sural nerve, but also on the superficial peroneal and occasionally the superficial radial nerve. For sural nerve biopsy, an incision is made, after local anesthesia, approximately 25 cm above the plantar surface of the heel and 1 cm lateral to the midline, and the nerve is dissected out. One segment is frozen for identification of immune deposits; immunocytochemistry studies are useful to stain for immunoglobulin and complement deposition. A second segment is placed in buffered formalin to be processed for paraffin sections, most useful for demonstration of vasculitis, inflammation, and granulomas. Another section is fixed in glutaraldehyde for preparation for light microscopy. Nerve fascicles are separated for single nerve fiber teasing, which allows detailed determination of nerve pathology, e.g., axonal vs. demyelinating. Special expertise in processing the nerve specimen is desirable.

Indications

- Peripheral nerve biopsy is indicated to evaluate for a specific cause of neuropathy, which may be diagnosed with certainty only by pathologic examination.
- Conditions for which peripheral nerve biopsy is most helpful for diagnosis include:
  - vasculitis
  - sarcoidosis
  - amyloidosis
  - tumor infiltration
  - leprosy
  - Fabry disease
  - storage diseases (Niemann–Pick disease, metachromatic leukodystrophy, sialidosis, Farber disease)
  - Hereditary neuropathy with liability to pressure palsies
  - Neuropathy associated with antibody to MAG (myelin-associated glycoprotein)

Strengths

- The nerve biopsy is especially useful to identify changes in blood vessels and connective tissue elements of the nerve. This makes it most useful to identify inflammatory changes in vasculitis, granulomatous disease such as sarcoidosis, neoplastic infiltration, and infection such as leprosy.
- If there is a clinical evidence of peripheral nerve involvement in suspected multisystem vasculitis, peripheral nerve may be the least invasive site for biopsy. The yield of biopsy is usually greater if a nerve is biopsied that is abnormal on electrophysiologic studies.

Limitations

Peripheral nerves respond to the myriad diseases that affect them with a narrow spectrum of pathologic responses. This limits the diagnostic utility of nerve biopsy in most patients presenting with common types of neuropathy. It should be emphasized that the diagnosis of peripheral neuropathy is generally based on neurologic examination and electrophysiologic study findings. In addition, sampling error may be an issue with nerve biopsy; sampling of a single segment of a single nerve may miss multifocal pathology such as vasculitic lesions that may occur in the nerve proximal or distal to the site of biopsy. In addition, nerve biopsy may fail to demonstrate significant pathology in small-fiber neuropathies. In that situation, skin biopsy to examine intraepidermal small nerve fibers may be a more powerful technique.

Risks

Nerve biopsy is a surgical procedure and is associated with the typical risks of hemorrhage, hematoma, wound infection, and wound dehiscence. It can also be painful, both during the procedure and in the postoperative period.

Contraindications

Uncorrected coagulopathy or thrombocytopenia. The risk/benefit ratio should be evaluated appropriately in patients with diabetes mellitus, peripheral vascular disease, and significant edema, as complications such as infection are more common in these groups.

Preparation/Special Instructions for Patients

There is no special preoperative preparation required except for temporary discontinuation of antiplatelet medications or anticoagulation if present (after judicious consideration of risk/benefit ratio for doing so and detailed instructions for the patient). However, patients should be apprised of what to expect after the biopsy. Patients often experience spontaneous paresthesias starting 24 to 48 hours after the biopsy, which may be precipitated by stretching of the proximal nerve stump by certain movements or positions of the involved limb. Pain usual wanes by 2 to 3 weeks, but lesser discomfort may persist for much longer. Electric dysesthesias or hypersensitivity to touch may persist for more than a year in a minority of patients. For sural nerve biopsies, there is a sensory deficit along the lateral aspect of the foot, which generally recedes or even resolves by 18 months.

ADDITIONAL READING

- Mendell JR, Erdem S, Agamanolis DP. The role of peripheral nerve and skin biopsies. In: Mendell JR, Kissel JT, Cornblath DR, eds. *Diagnosis and management of peripheral nerve disorders*. New York, NY: Oxford University Press, 2001: 90–123.
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COMPUTED TOMOGRAPHY OF BRAIN AND SPINE

Eric C. Bourekas, MD
H. Wayne Slone, MD

BASICS

DESCRIPTION

CT, or computed axial tomography, is an imaging technique that uses x-rays to obtain cross-sectional images. The appearance of x-ray-imaged structures depends on their density. Water is arbitrarily assigned the value of zero, with denser structures like bone having positive values and less dense tissues such as fat and air having negative values. Today, the most CT scanners are of fourth generation (multislice, volumetric acquisition). Multislice detectors allow faster imaging, acquisition of thinner slices, faster and better reconstructions, and improved image quality. The more the detectors the greater and faster the coverage, allowing for improved CT angiography among a number of improvements. Currently, 16- and 64-slice detector CT scanners are commonly used, with 160- and 256-slice scanners becoming available.

TECHNIQUES AND APPLICATIONS

- Conventional CT
  - Axial images only, except for head-direct coronal images can be obtained if the patient is able to lay prone with head extended. With modern scanners direct coronal imaging not necessary as reconstructed images are just as good.
- Reconstructions—computer generated: Sagittal, coronal, 3D
- Cisternography and myelography—after the intrathecal administration of contrast
- CT angiography (CTA)—requires contrast with 3D reconstructions
  - Circle of Willis
  - Carotid arteries
- Functional CT
  - CT perfusion—requires contrast, cerebral blood flow imaging
  - Xenon CT—cerebral blood flow imaging
- Interventional
  - CT fluoroscopy—real-time imaging
- Intraoperative CT, portable CT

INDICATIONS

Indications for Head CT

Examination of choice for evaluation of acute intracranial hemorrhage, calcifications, and cortical bone:

- Acute intracranial hemorrhage—subdural, epidural, subarachnoid, intraparenchymal, intraventricular
- Mental status/neurological change—rule out (R/O) hemorrhage
- Headache—for "worst headache of my life"; R/O subarachnoid hemorrhage. For chronic headaches MR is preferable, although imaging is generally not indicated.
- Stroke—R/O hemorrhage but also R/O arterial occlusion (CTA) and ischemia/infarction (CT perfusion);
  - early CT findings of acute ischemic stroke:
  - Hyperdense artery sign: Thrombus seen in 35–50% with clinical signs of acute middle cerebral artery stroke; poor prognostic sign
  - Obscuration of lentiform nucleus
  - Insular ribbon sign
  - Sulcal effacement
  - Parenchymal hypodensity
    - CT perfusion findings of ischemic stroke:
      - Decreased cerebral blood volume
      - Decreased cerebral blood flow
      - Increased mean transit time
      - Increased time to peak
- Trauma—R/O hemorrhage, edema, herniation, pneumocephalus, fracture
  - Any patient with loss of consciousness, neurologic deficit, anisocoria, fixed or dilated pupils, bleeding diathesis, or anticoagulation, and all penetrating head injuries
- Hydrocephalus
- New-onset seizure—R/O hemorrhage or mass
- Postoperative craniotomy—R/O hemorrhage, herniation
- In patients where MR is contraindicated (e.g., pacemaker) for:
  - Tumor
  - Infection—abscess, empyema, AIDS
  - Seizures
  - Multiple sclerosis
  - Neurodegenerative disorders
  - Granulomatous disease

Indications for Spine CT

- Trauma—R/O fracture
- Postoperative fusion—metal will cause some artifacts limiting the exam
- Spondylolysis
- Arthritis
- Spinal stenosis (MR is examination of choice)
- Disc disease (MR is examination of choice)
- Cord compression—only postmyelography with injection of intrathecal contrast
- Characterization of an isolated indeterminate bone lesion note on MR or nuclear medicine scan (e.g., hemangioma)
- In patients where MR is contraindicated (e.g., pacemaker) for:
  - Tumor—ideally after intrathecal contrast
  - Infection—epidural abscess, discitis, osteomyelitis, although even CT with contrast is relatively insensitive

Indications for Contrast with Head CT

- Tumor—(MR is exam of choice)
- Infection—abscess, empyema, AIDS, (MR is exam of choice)
- Seizure—R/O tumor (MR is exam of choice)
- Arteriovenous malformations
- CT angiography/venography
- CT perfusion

Indications for Intravenous Contrast with Spine CT

- Tumor—if MR contraindicated
- Infection—if MR contraindicated
- Disc disease—to enhance the epidural space/veins and better define the margins of the discs, although MR is still best

Indications for Intrathecal Contrast with Spine CT (Postmyelogram CT)

- Cord compression—when MR is contraindicated
- Disc disease, spinal stenosis, radiculopathy—if MR is contraindicated or if MR findings do not correlate with clinical findings.

STRENGTHS

- Readily available 24/7 even at small hospitals
- Noninvasive
- Fast—ideal for uncooperative and critically ill patients
- Extremely sensitive for acute intracranial hemorrhage
- Ideal for evaluation of calcifications and cortical bone

LIMITATIONS

- Beam-hardening artifacts limit posterior fossa evaluation
- Insensitive to acute ischemia although CTA and CT perfusion improve sensitivity
- Limited spinal cord evaluation
- Limited soft tissue contrast
- Metal streak artifacts
- Radiation dose—current hot topic because as CT scanner capabilities have improved, radiation doses have increased. Especially important in pediatric imaging. Newer techniques such as CT perfusion and CT angiography have significantly increased radiation doses.

ONGOING CARE

PATIENT EDUCATION

Patients who are scheduled for a CT with contrast are instructed to be NPO 2 hours prior to the exam. At the time of the exam they are asked to remove earrings, hair clips, hearing aids, glasses, and removable dental work.

Miscellaneous

Approximately 1% of patients are claustrophobic and require some sedation. Diazepam 5–10 mg PO is adequate for most.

ADDITIONAL READING

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CLINICAL PEARLS

Consider radiation dose when ordering studies such as CT perfusion.

MAGNETIC RESONANCE IMAGING OF THE BRAIN AND SPINE

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BASICS

DESCRIPTION OF PROCEDURE

Magnetic resonance imaging (MRI) uses a powerful magnetic field and radiofrequency waves to produce images. No ionizing radiation is involved. Most MRI units in clinical use are 1.5 Tesla units with 3 Tesla units are becoming more readily available.

Depending on imaging parameters, different pulse sequences can be obtained producing images yielding different information. Traditional imaging involves T1-weighted (T1W) and T2-weighted (T2W) spin echo imaging. Gradient echo imaging allows for faster imaging. T1W images are obtained after administration of IV contrast, which does not affect T2W images very much. Fat suppression images help to identify fatty lesions or lesions obscured by fat, such as those in the orbits. Proton density and fluid attenuated inversion recovery (FLAIR) images are useful in evaluation of white matter disease. Diffusion and perfusion imaging is invaluable in the evaluation of stroke. MR angiography (MRA) and MR venography (MRV) are noninvasive means of evaluation of the vasculature of the head and neck. Functional imaging is increasingly used in preoperative evaluation, especially of brain tumors, helping to noninvasively identify speech and motor centers. Spectroscopy can provide a measure of brain chemistry by identifying spectra that can help in the differential diagnosis of tumors, demyelination, and radiation necrosis to mention a few. Diffusion tensor imaging (DTI) can noninvasively identify white matter tracts and obtain information on connectivity of the brain. Susceptibility-weighted imaging is very sensitive in the evaluation of hemorrhage and calcifications.

INDICATIONS FOR BRAIN MRI

- Stroke—diffusion-weighted imaging is very sensitive for acute stroke.
- Tumor
- Infection—encephalitis, abscess, empyema
- Demyelinating disorders—MS
- Seizures
- Neurodegenerative Disorders—Alzheimer's, Parkinsonism
- Granulomatous disease—e.g., sarcoidosis
- Intracranial hemorrhage
- Negative Ct with continuing neurologic deficits

INDICATIONS FOR BRAIN MRI WITH CONTRAST

- Tumor
- Infection
- Demyelinating disorders—helpful to monitor disease activity
- Seizures—new onset to R/O tumor
- Granulomatous disease

INDICATIONS FOR SPINE MRI

- Tumor—primary spinal cord, metastatic to bone, R/O cord compression, leptomeningeal carcinomatosis, and R/O drop metastases
- Infection—osteomyelitis, discitis, and epidural abscess
- Trauma—cord or ligamentous injury with short tau inversion recovery (STIR) images
- Degenerative disc disease—R/O disc herniation and spinal or foraminal stenosis
- Cord abnormalities—tumor, demyelination, infarction, extremity weakness, incontinence, and paralysis

INDICATIONS FOR SPINE MRI WITH CONTRAST

- Tumor
  - NOT necessary for vertebral body metastases
  - Primary spinal cord or nerve root tumors, leptomeningeal carcinomatosis, and epidural tumor
- Infection—osteomyelitis, discitis, and epidural abscess
- Demyelination
- Granulomatous disease
- Any cord lesion
- Prior lumbar spine surgery—R/O epidural scar; not an issue in the cervical or thoracic region

Strengths

- Superior soft-tissue contrast/resolution
- Direct multiplanar imaging
- No ionizing radiation
- No beam-hardening artifacts related to bone

Limitations

- Length of exam—at least 20 minutes
- Sensitivity to motion
- Cost
- Difficulty in monitoring critically ill patients—ECGs work poorly during scanning even with MR-compatible equipment; pulse oximeter monitoring should be available; MR-compatible ventilator is required
- Difficulty in obtaining STAT off hours—technologist availability limited at many centers
- Metal artifacts
- Cortical bone, although MR is excellent for evaluation of bone marrow

CONTRAINDICATIONS

Many contraindications are relative and depend on magnetic field strength relating to heating issues. Need documentation of implants (make and model number). It is best to consult the MR facility for local policy and constantly changing policies. Do not just assume that something is contraindicated. Electrically, magnetically, or mechanically activated implants are generally contraindicated.

ABSOLUTE CONTRAINDICATIONS

- Pacemakers, although a new FDA-approved pacemaker by Medtronics is MR compatible, but as yet with limitations
- Defibrillators
- Neurostimulators
- Bone growth stimulators
- Cochlear implants
- Ocular metallic foreign bodies
- Swan–Ganz catheters
- Allergy to IV gadolinium (MR) contrast for contrast study

Relative Contraindications

- Aneurysm clips—most clips used currently are MR compatible; however, safety concerns exist and many facilities consider them absolute contraindications
- Heart valves—current valves are not contraindicated; old Starr Edwards (pre-6000 series) are contraindicated
- Inferior venacaval (IVC) filters—current filters mostly are MR compatible, although recommendations are to wait 2–6 weeks after insertion prior to imaging
- Inner ear implants—cochlear implants contraindicated, some stapes implants
- Drug-infusion pumps—generally not contraindicated, although MR may stop infusion and necessitate pump reprogramming
- Bullets, pellets, shrapnel—must use judgment; duration, proximity to vessel? Most bullets are not contraindicated.
- Stents—most are not contraindicated but many aortic stent grafts are

Not Contraindicated

Hemostatic clips, wire sutures, plates, pins, screws, nails, dental devices (e.g., braces, bridges despite artifacts), orthopedic implants (joint replacements, spinal rods), ocular implants, ventricular shunts.

PREPARATIONS/SPECIAL INSTRUCTIONS FOR PATIENTS

General Measures

- Patients must remove all jewelry and metal items from their body and clothing, including glasses, dentures and all other removable dental work, wigs, and hairpins.
- An extensive history and screening form, designed to ensure that there are no contraindications and safety of the exam, is filled out.

Miscellaneous

- Claustrophobia is a problem in 5–10% of patients. Often, this is transient and eliminated by reassurance from the technologist. Most are able to get through the exam with mild sedation, usually 5 mg PO of Valium. Approximately 1% will require heavy sedation in order to complete the exam in a closed MR. Open MRIs accommodate such patients at the cost of reduced image quality. Newer, wide-bore MRIs are also an option.

Pregnancy Considerations

- MR has not been proven safe in pregnancy, but is not believed hazardous. It is indicated in pregnancy if it will provide information critical to the patient's well-being or because the patient would otherwise require exposure to ionizing radiation.
- Contrast is generally contraindicated in pregnancy.

Pediatric Considerations

MRI is, generally, the preferred exam in the evaluation of the brain and spine due to the lack of ionizing radiation, but sedation is usually required in young children.

Geriatric Considerations

- Can be challenging in patients with dementia who forget the need to not move, thus necessitating sedation
- In the imaging of demyelinating disorders, higher field strength (i.e., 3 Tesla) magnets may increase the yield for T2– and proton–density-weighted lesions.

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- www.MRIsafety.com, maintained and frequently updated by Frank G. Shellock, Ph.D.

CLINICAL PEARLS

- MRI is an important tool for clinical diagnosis of abnormalities of the brain, particularly the posterior fossa and brain stem and the spinal cord.

MYELOGRAPHY

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BASICS

DESCRIPTION OF PROCEDURE

A lumbar puncture (LP) is performed with the patient in a prone or lateral decubitus position at L2–3 or more caudally, with a 20- to 26-gauge 3.5-inch spinal needle. Alternatively, if access is not obtainable secondary to lumbar spondylosis, a lateral cervical puncture may be performed at C1–C2 under direct fluoroscopic visualization. A maximum of 3 gm of watersoluble, nonionic, iodinated contrast is injected intrathecally and a series of plain radiographs are obtained. Care is taken to avoid or identify epidural and subdural injections. Evaluation of the anatomic relationships among nerve roots, intervertebral discs, osseous structures, and the spinal cord is not accurate with plain radiographs alone. Therefore, a post-procedure CT is usually performed and will permit a more detailed examination of the contents of the thecal sac.

INDICATIONS

- When MRI is contraindicated in:
  - Patients with a pacemaker, neurostimulator, some aneurysm clips, or metal within the globes
  - Patients with claustrophobia and those that exceed the MRI weight limit
  - Surgical hardware precluding optimal evaluation of the spine on an MRI secondary to artifact
  - Nondiagnostic prior MRI
  - Requirement for flexion and extension views to assess instability and stenosis
- When higher spatial and contrast resolution is required for evaluation of:
  - Osseous structures
  - Nerve roots
  - Intervertebral discs
  - Arachnoiditis
  - Vascular malformations
  - Meningeal cysts
  - Arachnoid cysts
  - Meningoceles
  - Perineural cysts
  - Spinal canal neoplasms
  - Cord compression

STRENGTHS

- High-resolution images when combined with CT
- Improved depiction of symptomatic pathology in patients with degenerative spine disease when combined with CT
- Improved evaluation of patients with surgical hardware involving the spine
- Collection of CSF

LIMITATIONS

- Suboptimal ability to identify intramedullary, extramedullary intradural, and epidural lesions
- Suboptimal ability to identify discitis and epidural abscess

RISKS

- Post-myelogram headaches
  - 5–30% of patients (22-G blunt needle) (1)
  - Can last 1 week
  - Onset up to 12 days after LP
  - Exacerbated by sitting up
  - Relieved or improved in supine position
  - Refractory headaches may be relieved by epidural blood patch (success rates between 70% and 90%) (2)
- Seizures
- Nausea and/or vomiting
- CSF leak
- Meningitis
- Trauma to the conus medullaris or nerve roots
- Vasovagal reaction
- Hemorrhage in the subarachnoid, subdural, or epidural space

CONTRAINDICATIONS

- Iodine allergy
- Coagulapathy (PT >15, Platelets <50,000)
- Pregnancy
- Infection at the puncture site
- Sepsis
- Bacteremia
- Altered mental status precluding cooperation
- Seizure disorder
- Elevated intracranial pressure
  - Risk of tonsillar herniation
- Medications
  - Anticoagulants
  - Antiplatelet agents
  - Antipsychotic agents
  - Metformin
    - Discontinue for 48 hours prior to myelography to minimize risk of renal failure
  - Phenothiazine derivatives (e.g., compazine, thorazine, stelazine)
  - Tricyclic antidepressants
  - Monoamine oxidase inhibitors
  - CNS stimulants

PREPARATION/SPECIAL INSTRUCTIONS FOR PATIENTS

Pre-Procedure Preparation

- No food or drink for 4 hours prior to procedure
- Medications may be taken except metformin, which should be discontinued for 48 hours prior to the procedure

Peri-Procedural Care

- Strict bed rest with the head of the bed elevated 30 degrees for 2–4 hours. If patient is unable to lie in bed, they may alternatively remain seated in a chair
- Keep patient under observation after contrast injection, during CT scanning, and for 1–4 hours after CT scanning

Post-Procedure Instructions

- Patients must not drive themselves home
- Refrain from operating a motor vehicle or machinery for 24 hours
- A competent adult should be with the patient for 24 hours
- Drink 8–10 glasses of fluids for the next 24 hours
- Provide contact number for the physician performing the procedure or covering physician
- No heavy lifting or strenuous physical activity for 24 hours
- Phenothiazines, tricyclic antidepressants, and Tigan should be withheld for 48 hours after the study

MR MYELOGRAPHY

Description of Procedure

A single-slice is acquired using a single-shot turbo spin-echo sequence with a very long TE (1200–1400). An inversion pulse may be applied to suppress fat signal. 3 images are obtained: coronal and bilateral oblique-coronal. Appropriate slice thickness is 40–60 mm. Images are heavily T2-weighted.

Strengths

- Noninvasive, no intrathecal contrast
- No ionizing radiation
- Reliable evaluation of subarachnoid space anatomy (3)[C]
- Assessment of morphology of the discs and cord
- Evaluates spinal canal even if there is CSF block

Limitations

- Metallic spine hardware artifact degrades image quality
- Patients must be screened and may be excluded due to surgically implanted metallic devices or history of metal within the orbits
- Multi-slice technique requires long imaging time resulting in image degradation from artifacts related to CSF pulsation
- Inversion pulse required to suppress background signal from paravertebral veins and fat

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CLINICAL PEARLS

If a complete myelographic block is seen with caudal approach, a C1–2 approach may delineate the upper extent of the block (when MRI is not available).

NERVE CONDUCTION STUDIES/ELECTROMYOGRAPHY

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BASICS

DESCRIPTION

Nerve conduction studies (NCS) and needle electromyography (EMG) are complementary electrophysiological diagnostic tests that evaluate the integrity and function of nerve and muscle.

- NCS rely on the ability of nerve fibers, specifically of large, myelinated nerves, to conduct electrical potentials. Surface percutaneous electrical stimulation generates a bidirectionally propagating nerve fiber action potential.
  - A summated compound muscle action potential (CMAP) is recorded, using surface electrodes, with the G1 or active electrode placed over the muscle endplate and the G2 or reference electrode placed at a short distance from the stimulation site. The amplitude of the CMAP reflects the number of functioning motor axons.
  - Incremental electric shocks at a distal and proximal site over the nerve are delivered until supramaximal stimulation is achieved. The electrical activity recorded by the 2 electrodes is amplified differentially and displayed on a computer screen. The distance between the proximal and distal sites is divided by the latency difference to calculate the motor conduction velocity expressed in meters per second (m/s). The calculated velocity correlates with the summated values of conducting fibers with the maximal velocity representing the fastest conducting fibers. The duration of the recorded CMAP at the 2 sites may be increased in disease processes that lead to summation with phase cancellation.
- Needle EMG records the electrical muscle activity at rest and with graded voluntary contraction. Concentric needle recording requires a surface ground electrode. Monopolar needle recording requires, in addition, a surface reference placed close to the muscle under examination.
  - Muscles of interest are identified using surface anatomical landmarks, and the needle electrode is inserted through the skin midway between the origin and insertion of the muscle across the joint near the endplate to evaluate insertional activity at rest, usually with a minimum of 5 insertions.
  - The needle electrode is slowly advanced with frequent pauses for a few seconds after each movement to assess for spontaneous activity.
  - The patient is instructed to perform graded volitional contractions while the needle electrode is held stationary and maximum voluntary recruitment and indices of amplitude and duration of voluntary motor unit potentials (MUP) are assessed on the computer screen. Disease processes that increase the duration and amplitude of the MUP are neuropathic in origin, while those that reduce the MUP duration and amplitude are myopathic in origin.

INDICATIONS

- Electrodiagnostic studies are an extension of the neurologic exam and help to localize peripheral nervous system disorders along the motor unit from the anterior horn cell or lower motor neuron to the muscle, through the spinal roots, plexus and peripheral nerve, across the neuromuscular junction to axon terminals at the motor endplate. They can occasionally provide useful information about dysfunction of upper motor neuron function in the CNS.
- NCS/EMG can elucidate the origin of neuropathic and myopathic symptoms including numbness, paresthesias, pain, cramping, and weakness.
- NCS/EMG can enable the clinician to:
  - Confirm a clinical diagnosis
  - Aid in the differential diagnosis and direct further evaluation if necessary
  - Identify subclinical disease
  - Characterize nature and severity of the disease

GOALS

- Localization of the lesion
  - Anterior horn cell: Motor neuron disease
  - Spinal nerve: Radiculopathy, polyradiculopathy
  - Plexus: Plexopathy
  - Peripheral nerve: Mononeuropathy, mononeuritis multiplex, polyneuropathy
  - Neuromuscular junction (NMJ): Presynaptic and postsynaptic
  - Muscle
- Identification of underlying nerve pathophysiology
  - Fiber type involved: Motor, sensory, or sensorimotor
  - Pattern of injury:
    - Distal or proximal involvement
    - Symmetric or asymmetric involvement
    - Focal, multifocal, or diffuse involvement
  - Pathology:
    - Primary demyelination: Acquired or inherited
    - Primary axonal loss
- Assessment of severity and correlation with clinical symptoms
- Assessment of temporal course: Hyperacute, acute, subacute, or chronic

STRENGTHS

- Minimally invasive
- Relatively inexpensive
- Characterize pathology and narrow differential diagnosis to direct future testing

LIMITATIONS

- NCS are useful in evaluating large-fiber neuropathies but are normal in primary small-fiber neuropathies. Alternative modalities may be necessary to define small-fiber neuropathies:
  - Quantitative sensory testing
  - Autonomic reflex testing
  - Epidermal nerve fiber (ENF) studies by punch biopsy of a proximal and distal site in the leg for ENF density and histology.
- Evaluation of proximal nerves can be useful and is complimentary to distal studies although they are technically more difficult to perform.
- Interpretation of NCS is subject to reference to age-normative values and recording conditions of surface temperature, and possible anomalous innervations.
- Timing of evaluation after onset of symptoms or acute injury is important.
  - NCS/EMG can help determine if nerve injury is present during the first 10 days when reversible demyelinative conduction block can lead to partial or complete cessation of nerve conductivity and clinical weakness, as for example facial or radial palsy.
  - By 21 days, the etiopathogenesis of a lesion will be definable as axonal or demyelinative in origin based upon the pattern of NCS as for example low CMAP and SNAP amplitude with preserved distal latency and velocity, and active spontaneous activity at rest in the former; and slow velocity, prolonged distal latency, and temporal dispersion of CMAP without active spontaneous activity in the latter.
- In long-standing and/or severe neuropathies, nerve responses may be unevocable.
- Specific etiology of pathology cannot be determined by electrodiagnostic testing.

RISKS

- Equipment must be properly grounded to avoid electrical injury to the patient.
- Patients must be properly grounded.
- Extra care should be taken with patients with indwelling cardiac pacemakers or defibrillators, particularly if stimulation site is located close to the chest wall.
- Care should be taken when performing needle EMG on patients with bleeding diatheses or coagulopathies. Deep muscles where local pressure cannot be applied should be avoided.

CONTRAINDICATIONS

- EMG in patients with platelets counts below 20,000 should be avoided or limited as much as possible.
- Needle EMG may induce artifactual histological chances in a muscle biopsy. Avoid placing a needle in a muscle that will be sampled at biopsy.
- Needle EMG may artificially elevate the serum creatine kinase. Obtain blood samples prior to EMG.
- Pacemakers and implanted cardiac defibrillators are relative contraindications for conventional NCS.

PREPARATION/SPECIAL INSTRUCTIONS FOR PATIENTS

- Inform the physician of any medications that thin blood or increase bleeding times or any hematological conditions.
- Inform the physician of pacemakers or implanted cardiac defibrillators in place.
- Wear loose-fitting clothing.
- Do not apply lotions or creams to skin on day of test.
- If referred for evaluation of a NMJ disorder (e.g., myasthenia gravis), hold pyridostigmine (Mestinon) for 12 hours before the test.

MISCELLANEOUS

- If patient has excessive anxiety regarding this test, administration of a benzodiazepine (e.g., diazepam 10 mg) before the test is acceptable.

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NEUROLOGICAL EXAMINATION

D. Joanne Lynn, MD

BASICS

Effective evaluation of neurological diseases still requires an examination of the nervous system. This examination primarily answers the question of *where* in the nervous system, or *what system* (e.g., cerebellar, sensory, motor) of the nervous system is affected in this patient. Using the history and a well-focused neurological examination, the physician should be able to narrow down the possibilities for localization. Once a localization is identified, the potential etiologies are narrowed down as only certain pathologies affect certain areas of the nervous system (e.g., neuromuscular junction disorder, myasthenia gravis or Lambert–Eaton). The following is a summary of nervous system examination techniques, but is by no means exhaustive.

MENTAL STATUS

- A rough assessment of mental status can be made by just observing the patient during history-taking and examination. Level of consciousness is assessed for acutely ill/hospitalized patients and may be documented by calculating a Glasgow Coma Scale score. Communicative patients should be asked about their handedness because of its relationship to cerebral hemispheric dominance for language and other cognitive functions. Patients should be observed for signs of self-neglect, depression, anxiety, inappropriate behavior, emotional lability, thought disorder, and disorders of memory, language, and other cognitive functions.
- Screening tests include:
  - Simple questions to test orientation to time, place, and person
  - Digit span to assess attention: Ask patient to repeat presented numbers forward or backward, starting with 3 or 4 digits and increasing up to 7 digits.
  - Assess registration: Ask patient to repeat back 3 objects.
  - Short-term memory: Ask patient to recall 3 objects at 5 minutes.
  - Assess calculations with tasks such as serial subtractions of 7's or 3's or simple addition problems.
  - Abstract thoughts such as proverbs, similarities, estimations
  - Spatial: Ask patient to draw in a clock face, place major cities on a map outline, draw interlocking pentagons.
  - Visual and body perception: Ask patient to recognize famous and familiar faces, identify his or her own index finger, touch right ear with left index finger, test stereognosis and graphesthesia.
  - Test for apraxias: Ask the patient to perform such motor actions as make movements pretending to kiss, suck through a straw, use a hammer or pair of scissors. Do not give any visual cueing.

CRANIAL NERVES

Cranial Nerve I (Olfactory)

- Cranial nerve I is tested by asking the patient to smell bedside objects such as food or formally prepared substances. Anosmia may be caused by rhinitis, trauma, degenerative illnesses such as Parkinson's and Alzheimer's disease, medications, and frontal meningiomas. Hyposmia is common with aging.

Cranial Nerve II (Optic)

- Cranial nerve II is tested by checking pupillary responses, visual acuity, visual fields, and fundi.
  - The pupillary light response is mediated via cranial nerve II as the afferent limb and parasympathetic fibers on both sides as the efferent limb. Note whether the pupils are equal or different in size (anisocoria). Shine a bright light in one pupil and observe the direct pupillary response in that eye and the consensual pupillary response in the other eye while the patient looks into the distance. Then have the patient look from the distance to your finger located a few inches from his or her nose and watch the pupils for the reaction to accommodation.
  - Swinging light test: Swing a bright light from one pupil to the other and assess pupillary constriction, which should be equal in both eyes. If one pupil dilates when the light is swung to it, a relative afferent pupillary defect or Marcus Gunn pupil is present, representing a lesion anterior to the optic nerve chiasm.
  - Assess visual acuity with Snellen chart, near vision chart or card, or ask if the patient can read bedside materials, count fingers, see hand movements, or perceive light.
  - Assess visual fields by simple confrontation technique. Ask the patient to cover one eye and then serially move your hand or an object into each quadrant of the patient's visual field, asking the patient to report when the object is seen. Repeat with the other eye.
  - Funduscopic examination: Examine the optic disk, blood vessels, and retinal background.

Cranial Nerves III, IV, and VI (Eye Movements)

- Look at position of eyes in primary gaze: Are they conjugate or dysconjugate?
- Test movements to cardinal positions, noting any positions in which the patient develops diplopia. Note any pathologic nystagmus.

Cranial Nerve V (Trigeminal)

- Sensory: Test light touch and pinprick for each division of the trigeminal nerve (V1 – forehead, V2 – cheek, V3 – lower lip). If a sensory deficit is found, map out the edges.
- Motor: Muscles of mastication
  - Look for wasting of the temporalis muscle.
  - Ask the patient to clench the jaw and palpate the masseter and temporalis muscles. Try to open the jaw.
  - Ask the patient to forcefully open the mouth against the resistance of your hand beneath the jaw. Look for deviation of the jaw to one side.
- Jaw jerk: Ask the patient to let the mouth hang open loosely. Place your finger on his or her chin and percuss it with hammer. Observe jaw movement.

Cranial Nerve VII (Facial)

- Motor: Examine facial symmetry, nasolabial folds, forehead wrinkles, smiling, eye closure. Ask patient to show teeth, close eyes tightly, look up at the ceiling, whistle.
- Upper motor neuron lesions spare forehead compared with lower face. Lower motor neuron or nuclear lesions involve upper and lower face equally. Taste may be altered because the facial nerve carries taste fibers for the anterior two-thirds of the tongue.

Cranial Nerve VIII (Auditory)

- Assess hearing acuity with whispered speech or a ticking watch, or rub fingers in each ear. If there is a decrease in acuity in one ear, perform the Rinne and Weber tests.
  - Rinne: Hold a 516-Hz tuning fork on the mastoid process and then in front of the ear and ask the patient which is louder.
  - Weber: Position the end of the tuning fork on the vertex of the head and ask if the sound is louder in the good ear or the deaf ear.
  - In conductive hearing loss, bone conduction via the mastoid is better than air conduction, and the sound is heard loudest in the affected ear on Weber testing. In sensorineural hearing loss, air is better than bone conduction, and the sound is heard loudest in the good ear.
  - Vestibular nerve dysfunction is associated with unilateral horizontal nystagmus that is associated with vertigo. Gait may be unsteady, veering toward the side of the lesion. In the Hallpike test, the patient is brought quickly from a sitting to a supine position, with head tilted below the horizontal and turned 45 degrees to the right or left. Fatigable rotary nystagmus with delay indicates a peripheral vertigo syndrome.

Cranial Nerves IX (Glossopharyngeal) and X (Vagus)

- Watch resting position and then movement of the uvula when the patient says "ahh." Touch the pharyngeal wall behind the pillars to elicit a "gag reflex" and observe the uvula: Does it lift, and is the movement symmetric or deviated to one side? Also ask about sensation in the pharynx. Movement of the uvula to one side suggests upper or lower motor neuron lesion of the vagus on the other side. If the uvula does not move at all, bilateral palatal muscle paresis may be suggested.

Cranial Nerve XI (Accessory)

- This nerve arises from the medulla with contributions from C2–4. The ipsilateral cerebral hemisphere innervates the ipsilateral sternocleidomastoid and the contralateral trapezius. Examine for wasting or fasciculation of the sternocleidomastoid muscle. Have the patient turn the head to either side against your resistance and to shrug shoulders, noting any asymmetry of the trapezius muscles.

Cranial Nerve XII (Hypoglossal)

- Examine the tongue for size and fasciculations (when the tongue is at rest in the mouth), and ask the patient to protrude the tongue, noting any deviation. Test power by asking the patient to push the tongue into each cheek. Deviation to one side suggests weakness on the side to which the tongue moves. This can be upper motor neuron weakness if associated with hemiparesis. Lower motor neuron weakness is associated with atrophy and fasciculations.

MOTOR/REFLEXES

- Motor examination assesses not only the strength of various muscle groups but also bulk, tone, and abnormal spontaneous movements of the muscles. Judgment should be made as to whether muscle tone is decreased, normal, or increased. Hypertonicity may be due to spasticity, rigidity, or paratonia. Patients with weakness should be assessed for atrophy and fasciculations.
- Power should be graded and reported on a scale such as the Medical Research Council scale:
  - 5 = Full strength
  - 4 = Movement against some resistance
  - 3 = Movement against gravity
  - 2 = Movement with gravity eliminated
  - 1 = Trace movement
  - 0 = No movement
- Muscle stretch reflexes are tested at the
  - Biceps C5
  - Brachioradialis C6
  - Triceps C7
  - Finger flexors C8
  - Knees L2–4
  - Ankles S1
- Reflexes are recorded on a scale of 0 = absent, 1 = normal or mildly pathologically reduced depending on the context, 2 = normal, 3 = hyperreflexic, and 4 = hyperreflexic with clonus. The examiner should note asymmetries and spread to adjacent segments of the body.
- Plantar reflex – Stimulate the sole of the foot with a blunt object. A normal response is downward flexion of the toes (flexor response). Extension of the great toe is abnormal and is termed a Babinski's sign or extensor response. An abnormal response indicates injury to the upper motor neurons in the cortex or corticospinal tract. Note that an extensor response is normal in an infant in the first year or so of life because of delayed myelination of the long tracts.

SENSORY

- The primary sensory modalities, that is, light touch, vibration, proprioception (position sense), pinprick (pain), and temperature sense, should be assessed in each limb starting distally and moving proximally as a quick screen. More extensive testing, such as touching upon each dermatome and major nerve distribution, is required if there are sensory complaints. A 128-Hz tuning fork is needed for testing of vibration.
- Higher integrative sensory modalities may be checked if the primary modalities are found to be intact. These include two-point discrimination and sensory inattention. A blunted pair of compasses or two pins can be used to test two-point discrimination; normal values include index finger <5 mm, little finger <7 mm, great toe <10 mm. In parietal lobe injury, primary modalities may be intact, but the patient may localize these inputs poorly with decreased two-point discrimination, astereognosis, and sensory inattention.

CEREBELLAR

- Note that while traditionally this testing is known as cerebellar testing, other systems can cause ataxia (e.g., sensory deafferentation in conditions such as a sensory ganglioneuropathy, brainstem relay systems, frontal systems). Caution should be exerted when interpreting such signs as emanating from the cerebellum.
- Several different tests assess cerebellar function.
  - Finger-to-nose testing and heel-to-shin testing to look for ipsilateral limb ataxia, which may manifest as intention tremor, dysmetria, and dysdiadochokinesia (incoordination or disorganization in tests of repeated movements or rapid alternating movements).
  - Rebound: Ask the patient to hold arms out and close eyes. Then push the arms up or down suddenly and see if the patient has an exaggerated correction.
  - Observation of gait may show evidence of midline cerebellar dysfunction with truncal ataxia with broad base and/or titubation. If there is very severe truncal ataxia, the patient may not be able to sit without falling to one side.
  - Dysarthria, cerebellar type

Stance and Gait

- Patients who can stand should be asked to do so normally, with feet touching and eyes closed for Romberg testing. Heel-to-toe walking stresses normal balance mechanisms. Patients should be assessed for narrow versus broad base, shuffling, ataxia, circumduction, footdrop, and apractic gait.

WEB RESOURCES

The University of Utah maintains a comprehensive collection of videos of demonstrations of the various components of the neurological examination. http://library.med.utah.edu/neurologicexam/html/home_exam.html. Accessed on July 1, 2011.

ULTRASONOGRAPHY, EXTRACRANIAL VASCULAR

Mei Lu, MD, PhD

DESCRIPTION OF PROCEDURE

- Extracranial vascular ultrasound is 1 of the commonly used imaging techniques (along with other techniques such as magnetic resonance angiogram, computed tomography angiography, and angiography) to evaluate carotid and vertebral arteries.
- Only extracranial artery ultrasound is discussed here.
- It is usually done with patient in supine position.
- An ultrasound probe with pulsed waves is used to emit and receive ultrasound signals to generate information about morphology and blood flow.
- To improve the transmission of sound wave between the interface of probe and skin, gel for ultrasound is used.
- Morphology of artery is evaluated by B-mode ultrasound, including the surrounding tissue, tortuosity of the vessel, intima thickening, plaque (simple versus complex, calcified, ulcerated, or mobile), dissection flap, pseudoaneurysm, suture line, and stent.
- Blood flow can be evaluated by color Doppler and power Doppler.
- Color Doppler can evaluate the blood flow velocity and direction and the characteristics of the flow (laminar versus turbulence).
- Power flow is more sensitive to detect slow flow, but does not provide directional information.
- Internal carotid artery (ICA) is low-resistance flow system, but external carotid artery is a high-resistance flow system normally.
- Morphology, blood flow characters, direction, velocity (diastolic and systolic and ICA/common carotid artery ratio) are analyzed, and spectral analysis is performed to determine the degree of stenosis, potential abnormal flow in the proximal or distal vasculature.
- Ultrasound of arteries can provide evaluation of stenosis reported in ranges rather than discrete numbers.

INDICATIONS

- Signs or symptoms suggesting following conditions:
  - *Carotid/vertebral stenosis or occlusion*
  - *Carotid/vertebral artery dissection*
  - *Fibromuscular Dysplasia (FMD)*
  - *Subclavian steal syndrome*
  - *Follow-up after Carotid endarterectomy (CEA) and/or stenting*
    - Carotid ultrasound is not indicated for lightheadedness, syncope, vertigo, or nonspecific cephalic sensations unless there are other focal symptoms or strong indicators of associated vascular disease.
    - Carotid ultrasound may be indicated to check for asymptomatic carotid disease where this may change management.

STRENGTHS

- Noninvasive, portable, and less expensive
- Causes less side effect and can be used in patients of all age groups
- Safe to be used in pregnant patients
- Providing more detailed morphological information, as well as flow characters and directions, besides degree of stenosis
- Providing real-time dynamic information

LIMITATIONS

- It is operator dependent.
- The sensitivity and specificity varies significantly between different labs.
- It may overestimate the degree of stenosis, especially near-occlusion versus occlusion.
- It may be technically difficult for evaluating carotid artery in individual patient due to variation of anatomy, neck length, or the position of carotid bifurcation.
- Inability to assess the carotid artery distally.
- Limited assessment for vertebral artery with only the flow direction, without the ability to provide the degree of stenosis and evaluation of entire vessel due to surrounding bony structures.
- The estimation of degree of stenosis in patient with FMD, or poststent placement, has not been validated yet.

RISKS

- Gel allergy
- Potential risk for heat production
- No confirmed side effect from current diagnostic ultrasound

Contraindications: Gel allergy

PREPARATION/SPECIAL INSTRUCTIONS FOR PATIENTS

- Exposing neck region as much as possible, avoiding necklace or other things around the neck to interfere with the scan
- Avoiding motion if possible while being scanned.

MISCELLANEOUS

- The criteria for carotid stenosis need to be validated in the individual ultrasound laboratory.
- In the presence of unilateral severe stenosis or occlusion, the degree of stenosis on the contralateral side may be overestimated based on the velocity, since this could be due to compensatory increased blood flow.
- Global blood flow, cardiac condition, and distal intracranial lesions can affect the velocity of the carotid/vertebral arteries.
- Combining with other examination modality may be helpful and necessary for the decision making of possible intervention (CEA versus stenting), since the sensitivity and specificity varies, and especially if distal lesions are suspected or there is discrepancy between stenosis based on the velocity and B-mode images.

ADDITIONAL READING

- Jahromi AS, Cina CS, Liu Y, et al. Sensitivity and specificity of color duplex ultrasound measurement in the estimation of internal carotid stenosis: a systematic review and meta-analysis. *J Vasc Surg* 2005;41:962–972.
- Wardlaw JM, Chappell FM, Best JJ, Non-invasive imaging compared with intra-arterial angiography in the diagnosis of symptomatic carotid stenosis: a meta-analysis. *Lancet* 2006;367(9521):1503–1512.
- Wolff T, Guirguis-Blake J, Miller T, et al. Evidence synthesis number 50, screening for asymptomatic carotid artery stenosis. AHRQ publications no. 08-05102-EF-1, December 2007.

CLINICAL PEARLS

Carotid ultrasound provides a noninvasive technique to assess for carotid stenosis, which is safe and well validated for this use.

Section III

Neurological Diseases and Disorders

AIDS: HIV DEMENTIA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

HIV dementia (i.e., AIDS dementia complex, HIV encephalopathy, HIV-1-associated cognitive/motor complex) is a syndrome of progressive deterioration of memory, cognition, behavior, and motor function in HIV-infected individuals during the late stages of the disease, when immunodeficiency is severe.

EPIDEMIOLOGY

Incidence/Prevalence

- Exact incidence and prevalence figures are not available. HIV dementia is the most common neurological complication of HIV infection and is estimated to have an overall incidence of 7.5–20% in retrospective studies. The incidence varies with CD4 counts: 7.3 cases/100 person years with CD4 counts less than 100, 3.0 cases/100 person years with CD4 counts between 101 and 200, 1.5 cases/100 person years with CD4 counts between 201 and 500, and 0.5 cases/100 person years with CD4 counts above 500. More recently, the incidence appears to be decreasing, most likely due to widespread use of highly active antiretroviral therapy (HAART).
- All races affected; most common in Caucasians and blacks. Any age can be affected; most common between 20 and 40 years of age. Both sexes can be affected; most often diagnosed in males.

RISK FACTORS

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 200/μL) and an advanced stage of disease, and lack of antiretroviral therapy.

Genetics

Genetic factors have not been identified.

GENERAL PREVENTION

Other than the use of HAART therapy, no other preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

HIV is neurotropic and can be cultured early from the nervous system. However, productive infection within neurons or astrocytes does not appear to be the major cause of HIV dementia or vacuolar myelopathy. Brain macrophages (i.e., microglia) can develop productive HIV infection and are the major vehicle for introducing the virus into the nervous system. Recent hypotheses suggest that neural injury and dysfunction may be due to an innocent-bystander effect. HIV does shed toxic substances, such as whole or fragmented gp120 envelope glycoprotein, which can cause neuronal death in vitro. In addition, other neurotoxic substances can be released in areas of productive infection and cause injury to neurons and astrocytes, such as tumor necrosis factor α, interleukin-1β, interleukin-6, and quinolinic acid. The proposed "final common pathway" of neurotoxicity is excessive stimulation of N-methyl-D-aspartate (NMDA) receptors. Overstimulation of NMDA receptors by gp120, quinolinic acid, and other substances could cause toxic build-up of intracellular calcium, thereby killing neuronal cells.

COMMONLY ASSOCIATED CONDITIONS

Vacuolar myelopathy

DIAGNOSIS

HISTORY

- Patients with HIV dementia demonstrate progressive dysfunction of memory, cognition, behavior, and motor function. During early stages of disease (stage 0.5, 1, 2), patients note difficulty with concentration, mild memory impairment, loss of mental agility, behavioral changes, and slowness of thinking. Mild motor dysfunction may affect strength, gait, balance, and coordination. The neurological examination often reveals subtle psychomotor slowing, mild memory deficits, reduced concentration, saccadic ocular pursuit movements, and soft motor signs (e.g., mild leg weakness, hyperreflexia, slowed rapid alternating movements, unsteady gait, tremor, frontal lobe release reflexes).
- In advanced stages of HIV dementia (stage 3, 4), patients develop progressively more severe neurological dysfunction with pronounced psychomotor slowing, reduced verbal output, apathy, confusion, disorientation, disinhibition, and reduced awareness of illness. Smooth-pursuit ocular movements become very saccadic, and frontal lobe release reflexes are common. Motor dysfunction becomes profound and may include ataxia, severe leg weakness and spasticity, hyperreflexia, Babinski's signs, tremor, myoclonus, and bowel and bladder incontinence.
- Vacuolar myelopathy usually develops as part of the motor component of HIV dementia, but can occur in isolation. It is clinically similar to subacute combined degeneration (i.e., vitamin B12 deficiency) and presents as a progressive myelopathy with spastic paraparesis, hyperactive reflexes, Babinski's signs, gait ataxia, tremor, and urinary incontinence. In some patients, a sensory level may be appreciated.

PHYSICAL EXAM

Progressive loss of memory and cognition, often with mild motor deficits, as outlined above.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

In general, HIV dementia is a diagnosis of exclusion after other infections, space-occupying lesions, and processes are ruled out. The most important tests will consist of blood counts (including CD4 counts to determine stage of HIV infection), infectious cultures of appropriate tissues, and serum antibody titers of various infectious agents. Other specific tests may be helpful in certain cases, such as Venereal Disease Research Laboratory test (VDRL) or vitamin B12 levels.

Imaging

Initial approach

MRI, with and without administration of gadolinium, is the most sensitive technique to evaluate HIV patients with loss of memory and intellectual function. HIV dementia may demonstrate atrophy or scattered, nonenhancing, white-matter lesions, as well as ventricular enlargement. Similarly, progressive multifocal leukoencephalopathy (PML) presents with patchy, nonenhancing, periventricular white-matter lesions that slowly enlarge and coalesce. Cerebral toxoplasmosis usually demonstrates multiple ring-enhancing lesions with surrounding edema. Primary CNS lymphoma (PCNSL) presents as a solitary or multifocal lesion within the deep periventricular white matter that typically enhances with contrast. Mild edema and/or mass effect may be noted. Tuberculous or fungal abscesses cause ring-enhancing lesions with surrounding edema.

Diagnostic Procedures/Other

Lumbar puncture is often helpful and should at least include routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL. In addition, surrogate markers of immune activation should be ordered, such as β2-microglobulin, quinolinic acid, and neopterin. Electroencephalography can rule out subclinical seizure activity as a cause for cognitive deterioration. Neuropsychological testing can establish a pattern of memory loss and cognitive dysfunction, and provide a baseline for subsequent follow-up testing.

Pathological Findings

Neuropathological evaluation of patients with HIV dementia often reveals cortical atrophy and ventricular dilatation, as well as abnormalities of deep structures including the hemispheric white matter, basal ganglia, and thalamus, consistent with a subcortical dementing process. Histologically, there is diffuse white-matter pallor and vacuolation, astrocytic gliosis, and cortical neuronal loss. Regions of HIV encephalitis contain multiple foci of multinucleated giant cells, foamy macrophages, lymphocytes, and microglia. The characteristic histological findings of vacuolar myelopathy consist of spongiform (vacuolar) changes of the dorsal and lateral columns, in association with lipid-filled macrophages.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes HIV-related and non-HIV-related diseases that can lead to deterioration of memory and cognition. HIV-related diseases to consider include PML, cerebral toxoplasmosis, PCNSL, bacterial or fungal abscess, and various toxic/metabolic encephalopathies.

TREATMENT

MEDICATION

First Line

All patients should be evaluated for zidovudine or HAART, since this may delay the onset or reduce the severity of HIV dementia. HAART usually consists of a combination of two nucleoside reverse transcriptase inhibitors (e.g., zidovudine, didanosine, lamivudine) plus one protease inhibitor (e.g., indinavir, saquinavir). Several randomized, placebo-controlled trials have shown benefit of single-agent zidovudine (1,000 or 2,000 mg/day) for delaying the onset of HIV dementia, or improving neuropsychological test performance in affected patients. Treatment with HAART can induce an improvement in clinical grading of HIV dementia, as well as reduce brain metabolite abnormalities as shown by magnetic resonance spectroscopy.

Second Line

Nimodipine (calcium channel blocker) was evaluated in a placebo-controlled clinical trial. Although the results did show a trend towards an effect for nimodipine, it was not statistically significant. Similar results have been noted in clinical trials of deprenyl (monoamine oxidase B inhibitor and anti-apoptotic agent) and lexipafant (platelet-activating factor inhibitor). A new promising agent is memantine, which blocks ion channels associated with NMDA receptors and inhibits gp120-associated neuronal injury in vitro. Clinical trials using memantine in patients with HIV dementia have shown the drug to be well tolerated. Efficacy trials are ongoing.

ADDITIONAL TREATMENT

General Measures

Antiretroviral therapy should be maximized, if possible (i.e., zidovudine, HAART). Nutritional and metabolic deficiencies should be corrected, especially those that might impact neurological function (e.g., hyponatremia). All systemic infections should be diagnosed and treated.

Additional Therapies

Patients with HIV dementia may stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART). Muscle relaxants such as baclofen may be helpful to reduce spasticity and muscle spasms in patients with advanced motor complications.

SURGERY/OTHER PROCEDURES

Biopsy may be required in rare cases to differentiate HIV dementia from other focal intracranial processes.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are generally admitted for acute neurological changes such as altered level of consciousness, confusion, focal or generalized weakness, seizure activity, headache, and focal neurological deficits (e.g., dysphasia, hemianopsia). Patients with persistent neurological deficits should be considered for rehabilitation.

Discharge Criteria

Will be variable, depending on the specific issue that caused the admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Follow-up of neurological status will be required, especially as patients enter more advanced stages of HIV dementia.

PATIENT EDUCATION

- Centers for Disease Control (CDC) AIDS Information: www.cdcnpin.org
- National AIDS Treatment Advocacy Project: www.natap.org

PROGNOSIS

The course and prognosis for HIV dementia is quite poor, since it occurs in patients with low CD4 counts and advanced disease. The 6-month cumulative mortality rate for stage 2–4 HIV dementia is 67%. However, the number of patients developing late-stage HIV dementia appears to be slowing with widespread use of HAART.

COMPLICATIONS

Potential for significant progressive loss of memory and cognition, along with motor deficits.

ADDITIONAL READING

- Lindl KA, Marks DR, Kolson DL, et al. HIV-associated neurocognitive disorder: pathogenesis and therapeutic opportunities. *J Neuroimmune Pharmacol* 2010;5:294–309.
- Xia C, Luo D, Yu X, et al. HIV-associated dementia in the era of highly active antiretroviral therapy (HAART). *Microbes Infect* 2011;13:419–425.

See Also (Topic, Algorithm, Electronic Media Element)

- HIV overview of neurological complications
- HIV neuromuscular complications
- HIV focal brain lesions

CODES

ICD9

- 042 Human immunodeficiency virus (HIV) disease
- 294.10 Dementia in conditions classified elsewhere without behavioral disturbance
- 348.30 Encephalopathy, unspecified

CLINICAL PEARLS

- AIDS dementia is less common now that most patients are receiving HAART therapy.
- Loss of memory and cognition in an AIDS patient requires an extensive work-up before AIDS dementia can be diagnosed.

AIDS: MANAGEMENT OF FOCAL BRAIN LESIONS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Central nervous system complications are frequent in patients with HIV infection and often manifest as enhancing or nonenhancing focal lesions of the brain. The most common focal brain lesions in HIV-infected patients are cerebral toxoplasmosis, primary CNS lymphoma (PCNSL), and progressive multifocal leukoencephalopathy (PML). If patients do not respond to an empiric trial of anti-toxoplasmosis therapy, surgical biopsy is required for a definitive histological diagnosis.

EPIDEMIOLOGY

Incidence/Prevalence

- Recent estimates suggest an overall incidence of intracranial mass lesions in roughly 10% of HIV-infected individuals. Cerebral toxoplasmosis occurs in approximately 5–12% of all AIDS patients. PCNSL is noted in 3–5% of all AIDS patients; incidence may be increasing. PML occurs in 2–4% of all AIDS patients. Incidence of focal brain lesions may be decreasing due to widespread use of highly active antiretroviral therapy (HAART). All races affected; most common in Caucasians and blacks. Any age affected; commonest between 20 and 40 years of age. Both sexes can be affected; most often diagnosed in males.
- Neuroimaging and autopsy studies demonstrate that cerebral toxoplasmosis accounts for 50–60% of all intracranial mass lesions, while another 20–30% are caused by PCNSL and 10–20% arise from PML.

RISK FACTORS

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 200/μL) and advanced stage of disease, and lack of antiretroviral therapy.

Genetics

Genetic factors have not been identified.

GENERAL PREVENTION

Other than the use of HAART therapy, no other preventive measures have been identified.

PATHOPHYSIOLOGY/ETIOLOGY

- Intracranial mass lesions usually develop in end-stage AIDS patients with CD4 counts below 200/μL. In rare patients, mass lesions can be the presenting manifestation of HIV infection. Cerebral toxoplasmosis is caused by reactivation of an endogenous infection by *Toxoplasma gondii*. Pathologically, the abscesses demonstrate regions of necrosis with mild inflammation and *Toxoplasma* cysts, endarteritis, lipid-laden macrophages, extracellular tachyzoites, and encysted bradyzoites.
- PCNSL develops from neoplastic lymphocytes (usually B cells). Epstein–Barr virus DNA is present in many of the tumors. Pathologically, the tumors show densely packed neoplastic lymphocytes with diffuse infiltration into surrounding brain, regions of necrosis, and a tendency to spread along perivascular spaces.
- PML is caused by reactivation of the JC papovavirus. Once reactivated, the JC virus infects oligodendrocytes, causing progressive demyelination. Histologically, swelling and degeneration of oligodendrocytes are noted, with minimal inflammation. Viral inclusion bodies may be present within infected cells.
- Less common causes of intracranial mass lesions include abscesses from other parasites (Cysticercosis), fungi (*Cryptococcus neoformans*), and bacteria (*Mycobacterium tuberculosis*); focal viral infections (e.g., cytomegalovirus, herpes simplex virus); gliomas; metastatic brain tumors (e.g., Kaposi's sarcoma, systemic lymphoma); and cerebrovascular disease.

DIAGNOSIS

HISTORY

- Cerebral toxoplasmosis is more acute than either PCNSL or PML; symptoms develop over several days. Initial symptoms are typically headache and confusion (>50% of patients). Other frequent symptoms include lethargy, low-grade fever, seizures, and focal neurological deficits (e.g., hemiparesis, dysphasia, ataxic gait, hemianopsia, sensory loss).
- With PCNSL symptoms evolve over a week to several weeks. Common symptoms are headache, confusion, lethargy, personality changes, seizures, and memory loss. Focal neurological signs and symptoms are frequent and similar to that noted above. Fever and other constitutional symptoms are generally absent.
- PML evolves over several weeks or more. Signs and symptoms of elevated intracranial pressure, fever, and constitutional symptoms are absent. Deterioration of memory and higher cognitive functions, focal signs.
- HIV dementia causes progressive impairment of short-term memory, cognition, concentration, and motivation. Associated motor abnormalities include unsteady gait, leg weakness, tremor, and incoordination.
- Less common causes of focal intracranial mass lesions present in a similar fashion.

PHYSICAL EXAM

Will be variable depending on the process involved and the region of brain affected, as outlined above.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

The most important tests consist of blood counts (including CD4 counts, to determine stage of HIV infection), toxoplasmosis serology, and serum antibody titers of other infectious agents.

Imaging

Initial approach

- MRI, with contrast, is the most sensitive technique to evaluate for a focal intracranial mass lesion. Cerebral toxoplasmosis: Multiple ring-enhancing lesions, surrounding edema, in the gray matter of the diencephalon and cortex. PCNSL: Solitary or multifocal lesions, deep periventricular white matter, diffuse enhancement. Mild edema and/or mass effect may be noted. PML presents with patchy, nonenhancing, white-matter lesions that slowly enlarge and coalesce. HIV dementia may demonstrate atrophy or scattered, nonenhancing, white-matter lesions that usually spare the subcortical fibers. Focal viral encephalitis: Mass lesions with minimal enhancement.
- For patients without access to an MRI facility, cerebral CT is still an excellent alternative, especially with double-dose iodinated contrast.
- Consider thallium-201 single photon emission computed tomography (SPECT) or fluorodeoxyglucose positron emission tomography (PET). A positive result is suspicious for PCNSL.

Diagnostic Procedures/Other
Lumbar puncture is selected to differentiate the etiology of focal brain lesions and should include routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and Venereal Disease Research Laboratory test.

Pathological Findings
The pathological findings will vary depending on the specific focal process involved, as outlined above.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis is extensive and includes any non-HIV-related diseases that can present as a focal lesion within the brain.

TREATMENT

MEDICATION
First Line
All patients should be evaluated for HAART, since this may prevent or reduce the risk of opportunistic infections and neoplastic complications. All other drug decisions have to be individualized to the neurological complications of each specific focal mass lesion.

ADDITIONAL TREATMENT
General Measures
Antiretroviral therapy should be maximized, if possible (i.e., HAART). Corticosteroids should be avoided unless brain herniation is suspected.

Additional Therapies
All patients, require an empiric trial of anti-toxoplasmosis therapy: Pyrimethamine (loading dose of 100–200 mg, then 25–50 mg/day), sulfadiazine (6–8 g/day in divided doses), and leucovorin (5–10 mg/day). Clinical and radiological improvement in 10–14 days confirms the diagnosis. PCNSL: Whole brain irradiation (4,000–5,000 cGy) and chemotherapy (e.g., methotrexate, temozolomide, or PCV [procarbazine, CCNU (Lomustine), vincristine]) are beneficial in selected patients with good performance status. Dexamethasone has cytotoxic effects against PCNSL and often reduces tumor size and edema. Although there are no proven beneficial therapies for PML, occasional patients may stabilize or improve with HAART or IV cytarabine therapy. HIV dementia may also stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART).

SURGERY/OTHER PROCEDURES
All large lesions with mass effect and impending herniation require biopsy with decompression. Biopsy is also warranted for patients with positive SPECT or PET studies, those with a single lesion and negative toxoplasma serology, and all patients that have failed an empiric trial of anti-toxoplasmosis therapy. Biopsy is accurate for diagnosis in 85–90% of cases.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Rx raised intracranial pressure, seizures, focal signs.

Admission Criteria
Patients are admitted for acute neurological changes related to the focal brain lesion, such as altered level of consciousness, confusion, seizure activity, headache, and focal neurological deficits. Rehab for persistent deficits.

Discharge Criteria
Variable

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Variable

Patient Monitoring
Follow-up of neurological status will be required, particularly for focal lesions that need long-term therapy and serial MRI scans (e.g., PCNSL, toxoplasmosis). Patients with cerebral toxoplasmosis require life-long maintenance therapy with pyrimethamine (25–50 mg/day) and sulfadiazine (2 g/day) to prevent relapses.

PATIENT EDUCATION
- Centers for Disease Control (CDC) AIDS Information: www.cdcnpin.org
- National AIDS Treatment Advocacy Project: www.natap.org
- AIDS Treatment Data Network: www.aidsnvc.org

PROGNOSIS
The course and prognosis for HIV patients with focal intracranial mass lesions is poor. Survival may be improving for this group because of HAART. 6-month cumulative mortality rate for cerebral toxoplasmosis is 51%, although many patients do respond to treatment with improvement of neurological symptoms and MRI scans. PCNSL: median survival; PML: median survival.

COMPLICATIONS
The complications will vary depending on the specific process involved, but may result in permanent focal deficits.

ADDITIONAL READING

- Berger J, Hall C, McArthur J, et al. Evaluation and management of intracranial mass lesions in AIDS. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1998;50:21–26.
- Cingolani A, Fratino L, Scoppettuolo G, et al. Changing pattern of primary cerebral lymphoma in the highly active antiretroviral therapy era. *J Neurovirol* 2005;11(Suppl 3):38–44.
- Cinque P, Koralnik IJ, Gerevini S, et al. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis* 2009;9:625–636.
- Newton HB. Common neurologic complications of HIV-1 infection and AIDS. *Am Fam Phys* 1995;51:387–398.

See Also (Topic, Algorithm, Electronic Media Element)
- HIV overview of neurological complications
- HIV dementia
- HIV neuromuscular complications

CODES

ICD9
- 046.3 Progressive multifocal leukoencephalopathy
- 200.51 Primary central nervous system lymphoma, lymph nodes of head/face/neck
- 294.10 Dementia in conditions classified elsewhere without behavioral disturbance

CLINICAL PEARLS
- Focal brain lesions are still common in AIDS patients, even in the HAART era.
- Biopsy will be necessary in all patients that fail a challenge with anti-toxoplasmosis therapy.

AIDS: NEUROLOGICAL COMPLICATIONS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Neurological complications are common in patients with HIV infection and AIDS, affecting all levels of the central and peripheral nervous system. The etiology of these disorders is variable and may result from direct effects of HIV infection, damage from inflammatory processes and cytokine production, neoplasms, opportunistic infections, metabolic abnormalities, vascular damage, and toxic effects of HIV therapy.

EPIDEMIOLOGY

Incidence

- Before highly active antiretroviral therapy (HAART), it was estimated that approximately 10% of AIDS patients presented with a neurological complaint, while 30–50% developed neurological complications during their disease. In addition, HIV dementia was estimated to have an incidence of 7.5–20% in retrospective studies. The incidence of neurological complications appears to be decreasing, most likely due to widespread use of HAART.
- All races affected; most common in Caucasians and blacks. Any age can be affected; most common between 20 and 40 years of age. Both sexes can be affected; most often diagnosed in males.

RISK FACTORS

No specific risk factors have been identified other than diagnosis of HIV infection, low CD4 counts (i.e., less than 100/μL), and lack of antiretroviral therapy.

Genetics

Genetic factors have not been identified.

GENERAL PREVENTION

Other than the use of HAART therapy, no other preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

- The etiology is variable and depends on the specific process involving the nervous system. In severely immunocompromised patients, opportunistic infections and neoplasms can involve the central or peripheral nervous system, including toxoplasmosis, cryptococcal and tuberculous meningitis, neurosyphilis, progressive multifocal leukoencephalopathy (PML; papovavirus), cytomegalovirus (CMV), herpes simplex virus (HSV), and primary CNS lymphoma (PCNSL).
- HIV is neurotropic and can be cultured early from the nervous system. However, productive infection within neural tissues does not appear to be the major cause of HIV dementia, vacuolar myelopathy, myopathy, or peripheral neuropathy. Although HIV does shed toxic substances such as gp120, viral initiation of inflammation and secretion of toxic cytokines (e.g., tumor necrosis factor α, interleukins 1β and 6) may be more critical in mediating neural tissue injury.
- Neurological complications can also develop as a result of treatment with antiretroviral therapy (e.g., zidovudine myopathy).

DIAGNOSIS

HISTORY

- HIV dementia (i.e., AIDS dementia complex) usually manifests with progressive impairment of short-term memory, cognition, concentration, and motivation. Associated motor abnormalities include unsteady gait, leg weakness, tremor, and incoordination. Late-stage patients have global dementia with severe psychomotor slowing, confusion, reduced verbal output, weakness, and spasticity.
- Space-occupying lesions include cerebral toxoplasmosis, PCNSL, PML, tuberculous or fungal abscess, focal viral encephalitis, and metastatic tumors (i.e., lymphoma or Kaposi's sarcoma). Symptoms consist of progressive headache, confusion, lethargy, personality changes, memory loss, seizures, nausea/emesis, and focal deficits (e.g., hemiparesis, dysphasia).
- Encephalitis typically develops from toxoplasmosis, CMV, and HSV while meningitis is most frequently caused by *Cryptococcus* and other fungi, tuberculosis, and leptomeningeal lymphoma. HIV can cause an aseptic meningitis syndrome. Encephalitic patients present with acute confusion, lethargy, seizures, fever, headache, and meningismus. Patients with meningitis develop subacute headache, fever, meningismus, lethargy, and nausea.
- Vacuolar myelopathy usually develops as part of HIV dementia, but can occur in isolation. It presents as a progressive myelopathy with spastic paraparesis, hyperactive reflexes, Babinski's signs, gait ataxia, tremor, and urinary incontinence. In some patients, a sensory level may be appreciated.
- For neuromuscular complications of HIV see chapter on that topic.

PHYSICAL EXAM

The neurological exam will vary depending on the specific syndrome involved, as noted above.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

In general, the most important tests will consist of blood counts (including CD4 counts, to determine stage of HIV infection), infectious cultures of appropriate tissues, and serum antibody titers of various infectious agents. Other specific tests may be helpful in certain cases, such as Venereal Disease Research Laboratory test (VDRL) or vitamin B12 levels.

Imaging

Initial approach

MRI, with and without administration of gadolinium, is the most sensitive technique to evaluate HIV patients with cranial or spinal neurological complaints. HIV dementia may demonstrate atrophy or scattered, nonenhancing white-matter lesions. Similarly, PML presents with patchy, nonenhancing, periventricular white-matter lesions that slowly enlarge and coalesce. Cerebral toxoplasmosis usually demonstrates multiple ring-enhancing lesions with surrounding edema. PCNSL presents as a solitary or multifocal lesion within the deep periventricular white matter that typically enhances with contrast. Mild edema and/or mass effect may be noted. Tuberculous or fungal abscesses cause ring-enhancing lesions with surrounding edema. Focal viral encephalitis (e.g., CMV, varicella-zoster virus, HSV) may produce mass lesions with minimal enhancement. Other potential enhancing mass lesions include metastatic systemic lymphoma and Kaposi's sarcoma.

Diagnostic Procedures/Other

Lumbar puncture is often helpful to differentiate the etiology of brain or spinal processes, and should at least include routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL. Other tests that may be helpful in selected patients include electroencephalography (i.e., seizure activity), electromyography and nerve conduction studies (i.e., neuropathy and myopathy), and neuropsychological testing (i.e., HIV dementia).

Pathological Findings
The pathological features will vary depending on the primary process and region of the nervous system, as noted above.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis is extensive and includes any non-HIV-related disease with a similar presentation affecting the central or peripheral nervous system.

TREATMENT

MEDICATION
First Line
All patients should be evaluated for HAART, since this may prevent or abrogate the direct effects of HIV on the central and peripheral nervous system. In addition, HAART may prevent or reduce the risk of opportunistic infectious and neoplastic complications. All other drug decisions have to be individualized to the specific neurological complication of each patient.

ADDITIONAL TREATMENT
General Measures
Antiretroviral therapy should be maximized, if possible (i.e., HAART). HAART consists of a combination of two nucleoside reverse transcriptase inhibitors (e.g., zidovudine, didanosine, abacavir) and at least one protease inhibitor (e.g., saquinavir, indinavir) and/or one non-nucleoside reverse transcriptase inhibitor (e.g., nevirapine, delavirdine). Nutritional and metabolic deficiencies should be corrected, especially those that might impact neurological function (e.g., hyponatremia). All systemic infections should be diagnosed and treated. Medications should be reviewed for potential central or peripheral neurotoxicity.

Additional Therapies
Patients with HIV dementia may stabilize or improve slightly on antiretroviral therapy (zidovudine or HAART). Cerebral toxoplasmosis usually responds to combination therapy with pyrimethamine (50–75 mg/day), sulfadiazine (6–8 g/day), and leucovorin (10 mg/day). Patients with PCNSL should receive whole brain irradiation (4,000–5,000 cGy), although chemotherapy can be beneficial in selected patients with good performance status. Infectious neurological complications require therapy specific to the agent involved.

SURGERY/OTHER PROCEDURES
Biopsy may be required to differentiate focal intracranial lesions. Less often, biopsy may be helpful to diagnose the cause of neuropathy or myopathy.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Will be variable according to the specific neurological complication.

Admission Criteria
Patients are generally admitted for acute neurological changes such as altered level of consciousness, confusion, focal or generalized weakness, seizure activity, headache, and focal neurological deficits (e.g., dysphasia, hemianopsia).

Discharge Criteria
Patients with persistent neurological deficits should be considered for rehabilitation, after stabilization.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Will be variable according to the specific neurological complication.

Patient Monitoring
Follow-up of neurological status will be required. This is particularly true for some of the infectious complications that need long-term therapy (e.g., toxoplasmosis, CMV).

PATIENT EDUCATION
- Centers for Disease Control (CDC) AIDS Information: www.cdcnpin.org
- National AIDS Treatment Advocacy Project: www.natap.org
- International Association of Physicians in AIDS Care: www.iapac.org

PROGNOSIS
The course and prognosis for many of the neurological complications mentioned above is quite poor, since most occur in patients with low CD4 counts and advanced disease. The 6-month cumulative mortality rate for stage 2–4 HIV dementia is 67%. Similar 6-month cumulative mortality rates are noted for PML (85%), PCNSL (70%), and cerebral toxoplasmosis (51%). Some infectious complications caused by specific agents may respond to appropriate therapy, such as CMV encephalitis and neurosyphilis.

COMPLICATIONS
Will be variable according to the specific neurological complication.

ADDITIONAL READING

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- Newton HB. Common neurologic complications of HIV-1 infection and AIDS. *Am Fam Phys* 1995;51: 387–398.
- Xia C, Luo D, Yu X, et al. HIV-associated dementia in the era of highly active antiretroviral therapy (HAART). *Microbes Infect* 2011;13:419–425.

See Also (Topic, Algorithm, Electronic Media Element)
- HIV dementia
- HIV neuromuscular complications
- HIV focal brain lesions

CODES

ICD9
- 042 Human immunodeficiency virus (HIV) disease
- 294.10 Dementia in conditions classified elsewhere without behavioral disturbance
- 336.9 Unspecified disease of spinal cord

CLINICAL PEARLS
- Neurological complications of HIV are less common in the era of HAART therapy.
- Can still affect any level of the CNS or PNS.

AIDS: NEUROMUSCULAR COMPLICATIONS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Neuromuscular (NM) complications are common in patients with HIV infection and AIDS, potentially affecting nerve roots, peripheral nerves, and muscles. The etiology of these disorders is variable and may result from direct effects of HIV infection, damage from inflammatory processes and cytokine production, opportunistic infections and neoplasms, metabolic abnormalities, and toxic effects of HIV therapy.

EPIDEMIOLOGY

Incidence/Prevalence

- Approximately 10–40% of patients with HIV-1 and AIDS develop some form of NM complication. The most common complication is distal symmetric polyneuropathy (DSP), which is diagnosed in 20–30% of patients. Asymptomatic HIV-1-infected patients can also be affected and have an incidence between 2% and 20%, as shown by detailed neurophysiological testing. NM complications are decreasing in HIV patients because of HAART therapy.
- All races affected; most common in Caucasians and blacks. Any age can be affected; most common between 20 and 40 years of age. Both sexes can be affected; most often diagnosed in males.

RISK FACTORS

Diagnosis of HIV infection, low CD4 counts (i.e., less than 100/μL), and lack of antiretroviral therapy.

Genetics

Genetic factors have not been identified.

GENERAL PREVENTION

Use of HAART therapy.

PATHOPHYSIOLOGY/ETIOLOGY

- Etiology depends on specific syndrome. In early stages of HIV-1 infection, NM complications are caused by immune dysregulation. Acute and chronic forms of inflammatory demyelinating polyradiculoneuropathy (AIDP, CIDP) and vasculitic neuropathy are thought to occur by this mechanism. In AIDP and CIDP, an autoimmune process develops which results in damage to peripheral nerve myelin (i.e., myelin antibodies). Vasculitic neuropathy appears to be caused by deposition of HIV-1 antibody/antigen immune complexes into blood vessel walls.
- DSP and autonomic neuropathy usually occur in the middle and late stages of HIV-1 infection. Although the etiology of DSP remains unclear, it does not appear to be caused by direct infection of nerves by HIV-1.
- During late stages opportunistic infections and neoplasms can directly involve nerve roots and peripheral nerves. The most common infection is cytomegalovirus (CMV), which can involve the nerve roots (i.e., polyradiculopathy) and/or peripheral nerves (i.e., mononeuropathy multiplex). Other less common infections include herpes zoster ganglionitis, syphilitic radiculopathy, and tuberculous polyradiculopathy. Lymphoma can directly invade nerve roots and cause polyradiculopathy after spreading to the spinal meninges. Infrequently, neuropathies can develop in patients with vitamin B6 and/or vitamin B12 deficiencies.
- Toxic neuropathies can arise in a dose-dependent manner from therapy for HIV-1, in particular the antiretroviral dideoxynucleotide analogues didanosine (ddI), zalcitabine (ddC), and stavudine (d4T). The neuropathy may result from damage to cellular mitochondria caused by inhibition of mitochondrial DNA-γ polymerase.
- Myopathies can develop as a result of HIV-1 infection or from toxicity of antiretroviral therapy. Productive HIV-1 infection has not been demonstrated in myofibers. Zidovudine is also implicated as a cause of myopathy and appears to damage myofiber mitochondria, resulting in "ragged-red fibers" and other evidence of dysfunction. The mechanism is through inhibition of mitochondrial DNA-γ polymerase.
- Rarely, opportunistic infections can directly involve muscle and present as a myopathy, such as toxoplasmosis or CMV.

DIAGNOSIS

HISTORY

- Patients with DSP usually complain of distal, symmetric numbness, paresthesias, and dysesthesias of the legs and feet that develops over weeks to months; upper extremities can become affected in late stages of disease. Typically, the pain is most severe on the soles of the feet. Light touch and pressure often exacerbate the pain. On examination, most patients have loss of reflexes at the ankles and a distal-to-proximal gradient to pinprick, cold, and vibration; muscle weakness and atrophy are usually mild or absent. Toxic neuropathies from HIV-1 therapy have signs and symptoms similar to DSP.
- HIV-1-related AIDP and CIDP have a similar clinical presentation to the idiopathic neuropathies. The patient notes either a rapid (i.e., weeks; AIDP) or slow (i.e., months; CIDP) onset of progressive weakness in two or more limbs, generalized areflexia, and mild sensory loss. Muscle atrophy may be noted in patients with long-standing disease.
- Patients with autonomic neuropathy complain of fainting, orthostatic dizziness, impotence, diminished sweating, diarrhea, and urinary dysfunction. In addition, cardiac conduction abnormalities may occur.
- The various forms of polyradiculopathy present with progressive lower extremity and sacral paresthesias, flaccid paraparesis, areflexia, sensory loss, and urinary dysfunction.
- Mononeuropathy multiplex is characterized by multifocal, asymmetric, dysfunction of cutaneous nerves, mixed nerves, and nerve roots that often presents with wrist drop, foot drop, facial palsy, and other focal neuropathic signs.
- Patients with myopathy complain of slowly progressive, generalized proximal muscle weakness that initially affects activities such as arising from a chair or climbing stairs. Myalgias are noted in 25–50% of patients. Reflexes are preserved and sensory function remains intact.

PHYSICAL EXAM

Varies depending on specific syndrome.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

The most important tests will consist of blood counts (including CD4 counts, to determine stage of HIV infection), infectious cultures of appropriate tissues (e.g., CMV), and serum antibody titers of various infectious agents. Serum creatine kinase levels are moderately elevated (450–500 U/L) in patients with myopathy. Other specific tests may be helpful in certain cases, such as Venereal Disease Research Laboratory test (VDRL) and vitamin B6 and vitamin B12 levels.

Imaging

Initial approach

MRI and CT have limited diagnostic value.

Diagnostic Procedures/Other

- Lumbar puncture is often helpful and should at least include routine CSF studies, bacterial/fungal antigens, cytology, CSF bacterial/viral/fungal cultures, smear and culture for acid-fast bacilli, and VDRL. The CSF cell count always demonstrates a pleocytosis (20–50 mononuclear cells) in patients with HIV-1-related AIDP and CIDP (usually hypocellular in HIV-negative cases). Patients with CMV mononeuropathy multiplex and polyradiculopathy have an elevated CSF protein and mononuclear cell pleocytosis.

- Electromyography and nerve conduction testing are helpful for diagnosis. In DSP, the findings are consistent with a distal, symmetrical sensory more than motor, axonal neuropathy, with evidence for acute and chronic partial denervation and reinnervation of muscles. A similar pattern is seen with toxic neuropathies. AIDP and CIDP demonstrate slowed motor nerve conduction velocities consistent with demyelination, as well as conduction block. Myopathy shows typical myopathic findings of early, polyphasic motor unit potentials, positive sharp waves, and fibrillation potentials.
- Autonomic function testing may be helpful to define the presence and extent of autonomic neuropathy.

Pathological Findings

Will vary depending on the specific NM complication involved, affecting various peripheral nerves or muscle as outlined above.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is extensive and includes any non-HIV-related disease with a similar presentation affecting the nerve roots, peripheral nerves, or muscles.

TREATMENT

MEDICATION

First Line

All patients should be evaluated for HAART, since this may prevent or abrogate the direct and indirect effects of HIV on nerve roots, peripheral nerves, and muscles. All other drug decisions have to be individualized to the specific NM complication of each patient.

ADDITIONAL TREATMENT

General Measures

Antiretroviral therapy should be maximized, if possible (i.e., HAART). All systemic infections should be diagnosed and treated. Medications that could contribute to a myopathic or neuropathic process (e.g., zidovudine, ddC) should be reviewed and possibly discontinued as a therapeutic trial.

Additional Therapies

Treatment for DSP is symptomatic and consists of a combination of tricyclic antidepressants, selected serotonin reuptake inhibitors, carbamazepine, gabapentin, lamotrigine, and topical agents (i.e., capsaicin). Toxic neuropathies receive similar treatment to DSP and may improve after cessation of the offending drug. Patients with AIDP and CIDP may respond to plasmapheresis or IV immunoglobulin, similar to HIV-negative patients. Therapy for autonomic neuropathy consists of fludrocortisone, antiarrhythmic agents, and management of fluids and electrolytes. CMV polyradiculopathy and mononeuropathy multiplex may respond to ganciclovir. HIV myopathy may respond to a course of prednisone (60 mg/day). Zidovudine myopathy should be treated with reduced dosage or cessation of the drug.

SURGERY/OTHER PROCEDURES

Biopsy of involved nerve roots, peripheral nerves, or muscles may be helpful for definitive diagnosis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are generally admitted for acute neurological changes related to the specific neuropathic or myopathic process. The most common causes for admission include focal extremity weakness, generalized weakness, progressive proximal weakness, and exacerbation of extremity pain. Patients with persistent neurological deficits should be considered for rehabilitation.

Discharge Criteria

Varies.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Varies.

Patient Monitoring

Follow-up of neurological status will be required. This is particularly true for conditions that require long-term therapy, such as distal painful neuropathy or infectious NM complications (e.g., CMV).

PATIENT EDUCATION

- Centers for Disease Control (CDC) AIDS Information: www.cdcnpin.org
- AIDS Treatment Data Network: www.aidsnvc.org

PROGNOSIS

The course and prognosis for many of the neuropathies and myopathies mentioned above is quite poor, since the majority occur in patients with low CD4 counts and advanced disease. However, in some cases, treatment may lead to stabilization or improvement. Infectious complications caused by specific agents may respond to appropriate therapies such as CMV polyradiculopathy or mononeuropathy multiplex, syphilitic radiculopathy, or tuberculous polyradiculopathy. Toxic myopathies and neuropathies may improve if the offending agent is discontinued at an early stage.

COMPLICATIONS

Varies.

ADDITIONAL READING

- Newton HB. Common neurologic complications of HIV-1 infection and AIDS. *Am Fam Phys* 1995;51: 387–398.
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- Simpson DM. Selected peripheral neuropathies associated with human immunodeficiency virus infection and antiretroviral therapy. *J Neurovirol* 2002;8(Suppl 2):33–41.

See Also (Topic, Algorithm, Electronic Media Element)

- HIV overview of neurological complications
- HIV dementia
- HIV management of focal brain lesions

CODES

ICD9

- 042 Human immunodeficiency virus (HIV) disease
- 341.9 Demyelinating disease of central nervous system, unspecified
- 356.9 Unspecified idiopathic peripheral neuropathy

ALCOHOL ABUSE: NEUROLOGICAL COMPLICATIONS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Alcohol addiction is a major social and economic public health problem, accounting for an estimated $117 billion in annual cost in the US, due to health expenses and lost productivity; ethanol-related neurological complications are diverse and can affect any level of the neuraxis, including brain, spinal cord, cranial and peripheral nerves, and muscles.

EPIDEMIOLOGY

Incidence

In the US, 7% of all adults and 19% of all adolescents are considered "problem drinkers," either addicted to ethanol or likely to get into trouble when they drink. All races affected; most common in Caucasians and blacks. Adults and adolescents can be affected; most commonly diagnosed between 30 and 50 years of age. Both sexes can be affected; most often diagnosed in males.

Prevalence

The estimated prevalence of alcohol abuse and dependence is 7.4–9.7%; ethanol-related deaths exceed 100,000 each year.

RISK FACTORS

The major risk factors for alcoholism are familial genetic susceptibility and environmental factors such as being raised in an alcoholic household and exposure to male role models with a tendency toward antisocial behavior and novelty-seeking behavior. The risk of developing neurological complications is related to the duration and severity of the patient's alcoholism.

Genetics

There is a strong genetic influence toward alcoholism, with heritability estimates of 50%. Alcoholism is 7 times more frequent in first-degree relatives of alcoholics than in the general population; 16–26% of fathers and 2–6% of mothers of alcoholics are alcohol abusers; identical twins have a significantly higher concordance rate for alcoholism than fraternal twins; no consistent genetic locus has been identified.

GENERAL PREVENTION

No general preventive measures except for regulated alcohol consumption.

PATHOPHYSIOLOGY/ETIOLOGY

- After ingestion of only 2 oz of 100% ethanol, the blood ethanol level will be 100 mg/dL and will require 6 hours to be metabolized; blood ethanol levels of 100 mg/dL and higher will result in symptoms of impaired concentration, poor judgment, reduced inhibitions, slurred speech, nystagmus, ataxic gait, and labile mood; levels of 300–400 mg/dL induce stupor and coma.
- Ethanol interacts with nervous system tissues in several ways, including intercalation into cell membranes, increasing membrane fluidity, and perturbing hydrophobic regions of membrane lipids and proteins; ethanol interacts directly with specific neurotransmitter receptors and ion channels in the brain; $GABA_B$ receptors, which regulate potassium and calcium channels, are modulated by ethanol; similarly, it is theorized that ethanol modulates $GABA_A$ receptors by augmenting their response to GABA; excitatory amino acid receptors are also affected by ethanol; ethanol inhibits N-Methyl-D-aspartate (NMDA)-activated Ca^{2+} currents and cellular responses to NMDA receptor activation; chronic ethanol exposure causes increased expression of glutamate receptors, which may contribute to the generation of alcohol withdrawal seizures.
- Chronic alcohol intake leads to poor dietary intake and deficiencies of protein, thiamine, folate, and niacin; in addition, chronic ethanol intake can lead to accumulation of potentially toxic substances (e.g., acetaldehyde).
- Wernicke's encephalopathy results from thiamine deficiency, causing demyelination, necrosis, gliosis, and vascular proliferation in the mamillary bodies, superior vermis, hypothalamic nuclei, and diencephalon; similarly, Korsakoff's syndrome is also due to thiamine deficiency, causing lesions of the dorsal medial nuclei of the thalamus; alcoholic cerebellar degeneration may also be related to thiamine deficiency, in addition to electrolyte derangements and direct neurotoxic effects of alcohol; pellagra is caused by niacin (nicotinic acid) deficiency, which induces chromatolysis of neurons in the motor cortex, basal ganglia, brain stem, cerebellum, and anterior horn cells; alcoholic dementia is multifactorial and can be related to thiamine deficiency, pellagra, hepatocerebral degeneration, Marchiafava–Bignami disease, and direct neurotoxic effects of ethanol; alcoholic polyneuropathy is most likely from nutritional deficiency (thiamine?); alcoholic myopathy is probably due to direct toxic effects of ethanol on muscle; the causes of Marchiafava–Bignami disease and central pontine myelinolysis (CPM) remain unknown; CPM usually occurs after overly aggressive correction of hyponatremia, with demyelination of the basis pontis.

Pregnancy Considerations

Pregnancy has not been shown to affect the course of neurological complications of alcohol abuse; alcohol abuse during pregnancy may cause the fetal alcohol syndrome (mental retardation, microcephaly, hypotonia, poor coordination, impaired growth, abnormal facies).

DIAGNOSIS

HISTORY

- Patients with minor alcohol withdrawal present with tremulousness, insomnia, agitation, flushing, sweating, nausea and emesis, tachypnea, tachycardia, and increased blood pressure; hallucinations and seizures may also occur; seizures are generally of tonic–clonic type and occur within 48 hours of abstinence; some patients may progress to delirium tremens, which has similar but more severe symptoms compared to simple withdrawal, as well as fever, delusions and hallucinations, and severe encephalopathy.
- Patients with Wernicke's encephalopathy present with an acute confusional state, ophthalmoplegia, and gait ataxia; ocular findings include nystagmus, unilateral or bilateral lateral rectus palsy, and conjugate gaze palsies; other findings may include hypotension, hypothermia, polyneuropathy, and somnolence; Korsakoff's syndrome often develops after Wernicke's and is characterized by severe anterograde and short-term retrograde amnesia, lack of concern and insight, and confabulation.
- Alcoholic cerebellar degeneration presents with gait ataxia and less severe limb ataxia; symptoms affect the legs more than the arms; dysarthria may occur; usually gradual in onset.
- Alcoholic dementia presents as progressive cognitive decline; in patients without a nutritional or other cause, it is often mild, with anterograde and retrograde memory deficits, and reduced cognition; on occasion, symptoms can be severe.
- Alcoholic polyneuropathy presents with paresthesias, pain, and weakness of the distal lower extremities, often in the feet; gait may be affected; pain and temperature sensation are reduced; distal muscle weakness and atrophy are often present; reflexes are often reduced.
- Chronic alcoholic myopathy presents with intermittent cramps and painless, progressive proximal weakness; symptoms can be mild or severe; atrophy may be present; acute alcoholic myopathy is a necrotizing process, often noted during alcoholic binges, which presents with pain, tenderness, weakness, muscle swelling, myoglobinuria, and cardiac arrhythmias.
- Pellagra presents with an acute confusional state, rigidity, and myoclonus; other signs may include hallucinations, seizures, pyramidal signs, ataxia, and neuropathy.
- Marchiafava–Bignami disease presents with a progressive, subacute confusional state, dementia, seizures, dysarthria, pyramidal signs, and incontinence; stupor and coma may occur.
- CPM presents with acute confusion or coma, spastic paraparesis or quadraparesis, dysarthria, and dysphagia; locked-in syndrome may occur.

PHYSICAL EXAM
The neurological examination findings will vary depending on the specific syndrome and the level of the nervous system involved, as noted above.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
Patients should be screened for thiamine, niacin, and other vitamin levels, transketolase level, liver panel (including ammonia), electrolytes, glucose, renal panel, calcium, and magnesium; ethanol level, toxicology screen, and infectious work-up may be of benefit in selected cases.

Imaging
Initial approach
MRI or CT, with and without contrast, is appropriate in patients with mental status changes, atypical seizures, or focal neurological findings to rule out intracranial processes (e.g., subdural hematoma, abscess).

Diagnostic Procedures/Other
Patients with seizures and/or encephalopathy should undergo lumbar puncture (meningitis?) and an electroencephalogram; electromyography and nerve conduction testing are helpful for patients with neuropathy and/or myopathy.

Pathological Findings
Will be variable depending on the specific process involved, as noted above.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis is extensive and includes any non-ethanol-related diseases that can have a similar presentation of encephalopathy, seizure activity, dementia, polyneuropathy, myopathy, or cerebellar degeneration.

TREATMENT
MEDICATION
First Line
There are no specific medications that cover all of the various alcoholic neurological complications.

ADDITIONAL TREATMENT
General Measures
Administration of thiamine, niacin, and multivitamins; correction of electrolyte, glucose, and fluid imbalances; hyponatremia should be corrected slowly (i.e., ≤10–12 mmol/L/day); monitoring of heart rhythm; calming environment; seizure precautions; treatment of general medical complications and infections as appropriate; improve general nutrition and protein intake.

Additional Therapies
- Treatment of early alcohol withdrawal consists of oral diazepam (10–40 mg) or chlordiazepoxide (25–100 mg) every 2–4 hours; the addition of atenolol (50 mg q.d. or b.i.d.) or clonidine (0.3 mg b.i.d.) may be of benefit; treatment of delirium tremens consists of IV diazepam (10–40 mg) every 5–10 minutes, titrated to clinical effect; maintenance doses of 5–20 mg every 1–4 hours; oral atenolol (50 mg q.d. or b.i.d.) should be considered; hydration, electrolyte replacement, and cooling as needed; withdrawal-related seizures are typically self-limited once treatment has begun; persistent seizures or status epilepticus require IV diazepam or lorazepam and IV phenytoin, similar to the protocol used for non-ethanol-related patients.
- Wernicke's encephalopathy should be treated with thiamine 500 mg IV t.i.d. for 2–3 days, followed by 250 mg IV or IM for another 3–5 days, converting to oral therapy at discharge; Korsakoff's syndrome should be treated with thiamine, although it typically does not improve; pellagra responds to multivitamin and niacin (nicotinic acid) replacement; alcoholic polyneuropathy may respond to thiamine and multivitamin replacement.
- There is no specific therapy for alcoholic cerebellar degeneration; it may improve with thiamine and multivitamins; there is no treatment for Marchiafava–Bignami disease or CPM; alcoholic myopathy usually improves with abstinence and supportive care.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
As above.

Admission Criteria
Seizure activity, mental status alterations, and focal neurological deficits are the most common causes for admission; alcohol withdrawal and delirium tremens usually occur after admission and cessation of alcohol intake.

IV Fluids
As above.

Discharge Criteria
Discharge is appropriate when symptoms of withdrawal, seizures, and other neurological and medical complications have either stabilized or resolved.

ONGOING CARE
FOLLOW-UP RECOMMENDATIONS
Neurological follow-up will be required; monitoring of abstinence, nutritional status, and compliance with thiamine, multivitamins, and other medications is critical.

Patient Monitoring
As above.

DIET
Will be specific to the type of alcoholic neurological complication involved.

PATIENT EDUCATION
- National Institute on Alcohol Abuse and Alcoholism: www.niaaa.nih.gov
- Medical Council on Alcohol: www.medicouncilalcol.demon.co.uk
- Alcoholism/Treatment: www.alcoholismtreatment.org
- American Council on Alcoholism: www.nca-usa.org

PROGNOSIS
The course and prognosis for early alcohol withdrawal is favorable, but becomes more guarded with delirium tremens, due to frequent medical complications; patients with Wernicke's encephalopathy and Korsakoff's syndrome often have residual neurological dysfunction (dementia, ataxia); alcoholic cerebellar degeneration and polyneuropathy usually improve with abstinence and nutritional therapy; recovery from pellagra is excellent with treatment; recovery of myopathy is excellent with abstinence; recovery from Marchiafava–Bignami disease and CPM is typically poor.

COMPLICATIONS
As noted above.

ADDITIONAL READING

- Brust JCM. Alcoholism. In: Rowland LP, ed. *Merritt's neurology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000;157:921–929.
- Harper C. The neurotoxicity of alcohol. *Hum Exp Toxicol* 2007;26:251–257.
- Harper C, Matsumoto I. Ethanol and brain damage. *Curr Opin Pharmacol* 2005;5:73–78.

See Also (Topic, Algorithm, Electronic Media Element)
Chapters on encephalopathy, neuropathy, myopathy, and nutritional disorders.

CODES
ICD9
- 265.1 Other and unspecified manifestations of thiamine deficiency
- 291.2 Alcohol-induced persisting dementia
- 305.00 Nondependent alcohol abuse, unspecified drinking behavior

CLINICAL PEARLS
Will be specific to the type of alcoholic neurological complication involved.

AMNESIA, TRANSIENT GLOBAL

Dean Sherzai, MD, MAS
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BASICS

DESCRIPTION
- Sudden onset of an anterograde and retrograde amnesia that lasts up to 24 hours
- Mild subclinical neuropsychological deficits with concomitant vegetative symptoms can last for days after the episode

EPIDEMIOLOGY
Incidence
- about 3–8/100,000 annually
- 75% between 50 and 70 years
- Rare in patients younger than 40 years
- No clear sex differences
- 6–10% annual recurrence

RISK FACTORS
- Age >50 years
- History of migraines
- Events involving a stress response
- Sudden immersion in cold or hot water
- Physical exertion
- Emotional or psychological stress
- Acute pain
- Medical procedures
- Sexual intercourse
- Valsalva-associated maneuvers

Genetics
- No genetic factors determined

PATHOPHYSIOLOGY
- Exact mechanism is not well known
  - Migraine-related mechanisms, focal ischemia, venous flow abnormalities, and epileptic phenomena have been implicated
  - Temporal lobe structures involved, especially the hippocampus
  - Hyperintense MRI lesions can be detected in the hippocampal formation

ETIOLOGY
- No cause has been found. There is speculation around cerebral ischemia, seizures, and migraines, yet these patients are not at increased risk for strokes, transient ischemic attacks, or seizures.

COMMONLY ASSOCIATED CONDITIONS
- Events involving a stress response
- Psychological or emotional disorders

DIAGNOSIS

HISTORY
- Abrupt onset of memory loss, lasting for hours, inability to learn new material
- Diagnostic criteria
  - Presence of an anterograde amnesia that is witnessed by an observer
  - No clouding of consciousness or loss of personal identity
  - Cognitive impairment limited to amnesia
  - No focal neurological or epileptic signs
  - No recent history of head trauma or seizures
  - Resolution of symptoms within 24 hours
  - Mild vegetative symptoms (headache, nausea, dizziness) during the acute phase
  - Patients repeatedly ask 'Where am I?', 'How did I get here?' during the amnestic event

PHYSICAL EXAM
- Normal physical exam
- No focal neurological signs
  - Cognitive impairment limited to amnesia, predominantly anterograde; repetition of questions or tasks, sometimes confabulation
  - Intact remote memory, including personal identity

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- CBC and metabolic panel, drug screen, infectious work-up
- There are no specific laboratory studies for transient global amnesia (TGA)

Follow-up & special considerations
- Neurological consultation

Imaging
Initial approach
- CT head scan to rule out stroke and head trauma
- Diffusion-weighted MRI of the brain

Diagnostic Procedures/Other
- EEG to rule out transient epileptic amnesia
- Urine drug screen and toxicology panel
- If patient is on medication, consider checking levels, rule out overdose

Pathological Findings
- Diffusion-weighted MRI of the brain, preferably 3T, may show abnormalities in the hippocampus within 24–72 hours

DIFFERENTIAL DIAGNOSIS
- Hypoglycemia
- Ischemia in the posterior cerebral circulation
- Adverse drug side-effects, intoxication
- Complex partial seizures, transient epileptic amnesia, postictal conditions
- Post-traumatic amnesia
- Psychogenic amnesia, dissociative disorders
- Alcoholic "blackouts"
- Thiamine deficiency (Wernicke–Korsakoff syndrome)
- Encephalitis, especially herpes simplex encephalitis

TREATMENT

MEDICATION
First Line
- Treatment of reversible conditions, such as metabolic disturbances and toxicity if suspected.

Second Line
- Based on primary etiological factor

ADDITIONAL TREATMENT
General Measures
- Patient and family reassurance
- Frequent patient re-orientation

Issues for Referral
- Neurology
- Psychiatry

SURGERY/OTHER PROCEDURES
- No surgery or instrumentation indicated

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Avoidance of activities that may increase breathing effort and intrathoracic pressure

Admission Criteria
- Rule out stroke or seizure

Discharge Criteria
- Stabilization of vital signs, reversal of cognitive deficits and constitutional symptoms, enough to be sent home safely without undue anxiety

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Neurology

Patient Monitoring
- Avoidance of stress factors if any

DIET
- No restrictions

PATIENT EDUCATION
- Knowledge of basic health education and risk factor management
- TGA is not indicative of cerebrovascular disease

PROGNOSIS
- Recurrence rate up to 6–10% annually
- Gradual abatement of constitutional symptoms

COMPLICATIONS
- None

ADDITIONAL READING

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CODES

ICD9
437.7 Transient global amnesia

CLINICAL PEARLS
- Normal physical exam
- Cognitive impairment limited to amnesia only
- Diffusion-weighted MRI within 24–72 hours of onset may show restriction in the hippocampus

AMYOTROPHIC LATERAL SCLEROSIS

Glenn A. Mackin, MD, FAAN, FACP

BASICS

DESCRIPTION

- Amyotrophic lateral sclerosis (ALS), or "Lou Gehrig's Disease," is a neurodegenerative disease of unknown cause of corticospinal upper motor neurons (UMNs), brainstem bulbar motor neurons, and spinal cord lower motor neurons (LMNs), causing progressive skeletal muscle weakness.
- Recently recognized, measurable cognitive impairments develop in up to half of ALS patients, from mild to full frontotemporal dementia (FTD).
- ALS starts in a bulbar or limb muscle, spreads to contiguous spinal segments. Progressive loss of strength proceeds at a constant rate in affected persons and varies substantially between individuals. Death usually occurs by progressive ventilatory failure.

EPIDEMIOLOGY

Incidence

- 2 per 100,000/year
- All ages: Highest between 45 and 70 years, mean approximately 60, uncommon under age 40
- Overall male predominance 1.5:1, especially in younger age groups; closer to 1:1 over age 60
- Fairly uniform geographic and ethnic distribution; highest incidence in Caucasians

Prevalence

- 6 per 100,000 (approximately 30,000 in the US)

RISK FACTORS

- Slim body habitus
- History of varsity or professional sports
- Cigarette smoking
- Environmental factors
  - ALS–Parkinson–dementia complex of Guam
  - Gulf war service
  - Exposure to heavy metals, radiation, pesticides, electricity
  - Occupations (crafts, trade workers)
- Lymphoma with M protein
- Other neurodegenerative diseases in family

Genetics

- Familial ALS (FALS, 5–10% of all ALS): Younger onset, mean 45. Some subtypes, rapid.
- Multiple mutations; most autosomal dominant.
  - 20% of FALS is due to a mutation in copper zinc superoxide dismutase (SOD_1) gene.
  - 2–5% TARDBP (TDP-43) gene mutations.

Pregnancy Considerations

- Prenatal gene tests (SOD_1 in 1–2% of all ALS)

PATHOPHYSIOLOGY

- Loss of motor neurons with intraneuronal ubiquitin-positive inclusions in degenerating UMNs and TDP-43 reactive inclusions in LMNs
- Variable TDP-43 inclusions in frontal neurons

ETIOLOGY

- Unknown
- Suspected interplay between aberrant gene expression, aging, and environmental triggers
- Cause of cell death—upon which dramatically effective pharmacotherapy depends—is unknown
- Proposed mechanisms: Oxidative stress, excitotoxicity, proteosomes, mitochondrial dysfunction, impaired axonal transport, protein aggregation, inflammation, neurotrophic factor deficiency, retroviruses, and accelerated apoptosis

COMMONLY ASSOCIATED CONDITIONS

- FTD
  - In ALS, measurable neuropsychological deficits eventually in 50%, dementia in 5–10%
  - May follow, overlap, or precede weakness
  - Abnormal intraneuronal TDP-43 expression
  - Loss of executive function, lack of empathy for caregivers, euphoria, apathy, maladaptive
  - Relative preservation of episodic memory, language, and visuospatial capabilities

DIAGNOSIS

HISTORY

- Progressive painless weakness and atrophy without numbness in 1 or more limbs
- Progressive dysarthria, dysphagia, or dyspnea
- Muscle fasciculations, cramps (esp. calves)
- Gait unsteadiness and/or hand clumsiness
- Weight loss (usually mild in early onset of disease)

PHYSICAL EXAM

- UMN signs: Hyperreflexia, spasticity, Babinski's sign, emotional lability (pseudobulbar affect)
- LMN signs: Weakness, hyporeflexia, atrophy, diffuse fasciculations, flaccidity, cramps (calves)
- Bulbar (ALS onset 20–30%): Tongue atrophy or fasciculations, dysarthria (flaccid or spastic), jaw jerk/gag (reduced or hyperactive), dysphagia
- Respiratory: Exertional dyspnea, orthopnea
  - Chronic ventilatory insufficiency: Heralded by fitful sleep, orthopnea, nightmares, morning headache, drowsiness, change in snoring
- Cognitive: Frontotemporal dysfunction
- El Escorial Criteria [C] (World Federation of Neurology): *Progressive* weakness or electromyographic (EMG) signs in bulbar, cervical, thoracic, lumbosacral "regions"
  - Definite ALS: UMN and LMN signs in 3 regions (bulbar + 2 spinal or 3 spinal)
  - Probable ALS: UMN and LMN signs in 2 regions, some UMN rostral to LMN
  - Possible ALS: UMN and LMN signs in 1 region

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- No confirmatory serologic or CSF test for ALS
- EMG and nerve conductions: Mandatory test!
  - Looking for evidence of denervation in 3 body regions (bulbar, individual limbs, trunk)
  - May show widespread acute and/or chronic LMN axon loss that is not clinically apparent
- Lab tests performed in most patients
  - CBC, comprehensive metabolic panel (CMP), CK (normal or mildly elevated)
  - ESR, antinuclear antibody (ANA), rheumatoid factor (RF), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), B_{12}
  - SIEP/SIFX, UIEP/UIFX (monoclonal)
- Optional tests, based on suspicion and risks
  - Gene tests (if possibility of familial ALS is present)
  - Lyme titer, rapid plasma reagin (RPR), and/or HIV-1/2 titer
  - 24-hour urine heavy metal test (lead, mercury)
  - Acetylcholine receptor antibody (bulbar)
  - Purely LMN presentations
    - GM_1 ganglioside antibody (high titers, 40–60% multifocal motor neuropathy, MMN)
    - SBMA gene (spinal bulbar muscular atrophy)
    - SMN gene (survival of motor neurons 1, 2)
    - Hexosaminidase A deficiency (multisystem)
  - Purely UMN presentations
    - HTLV-1 (tropical spastic paraparesis)

Follow-up & special considerations

- Breaking the news
  - Give the diagnosis in person, never by phone (B)
  - Discuss implications, respect background (B)
  - Give written information, support groups (B)

Imaging

Initial approach

- Cervical MRI (to exclude cervical stenosis, especially if all UMN and LMN signs occur below neck)
- Brain, thoracic, lumbosacral MRI (as needed)

Diagnostic Procedures/Other

- Muscle biopsy: EMG of chronic myopathy may mimic denervation [e.g., inclusion-body myositis (IBM), dystrophies]; ALS biopsy confirms acute/chronic denervation.
- Lumbar puncture: In atypical cases, CSF may show meningeal lymphoma, carcinomatosis, and Lyme.

DIFFERENTIAL DIAGNOSIS

- ALS phenotype
  - Familial ALS (often autosomal dominant)
  - ALS with lymphoproliferative disease, monoclonal gammopathy, other malignancies
  - ALS-like disease with HIV infection
  - ALS–Parkinson–dementia complex (Guam)
- LMN disorders
  - Progressive muscular atrophy (PMA): Adult onset; minimal bulbar signs; slower than ALS, similar course, and care. "PMA" LMN onset often develops UMN signs of ALS
  - Spinal muscular atrophy: Autosomal recessive (5q11.2–13.3); from birth to young adult. More copies of SMN2 predict longer survival
  - Spinal bulbar muscular atrophy (SBMA, "Kennedy's disease"): X-linked, CAG trinucleotide repeat in androgen receptor gene; young adults; slow, proximal > distal LMN signs; chin fasciculation; gynecomastia
  - Viral: Poliomyelitis, enteroviruses, West Nile
- UMN disorders
  - Primary lateral sclerosis (PLS): Rare, occurring in sporadic middle age/older; purely UMN signs; spastic dysarthria, dysphonia, dysphagia, gait; normal EMG; slower than ALS, but most "PLS" onset will develop LMN signs of ALS
  - Hereditary spastic paraplegia (HSP)
  - Viral myelopathies: HIV-1 and 2, HTLV-1
- Disorders that may be confused with ALS
  - Structural myelopathy (especially at cervical but also at thoracic and lumbosacral levels)
    - Compression, Chiari, tumor, syringomyelia
  - Lumbosacral or thoracic spinal stenosis
  - B_{12} deficiency (subacute combined degeneration)
  - Copper deficiency (gastric bypass, nutritional)

– IBM: Occurring in older males > females; slowly progressive weakness of finger and hip flexors; possible dysphagia
– MMN: Sporadic antibody-mediated multifocal demyelinating motor neuropathy; occurring in middle aged and older patients; male > female; weakness out of proportion to atrophy; nerve conduction study (NCS), motor conduction blocks, high-titer G_{M1} ganglioside antibody (50%)
– Chronic inflammatory demyelinating polyneuropathy
– Amyotrophies (diabetic, inflammatory, tumor)
– Neuromuscular junction: Myasthenia, Lambert–Eaton myasthenic syndrome (LEMS)
– Heavy metal intoxication
– Hyperthyroidism, hyperparathyroidism
– Benign cramp-fasciculation syndrome
– CNS diseases: Cerebrovascular disease, multiple sclerosis (MS)
– Multisystem CNS: Hexoaminidase A deficient (adult Tay–Sachs), Creutzfeldt–Jakob, progressive supranuclear palsy, corticobasal degeneration, diffuse Lewy body disease, multiple systems atrophy, neurosyphilis

TREATMENT

MEDICATION

First Line

- Riluzole: FDA-approved, disease-modifying ALS drug; 3-month survival advantage in placebo trials (2)[A]; mechanism uncertain; expensive
  – Dosing: 50 mg PO q12h
  – Cautions: Impaired hepatic or renal function
  – Side effects: Fatigue, nausea, diarrhea
- Stop statins if possible, deleterious in ALS [C]

Second Line

- All unproven, but commonly used by patients
  – Vitamin C (1,000–2,000 mg daily)
  – Vitamin E (800–1,200 IU daily)
  – Coenzyme Q10
  – β-Carotene

ADDITIONAL TREATMENT

General Measures

- Accurate diagnosis is essential to enable the patient and family to come to terms with diagnosis
- Compassion in "breaking the news" is the basis for trust essential to optimal ALS care (2)[B]
- Early diagnosis prevents unnecessary surgery
- Second diagnostic opinions are indispensable for any question and to help some reach "cloture"
- Multidisciplinary ALS care optimizes symptom management and access to adaptive measures
  – Intervention by ALS-specialized neurologist, ALS nurse, case manager, therapy services [physical therapy (PT), occupational therapy (OT), speech/swallowing, nutrition], pastoral/spiritual care
- Promptly treat new and changing symptoms
- Broach early and periodically review end-of-life wishes [percutaneous endoscopic gastrostomy (PEG), intubation, long-term ventilation, LTV] advance directives, and power-of-attorney
- Respite care and psychological support for spouse or caregiver; ALS support groups are helpful
- Keep vaccinations current (flu, Pneumovax)
- Respect patient's right to refuse or withdraw any treatment, including mechanical ventilation

Issues for Referral

- Outpatient PT/OT, speech/swallowing, VNA
- Communication specialist (voice synthesizers)
- Wheelchair clinic (power chairs) and orthotists
- PRN: Pulmonary, physiatry, psychiatry, heme

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  – Dyspnea
    ○ Initiate noninvasive ventilatory support [using bilevel positive airway pressure (biPAP)] >4 hours/night, if symptoms of hypoventilation exist (2)[B]. Indications are dyspnea, daytime sleepiness, morning headaches, awakenings, or if forced vital capacity (FVC) <50%
    ○ Nocturnal biPAP: Prolongs survival if used >4 hours nightly, especially initiated if FVC >50% (2)[B]. Nasal O_2 is not germane
    ○ Elevate head of bed or home hospital bed
    ○ Promptly treat emerging respiratory infection
    ○ Ensure palliative/hospice care at end-of-life, whether LTV is declined or withdrawn. Treat dyspnea with opioids alone or with oxygen; anxiety with anxiolytics (2)[B]
  – Speech: Communication aids range from low tech (notepads, letter boards) to high tech (voice synthesizers, headset laser pointer)
  – Sialorrhea: Glycopyrrolate, benztropine, hyocosine, trihexyphenidyl, atropine, amitriptyline (2)[C]. Also, suction, parotid botulinium injections, scopolamine patches
    ○ Parotid radiation may cause excess dryness
  – Thick phlegm: Cough assist devices, suction, acetylcysteine, propranolol, and guaifenesin
  – Nasal congestion, postnasal drip: Loratadine
  – Dysphagia: Consider placing PEG as soon as symptomatic. Optimal safety and efficacy for PEG placement when FVC >50% (2)[B]
  – Spasticity: Lioresal, tizanidine, diazepam
  – Cramps: Calcium/magnesium/zinc, quinine sulfate, gabapentin, vitamin E (2)[C]
  – Pain control [immobility, degenerative joint disease (DJD)]: NSAID, opioid
  – Cognitive (FTD): Family understanding key; consider donepezil, behavioral medications
  – Depression and anxiety: Antidepressants, anxiolytics, psychiatry/psychology liaison
  – Pseudobulbar affect: Dextromethorphan–quinidine (2)[A]; amitriptyline, fluoxetine
  – Insomnia: Consider nocturnal hypoventilation, sleep apnea, depression, anxiety, and/or pain
  – Constipation: Stool softener, fiber, laxatives
- Adjunctive treatment
  – Durable goods: Ankle foot orthosis (AFO), resting splint, cane, walker, wheelchairs (manual, motorized), head support (head drop), hospital beds
  – Home adaptation: Chair lifts, stair glides, shower benches, grab bars, ramps, and vans
  – Surgery/other procedures
    ○ Muscle biopsy, PEG tube, tracheostomy
    ○ Botulinium injections (parotid, masseter)

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Avoid hospitalization, as much as possible
  – Verify hospital, intubation wish before need
  – Pneumonia (biPAP may avoid intubation)
  – PEG placement, teaching on care and use

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- ALS clinic: Every 3 months, sooner as needed
  – FVC, weight, assess dysphagia—at each visit
  – On riluzole, LFTs and CBC every 3–6 months
  – Hospice (home, inpatient): Initiate well before end stage for symptom control, end-of-life comfort

DIET

- Food consistency: Monitor swallow function
- Weight stability: Administer supplements, PEG formula

PATIENT EDUCATION

- ALS Association, 1275 K Street NW, Suite 1050 Washington, DC 20005. Website: www.alsa.org

PROGNOSIS

- Average disease duration to death is 3 years; lesser than 10% survive more than 10 years
  – Survival after onset: Bulbar 2–3, limb 3–5, years

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CODES

ICD9

- 294.10 Dementia in conditions classified elsewhere without behavioral disturbance
- 335.20 Amyotrophic lateral sclerosis

CLINICAL PEARLS

- High priority on patient self-determination in decision-making. Multidisciplinary care, detailed symptom management, and timely hospice crucial.
- Riluzole extends survival, mean 3 months (2)[A].
- BiPAP as early as possible, FVC 50–70% and >4 hours nightly, extends survival mean of months (2)[B].
- Broach PEG early, place as soon as possible for symptomatic dysphagia; extends survival (2)[B].
- Quality of life is often rated high by persons with ALS (spiritual) and low by healthy observers.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME, NEUROLOGICAL COMPLICATIONS

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BASICS

DESCRIPTION

Antiphospholipid syndrome (APS) is an autoimmune condition associated with thrombotic events, thrombocytopenia, and recurrent fetal loss in the presence of circulating antiphospholipid antibodies (aPLs). APS can be primary or secondary to connective tissue disorders such as systemic lupus erythematosus (SLE), infectious diseases, or neoplastic disorders. Neurological manifestations of APS are variable and are most often due to recurrent cerebral ischemia (1).

EPIDEMIOLOGY

Incidence

The incidence of APS increases with age and chronic disease.

Prevalence

The prevalence of aPLs in the population is 2–5%, with the majority of subjects being asymptomatic.

RISK FACTORS

- SLE
- Race
  - While APS is less common in African-Americans, IgA and IgM anticardiolipin antibody (aCL) isotypes appear to be more prevalent in this subgroup.
- Age
  - Although the syndrome is more common in younger patients, 27% of patients with APS are over 60. It is estimated that 20–30% of young adults with thromboembolic events have positive aCLs and/or lupus anticoagulant (LA), and 7–10% of total patients with stroke are aPL positive if all ages are considered. Clinical manifestations of APS occur at a mean age of 31 years.
- Sex
  - The female-to-male ratio varies from 1.5–2:1 in primary APS up to 9:1 in patients with APS associated with SLE.

Pregnancy Considerations

aPLs can cause early and late spontaneous abortion. Pregnant women with APS are at increased risk of pre-eclampsia and placental insufficiency.

Genetics

- Familial aPLs positivity has been linked to HLAs DR7, DR4, DQw7, and DRw53. Familial coexistence has been linked to factor V Leiden mutation.
- An HLA-DQB1 sequence, called TRAELDT, may represent an autoantibody predisposing 'candidate epitope' in patients with connective tissue disorders.

ETIOLOGY

- APS is linked to the presence of aPLs—acquired antibodies against anionic phospholipid containing moieties in cell membranes. LA and aCL, especially the IgG isotype, were identified as risk factors for ischemic strokes. Although the mechanism of thrombosis is uncertain, it is believed that aPLs promote platelet aggregation and disruption of coagulation cascade with subsequent inhibition of the production of prostaglandin E_2—a potent vasodilator.
- The binding of aCL phospholipid is dependent on the presence of a β_2-glycoprotein (β_2-GPI), a plasma protein with high affinity to anionic phospholipids, creating an immunologic reaction that may lead to thrombosis.
- APL can interfere with protein C activity and decrease protein S levels, leading to inhibition of plasminogen activator protein.

COMMONLY ASSOCIATED CONDITIONS

- Frequent (>20% of cases) (1)[C]
  - Venous thromboembolism
  - Thrombocytopenia
  - Miscarriage or fetal loss
  - Stroke or transient ischemic attack
  - Migraine
  - Livedo reticularis
- Less common (10–20% of cases)
  - Heart valve disease
  - Pre-eclampsia or eclampsia
  - Premature birth
  - Hemolytic anemia
  - Coronary artery disease
- Unusual (<10% of cases)
  - Epilepsy
  - Vascular dementia
  - Chorea
  - Retinal artery or vein thrombosis
  - Amaurosis fugax
  - Pulmonary hypertension
  - Leg ulcers
  - Digital gangrene
  - Osteonecrosis
  - APS nephropathy
  - Mesenteric ischemia
- Rare (<1% of cases)
  - Adrenal hemorrhage
  - Transverse myelitis
  - Budd–Chiari syndrome

DIAGNOSIS

DIAGNOSTIC TESTS AND INTERPRETATION

Primary APS occurs without an identifiable cause and is characterized by the diagnostic criteria below. Secondary APS occurs in the setting of an autoimmune disorder, most commonly SLE.

Lab

Initial lab tests

- APS is present if at least one of the following clinical and one lab criteria are met (2)[C]:
  - Clinical criteria:
    - Vascular thrombosis, arterial or venous.
    - Obstetric morbidity including (a) fetal death at or beyond 10 weeks' gestation, (b) premature birth before 34 weeks' gestation due to eclampsia or placental insufficiency, or (c) 3 or more consecutive spontaneous abortions before 10 weeks' gestation.
  - Laboratory criteria:
    - LA+ in plasma ≥2 occasions at least 12 weeks apart.
    - ACL IgG and/or IgM+ in serum or plasma at medium or high titer ≥2 occasions at least 12 weeks apart.
    - Anti-B_2 glycoprotein IgG and/or IgM+ in serum or plasma with titer >99 percentile ≥2 occasions at least 12 weeks apart.
- Hematologic abnormalities that may be associated with APS include:
  - Thrombocytopenia (26–31%)
  - Prolonged aPTT (50%)
  - Positive Coombs' test
  - False-positive rapid plasma reagin or venereal disease research laboratory
  - Neutropenia
  - Lymphopenia
  - Decreased C_4 levels

Follow-up & special considerations

- Persistently positive antibody titers after 12 weeks is required for diagnosis.
- Phenothiazines may induce aPLs.

Imaging

Initial approach

- CT and MRI findings are nonspecific. At least 50% of patients with APS will show a single lesion on CT, and about half this number will have multiple infarcts. Less common findings include white matter abnormalities, cortical atrophy, and venous sinus thrombosis.
- Conventional cerebral angiography, CT angiography, or magnetic resonance angiograph may show evidence of intracranial stenosis in 40% of patients, half of which are in the middle cerebral artery branches. Only 22% of patients may show extracranial lesions. Dural sinus thrombosis is a common finding. Rarely, the angiogram picture may be suggestive of vasculitis.

DIFFERENTIAL DIAGNOSIS

APS should be considered in patients with cryptogenic stroke. Other causes of unexplained arterial or venous thrombosis should be excluded:

- Protein C or S deficiency
- Homocystinuria
- Antithrombin III deficiency
- CNS vasculitis
- Coagulation factors disorders
- Factor V Leiden mutation
- Sickle cell disease
- Underlying malignancy with hypercoagulability
- Conditions associated with transient elevation of aPLs, such as AIDS, neuroleptic agents (in particular phenothiazines), recombinant tissue plasminogen activator (rt-PA), aging (50% of patients over 80 are aPLs positive), and insulin-dependent diabetes mellitus
- aPLs positivity in patients with multiple sclerosis without APS ranges from 8 to 33%

TREATMENT

- Asymptomatic patients with aPLs do not benefit from low-dose aspirin for prophylaxis of thrombosis, but may develop vascular events if additional thrombosis risk factors are present (3)[C].
- Secondary prophylaxis: Antiplatelet agents or anticoagulants depending on patient risks.

MEDICATION

First Line

- Antiplatelet agents
  - Aspirin: Aspirin reduces the risk of stroke recurrence by inhibiting platelet aggregation through inhibition of endothelial prostacyclin synthesis. Aspirin can be used in variable doses of 81 to 1,300 mg in patients with a single thromboembolic event and positive aCLs (4,5)[A].
  - Other antiplatelet agents: Ticlopidine, clopidogrel, and dipyridamole have not been studied in the aCL-positive subgroup of stroke patients (5)[C].
- Anticoagulants
  - Warfarin is an effective therapy for recurrent thromboembolic events, with an international normalized ratio aim of 2–3 (5)[B]. Abrupt discontinuation of warfarin may increase the probability of recurrent thrombosis. A combination of aspirin and warfarin has been used for patients with recurrent events on warfarin alone (4)[B].
  - Heparin: High doses of unfractionated heparin or low molecular weight heparin appear to be efficacious in protecting against recurrent thrombosis.
- Thrombolytics
- Alteplase rt-PA has been successfully used in patients with APS and can be used in selective patients with acute stroke.
- Contraindications: Known hypersensitivity reactions for any of the above drugs. Warfarin is contraindicated in those with active or potential sources of bleeding or frequent falls.

Second Line

- Plasma exchange
  - Plasma exchange may lower the level of circulating antibodies; repeated exchanges may be required to avoid a rapid rise in aPLs titers. May be helpful in catastrophic APS (CAPS).
- Steroids
  - There is no conclusive evidence that steroids are beneficial in aCL-positive stroke patients. Its use in pregnant women is associated with decreased incidence of fetal loss, especially in patients with SLE.
- Immunoglobulin therapy
  - The role of intravenous immunoglobulin in APS is not well understood but is thought to bind to endothelial receptors, prohibiting the interaction of aPLs with their targets. Immunoglobulin therapy may cause thrombosis especially in elderly patients or those with other risk factors for thrombosis.
- Immunosuppressive agents
  - Azathioprine, cyclophosphamide, and methotrexate, with or without corticosteroids, have been used in refractory APS, with decreased aCL titers and LA activity.

ADDITIONAL TREATMENT

General Measures

- Some studies suggest that combination therapy with anticoagulants and antiplatelet therapy has shown to be more effective in secondary prevention of stroke in APS patients (2)[C].
- Control of risk factors
  - Avoid smoking, excessive alcohol intake, and oral contraceptive pills.
  - Management of blood pressure.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Fish oil derivatives may help in preventing recurrent miscarriage in APS women.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Admission is required for the management of acute stroke or neuropsychiatric symptoms.

ONGOING CARE

PATIENT-MONITORING

- Patients should be reevaluated for new neurological complaints. Those on warfarin require routine monitoring of coagulation parameters.

PATIENT EDUCATION

- Patients should be educated regarding symptoms and signs of stroke and to consult with their physician regarding treatment or monitoring during pregnancy.

PROGNOSIS

- The disease duration is thought to be longer in secondary APS. The rate of recurrence of stroke or transient ischemic attack in patients with APS is 35–50%.
- A long-term study of primary APS patients showed that 8% develop SLE, 5% developed lupus-like disease, and 1% developed myasthenia gravis.

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See Also (Topic, Algorithm, Electronic Media Element)

- Hughes' syndrome
- Asherson's syndrome

CODES

ICD9

- 289.81 Primary hypercoagulable state
- 434.91 Cerebral artery occlusion, unspecified with cerebral infarction
- 435.9 Unspecified transient cerebral ischemia

CLINICAL PEARLS

- APS is associated with arterial and venous thrombosis.
- APS may be treated with antithrombotics or anticoagulants.
- Treatment is important in order to avoid sequelae of the condition including stroke and fetal loss.

ARACHNOIDITIS

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BASICS

DESCRIPTION
Arachnoiditis is defined as nonspecific inflammation of the arachnoid membrane, the middle layer of the meninges. It is classically caused by irritant, infectious, or foreign body exposure of the spinal cord subarachnoid space. Lumbosacral arachnoiditis is a continuum ranging from clinically minimally symptomatic thickening of the arachnoid membrane to symptomatic progressive adhesive scarring with associated sensory and motor disturbances in the legs, urinary, bowel and sexual deficits due to tethering effect on the spinal cord.

EPIDEMIOLOGY
- Incidence of 1.6%
- Race
  - – No demonstrated ethnic predominance
- Age
  - – Risk increases with age due to proportionately increased degenerative lumbar spine disease
- Sex
  - – Men more often affected than women

RISK FACTORS
- Myelography employing oil-based agents
- Postoperative lumbar spine wound infection
- Repeated lumbar surgery
- Congenital spinal stenosis
- Intrathecal or epidural injections
- Spinal anesthesia
- Epidural blood patches

Pregnancy Considerations
- None

ETIOLOGY
- Arachnoiditis is associated with heightened rostrocaudal CSF pulse waves directed into the spinal cord
- Elevated intramural pressures and decreased compliance of the subarachnoid space favor CSF flow into the spinal cord through perivascular spaces
  - – Cavitary injury
  - – Syrinx formation
  - – Compression by collagen bands and scar tissue with resultant myeloradiculopathy
- Histopathological changes
  - – Fibroblast proliferation
  - – Collagen deposition causing adhesions
  - – Obliteration of the subarachnoid space due to calcified scar tissue

COMMONLY ASSOCIATED CONDITIONS
- Repeated lumbar spine surgery
- Ankylosing spondylitis

DIAGNOSIS

HISTORY
- Chronic persistent pain in the lower back and legs
- Numbness, tingling, or other bizarre sensations in the legs
- Severe shooting pains in the legs
- Urinary frequency, urgency, bladder and bowel incontinence, and sexual dysfunction

PHYSICAL EXAM
- Low-grade fever
- Unilateral or bilateral leg and back hyperesthesia that increases with activity, straight-leg raising, and sciatic notch palpation
- Spasms and cramps
- Limitation of spinal flexion and extension
- Deep tendon reflex changes in the legs

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
There are no reliable blood or CSF tests to diagnose arachnoiditis.

Imaging
- Gadolinium-enhanced MRI employing axial T1-weighted sequences reveals clumping of multiple nerve roots while T2-weighted sequences are more useful for advanced fibrosis and more widespread adhesions that have the appearance of a mass lesion. Three MRI patterns can be discerned:
  - – Central (type 1) with roots clumped to the center of thecal sac
  - – Peripheral (type 2) with roots adherent to the margins of the thecal sac
  - – Unilateral (type 3) with adherent roots to the thecal sac that resemble a soft tissue mass
- Conventional MR may be augmented for high-resolution T2 3D images:
  - – Constructive interference steady state (CISS) imaging employing gradient echo sequences to a stimulated T2 echo
  - – True fast imaging with steady state precession (FISP) sequences acquired with differing RF pulses
  - – CISS imaging and myelographic MRI with TrueFISP detects nerve root details, neural tethering, subarachnoid adhesions, and cavity (syrinx) formation
  - – Improves selection of patients for surgery
- Patients with incidental asymptomatic arachnoiditis on neuroimaging should avoid intraspinal interventions

Diagnostic Procedures/Other
Lumbar CSF to exclude concomitant infection

DIFFERENTIAL DIAGNOSIS
- Herniated nucleus pulposis (HNP)
- Degenerative disk disease
- Chronic back pain
- Infection
- Lumbar sprain
- Metastatic bone disease
- Lumbar osteopenia
- Paget's disease
- Congenital spinal anomalies
- Multiple myeloma

TREATMENT

MEDICATION

- Gabapentin (Neurontin), 100 mg PO t.i.d.
  - Increase by 100 mg PO t.i.d. every 2–3 days to maximum of 2400–3600 mg
- Amitriptyline (Elavil) 25 mg PO q.h.s.
  - Increase by 25 mg PO q.h.s. every 2–3 days to a maximum of 100 mg PO q.h.s.
- Contraindications: Intractable pain
- Precautions
  - Gabapentin: Renal insufficiency
  - Tricyclic antidepressant mediated orthostatic intolerance and cardiac arrhythmias
- Adjunctive measures and alternative agents
  - Muscle relaxant for muscle spasm

ADDITIONAL TREATMENT

General Measures

- Since arachnoiditis responds poorly to therapy, it should be considered a chronic condition emphasizing prevention of worsening and supportive care treatment measures.
- Treat disorders that may worsen arachnoiditis such as HNP and concomitant focus of spinal infection.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Anti-inflammatory and analgesics
  - Education
  - Behavior modification
  - Acupuncture
- Adjunctive treatment
  - Dorsal column stimulation
  - Transcutaneous electrical nerve stimulation (TENS)
  - Intrathecal preservative-free hyaluronidase, but is not FDA approved

SURGERY/OTHER PROCEDURES

- Appropriate surgical patients are probably those with progressive neurological deficits, refractory pain, and potential for surgical remediation employing microscopic neurosurgery for decompression and lysis of scar tissue
- Long-term symptomatic relief <50%
- Unfavorable prognosis when arachnoiditis is most advanced

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Treatment is generally outpatient
- Admission reserved for those with intractable pain and acute change in neurological status

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Regular clinical follow-up in all patients
- Serial neuroimaging for those with unstable neurological function or complaints

PATIENT EDUCATION

- National Organization for Rare Disorders, Inc. (NORD), P.O. Box 8923, New Fairfield, CT 06812-8923, USA; website: www.nord-rdb.com
- National Institute of Neurological Disorders and Stroke, 31 Center Drive, MSC 2540, Building 31, Room 8A16, Bethesda, MD 20892, USA; website: www.ninds.nih.gov

PROGNOSIS

- The majority of affected patients do not evolve from the condition at the time of diagnosis
- The majority of patients are able to ambulate and drive a car
  - Ability to return to full-time work is generally limited
  - A majority of patients need daily analgesic including narcotic medication

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See Also (Topic, Algorithm, Electronic Media Element)

- Lumbosacral adhesive arachnoiditis
- Chronic adhesive arachnoiditis
- Serous circumscribed meningitis
- Spinal arachnoiditis

CODES

ICD9

322.9 Meningitis, unspecified

CLINICAL PEARLS

- Arachnoiditis is a debilitating condition associated with chronic pain and significant disability.
- There is no cure, and treatment is focused on approaches to symptomatic pain relief.

ARSENIC POISONING

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David H. Garabrant, MD, MPH

BASICS

DESCRIPTION
Arsenic neuropathy is part of a systemic illness due to excessive exposure to this toxic metalloid in the form of inorganic arsenic. Arsenic has a long history of medicinal applications, but it is also a notorious homicidal or suicidal agent. The neurological consequences of recurrent or chronic intoxication are similar to those of acute poisoning.

EPIDEMIOLOGY
Incidence
Unknown

Prevalence
Unknown

RISK FACTORS
The primary risk factor is excessive arsenic exposure from some sources.

Genetics
There is no known predilection for race or sex.

GENERAL PREVENTION
Avoid access to arsenic-containing products.

Pregnancy Considerations
There is no known relationship with pregnancy nor any particular danger to the fetus at typical environmental concentrations.

PATHOPHYSIOLOGY
Arsenic is a general protoplasmic poison that interferes with cellular energy metabolism. Trivalent arsenic compounds (As^{III}) inhibit the tricarboxylic acid cycle and glycolysis by binding to enzymes' sulfhydryl groups. Pentavalent arsenic compounds (As^{V}) uncouple mitochondrial oxidative phosphorylation.

ETIOLOGY
- Homicidal and suicidal applications account for most cases of acute intoxication.
- Iatrogenic medicinal exposures (usually folk medicines).
- Inadvertent exposure to contaminated foods, beverages, water, or combustion fumes.

COMMONLY ASSOCIATED CONDITIONS
- CNS depression, encephalopathy, gastroenteritis, cardiomyopathy, cardiovascular collapse, chemical hepatitis, renal tubular necrosis, dermatitis with hyperkeratosis and hyperpigmentation, pancreatitis, and pancytopenia.
- Inorganic arsenic compounds cause hepatic angiosarcoma, lung cancer (by inhalation), skin cancer, and urothelial cancers (bladder and renal pelvis).

DIAGNOSIS

HISTORY
- Acute poisoning: Abdominal pain, vomiting, and diarrhea.
- Distal numbness and tingling, intense paresthesias, burning pain, muscle tenderness, and weakness develop 5–10 days later.
- Chronic poisoning: Malaise, weakness, loss of appetite, and weight loss.

PHYSICAL EXAM
- Peripheral signs: Profound length-dependent sensory loss, weakness (sometimes progressing to quadriplegia with respiratory failure), areflexia, and dysautonomia.
- CNS signs: Confusion, stupor, and coma.
- Neurological signs reflect the magnitude of exposure and progress for several weeks.
- Additional signs include Mees' lines (transverse bands in all nails appearing about 1 month after acute ingestion, limiting their usefulness) and pigmented dermatitis.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Arsenic is readily absorbed and rapidly excreted in the urine, reflecting the magnitude of exposure. A 24-hour urine collection is most reliable for establishing recent or ongoing exposure, not intoxication. Total urinary arsenic can be used as a screening test to rule out acute intoxication. Arsenic is rapidly cleared from the blood (half-life of about 60 hours), and blood levels are helpful only within days of acute poisoning.
- CSF protein is elevated (150–300 mg/dL) early in the course of neuropathy.
- Other laboratory abnormalities reflect systemic involvement and include abnormal liver function studies, pancytopenia, and basophilic stippling of red blood cells (RBCs) (a nonspecific but important indication of a toxic exposure).

Follow-up & special considerations
- If elevated total urinary arsenic is found, speciation into organic and inorganic forms (As^{III} and As^{V}) is important. The organic forms of arsenic that occur naturally at high levels in fish, shellfish, and seaweed are nontoxic but may result in elevated total urine arsenic levels. The inorganic forms, when elevated, may indicate suicidal, homicidal, or inadvertent poisoning. Inorganic arsenic is excreted unchanged as ionic arsenite (As^{III}), arsenate (As^{V}), and as their metabolites, monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) (1).
- Inorganic arsenic is bound to keratin, and remote exposures can be documented by the amount of arsenic present in hair or nails. External contamination must be excluded. Organic arsenic (from seafood) does not accumulate in hair.

Imaging
There are no specific imaging abnormalities. Chest x-ray film may demonstrate cardiomegaly.

Diagnostic Procedures/Other
- Nerve conduction studies (NCSs) at onset may include features suggestive of an acquired demyelinating neuropathy (2):
  - Motor responses showing abnormal temporal dispersion, partial conduction block, slow conduction velocity, and long distal latency.
  - Sensory responses may be of low amplitude or unobtainable.
- NCS and needle electromyography (EMG) findings progress to those of an axonal sensorimotor neuropathy, often with loss of distal responses and profuse fibrillation potentials.
- Sural nerve biopsy occasionally is required to exclude other considerations such as vasculitis.

Pathological Findings
- Nerve biopsy results are nonspecific and include a decreased number of myelinated fibers, with axons in varying stages of degeneration.
- Toxicology examination at autopsy (e.g., liver or kidney) can establish intoxication.

DIFFERENTIAL DIAGNOSIS
Neuropathies having similar features:
- Inflammatory: Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), HIV, confluent vasculitic mononeuritis multiplex, systemic lupus erythematosus (SLE).
- Metabolic: Acute porphyria.
- Dysimmune: Monoclonal gammopathy, Waldenström's macroglobulinemia, γ heavy-chain disease, cryoglobulinemia, Castleman's disease.
- Paraneoplastic: Lymphoma or occult malignancy.
- Other toxicants: Amiodarone, ara-C, carbon disulfide, disulfiram, methyl-butyl-ketone, *n*-hexane.

TREATMENT

MEDICATION
First Line
Activated charcoal in association with gastric lavage is used to treat acute intoxication. Diuresis should be maintained. Chelation is effective in acute poisoning if started within a couple of hours of exposure.

Second Line
By the time neurological signs develop weeks after a single toxic exposure, it is questionable whether chelation or related treatments (e.g., hemodialysis) influence the rate or extent of neurological progression or recovery. Further, the arsenic eliminated by chelation or dialysis may be negligible relative to that ingested or to that spontaneously excreted in urine. Nevertheless, the prompt use of chelating agents in acute, life-threatening arsenic intoxication is supported by experimental animal studies (3)[C].

- Chelation is not recommended for urinary inorganic arsenic levels below 50 μg/L.
- DMPS (2,3-dimercapto-1-propanesulfonic acid; unithiol), is recommended for urine levels above 50 μg/L in symptomatic patients, and for urine levels above 200 μg/L in asymptomatic patients, but it is not approved by the FDA.
- Treatment should continue until the urine arsenic is below 50 μg/L.
- Chelation following chronic, low-level inorganic arsenic exposure may not only be ineffective but possibly deleterious (3)[C].

ADDITIONAL TREATMENT

General Measures

- Establish the diagnosis and remove the patient from exposure, although removal from exposure frequently is impossible because most cases involve single massive exposures.
- The treatment of acute arsenic poisoning is beyond the scope of this section but may include gastric lavage, hemodialysis, and chelation (discussed above) to increase arsenic excretion.

Issues for Referral

- Possible pulmonary, cardiology, or renal medicine consultations.
- Psychiatry (if suicidal ingestion); social services or law enforcement (if homicidal); and occupational medicine (if environmental).
- Physical Medicine and Rehabilitation consultation

Additional Therapies

- Symptomatic treatment.
  - Painful paresthesias may require analgesic treatment.
- Adjunctive treatment.
  - Supportive care includes monitoring and management of respiratory function and prevention or treatment of infection, circulatory failure, and thromboembolism.
  - Intubation is generally required when the forced vital capacity (FVC) approaches 15 mL/kg, but elective intubation should be considered when there is a rapid decline in FVC, independent of the absolute level.
  - Autonomic dysfunction may require management of hypotension or cardiac dysrhythmia.
  - Acute renal failure may require hemodialysis.
  - Anecdotal reports suggest that therapeutic plasma exchange does not influence the course of neuropathy.
  - Physical therapy to prevent contractures and promote reconditioning

SURGERY/OTHER PROCEDURES

Not applicable, other than sural nerve biopsy

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Nothing specific for arsenic.

Admission Criteria

- Admission criteria reflect the type and severity of systemic involvement and the magnitude and rate of progression of the neuropathy.
- All patients with progressive quadriparesis, respiratory decline, or evidence of dysautonomia require hospitalization and monitoring.

IV Fluids

Fluid management as determined by presence of dysautonomia with fluctuating blood pressure and possible renal failure.

Nursing

Special precautions may exist due to the frequent association of suicidal or homicidal origin.

Discharge Criteria

Discharge is usually to a rehabilitation facility, depending on the magnitude of the residual impairment and deconditioning.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Arsenic neuropathy may progress for weeks, and monitoring is required for the development of respiratory distress or dysautonomia until a plateau is reached or improvement appears. Respiratory monitoring includes interval measurement of FVC. Arterial blood gases are poor indicators of impending respiratory failure. Autonomic dysfunction requires monitoring of vital signs for hypotension or cardiac dysrhythmia. Systemic manifestations, such as renal failure or hepatic dysfunction, usually appear early in the course, shortly after the resolution of the acute gastrointestinal syndrome.

PROGNOSIS

- For patients who survive the acute systemic illness, including the complications of respiratory support, the prognosis for recovery is good.
  - Bone marrow suppression resolves rapidly, as does the chemical hepatitis and other non-neurological features.
- The neuropathy becomes the most feared residual manifestation. The degree of axonal degeneration may be severe and recovery protracted.
  - Patients who remain respirator dependent and nonambulatory for months require long-term rehabilitation.
  - Neurological improvement occurs over years.

COMPLICATIONS

- Medical complications related to pulmonary, gastrointestional, hematologic, cardiac, or renal involvement.
- Neuromuscular residua are common.
  - Sensory and motor deficits, similar to those observed after severe GBS or other acute neuropathies.

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See Also (Topic, Algorithm, Electronic Media Element)

- Toxic neuropathy, arsenical polyneuropathy, neuropathy due to arsenic.

CODES

ICD9

- 357.7 Polyneuropathy due to other toxic agents
- 985.1 Toxic effect of arsenic and its compounds

CLINICAL PEARLS

- An acute gastrointestinal illness followed by a GBS-like neuropathy in the presence of pancytopenia—consider arsenic intoxication.
- Aside from the prompt use of gastric lavage and possibly chelating agents (if the diagnosis is recognized early in its course), there is no evidence that any specific treatments influence the progression or recovery of the neuropathy.
- The mainstay of initial treatment involves the general medical care of respiratory, autonomic, cardiovascular, and renal involvement.
- A 24-hour urine collection is most reliable for establishing arsenic exposure (not necessarily intoxication).
- Increased urine arsenic levels may reflect nontoxic organic arsenic from recent ingestion of some shellfish.

ARTERIOVENOUS MALFORMATION

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BASICS

DESCRIPTION
- An arteriovenous malformation (AVM) is a congenital vascular lesion consisting of a direct connection between arteries and veins without an intervening capillary bed.
  - AVMs are high-flow, low-resistance systems.
  - Growth of an AVM within the parenchyma leads to reorganization and displacement of functional tissue.
  - AVMs may involve the cerebral hemispheres (65%), deep midline structures (15%), or the posterior fossa (20%).

EPIDEMIOLOGY
Incidence
- Prevalence in the general population is 0.005–0.6% (1,2)
  - Mean age at diagnosis is 31.2 years with slight male predominance (55%)
  - Annual risk of hemorrhage among patients harboring an AVM is 2–4%
  - Lifetime risk (%) can be estimated by the formula: Risk (%) = 105 – the patient's age in years.
  - Risk factors for hemorrhage: Prior hemorrhage, smaller size, deep venous drainage, impaired venous outflow, infratentorial or deep brain location, presence of associated aneurysm, hypertension, pregnancy.

RISK FACTORS
Genetics
- Most AVMs are sporadic. However, patients with multiple AVMs frequently have an associated vascular syndrome (see "Commonly Associated Conditions").
  - Familial AVMs, defined as AVM occurrence in 2 or more relatives (up to third-degree relatives) in a family without any associated disorders, are very rare and have been linked to 5p13-q14, 15q11-q13, or 18p11 (3).

GENERAL PREVENTION
The only modifiable risk factor associated with AVM hemorrhage is hypertension and pregnancy.

PATHOPHYSIOLOGY
Estimates of mortality (5–30%) and morbidity (20–30%) from an AVM hemorrhage are lower than that from an aneurysm.

ETIOLOGY
- The precise etiology of AVMs is unclear and still up for debate.
- AVMs form during fetal development and may continue to grow after birth.

COMMONLY ASSOCIATED CONDITIONS
- Hereditary hemorrhagic telangiectasia
- Wyburn–Mason syndrome
- Sturge–Weber syndrome

DIAGNOSIS

HISTORY
- Hemorrhage and headache are the most common forms of presentation.
- Seizures are the second-most common presentation and can be partial or generalized.

PHYSICAL EXAM
- Patients may present with focal deficits from either hemorrhage into brain parenchyma or seizures.
  - If the hemorrhage is of sufficient size to cause mass effect, shift, or a global increase in intracranial pressure, patients may present with coma.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Platelet count, international normalized ratio, and PTT to assess for a coagulopathy; basic metabolic panel and CBC.
  - Type and screen in the event of an emergent procedure is required.

Follow-up & special considerations
For patients presenting with either seizure or hemorrhage in an area at high risk for the development of seizures (e.g. temporal lobe), checking serum antiepileptic drug levels may be appropriate.

Imaging
Initial approach
Noncontrast brain CT to evaluate for acute hemorrhage; may also show a partially calcified lesion extending towards the ventricles.

Follow-up & special considerations
- CT angiogram is of limited use.
- MRI is required to provide more information about the precise region of brain involved.

Diagnostic Procedures/Other
Catheter angiography remains the gold standard for fully interrogating an AVM including the identification of high-risk features and should be performed in every patient found to have an AVM.

Pathological Findings
- Gross appearance:
  - AVMs resemble a ball or tangle of red and blue vessels.
    - Frequently are cone-shaped lesions with the base at the cortical surface and the apex directed towards the ventricle.
    - Gliosis, fibrosis, and calcification may be present in the adjacent parenchyma which may also be stained with hemosiderin from prior hemorrhages.
    - Histology: Arteries are abnormally dilated with thinning and degeneration of the media and elastic lamina. Sclerotic tissue is present within the nidus. Veins are arterialized with wall thickening from cellular proliferation.

DIFFERENTIAL DIAGNOSIS
- Spontaneous intracerebral hemorrhage
  - Aneurysmal subarachnoid hemorrhage
  - Dural arteriovenous fistula

TREATMENT

MEDICATION
- N/A

ADDITIONAL TREATMENT
General Measures
- *Options should be individualized to each patient and include:*
  - *Expectant management*: Observation of some patients with asymptomatic AVMs may be appropriate, considering the natural history of relatively low morbidity associated with hemorrhage from AVMs.
  - *Early surgery*: For patients in a comatose state or rapidly deteriorating level of consciousness, with surgically accessible AVM, for whom hematoma evacuation would be beneficial.
  - Otherwise, late surgery (several weeks), once the hematoma has resolved and the possibility of partial AVM obscurement is no longer a possibility, is preferable.
  - Intraoperative or postoperative catheter angiography to verify AVM eradication.
  - *Radiosurgery*: Radiation damages to endothelial cells of the AVM, leading to cell proliferation and progressive lumen occlusion. It is generally reserved for surgically inaccessible lesions. Obliteration rates of 75–95% can be achieved for AVMs <3 cm in size. Advantages: Minimally invasive, low risk.
  - *Embolization*: Includes transarterial delivery of either *N*-butyl-2-cyanoacrylate (glue) or ethylene vinyl alcohol copolymer (Onyx) through selective catheterization of the arterial pedicle feeders. Cure is rarely achieved; embolization is used to reduce the size of the nidus prior to surgical resection or radiotherapy or to eliminate high-risk features such as an associated intranidal aneurysm.
  - *Multimodal treatment*: A combination of the above treatments.

Issues for Referral
Neurosurgical referral should be obtained for every newly diagnosed AVM.

SURGERY/OTHER PROCEDURES
Classically, risk of operative morbidity has been related to the Spetzler–Martin (SM) scale which scores AVM on 3 features for a grading score of 1 to 5 (4)[C].

AVM characteristic	Points
Size	
Small (>3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Location	
Noneloquent	0
Eloquent	1
Pattern of Venous Drainage	
Superficial only	0
Deep	1

- SM grades I–III: Morbidity 0–5%, mortality 0–4%
- SM grades IV–V: Morbidity 12.2–21.9%, mortality 11.1–38.4%
  – Recently, with the widespread adoption of adjunct treatment strategies, AVMs have been classified into a 3-tier system [C]:

Class	Spetzler–Martin grade	Management
A	I and II	Surgical Resection
B	III	Multimodal Treatment
C	IV and V	No Treatment*

*Exceptions for the treatment of class C AVMs include recurrent hemorrhages, progressive neurological deficits, steal-related symptoms, and AVM-related aneurysms or multi-stage radiosurgery.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- For patients presenting with hemorrhage, initial assessment should include establishing the ABCs (airway, breathing, circulation).
  – Raise the head of bed to 30 degrees
  – Strict blood pressure management to maintain SBP <160 mm Hg
  – Assess the neurological status
  – Repeat noncontrast brain CT in the first 4–6 hours
  – Admission to a neurological intensive care unit for close observation

Admission Criteria

For preoperative workup as needed

IV Fluids

Intravenous hydration with isotonic solution; avoid hypotonic infusions with dextrose.

Nursing

Hourly neurological assessments until the patient has stabilized. Strict blood pressure control with antihypertensive infusions as needed.

Discharge Criteria

Patients presenting with hemorrhage who will undergo delayed surgery can be discharged once their neurological status has been stabilized; repeat brain imaging demonstrates a stabilized intracerebral hematoma; catheter angiography has been performed and any high-risk features have been addressed; and blood pressure is managed on PO antihypertensive medication.

Pediatric Considerations

Any child with a spontaneous intracerebral hemorrhage should be considered to harbor an AVM until proven otherwise. All should undergo catheter angiography. AVM recurrence and de novo formation in pediatric patients is more common than adults, while the prognosis after hemorrhage is better than adults.

Pregnancy Considerations

AVM hemorrhage is a relatively common cause of intracerebral hemorrhage in pregnant women, occurring at a mean gestational age of 30 weeks. Women of childbearing age should be counseled to defer pregnancy until the AVM has been treated.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Follow-up imaging after treatment can be performed with serial MRI and catheter angiography. There is no standard of care for duration or frequency of follow-up imaging surveillance. Children under the age of 18 should be surveillance imaged for recurrence or de novo formation.

Patient Monitoring

Patients should be followed expectantly.

DIET

No specific diet.

PATIENT EDUCATION

Patients and their family members should receive education about signs and symptoms of AVM recurrence of hemorrhage as well as education on any medications including antiepileptic drugs that may be initiated.

PROGNOSIS

Related to the initial symptoms at presentation including hemorrhage and any neurological deficits that may occur during treatment or rehemorrhage. See Spetzler–Martin grade.

COMPLICATIONS

- Complications relate to rehemorrhage for AVMs that are followed expectantly.
- Complications may also occur during treatment of the AVM:
  – *Surgery*: Seizures, infarction, failure to fully resect the lesion requiring reoperation and rehemorrhage. Normal perfusion pressure breakthrough causing cerebral edema and rehemorrhage is a unique postoperative complication that can develop following the resection of an AVM. Since the AVM is a low-resistance shunt, adjacent brain parenchyma compensates by vasodilation of its arterial supply. Once the shunt is removed, the vasodilated arteries of the adjacent brain can become overloaded even in the presence of normal cerebral perfusion pressures.
  – *Radiotherapy*: Radiation injury to adjacent parenchyma and hemorrhage as the risk is reduced but not eliminated during the latent period between treatment and AVM obliteration.
  – *Embolization*: Arterial or venous infarction, hemorrhage, and radiation exposure during the angiographic procedure.

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CODES

ICD9

- 747.60 Anomaly of the peripheral vascular system, unspecified site
- 747.81 Anomalies of cerebrovascular system
- 448.0 Hereditary hemorrhagic telangiectasia

CLINICAL PEARLS

- Hemorrhages resulting from AVMs are associated with lower morbidity and mortality rates than from intracranial aneurysms.
- Treatment options for AVMs are individualized and complex.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

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BASICS

DESCRIPTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental syndrome with symptom onset typically by age 7, most often between ages 3 and 5. It is primarily characterized by two symptom types: (a) inattention and (b) hyperactive and impulsive behaviors. The DSM-IV (1994) categorizes ADHD into 3 major subtypes: (a) predominantly inattentive type, (b) predominantly hyperactive/impulsive type, and (c) combined type.

EPIDEMIOLOGY

Report rates of 3–7% within a school-aged population (1). Rates of ADHD diagnosis increased an average of 5.5% per year from 2003 to 2007, and the percentage of children with a parent-reported ADHD diagnosis increased by 22% during this same time period (2). ADHD occurs across cultures and genders. Boys (13.2%) > girls (5.6%). As of 2007, 2.7 million youth aged 4–17 years (66.3% of those with a current diagnosis) were receiving medication treatment for the disorder. About 60% of children have residual symptoms into adulthood. In adulthood, 5% of adults may have ADHD (3), and the gender ratio shifts to approximately 1:1 (4).

RISK FACTORS

- Family history of ADHD
- Significant environmental factors such as premature birth, *in utero* exposure to substances, lead exposure, and psychosocial adversity.
- Traumatic brain injury
- Neurologic disorders such as Tourette's syndrome and seizure disorder.
  - Factors, such as food additives (5) and environmental toxins, have been implicated but definitive scientific data substantiating such links are lacking.

Pregnancy Considerations

Pregnant women who smoke, ingest alcohol or other illicit substances, or deliver prematurely are at higher risk for having a child with ADHD.

ETIOLOGY

Exact etiology of ADHD is not yet known, perhaps due to diagnostic heterogeneity (6). Genome-wide association studies have been inconclusive (6–10). Structural and functional neuroimaging from patients with ADHD are inconclusive (11).

COMMONLY ASSOCIATED CONDITIONS

Approximately 65% of children with ADHD will have a comorbid psychiatric condition. Most common are oppositional/defiant disorder (40–50%; predominantly boys), anxiety and mood disorders (10–35%; predominantly girls), learning disabilities (30–40%), and conduct disorder (10%) (12). Children with untreated ADHD are at high risk for developing significant comorbidities as they age (4). Children with seizures and Tourette's may have ADHD. Adults with ADHD tend to exhibit comorbid depression, anxiety, and higher rates of substance abuse (13).

DIAGNOSIS

The first signs of ADHD in children are often observed in a school setting, with teacher complaints initiating a referral. Children with ADHD can be excessively active, unable to sit still, disruptive to others, loud, inattentive, distractible, unable to focus on a task at hand, and impulsive. Academic performance is often below expected for their age and IQ. Peer and interpersonal interactions are also impaired. Observational data from outside sources (e.g., teachers) are necessary for accurate diagnosis. No specific diagnostic criteria for adults with ADHD at present (14).

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

To date, none of the imaging modalities have been accepted as proven diagnostic methods (15).

Diagnostic Procedures/Other

In children, observational data are obtained from teacher and parent rating scales of childhood behaviors. Conners' Parent (CPRS) and Teacher (CTRS) Rating Scales are commonly used (16). The adult counterpart is the Conners' Adult ADHD Rating Scale (CAARS) (17).

DIFFERENTIAL DIAGNOSIS

Rule out other psychiatric conditions: Pervasive developmental disorders, obsessive-compulsive disorder, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections), other anxiety and mood disorders, especially bipolar disorder. Neurologic conditions, such as seizure disorder, head trauma, birth trauma, mental retardation, and Tourette's syndrome, must also be taken into consideration.

TREATMENT

MEDICATION

- Stimulants are considered first-line therapy in most cases. Approximately 70% of children with ADHD will have a therapeutic response to stimulant treatment. Of the 30% who do not get a good response, switching to a different stimulant will often result in efficacy. Studies also demonstrate that, for the majority of ADHD patients, efficacy from stimulant therapy is not achieved until reaching a methylphenidate (MPH) dose of at least 15–20 mg/day (equivalent amphetamine dose is 10 mg/day). Most treatments are approved for use in both adults and children.
- Long-acting stimulants are the treatment of choice over short-acting treatments for various reasons, including improved treatment compliance and more consistent drug delivery. Long-acting MPH treatments include: Concerta® (18–72 mg/day), Ritalin-LA® (10–60 mg/day), Metadate CD® (20–60 mg/day), Focalin XR® (5–30 mg/day), and Daytrana®, a transdermal system that delivers 10–30 mg/day of MPH depending upon size of the patch. Long-acting amphetamine-derived treatments include: Adderall XR® (10–40 mg/day) and Vyvanse® (Lisdexamfetamine, 30–70 mg/day). These medications are given once daily in the morning with a duration of approximately 9–12 hours.
- The short-acting MPH, Ritalin® (5–60 mg/day), is highly effective and available in generic form, but wears off in 3–4 hours, necessitating multiple dosing and possibly causing rebound of symptoms during wear-off. One form of MPH, *d*-MPH (Focalin®), is MPH minus the *l*-isomer and is purported to have fewer side effects than *d,l*-MPH. This comes in short-acting and long-acting formulations.
- Adderall® (2.5–40 mg/day) is a mixed amphetamine salts compound and is a commonly used short-acting stimulant available in generic form. It lasts about 6 hours. The side-effect profile for amphetamines, including Adderall, is somewhat higher than that for MPH.

Non-Stimulant Therapies

- α-Adrenergic agonists (clonidine, guanfacine) are second-line therapies that can have a synergistic effect when used in conjunction with stimulants (1). Intuniv® (long-acting guanfacine, 1–4 mg/day) is a once-daily ADHD medication approved for administration as a primary ADHD treatment and as adjunctive therapy to stimulants in children and adolescents aged 6–17.
- Both guanfacine (0.5–4.0 mg/day) and clonidine (0.1–0.3 mg/day) have short-acting generic versions that can be used effectively as add-on ADHD therapy. The clonidine patch provides 0.1, 0.2 or 0.3 mg/day. However, using these short-acting formulations to treat ADHD is considered an off-label use.

- Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor approved to treat children and adults with ADHD. Data has shown less robust efficacy than achieved with stimulant treatment; however, atomoxetine can be useful for those who cannot tolerate stimulants or as add-on therapy. Strattera® is dosed according to body weight: Patients weighing over 70 kg start at 40 mg dose and titrate up to 80 mg, up to a maximum of 100 mg. Those weighing up to 70 kg start at 0.5 mg/kg and titrate up to 1.2 mg/kg, up to a maximum of 1.4 mg/kg.
- For children with comorbidities, combination pharmacotherapy is often necessary (18,19).

Precautions

Common side effects of stimulants include loss of appetite, insomnia, headache, nausea, irritability, and depression. In general, stimulants are well tolerated, and side effects tend to be mild and wane over a few days after initiating treatment. Sleep disturbance and appetite loss should be carefully monitored and managed clinically if necessary. (Note: many children with ADHD have preexisting sleep disturbance unrelated to medication therapy.) Preschoolers with ADHD tend to require lower doses of stimulants than school-aged children (20). Long-term effects of stimulants are not well established. Abuse and diversion potential is limited with some longer-acting agents.

ADDITIONAL TREATMENT

General Measures

Educational accommodations are almost always required in addition to medication management of symptoms. Psychoeducational evaluations and individual education programs should be pursued via the school system. Although behavioral therapy alone typically is not effective in fully controlling ADHD symptoms, behavioral treatments are a powerful adjunct to management with medication.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - The most effective treatment of ADHD is multimodal and includes medication, academic or occupational accommodations, and behavioral interventions. The MTA (Multimodal Treatment Study of Children with ADHD) (21) demonstrated that when a multimodal approach to ADHD treatment was implemented, 68% of the subjects attained "normalized" behavior. Educational accommodations are necessary and implemented via the school system. For the vast majority of cases, drug "holidays" are neither necessary nor advisable.
- Adjunctive treatment
  - Cognitive behavioral therapy, parent training, social skills groups, occupational and physical therapy, and academic interventions may be needed depending upon the specifics of the case.
- Alternative therapies have not been validated as effective treatments and their use is not supported by well-controlled clinical studies at this time. However, athletic activities (such as karate, tennis) or organized team sports are a good outlet for excessive energy and can help improve socialization and should be considered for patients with ADHD as an adjunct to treatment.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission for evaluation of ADHD is rarely needed.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Monitor for side effects.

PATIENT EDUCATION

- CHADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder). Website: www.chadd.org
- ADDA (Attention Deficit Disorder Association). Website: www.add.org
- National Resource Center on AD/HD. Website: www.help4adhd.org
- NIH/NIMH has a web page devoted to diagnosis and treatment of ADHD. Website: http://www.nimh.nih.gov

PROGNOSIS

Highly variable, depending upon severity of comorbidities, environmental surroundings, and treatment compliance, especially for adults with ADHD (2).

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CODES

ICD9

314.01 Attention deficit disorder with hyperactivity

AUTISM

David Q. Beversdorf, MD

BASICS

DESCRIPTION
Autism is a condition characterized by delayed language, impaired social interaction, and stereotyped behavior with onset before age 3 years.

EPIDEMIOLOGY
Incidence
- The incidence of autism spectrum disorders [autism, Asperger syndrome, pervasive developmental disorder (PDD)] has been recently reported as 1 in 150, and subsequent reports have suggested an even higher incidence. There is no racial predilection known for autism, and the age of onset, by definition, is before the age of 3 years. There are 4–5 times as many males as females with autism.
- The incidence of autism is increased when a first-degree relative is affected. A modest percentage of cases of autism have been associated with a range of copy number variations and other mutations within genes associated with several neurotransmitter systems and genes involved with synaptogenesis.

Prevalence
Estimated at 30–60 cases per 10,000. Incidence is not precisely known as diagnosis was made less frequently in the past.

RISK FACTORS
Patients with fragile X syndrome or tuberous sclerosis have an increased incidence of autism. Preliminary evidence suggests perinatal stressors may be a risk factor as well as certain maternal immune markers.

Pregnancy Considerations
There are no known issues specific to managing autism during pregnancy.

Genetics
As above, a modest percentage of autism cases have been associated with a range of copy number variations and other mutations within genes associated with several neurotransmitter systems and genes involved with synaptogenesis. In general, a strong genetic component has been supported by a 60–92% concordance in monozygotic twins and a 5–10% risk in siblings. However, it is not monogenic and appears to be multifactorial.

GENERAL PREVENTION
There are no known preventative measures.

PATHOPHYSIOLOGY
The pathophysiology of autism is not fully understood, but active research is rapidly increasing our understanding in this area.

ETIOLOGY
As described above, the etiology is multifactorial, with a significant genetic component.

COMMONLY ASSOCIATED CONDITIONS
There is a high incidence of mental retardation with autism. There is also an increased incidence of seizures in patients with autism. A variety of behavioral disturbances are also associated with autism. Although frank macrocephaly is uncommon, there is a tendency toward a larger head size in autism.

DIAGNOSIS

HISTORY
- Signs and symptoms of autism develop by age 3 years, usually without a period of normal development previously (except in occasional patients in whom the development is normal in the first 1–2 years: Regression), in 3 domains:
  - Impaired social interaction: There is a lack of eye-to-eye gaze, blunted or abnormal facial expression, impaired use of social gesture, poor development of peer relationships (either lack of interest or lack of ability), lack of sharing enjoyment or interests with others, lack of social reciprocity, and inappropriate response to others' needs or distress.
  - Impaired communication: There is a delay in verbal output, impaired ability to build a conversation, stereotyped or repetitive language, monotone or otherwise abnormal prosody to speech, idiosyncratic use of language, and inability to understand subtleties of language (jokes and irony).
  - Restricted, repetitive, and stereotyped behavior: There is preoccupation with strange interests or interests held with an abnormal degree of intensity, inflexibility in rituals and routines, preoccupation with parts of objects, stereotyped motor behaviors, a restricted range of interests, and repetitive mimicry and a compulsion to line up objects or place them in a row.

PHYSICAL EXAM
Aside from direct observation of the behaviors associated with autism as described above, there are no examination findings specific for autism.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
There are no specific laboratory procedures for the diagnosis of autism, except possibly testing to exclude fragile X syndrome or other genetic syndromes. If pica is present, lead screening is indicated.

Follow-up & special considerations
Patients on neuroleptics need monitoring for metabolic issues associated with neuroleptic use.

Imaging
Initial approach
There are no imaging findings specific to autism, but some report cerebellar vermis hypoplasia. Imaging is performed to exclude other issues.

Follow-up & special considerations
Repeat imaging would be recommended if there is a change in neurological status (new onset seizure, change in neurological exam).

Diagnostic Procedures/Other
- Diagnosis is established by clinical evaluation by a child psychologist, child psychiatrist, pediatric neurologist, developmental pediatrician, or behavioral neurologist. The Autism Diagnostic Interview-Revised and or the Autism Diagnostic Observation Schedule are considered the gold standard clinical evaluation tools.
- EEG is recommended in cases of episodes suspicious for seizures or language regression.

Pathological Findings
There is no role for biopsy in autism. However, decreased aminobutyric acid (GABA) receptor density and various histological changes (differences in neuronal size, neuronal density, and denditic arborization) in limbic structures have been observed in postmortem samples.

DIFFERENTIAL DIAGNOSIS
- Asperger syndrome resembles autism with relatively preserved language
- Pervasive developmental disorder-not otherwise specified (PDD-NOS) describes the condition where features of autism are present, but the criteria for autism or Asperger syndrome are not met.
- Collectively, the related conditions of autism, Asperger syndrome, and PDD-NOS are referred to by some specialists as "autism spectrum disorder." The collective incidence of autism spectrum disorders has been reported as high as one in 150.
- Rett syndrome consists of normal development for the first 5–48 months, followed by deceleration of head growth, stereotyped movements (typically midline hand movements), axial incoordination, loss of language skills, and retardation. Only females are affected.

- Fragile X syndrome is a genetic disorder that can present with some autistic features.
- Landau–Kleffner syndrome consists of seizures originating in the language area, and occasionally this can resemble autism.
- Childhood-onset schizophrenia is characterized by early normal development followed by the development of schizophrenia and can sometimes resemble autism.
- Mental retardation sometimes can be difficult to distinguish from autism with mental retardation when retardation is sufficiently severe.

TREATMENT

MEDICATION

First Line

- Risperidone and aripiprazole have been approved by the FDA for autism-related irritability. However, patients must be monitored for metabolic issues associated with atypical neuroleptic use.
- In general, symptomatic treatment is recommended for any other neuropsychiatric symptoms sometimes associated with autism, such as obsessive compulsive behavior, anxiety, depression, behavioral disturbances, self-injurious behavior, mood stabilization issues, and sleep disturbances.

Second Line

New agents are currently under study, exploring the potential avenues for treatment targeting the GABAergic, glutamatergic, adrenergic systems, and the potential role of oxytocin.

ADDITIONAL TREATMENT

General Measures

- Early and intensive behavioral intervention appears to be critical to optimizing development of functional ability in autism. This should be initiated as soon as possible after diagnosis and continued throughout schooling.
- Appropriate vocational rehabilitation services would be needed for those with sufficient cognitive ability to handle work, and social supports for the families.

Issues for Referral

Referral would be recommended for questions regarding the diagnosis, behavior management, management of neurological comorbidity and questions regarding whether the autism is associated with a broader syndrome which might affect treatment (genetic syndrome, mitochondrial, presence of dysmorphic features).

Additional Therapies

Occasionally, behavior disturbances can result from gastrointestinal disorders, so if there is any suggestion that this is the case, referral may be indicated.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Behavioral therapy, sensory integration occupational therapy, auditory integration therapy, speech therapy, and cognitive therapy are options, as is vocational rehabilitation for older and higher functioning individuals.
- Families in desperation to seek a solution to the tremendous impact of autism often seek unproven therapies. It is important for the physician to be aware of these as it might impact care.

SURGERY/OTHER PROCEDURES

There are no surgical measures specific to autism.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Admission specifically for autism is usually associated with severe behavior disturbances, so ensuring patient safety would be the initial goal.

Admission Criteria

There are no admission/discharge criteria specific to autism, other than if the behavior disturbance makes the patient a threat to self or others.

Nursing

Ensuring patient safety is the top nursing priority. Consulting with someone knowledgeable about autism would be of benefit.

Discharge Criteria

Discharge is possible when the patient is no longer a threat to self or others.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

As the patient grows and matures, it is critical for the family to have optimal access to all educational and support avenues appropriate for the patient at their level.

Patient Monitoring

Monitoring should include follow-up visits to monitor effects of drugs used to treat neuropsychiatric conditions associated with autism and to monitor for adequacy of behavioral intervention strategies.

DIET

Patients with autism occasionally have restricted diets due to their refusal to eat foods beyond a narrow range. Parents also occasionally place patients on restrictive diets in hopes of a therapeutic benefit. Physicians need to be aware of the potential impact of these on the patient's nutritional status.

PATIENT EDUCATION

- Families should be informed of the importance of early intervention and should be given information on regional chapters of the Autism Society of America to help them locate other appropriate resources and support.
- Autism Society of America, 7910 Woodmont Avenue, Suite 300, Bethesda, MD 20814-3015. Phone: 1-800-3, website: www.autism-society.org
- Families should be given access to all local and regional resources which might improve access to therapeutic, educational, and social support resources.

PROGNOSIS

Individuals with autism often slowly improve with regard to their impairments as they develop through school years and adolescence, but seldom improve to the point of independent functioning. Occasional patients have a behavioral decline during adolescence, often associated with difficulty handling the increase in complexity of social interaction in adolescence. Improvement is the greatest in individuals with better language skills and higher overall intelligence.

COMPLICATIONS

Aside from the medical issues mentioned above (sleep disturbances, increased risk of seizures, psychiatric comorbidity, and occasional gastrointestinal disturbances), the main concern is monitoring patients regarding personal safety, as they often do not have the judgment to function safely in their environment.

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See Also (Topic, Algorithm, Electronic Media Element)

- Asperger syndrome
- Autism
- Infantile autism
- Kanner's syndrome
- Progressive developmental disorder

CODES

ICD9

- 299.0, Autistic disorder, Infantile autism, Primary autism
- 299.8, Other pervasive developmental disorders (Asperger disorder)
- 299.9, Pervasive developmental disorder NOS

CLINICAL PEARLS

The DSM-V will soon come out, which will group autism, Asperger syndrome, and PDD-NOS into 1 group, autism spectrum disorders (ASD).

BACK PAIN, SPONDYLOSIS, LUMBAR CANAL STENOSIS

P. Mark Li, MD, PhD

BASICS

DESCRIPTION

Lumbar spondylosis (LS) refers to degenerative changes including disk disease, osteophyte formation, facet joint disease, and ligamentous laxity, which can cause stenosis, segmental instability, and/or neurological deficits. Lumbar canal stenosis (LCS) refers to a decrease in total cross-sectional area of the spinal canal, lateral recess, or neural foramen. Other commonly used terms are spondylolisthesis (forward position of 1 vertebral body in relation to the vertebral body below it) and spondylolysis (congenital or degenerative/posttraumatic absence of the pars interarticularis between the superior and inferior articular processes, frequently associated with spondylolisthesis).

EPIDEMIOLOGY

- About 80% of the adult population suffers from low back pain at some point during their lifetime. LS is 1 of the most frequent causes of low back and/or leg pain. The prevalence of LS by MRI studies ranges from 33% at age 20 years to 95% in women aged >70 years. About 95% of males and 80% of females aged >65 years show MRI evidence of LS. Plain radiographic evidence of LS is seen in about 80% of patients aged >65 years.
- Spondylosis is most frequent in the cervical and lumbar spine, the most mobile regions of the spinal column.
- LCS most commonly involves the L4-5 level, followed by L3-4, L2-3, L5-S1, and L1-2.
- Age
  - Both LS and LCS are seen with increasing frequency after the fifth decade of life.
- Sex
  - Males are affected more often than females.

RISK FACTORS

Prior trauma

Pregnancy Considerations

Back pain is frequent during the third trimester of pregnancy (due to additional abdominal weight) and usually resolves postpartum.

ETIOLOGY

- LS results from a complex process of disk degeneration, bilateral facet joint arthropathy, and osteophyte formation. Facet joint cartilage destruction and capsular laxity can lead to subluxation and segmental lumbar instability
- LCS:
  - Congenital: Idiopathic/achondroplastic
  - Acquired: Degenerative stenosis
    - Iatrogenic: Post lumbar fusion stenosis
    - Metabolic: Paget's disease, fluorosis
    - Posttraumatic
- Location of LCS: Central canal/lateral recess/foraminal stenosis/far-out foraminal stenosis (compression between L5 transverse process and sacral ala)
- Narrowing of spinal canal diameter in extension by hypertrophied facets, buckling of ligamentum flavum, and protruding intervertebral disk aggravates symptoms, which are relieved by flexion
- Etiology of neurogenic claudication: Narrowed canal prevents vasodilation of blood vessels with activity, causing ischemic neuritis of the nerves

COMMONLY ASSOCIATED CONDITIONS

Cervical canal stenosis

DIAGNOSIS

- Pain from LCS can be grouped into 3 general categories: *Midline low back pain* (lumbar instability, paraspinal muscle spasm); *radiculopathy* (nerve/nerve root irritation secondary to lateral recess and/or foraminal stenosis); *neurogenic claudication* (pain; sensory and/or motor changes when standing and walking, relieved with rest and/or flexion).
- Absent or minimal neural signs. Neural deficits are reproducible with walking in LCS.
- Patients usually stoop forward to relieve symptoms (stoop sign) and may use a shopping cart to maintain flexion. Extension is limited and painful.
- Walking *down* stairs (i.e., extension) is more painful in LCS/neurogenic claudication; walking *up* stairs (i.e., flexion, exertion) is more painful in vascular claudication.
- Patients tend to walk with slight hip and knee flexion (simian stance).
- Straight-leg raising test usually is negative.
- Loss of lumbar lordosis is common.
- Examination of hip joints, abdomen, and peripheral vessels should be performed to rule out other etiologies or coexisting pathologies.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

CBC and differential; sedimentation rate; C-reactive protein to rule out infection or inflammatory process

Imaging

- Plain radiographs: Sagittal diameter of lumbar canal (normal 15–25 mm) is reduced below 12 mm in most patients with LCS. Lateral recess diameter (normal 3–5 mm) is reduced below 3 mm in patients with lateral recess stenosis. Foraminal height is reduced below 15 mm in patients with foraminal stenosis. Flexion-extension dynamic x-ray films may show subluxation of the involved spinal segments. Findings in LS include disk space narrowing, facet joint hypertrophy, LCS, foraminal stenosis, subluxation, and scoliosis.
- Myelography often reveals multiple areas of contrast compression (hourglass constriction). With lateral recess stenosis, myelography shows root sleeve cutoff. Complete block produces a characteristic paint brush appearance.
- CT without contrast provides details of the bony anatomy and may provide information necessary for complex cases. Patients with previous lumbar instrumentation may show less artifact on CT than MRI; those with implanted devices (e.g., cardiac pacemakers) may be limited to CT or CT myelography.
- MRI is the preferred imaging modality. It is noninvasive, highly sensitive, provides excellent soft-tissue resolution and shows the extent of neural compression without risk of radiation. Asymptomatic degenerative changes may be seen in 60% of patients on MRI. Hypertrophied bone is low signal on T1 and T2 images, whereas hypertrophied ligamentum flavum is intermediate signal on T1 and T2 images.

Diagnostic Procedures/Other

Neurophysiologic studies [EMG and nerve conduction velocity (NCV)] can be very helpful in difficult cases of suspected peripheral neuropathy, nerve root compression, or paraspinous muscle syndromes. Somatosensory-evoked potential recording also can be helpful, especially when performed before and after a walking stress test.

DIFFERENTIAL DIAGNOSIS

- Vascular claudication
- Referred pain from leg, hip joint disease
- Lumbar disk disease
- Peripheral neuropathy (e.g., diabetes)
- Vertebral osteomyelitis
- Spinal tumors (bone tumors/metastasis)
- Myofascial syndromes

TREATMENT

MEDICATION

- Nonsteroidal antiinflammatory drugs: Ibuprofen, naproxen, celecoxib, rofecoxib
- Contraindications: Known history of gastrointestinal bleeding, hypersensitivity reaction to nonsteroidal antiinflammatory drugs, bronchial asthma
- Precautions: History of peptic ulcer, or renal, hepatic, or hematologic disease
- Alternative drugs
  – Narcotic medications can be helpful for severe pain and muscle relaxants for muscle spasms.

ADDITIONAL TREATMENT

General Measures

Conservative measures are helpful in most patients with LS and about 50% of patients with LCS. Physical therapy (spinal exercises, traction, heat or cold pack application), weight reduction, or spinal epidural/foraminal injections can be tried in patients with LS or LCS. Flexion spinal exercises, which decrease lumbar lordosis, can be useful in patients with LCS. In LS patients with facet joint pain, facet joint injections are a useful option. A well-fitted lumbosacral corset can be helpful for low back pain secondary to instability.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  – See "General measures"
- Adjunctive treatment
  – See "General measures" and surgical measures

SURGERY/OTHER PROCEDURES

Indications for surgery include cauda equina syndrome, progressive neurologic deficits, and severe unrelenting pain. The onset of bowel or bladder dysfunction (incontinence or retention) is a surgical emergency, because permanent impairment in bowel or bladder function can quickly ensue. Surgery often is required in the presence of severe canal stenosis segmental instability or spondylolisthesis with unremitting/progressive pain. Decompressive surgery (laminectomy, laminoforaminotomy, window laminotomy) of the stenotic segments by either open or endoscopic techniques is effective in most cases. Fusion should be considered for severe unrelenting back pain due to lumbar instability or when stenosis requires complete excision of more than 1 facet joint at a particular level.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Emergent admission (and usually surgical treatment) is indicated for bowel or bladder dysfunction, sudden progressive neurologic deficits, or cauda equina syndrome.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be encouraged to keep a journal of activities performed and medication taken in order to have objective evidence of trends toward improvement or deterioration. Follow-up neurological assessment should include, in addition to the standard motor and sensory examinations, the claudication distance in cases of LCS to assess progression of disease in functional terms. Serial EMG and/or NCV studies can be helpful to assess progression or improvement in selected cases.

PATIENT EDUCATION

Physical therapy can be very helpful in educating the patient about low back care, activities of daily living, risk avoidance, and use of walkers and other aids.

PROGNOSIS

About 50% of cases experience progressive worsening; 50% tend to be stationary or improve. About 80% of patients will have a satisfactory outcome after surgery; limited decompressive procedures (e.g., window laminotomy) have a quicker recovery time than more extensive decompressive surgery and/or fusion procedures. Operative morbidity ranges from 1–2% up to 15%, depending upon the extensiveness of the procedure performed, initial versus reoperation, and the surgical risk status of the patient (e.g., age, medical conditions).

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

Degenerative disk disease

CODES

ICD9

- 721.3 Lumbosacral spondylosis without myelopathy
- 724.02 Spinal stenosis, lumbar region, without neurogenic claudication
- 724.2 Lumbago

BELL'S PALSY

Ronnie Bergen, MD

BASICS

DESCRIPTION

- Facial palsy is a syndrome of weakness of the facial musculature that may be due to a number of causes. Bell's palsy was traditionally considered to be idiopathic. It describes usually unilateral facial weakness due to disease of the seventh nerve of various causes.

EPIDEMIOLOGY

Incidence

- 20–30 per 100,000 annually.
- Incidence increases with age, highest over age 70.

RISK FACTORS

- Diabetes mellitus
- Multiple sclerosis in younger patients

Genetics

- No genetic predisposition known.

PATHOPHYSIOLOGY

- Imaging and surgical intervention demonstrate swelling and entrapment of facial nerve in facial canal.

ETIOLOGY

- Herpes Simplex Virus Type I (HSV-1): Approximately 70% of cases. Endoneurial fluid cultures have been positive for HSV-1.

COMMONLY ASSOCIATED CONDITIONS

- Diabetes Mellitus

DIAGNOSIS

HISTORY

- Acute or subacute facial weakness, often preceded by retroauricular pain and/or dysgeusia.
- Half of patients reach maximal paralysis 48 hours after onset, the vast majority of cases by 5 days.

PHYSICAL EXAM

- Unilateral paralysis of facial muscles, partial or complete
- Subjective "numbness" or hypesthesia present in the branches of the ipsilateral trigeminal nerve.
- Ipsilateral excess tearing or insufficient tearing
- Ipsilateral hyperacusis or distortion of sound with paralysis of the stapedius muscle (one-third to one-half of cases)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Complete blood count if infection suspected.
- Hemoglobin A1C to screen for diabetes mellitus
- Lyme serology if history of tick bite, erythema migrans or arthralgias

Follow-up & special considerations

- Bilateral or recurrent palsies warrant lumbar puncture.

Imaging

Initial approach

- Routine imaging not recommended,
- For cases of trauma, recurrent facial palsy, slowly progressive facial palsy, abnormal examination or failure to show any improvement of paresis within 3 months, MRI and CT of the temporal bone and posterior fossa and MRI of the parotid glands should be done with and without contrast.
- Imaging recommended for bilateral facial nerve palsy.

Follow-up & special considerations

- 3T MRI failed to show any value for predicting outcome.

Diagnostic Procedures/Other

- Nerve conduction and EMG of the facial nerve may be used prognostically after several days to distinguish a temporary conduction defect from axonal injury.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of idiopathic facial palsy includes, in addition to traumatic injury, the numerous diseases that can injure the facial nerve by inflammation, infection, infiltration, or compression.
- Neoplastic:
  - Carcinomatous meningitis
  - Leukemic meningitis
- Tumors (primary and metastatic) of the base of the skull:
  - Parotid gland tumors
  - Cranial nerve VII neurinoma
  - Cranial nerve VIII Schwannoma
- Inflammatory or Demyelinating:
  - Sarcoidosis
  - Guillain-Barre syndrome
  - Multiple Sclerosis
  - Other granulomatous diseases
- Infectious
  - HIV infection
  - Tuberculosis
  - Lyme disease
  - Ramsay-Hunt syndrome (due to varicella-zoster infection of the geniculate ganglion with vesicles in the external auditory meatus, facial palsy, and other neurological findings)
  - Leprosy

- Idiopathic:
  - Melkersson-Rosenthal syndrome (recurrent facial paralysis with facial edema, especially labial)
  - Idiopathic cranial polyneuropathy
  - Mobius syndrome
- Trauma:
  - Facial injuries
  - Temporal bone fractures
  - Birth trauma
  - Latrogenic (post-surgical)
- Metabolic:
  - Diabetes mellitus
- Pregnancy: Third trimester
- Medications:
  - Interferon alpha
  - Linezolid
  - Vaccines (influenza, and hepatitis)
- Supranuclear facial palsy:
  - Cerebrovascular accident
  - Pontine mass lesion

TREATMENT

MEDICATION

First Line

- Corticosteroids: Prednisone, best within 72 hours of symptom onset. Several different regimens proposed, ranging from 80 mg daily tapering in 20 mg increments over 10–12 days to 30 mg twice daily for 5 days with gradual taper to 5 mg daily by day 10.

Second Line

- Use of anti-viral agents controversial. No benefit of anti-viral medications either alone (without corticosteroids) or in combination with corticosteroids over corticosteroids and placebo except possibly in most severe cases.

ADDITIONAL TREATMENT

General Measures

- Protection of the eye with patching, taping, and lubricating agents

Issues for Referral

- Recheck after 1 month. Severe cases with poor eyelid closure should be seen monthly for 6–12 months to look for corneal abrasions (Ophthalmology referral).

Additional Therapies

- Physical therapy (e.g., electrostimulation, exercises): No evidence for either benefit or harm.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Abobotulinum toxin A for chemodenervation of eyelid muscles to induce protective ptosis has been tried.

SURGERY/OTHER PROCEDURES

- Surgical decompression of the facial nerve for traumatic paralysis.
- Surgery for idiopathic facial nerve palsy: Insufficient evidence to decide whether surgical intervention is beneficial or harmful.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Continued failure to recover eyelid closure warrants ophthalmological referral.

DIET

- n/a except diabetes.

PATIENT EDUCATION

- Eye protection.
- www.ninds.nih.gov/disorders/bells/bells.htm

PROGNOSIS

- High rate of spontaneous recovery (full, approximately 66%, moderate 10–12%, poor, 5%). Recovery typically begins in 3 weeks, may continue 6–9 months. Early recovery of some motor function within the first week is a very favorable prognostic sign.
- Better prognosis with: Incomplete paralysis, younger age group, non-diabetic.
- Presence of pain has no prognostic value, but severe pain associated with Ramsay-Hunt syndrome.
- Imaging typically abnormal, but no prognostic value in idiopathic palsy.

COMPLICATIONS

- Permanent facial weakness and contractures.
- Aberrant regeneration with synkinesis ("crocodile tears").
- Corneal abrasion.
- Postparalytic hemifacial spasm.

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CODES

ICD9

351.0 Bell's palsy

CLINICAL PEARLS

- Corticosteroids helpful for retro-auricular pain even if after 72 hours.
- Typical cases do not require neuroimaging.
- Consider new onset Multiple Sclerosis or Lyme disease in the differential in young patient presenting with Bell's palsy.

BOTULISM

Sara Khan, MD
Kerry H. Levin, MD

BASICS

DESCRIPTION

Botulism is an acute paralytic disease caused by a potent neurotoxin produced by the gram positive, anaerobic, spore-forming bacterium *Clostridium botulinum*. Currently, five clinical forms are recognized:

- Foodborne (classic).
- Infant.
- Wound.
- Hidden (adult form of infant botulism).
- Inadvertent.

EPIDEMIOLOGY

According to the CDC, an average of 110 cases of botulism are reported annually in the U.S. Approximately, 65–70% are infant and 25% foodborne. These numbers are thought to be an underestimate due to under reporting. Recently, there has been an increase in wound botulism mostly amongst IV drug users. The number of cases of hidden and inadvertent botulism secondary to *botulinum* toxin injections remains very small.

RISK FACTORS

- Foodborne:
  - Ingestion of toxin in food contaminated with toxin producing bacteria.
  - Home canned foods.
  - Contaminated fish and seafood (Type E).
  - Low acidity, low oxygen and high water content favor spore germination.
  - Exotoxin is heat labile, but spores are heat resistant.
- Infant:
  - Immature infant GI tract more susceptible to colonization by *C. botulinum* due to lack of protective intestinal flora and bile acids. Ingested spores germinate in GI tract.
  - High spore density environment.
  - Weaning from breast feeding?
  - Introduction of formula?
  - Spores can be found in honey (Type B) but due to increased awareness, now associated with only 20% of infant cases.
- Wound:
  - Contamination of traumatic or surgical wounds with environmental spores. Skin and nasal abscesses due to IV drug and cocaine abuse respectively.
- Hidden (undetermined or unclassified):
  - Adult form due to GI tract abnormality, e.g., achlorhydria, Crohn's disease, recent surgery, or antibiotic use.
  - Abnormal GI environment allows germination of spores and formation of toxin.
- Inadvertent:
  - Due to injection of therapeutic *botulinum* toxin A and B.

Pregnancy Considerations

Cases of maternal botulism have not been transmitted to the fetus. Therapeutic injections of *botulinum* toxin have no adverse fetal effects. The role of breast feeding is not clear.

GENERAL PREVENTION

- Proper processing and storage of food to kill spores.
- pH <4.5, temperature >121°C or <3.3°C.
- Toxin can be inactivated by heating food to 100°C for 10 minutes.
- Avoid feeding honey to infants <1 year of age.

PATHOPHYSIOLOGY

- Paralysis caused by failure of release of acetylcholine from nerve terminal (presynaptic) membrane.
- Toxin is internalized by presynaptic membrane and cleaves proteins required for docking of synaptic vesicles on nerve terminal membrane; thereby, inhibiting the release of acetylcholine.
- Toxins A, C, and E cleave protein SNAP-25; types B, D, F, and G cleave synaptobrevin; type C cleaves syntaxin.
- Also inhibits autonomic synaptic transmission.

ETIOLOGY

- Most potent toxin known.
- Most cases of foodborne caused by types A and B (E associated with seafood).
- Infant botulism usually caused by types A and B.
- Wound botulism caused by type A.

DIAGNOSIS

HISTORY

- Foodborne
  - Onset of symptoms 2–35 hours after ingestion.
  - Early GI symptoms: nausea, vomiting, diarrhea.
  - Oculobulbar symptoms: blurred vision, diplopia, ptosis, opthalmoplegia, dysarthria, dysphagia.
  - Descending weakness.
  - Respiratory difficulty.
  - Autonomic instability: Constipation, urinary retention, dry mouth, orthostatic hypotension and pupillary dysfunction.
- Infant:
  - Usually occurs in infants <6 months of age.
  - Incubation period 3–30 days.
  - Early signs: Constipation, weak cry, poor sucking or feeding.
  - Progression to loss of head control, limb and bulbar weakness, respiratory distress.
- Wound and Hidden:
  - Similar to foodborne except lack of early GI symptoms.
  - Mean incubation period 7.5 days.
- Inadvertent:
  - Weakness in the area of injection or generalized weakness with autonomic dysfunction.

PHYSICAL EXAM

- Pupillary dilation that does not respond to light stimulus.
- Ophthalmoparesis.
- Ptosis.
- Diffusely low tone.
- Descending proximal to distal weakness. Can be asymmetric.
- Reflexes usually spared.
- Respiratory difficulties.
- Afebrile.
- No sensory findings.

DIAGNOSTIC TESTS AND INTERPRETATION

Diagnostic Procedures/Other

- Diagnosis is based on clinical features and electrodiagnostic studies as laboratory confirmation is usually delayed.
- Electrodiagnostic studies:
  - Reduced compound muscle action potential (CMAP) amplitude of affected muscles with normal conduction velocities.
  - 30–100% increment of CMAP with rapid repetitive stimulation (50 Hz) or isometric exercise. Facilitation is less than that seen in Lambert–Eaton myasthenic syndrome (LEMS), but can be more prolonged.
  - Small polyphasic voluntary motor units with spontaneous denervation potentials can be seen on needle electrode examination.
  - No response to acetylcholinesterase inhibitors (edrophonium or neostigmine).

Lab

Initial lab tests

- Routine blood, urine, and cerebrospinal tests are usually normal.
- Toxin detection in serum, stool, wound, and food (if available) samples, by mouse inoculation test with antitoxin neutralization.
- *C. botulinum* detection in stool by culture.
- Chances of toxin detection drop to <30% for sample collection >2 days after toxin ingestion.

Imaging

Initial approach

Neuroimaging can be done to rule out diagnoses such as brainstem disease (stroke, infection, etc.).

DIFFERENTIAL DIAGNOSIS

- Myasthenia gravis.
- Guillain–Barré syndrome (Miller Fisher Variant).
- LEMS.
- Poliomyelitis (and other brainstem encephalitis).
- Tick bite paralysis.
- Stroke.
- Brainstem lesion.
- Diphtheritic neuropathy.
- Intoxication with depressants, organophosphates.

TREATMENT

MEDICATION

First Line

- For infant botulism; human derived *botulinum* immunoglobulin (BIG), from pooled plasma of adults immunized with *botulinum* toxoid, within 3 days of symptom onset (1,2)[A]. Recommended dose 75 mg/kg as a single IV infusion. (Contact CDHS Infant Botulism Treatment and Prevention Program at 510-231-7600).
- Equine-derived trivalent (Types A, B and E) antitoxin for foodborne and wound botulism (2)[C].
- Both neutralize circulating toxin in blood but do not affect internalized toxin in nerve terminals, therefore do not reverse paralysis.
- Equine-derived antitoxin is not used in infants due to the risk of hypersensitivity reactions.

Second Line

- Studies with Guanidine, 3,4-diaminopyridine, steroids, plasmapharesis and intravenous immunoglobulin have shown conflicting results with some suggesting benefit. These remain experimental treatments.

ADDITIONAL TREATMENT

General Measures

- Supportive management in an intensive care setting is paramount and takes precedence over specific therapy for severe cases.

Additional Therapies

- Symptomatic Treatment:
  - Respiratory distress:
    - Airway protection.
    - Ventilatory support.
  - Dysphagia:
    - Swallowing assessment.
    - Tube feedings.
  - Nutritional support.
  - Urinary retention and constipation:
    - Intermittent straight catheterization.
    - Stool softeners.
    - Timed evacuation.
- Adjunctive treatment:
  - Prevention of decubitus ulcers.
  - Physical and occupational therapy.

SURGERY/OTHER PROCEDURES

Early drainage of wound with systemic antitoxin administration for wound botulism (3)[C].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Patients with suspected botulism need to be admitted for careful monitoring of neurological and respiratory status.
- Elective intubation with worsening respiratory status has better outcomes when compared to emergent intubation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Respiratory care and rehabilitation in a long-term care facility may be required.

PROGNOSIS

- Severe cases usually require hospitalization for 2–3 months.
- Mortality rate for untreated botulism is 40–50%.
- With adequate treatment, mortality ranges from 5–8%. For infant botulism alone it is <1%.
- 36% decrease in mortality reported when antitoxin given within 24 hours and a 31% decrease when given >24 hours of symptom onset.
- BIG has been shown to significantly reduce the duration of hospitalization, mechanical ventilation and parenteral feeding in infants.
- Similar outcomes noted with the use of antitoxin although not supported by a randomized control trial.

COMPLICATIONS

- Secondary infections such as pneumonia, UTI, sepsis due to aspiration and indwelling catheters.
- Some reports of long-term dyspnea, fatigue, and psychosocial impairment.

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CODES

ICD9

- 005.1 Botulism food poisoning
- 040.41 Infant botulism
- 040.42 Wound botulism

CLINICAL PEARLS

- Botulism presents with descending paralysis, oculobulbar weakness, autonomic instability, and respiratory failure.
- Supportive management is the mainstay of treatment
- BIG or antitoxin can reduce mortality and shorten intensive care stay.
- Electrodiagnostic studies may be the earliest support for diagnosis

BRAIN ABSCESS

Adarsh Bhimraj, MD
Carlos Isada, MD

BASICS

DESCRIPTION

Brain abscess is a focal collection of pus in the brain parenchyma. It begins as a localized area of cerebritis and develops into a collection of pus surrounded by a capsule.

EPIDEMIOLOGY

It is a rare but devastating disorder, the incidence of which is further decreasing. What was considered an almost fatal disorder in the late 1800's, now has reported case fatality rates as low as 0–9.5% in some studies (1,2). This has been attributed to better imaging tests like CT's and MRI's facilitating early diagnosis, more effective antibiotics and newer less invasive surgical techniques.

ETIOLOGY AND RISK FACTORS

The microorganisms can reach the brain by different routes. The most common mechanisms are

- Spread from a contiguous focus of infection from the middle ear/mastoids (otogenic), fronto-ethmoid or sphenoid paranasal sinuses (sinugenic) or from a dental infection.
- Secondary to cranio-cerebral trauma or neurosurgical procedures like craniotomies.
- Hematogenous spread from a distant focus of infection. The most common distant foci are pyogenic lung infections (lung abscesses, empyema and bronchiectasis), cyanotic congenital heart diseases and AV malformations. Infective endocarditis is an uncommon cause of brain abscess, despite the persistent bacteremia. In a recent, multi-center ICU study, less than 8% of patients with endocarditis developed brain abscesses (3).
- The cause is unknown in 20–40% of cases (4).

The microbiologic flora and location of the abscess in the brain depends on the route of acquisition. The infections from contiguous spread tend to be polymicrobial and those from hematogenous spread tend to be monomicrobial.

Predisposing condition	Site of the abscess	Microbiology
Otogenic	Temporal lobe, cerebellum	*Streptococci* (aerobic and anaerobic) gram negative aerobes and anaerobes
Sinugenic	Frontal lobe	*Streptococci* (aerobic, anaerobic and microaerophilic), *Staph* aureus, gram negative aerobes and anaerobes
Odontogenic	Frontal lobe	*Streptococci*, Actinomycosis and other oral anaerobes
Pyogenic pulmonary	Multiple at grey–white matter junctions	*Streptococci*, anaerobes, nocardia
Congenital heart disease	Multiple at grey–white matter junctions	*Streptococci*, *Staph*, *Hemophilus* spp.
Bacterial endocarditis	Multiple at grey–white matter junctions	*Strptococci* and Staph aureus
Penetrating trauma, post-neurosurgical	Contiguous site of wound or surgery	*Staph* spp, *Streptococci*, Gram negative aerobes, propionobacter

Immuno-compromised patients can be infected by a broader spectrum of opportunistic pathogens like fungi and parasites.

DIAGNOSIS

- The diagnostic accuracy of symptoms, signs, lab, and imaging findings have not been evaluated in well-designed studies. Most of the studies have been retrospective case series and the few prospective studies performed did not have blinded and independent comparison, consistently, to a reference standard. This precludes us from calculating clinically meaningful likelihood ratios and specificities (C).
- Clinical signs depend on location, virulence of the organism and the host's immune status.
- The classic triad includes fever, headache, and focal neurologic deficit; however, it is present in around 50% of patients (2).
- In most studies, headache was the most common symptom followed by mental status changes, focal deficits and fever. The clinical presentation can range from an acute fulminant to an indolent process and can often lack features like a fever to suggest an infection. Fever was present in less then 50% of patients in some studies (5).
- Sudden worsening of a preexisting headache or new-onset meningismus may signal rupture of the abscess into the ventricles, an often fatal complication.
- Signs and symptoms are suggestive, but further testing, especially imaging is required for diagnosis.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Routine labs like WBC counts, CRP and ESR are nonspecific and not very useful.
- A lumbar puncture and CSF Studies, have limited value, a low yield for cultures, and carries the risk of cerebral herniation in patients with a space occupying lesion like an abscess.
- Routine blood cultures are infrequently positive but when positive can provide important information to direct antimicrobial therapy.

Imaging

- Newer imaging modalities have facilitated early detection and treatment of brain abscess and are partly responsible for the recent trends in decreasing mortality rates (1).
- Abscess due to spread from a contiguous site are usually solitary and those from hematogenous spread are multiple mostly in the MCA territory at grey–white junctions.
- The MRI findings in the cerebritis stage are ill defined. It is hypointenste on T1, hyperintense on T2 and enhances with gadolinium.
- The findings in the later capsular stage are more characteristic. The following features are more suggestive of a brain abscess than other entities like a necrotic tumor that can mimic an abscess.

CT brain with contrast	Low density abnormalities with mass effect. Ring enhancing with contrast
MRI T1 non-contrast	Round, well-demarcated low-intensity center with mass effect. Iso or hyperintense capsule with peripheral low intensity (edema)
MRI T1 with contrast	Ring enhancement. The rim of the abscess, in all imaging modalities, is smoother on the inside than outside and thinner on the ventricular side compared to the cortical side.
MRI T2/FLAIR	Hyperinteinsity in the center/ cavity with a hypointense rim and hyperintensity in the surrounding parenchyma (edema) and mass effect.
DWI/ADC	The center is hyperintense on DWI and hypointense on ADC

Microbiologic tests

- Stereotactic brain biopsy, aspiration, or excision must be strongly considered for diagnostic and therapeutic purposes, preferably prior to administering antimicrobial, or at least within 1–3 days of starting antimicrobials. In one study, the yield fell from 100% to around 30% even after a day of antimicrobial therapy (6).
- The specimens should be sent for gram stain, aerobic, anaerobic culture, fungal stain and cultures, acid-fast stain and culture and other tests/cultures for specific organisms depending on clinical suspicion.

TREATMENT

There are no randomized controlled trials that evaluated the efficacy of surgical vs conservative treatments, different antimicrobial regimens or various surgical approaches. The recommendations are based mostly on cohort studies and case series. There is limited pharmacokinetic and pharmacodynamic data to guide the choice of antimicrobials (7)[B].

ANTIMICROBIAL THERAPY

After the samples for cultures are obtained, empiric therapy can be started. Therapy should target the suspected organisms and use agents at doses that reach therapeutic concentrations in the brain abscess. Due to the blood–brain barrier, the doses of antimicrobials used to treat brain abscess are often much higher than for other indications. Empiric therapy depends on the route of acquisition and is as follows:

Predisposing condition	Microbiology
Otogenic	Third-generation cephalosporin (e.g., ceftriaxone 2 g IV q12h) and metronidazole (500 mg IV q6h)
Sinugenic	Third-generation cephalosporin and metronidazole
Odontogenic	Penicillin (2–4 million units q4h) and metronidazole
Pyogenic pulmonary	Penicillin and metronidazole Add trimethoprim–sulfamethoxazole if Nocardia is suspected
Congenital heart disease	Third-generation cephalosporin (ceftriaxone)
Bacterial Endocarditis	Vancomycin 40–60 mg/kg daily dose—divided into 2 –3 dose q12 to q8h. Goal troughs of 20 mg/L
Post-neurosurgical	Vancomycin and Ceftazidime 2 g IV q8h
Penetrating trauma	Third-generation cephalosporin (ceftriaxone) and vancomycin

- Treatment should be tailored to the organism and the susceptibilities after the microbiology results are available.
- Duration of therapy is usually 4–6 weeks of IV antimicrobials, but should be determined by clinical and radiologic response (see algorithm).

SURGICAL MANAGEMENT

- In general, surgical drainage or excision is needed. Conservative or only antimicrobial therapy for treatment is controversial. Medical therapy alone may be attempted when the diameter of the abscess is less than 3 cm, in early cerebritis stage, or if the abscesses are located in an inaccessible site or in vital areas (8).
- Studies have shown that aspiration by a sterotactic approach can be as effective as craniotomy and excision in appropriate cases (7).

OTHER THERAPIES

Adjunctive Treatment

- Steroids (e.g., dexamethasone 6–12 mg q6h) are indicated if the patient has significant edema or mass effect. Steroids may decrease response to antimicrobial treatment and should be tapered as soon as feasible.
- The below algorithm can be used as a guideline, but has not been systematically evaluated in studies.

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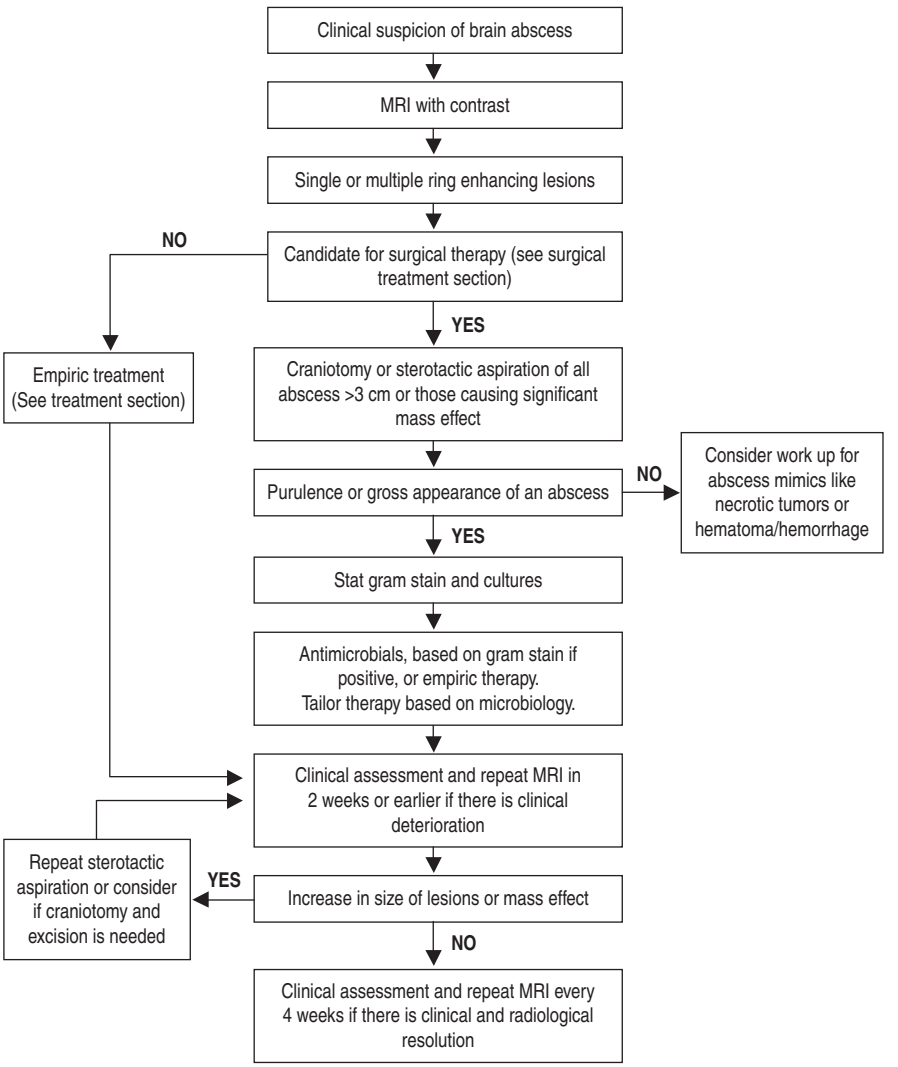
CODES

ICD9

- 324.0 Intracranial abscess
- 039.8 Actinomycotic infection of other specified sites



BRAIN DEATH

G. Bryan Young, MD

BASICS

DESCRIPTION

- Brain death is defined as the irreversible loss of function of the entire brain, including the brainstem. Brain death was first proposed as a criterion of death in 1968 and was endorsed in 1981 by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. In the USA, properly documented brain death meets the legal standard for the declaration of death.
- Most developed countries accept death of the brain as equivalent to death of the individual, although specific guidelines differ from country to country.
- Brain death or the neurological determination of death allows for the transplantation of solid organs.

EPIDEMIOLOGY

Incidence

- There are no accurate statistics on the annual rate of brain death declaration. However, there are 13 donors, at least half of whom are brain dead, per million persons in the USA annually.

Pregnancy Considerations

- Brain death occurring during pregnancy is a complex and controversial issue. There is a general consensus that attempts to maintain the brain-dead maternal body are appropriate if there is a reasonable possibility of delivering a healthy fetus. Who should make medical decisions is less clear: If the patient is married, the husband is generally considered the most appropriate surrogate decision maker; if unmarried, both the father of the fetus (if identified and involved) and the mother's immediate family should be included in the decision-making process. The basis for decision making also is controversial: Many consider the interests of the fetus to be paramount, but others believe that the mother's interests are equally important.

Pediatric Considerations

- Brain death is declared in 0.65 to 1.2% of children admitted to pediatric ICUs; it is uncommonly declared in neonates.

ETIOLOGY

- The main causes are intracranial catastrophes, including traumatic brain injury, spontaneous intracerebral hemorrhage, subarachnoid hemorrhage. Less common causes include cerebral edema from ischemic stroke, anoxic-ischemic encephalopathy, acute fulminant hepatic failure, encephalitis, or other central nervous system infections and inflammations.

PATHOPHYSIOLOGY

- The usual mechanism for brain death is an increase in intracranial pressure sufficient to prevent blood perfusing the brain tissue. This is often preceded by an increase in mass effect from brain swelling or blood, causing herniation and compression of brain stem structures. Lack of oxygenation of neurons with subsequent neuronal death is the mechanism in anoxic-ischemic encephalopathy.

DIAGNOSIS

PREREQUISITES

- It is essential that the cause of coma is known and that this etiology is one that is capable of causing neuronal death.
- For the *clinical* determination of brain death, there should be no confounding issues (that can mimic brain death), e.g., massive overdoses of sedative drugs or anesthetic agents, neuromuscular paralysis, profound hypothermia, or severe metabolic disturbance, (e.g., profound hypophosphatemia, hypoglycemia or hypokalemia), or profound shock/hypotension.

CLINICAL FEATURES

- The diagnosis of brain death is primarily clinical; ancillary tests are needed when the clinical criteria cannot be applied. The main features used in the clinical examination are:
  - The patient is in coma and on a ventilator.
  - Brainstem reflexes are absent: The pupillary light reflex, corneal reflexes bilaterally (tested by touching the cornea with a tissue or swab), the vestibular-ocular reflex [using ice water (at least 50 cc) in each ear canal with the head up 30 degrees from horizontal, with at least a 5-minute interval between each ear being tested], the gag reflex (usually using a suction device applied to the pharynx) and the cough reflex (usually tested with a suction catheter inserted below the endotracheal tube).
  - The patient is apneic. (*Note that the apnea test is not valid if the patient is a chronic retainer of carbon dioxide, e.g., with chronic lung disease.*) The test is done after the patient has been pre-oxygenated with 100% O_2 for at least 10 minutes. The targets are: A rise of $PaCO_2$ of at least 20 mm Hg, a final $PaCO_2$ of 60 mm Hg or greater (a final arterial pH of 7.28 or less is required in Canada but not in the USA).
  - States and countries differ in some procedures. In patients with anoxic-ischemic encephalopathy it is advisable to wait for 24 hours from the time of the arrest, as some brainstem reflexes show a delayed recovery of function after resuscitation. Most centers require two qualified physicians who do not have a perceived conflict of interest (e.g., are not involved with the potential organ recipient) to test the patient. Some states and countries require two separate tests by each physician tested several hours apart.
  - Movements after brain death: Some spinal cord-originating movements can persist after brain death, e.g., Lazarus sign (crossing arms, sitting up), tonic neck and tonic foot reflexes, abdominal contractions, plantar withdrawal and deep tendon reflexes. These do not preclude the diagnosis of brain death. When uncertainty exists, a brain blood flow study is helpful to confirm the diagnosis of brain death.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- As mentioned above, testing of expanded electrolytes, serum glucose and, when appropriate, drug screens are done.

Imaging

Tests of brain blood flow

- The only valid confirmatory tests are ones that demonstate absence of brain perfusion. These are used only when the clinical criteria cannot be applied [e.g., when all the cranial nerve reflexes cannot be assessed (e.g., enucleation of an eye, fracture involving the inner ear, chronic resipiratory failure with CO_2 retention, metabolic derangement)]. The testing modalities include:
  - 4-vessel angiography: Injection of dye into the carotid and vertebral arteries to show lack of intracranial circulation. It should be assured that the patient has a normal blood pressure and is not in shock when this is performed, as such could produce a "false positive" confirmatory test.

– CT angiography: This is often easier to arrange than 4-vessel angiography, but has the same requirements.
– MR angiography.
– Nuclear medicine brain flow tests: Traditionally radionuclide tests were conducted to show absence of brain flow. However, single photon emission tomography and tracers, which penetrate into the brain as it is perfused, offer a refinement.
– In general, transcranial Doppler tests are too operator-dependent (and also some patients cannot be properly insonated) to be recommended.

Diagnostic Procedures/Other

- Electrophysiological tests, e.g., EEG and evoked responses, are not sufficient as ancillary tests to confirm the diagnosis of brain death when the clinical criteria cannot be applied. However, they provide some additional supportive evidence.

Pediatric Considerations

- Guidelines for the declaration of brain death in children are not substantially different from those of adults. The American Academy of Pediatrics (1987) added the following additional protocol based on age:
  – 7 days to 2 months: 2 clinical examinations and EEGs 48 hours apart.
  – 2 months to 1 year: 2 clinical examinations and EEGs 24 hours apart; or 1 examination and an initial EEG showing ECS, combined with a radionuclide angiogram showing no CBF; or both.
  – More than 1 year: 2 clinical examinations 12–24 hours apart; EEG and isotope angiography optional.

Pathological Findings

- The brain often shows autolysis (respirator brain) depending how long the patient has been supported on a ventilator while brain dead.
- In up to 1/3 of patients, the pituitary gland receives a separate blood supply from the brain and may be viable (such patients do not develop diabetes insipidus or pituitary failure).

DIFFERENTIAL DIAGNOSIS

- Some conditions, e.g., profound hypothermia and massive barbiturate overdose, Guillain-Barré syndrome with complete ophthalmoplegia and pupillary non-reactivity. These should not be confounders if guidelines are followed.

TREATMENT

ADDITIONAL TREATMENT

General Measures

- Not applicable. Once brain death is officially declared and consent for transplantation is issued, there may be procedures to support somatic survival until organ harvesting has occurred.

Issues for Referral

- The transplant team should not in any way be involved in decision making about determining brain death.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- There are protocols for maintaining the viability of organs by supporting the brain dead donor. These involve the administration of vasopressin, ACTH and T3.

IV Fluids

- Per ICU support protocols.

Nursing

- Per ICU protocols.

ONGOING CARE

PATIENT MONITORING

- Per ICU protocol.

ADDITIONAL READING

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CODES

ICD9

- 348.1 Anoxic brain damage
- 348.89 Other conditions of brain

CLINICAL PEARLS

- Brain death is predominantly a clinical diagnosis.
- In the diagnosis of brain death the only truly confirmatory ancillary tests are those of brain blood flow.
- Some spinal cord-originating movements may persist after brain death.

BRAIN TUMOR: ACOUSTIC SCHWANNOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

- Acoustic schwannomas are extra-axial benign neoplasms that arise from the vestibular branch of the 8th cranial nerve in the cerebellopontine angle (CPA) region, near the porus acusticus. They are typically slow growing, with a growth rate of 1 to 2 mm/year. In some cases, especially older patients, the tumor may remain dormant. There are three stages of growth: canalicular, cisternal, and brainstem compressive. In late stages of growth, the seventh cranial nerve becomes draped over the mass, as it grows into the cistern toward the brainstem.

EPIDEMIOLOGY

Incidence/Prevalence

- Schwannomas account for 6 to 8% of all primary brain tumors. The majority of schwannomas (85 to 90%) are of the acoustic type and are usually unilateral (95%). The annual incidence is 1 case in 100,000 persons. Bilateral tumors occur in patients with Neurofibromatosis (NF) type II.
- All races and ethnic groups equally affected. Typical presentation is between 44 and 64 years of age. Females have a higher incidence than males: 1.5:1.

RISK FACTORS

- There are no known definite risk factors for acoustic schwannomas except for NF types I and II. Prior cranial radiation may be causally related in rare cases.

Genetics

- The majority of acoustic schwannomas are sporadic and unilateral. Approximately, 5% can develop in association with NF type I or II. In all NF-related tumors and between 65% and 70% of sporadic tumors, there are mutations of a tumor suppressor gene located at 22q12, the NF2 gene. NF2 codes for a protein, schwannomin, that interacts with cytoskeletal proteins involved in regulation of cell adhesion and proliferation.

GENERAL PREVENTION

- No preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

- The cells of origin of acoustic schwannomas are transformed Schwann cells from the 8th cranial nerve. In most cases, the initial genesis of transformation is unknown. The tumor appears as a discrete, rounded, encapsulated mass of a milky white color, arising from a nerve fascicle.

COMMONLY ASSOCIATED CONDITIONS

- NF types I and II.

DIAGNOSIS

HISTORY

- Common symptoms include unilateral sensory hearing loss (96%), unsteadiness (77%), tinnitus (71%), headache (29%), mastoid pain or otalgia (28%), facial numbness, diplopia, and vertigo. The mean time from onset of symptoms to diagnosis is 3.7 years. The loss of hearing and balance is slow and gradual in most cases. Tinnitus is typically unilateral, mild, and constant.

PHYSICAL EXAM

- Common neurological signs include unilateral sensorineural hearing loss in 90 to 95% of patients. Preserved hearing suggests the tumor will be less than 1.5 cm in size. In 50% of patients at presentation, hearing loss is the solitary neurological sign. Gait is either normal or only mildly affected. Large tumors (i.e., greater than 3 cm) can cause gait ataxia, dysmetria, nystagmus, facial hypesthesia, and papilledema.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Regular lab testing is not indicated, unless for pre-surgical screening.

Imaging

Initial approach

- MRI, with and without gadolinium contrast, is the most critical diagnostic test. Axial and coronal enhanced images should be obtained. MRI is more sensitive than CT for small intracanalicular tumors and vascular structures, although both modalities properly visualize large masses. On T1 images, the tumor is usually isointense to brain while on T2 images it is hyperintense. Schwannomas enhance densely after administration of gadolinium. An MRI negative for an enhancing mass in the internal auditory canal rules out an acoustic schwannoma.

Diagnostic Procedures/Other

- Screening tests that are sometimes used before MRI or CT in patients with hearing loss include pure tone audiometry, speech discrimination assessment, and auditory-evoked brainstem responses (AEBR). In 60 to 70% of patients, high-frequency loss is present on audiometry. Speech discrimination is abnormal in 45 to 80% of cases. AEBR is the most sensitive non-imaging test and shows delayed latency or loss of wave V in approximately 95% of patients.

Pathological Findings

- Microscopically, schwannomas have biphasic architecture, with Antoni A and B regions. Antoni A is most common, with features of dense, compact rows of elongated spindle-shaped cells. Antoni B regions demonstrate loosely organized areas of stellate cells, lipid, and microcystic change. Mitoses and nuclear pleomorphism may be seen. Abnormalities of chromosome 22 are common, including monosomy and alterations of the long arm (i.e., deletions, inversions, translocations).

DIFFERENTIAL DIAGNOSIS

- Acoustic schwannomas account for 80% of tumors in the CPA region. The differential diagnosis includes other masses or processes that can cause a progressive syndrome in the CPA: meningioma, epidermoid cyst, exophytic brainstem glioma, ependymoma, choroid plexus papilloma, schwannomas of other cranial nerves (V, VII, IX, X, XI), jugular foramen paraganglioma, metastatic tumor, vascular processes (aneurysm, arteriovenous malformation), and abscess.

TREATMENT

MEDICATION

First Line

- Dexamethasone (8–16 mg/d) may be of benefit to reduce edema and swelling for patients in the brainstem compressive stage of growth. It may also improve transient symptoms of pressure and swelling after radiotherapy (RT) or radiosurgery.

ADDITIONAL TREATMENT

General Measures

- In certain patient cohorts, tumors are followed conservatively after diagnosis, including those with poor health, elderly patients with small lesions (less than 10 mm) or who are reluctant to proceed to surgery, and any patient with poor hearing in the contralateral ear. Tumors are likely to remain quiescent if they remain stable during the initial observation period (usually 6 months). Conservative approaches are unjustified in most young patients due to accelerated growth rates.

Issues for Referral

- Evaluation for hearing aids in patients with residual hearing; physical therapy as needed (e.g., dysmetria, ataxia); facial nerve grafting and reconstruction can be of benefit in selected patients.

Additional Therapies

- Conventional external beam RT and stereotactic radiosurgery (linear accelerator, proton beam, Gamma Knife) can be adjunctive or alternative forms of treatment in selected patients. RT (30 to 50 Gy) should be considered in patients with large residual tumors after surgery, large recurrent tumors, and patients with large tumors that are poor surgical candidates. RT can lengthen progression-free survival. Patients most appropriate for radiosurgery include those that are medically unstable, elderly (>65 years of age), contralaterally deaf, have failed previous surgery, or refuse surgical intervention. Tumors <3 cm in diameter are most suitable. Dosing is usually between 16 and 18 Gy in a single fraction to the 50% isodense line. Local control rates range from 90 to 95%, with variable amounts of tumor shrinkage. Complications of radiosurgery include hearing loss, nausea and emesis, headaches, and delayed facial neuropathy.

- Recent data suggest that molecular chemotherapy can be of benefit in the treatment of selected patients with acoustic schwannomas. Bevacizumab is a monoclonal antibody with activity against vascular endothelial growth factor (VEGF). VEGF appears to be active in progressive acoustic schwannomas. Treatment of some tumors will result in modest tumor shrinkage, and the potential for improved hearing.

SURGERY/OTHER PROCEDURES

- Complete surgical resection is the treatment of choice in most patients. Tumors <1 cm in diameter are most likely to be completely resected while preserving cranial nerve function. Three surgical approaches are commonly used, the choice between techniques depends on tumor size, depth of internal auditory canal penetration, hearing status, exposure of the facial nerve, and patient age. The suboccipital or retrosigmoid approach allows for excellent exposure of the tumor and the CPA, and hearing may be preserved; this approach is excellent for large tumors. The translabyrinthine or the anterosigmoid approach allows for good exposure of the internal auditory canal, CPA, and course of the facial nerve; although postoperative complications are reduced (especially facial nerve paralysis), hearing is abolished. The middle fossa or subtemporal approach does not give good exposure of the CPA, but does allow for removal of intracanalicular or small cisternal tumors, while sparing hearing and minimizing complications. Traction of the cerebellum during the suboccipital approach can cause dysmetria. Traction of the temporal lobe during the middle fossa approach can cause epilepsy or dysphasia.
- Intraoperative monitoring of cranial nerves V, VII, and XI during surgical resection is an excellent method for reducing morbidity of these nerves. Monitoring of cranial nerve VIII remains controversial, it may reduce morbidity during resection of tumors <2 cm in size.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Admissions are unusual, except in the setting of surgical resection of the tumor.

Admission Criteria

- Admission is generally reserved for pre-surgical evaluation and surgical resection; angiography may be included in the work-up to assess regional vascular anatomy and rule out aneurysms and vascular malformations of the CPA; patients with brainstem compression might benefit from admission for intravenous dexamethasone.

Discharge Criteria

- Appropriate after recovery from surgery.

ONGOING CARE

PATIENT MONITORING

- Patients are followed with serial MRI scans and assessment of neurological function every 6 to 12 months.

PATIENT EDUCATION

- Acoustic Neuroma Association: www.anausa.org
- National Institute of Health—Acoustic Neuroma: text.nlm.nih.gov/nih/cdc/www/87.html

PROGNOSIS

- Overall prognosis for survival and neurological function is good for sporadic tumors if diagnosed in the canalicular or cisternal phases. The recurrence rate after a gross total resection is 1 to 2%. Surgical complications include mortality (0.5to 2%), hemorrhage, cerebellar injury, cranial nerve injury (V, VII, VIII, XI), headache, aseptic meningitis, and cerebrospinal fluid leak. Incomplete resection will result in recurrent tumor within 7 years in 44% of patients. Almost two-thirds of patients are able to return to work within 4 months after surgical resection.

COMPLICATIONS

- Complications of acoustic schwannomas and their treatment include partial or complete hearing loss, facial weakness, vertigo, and dysmetria; less common sequelae include impairment of other cranial nerves, ataxia, and hydrocephalus.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- NF types I and II

CODES

ICD9

225.1 Benign neoplasm of cranial nerves

CLINICAL PEARLS

- Acoustic schwannomas are slow-growing benign tumors that arise on CN VIII, often with symptoms of hearing loss and/or tinnitus.
- Surgical resection is the mainstay of treatment, although RT and chemotherapy may be beneficial in selected patients.
- Bilateral acoustic neuromas is strongly suggestive of NF type II

BRAIN TUMORS: EPENDYMOMA

Dr. Kevin T. Palka, MD
Dr. Paul L. Moots, MD

BASICS

DESCRIPTION

- Ependymomas are gliomas that arise from cells forming the ependymal surfaces of the ventricles and central canal of the spinal cord, or from developmental rests of ependymal cells within the brain parenchyma. The symptoms associated with ependymomas primarily reflect local compressive effects. Infiltration into the surrounding brain tissue tends to be limited compared with other gliomas. By arising from the ependymal surface, frequently in the fourth ventricle, these tumors are more often associated with hydrocephalus and with subarachnoid metastases than most gliomas, although less often than medulloblastoma/primitive neuroectodermal tumor (PNET). Systemic metastases are rare.
- Ependymomas comprise a higher percentage of the gliomas in patients under age 19 (7%) than in adults (3%) (CBTRUS). In children, they are usually intracranial tumors, with 60–70% occurring in the fourth ventricle. Most are histologically low grade but often behave aggressively. Ependymomas in adults may be intracranial, occurring with a higher frequency supratentorially, but spinal ependymomas are also common. Ependymomas account for 23% of primary spinal cord tumors.

EPIDEMIOLOGY

Incidence

- The incidence of ependymomas in children is 0.27 per 100,000 patient years, comprising 4.9% of all CNS tumors and 7% of all gliomas. The incidence in adults is 0.26 per 100,000 patient years, comprising 1.3% of all CNS tumors and 3% of all gliomas. Males are affected marginally more frequently than females. The incidence in whites (0.28) is greater than blacks (0.16). (CTBRUS)

RISK FACTORS

- Family History of Neurofibromatosis (NF) Type I or II.

Genetics

- Most are sporadic.
- Highly associated with NF Type II and occasionally NF Type I.

PATHOPHYSIOLOGY

- Radial glia of the developing brain may serve as stem cell precursors for ependymomas.
- Loss of heterozygosity on chromosome 22q probably related to the NF II locus is found in some ependymomas.
- Mutations of the multiple endocrine neoplasia type 1 (MEN 1) gene or loss of heterozygosity (LOH) on chromosome 11q13 at the MEN 1 locus have been associated with ependymoma.
- Clear cell variant of supratentorial ependymoma is associated with partial trisomy 19, and is usually anaplastic.
- High levels of MGMT expression, a DNA repair enzyme, may explain the low sensitivity to chemotherapy.
- Over-expression of ErbB2 and ErbB4, mutations in platelet-derived growth factor receptor (PDGF-R) alpha and altered integrin expression provide possible therapeutic targets.

COMMONLY ASSOCIATED CONDITIONS

- Meningiomas and other gliomas are commonly associated with NF II.
- Cervical spinal cord tumors of many types are often associated with adjacent syringomyelia.

DIAGNOSIS

HISTORY

- Symptom progression over many weeks or a few months is common.
- Headache.
- Lethargy.
- Nausea and vomiting.
- Rapidly increasing head circumference in children.
- Ataxia/dysequilibrium.
- Diplopia.
- Seizures.
- Weakness.

PHYSICAL EXAM

- Papilledema.
- Gait difficulty.
- Limb ataxia.
- Cerebellopontine angle syndrome, including cranial nerves (CN) V, VII, and VIII.
- CN VI palsies related to hydrocephalus.
- Myelopathy or cauda equina syndrome in adults.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Helpful for pre-surgical screening.

Imaging

Initial approach

- CT scanning is often done in the ER evaluation of patients with a suspected brain tumor, or if MRI is contraindicated. CT scanning is able to demonstrate intracranial ependymomas well, but MRI scanning tends to be more informative, particularly with regard to posterior fossa lesions and meningeal dissemination.
- MRI of the brain without and with contrast is the prefered imaging modality. MRI scanning usually demonstrates a solitary well-demarcated, contrast-enhancing mass.
- Hydrocephalus is common with fourth ventricle ependymomas.
- The MRI scan should be reviewed carefully for subarachnoid metastases.
- If a mass lesion suggestive of ependymoma is found, then MRI scanning of entire spine is recommended. For patients who cannot undergo MRI scanning, CT myelography performed after surgery is used as an alternative for assessment of the spinal axis if an LP is not contraindicated.
- Neither CT nor MRI scanning can distinguish ependymomas from other CNS neoplasms with sufficient certainty to be considered diagnostic. Diffusion-weighted abnormalities are less common with ependymoma than with medulloblastoma, a useful finding when assessing posterior fossa masses.

Diagnostic Procedures/Other

- The definitive diagnosis is achieved by pathologic assessment of the tumor. Resection is highly preferable to biopsy alone and sometimes is curative.
- CSF cytology is an important part of staging. It is usually done 2–3 weeks post-surgery. Elevated intracranial pressure or tumor-related mass effect sometimes contraindicates performing a lumbar puncture.

Pathological Findings

- The WHO classification includes two main types: (a) Ependymoma (WHO grade II) and (b) Anaplastic Ependymoma (WHO grade III). Both show a monotonous population of cells with round nuclei and finely dispersed chromatin. Grade III has more anaplastic nuclear features, higher cellularity, higher mitotic index, wider infiltration, microvascular proliferation, and sometimes necrosis. Four histologic variants occur: Clear cell (resembles oligodendroglioma), cellular, tanycytic, and papillary. These can be either grade II or III.
- Grade I subtypes include (spinal) Myxopapillary Ependymoma (WHO grade I), and Subependymoma (WHO grade I). These are more likely to be cured by resection due to a lack of infiltration of surrounding tissue.
- Perivascular rosettes are a hallmark of all types. True ependymal rosettes or tubules are rare.
- Immunohistochemical stating is positive for glial fibrillary acidic protein (GFAP), neural cell adhesion molecule (NCAM), and epithelial membrane antigen (EMA). Neuronal markers are negative.
- PNET with ependymal differentiation, also called ependymoblastoma, has biologic and clinical features that relate it to the medulloblastoma/PNET group of neoplasms. The prognosis and treatment are distinct from that of ependymomas.

DIFFERENTIAL DIAGNOSIS

- Medulloblastoma, high grade glioma, pilocytic astrocytoma, choroid plexus papilloma, and metastasis.
- Nonneoplastic conditions such as Chiari malformations and other craniocervical junction anomalies may present similarly.
- Postviral, toxic, and other subacute ataxias may present similar clinical features.

TREATMENT

MEDICATION

First Line

- Corticosteroids, usually dexamethasone, typically 2–6 mg every 6 to 8 hours and occasionally higher, are used for rapidly treating cerebral edema.

ADDITIONAL TREATMENT

General Measures

- Initial measures are aimed at controlling rapidly progressive neurologic symptoms and increased intracranial pressure. Both cerebral edema and hydrocephalus may be contributing factors. Steroids (dexamethasone) are commonly used. Osmotic diuretics (mannitol or hypertonic saline) are reserved for extreme circumstances.
- Ventriculostomy, often temporary, is used if hydrocephalus is present.

Issues for Referral

- Urgent neurosurgical intervention for tumor-related mass effect or hydrocephalus is indicated.
- After stabilizing the symptoms and establishing a diagnosis by surgery radiation oncology is consulted. There is little role for urgent radiation oncology referral in this setting.

Additional Therapies

- Anticonvulsant therapy is indicated only when seizures have occurred, although perioperative antiseizure prophylaxis is sometimes recommended, particularly if elevated intracranial pressure is present.
- Anticonvulsants available in both IV and PO formulations (phenytoin, divalproex, levateracitam) are preferable.
- Anticonvulsants with frequent drug interactions or hematologic toxicity (phenytoin, carbamazepine, divalproex) should be avoided in patients receiving chemotherapy.

SURGERY/OTHER PROCEDURES

- SURGERY:
  - Tumor resection is the primary mode of antineoplastic therapy.
  - Gross total resection is associated with better prognosis compared to partial resection. Complete resection can lead to longterm control without other modalities of treatment for all grade I and many grade II ependymomas.
  - Since complete can be curative, second operations to resect any residual tumor is sometimes appropriate.
  - Emergency ventriculostomy may be indicated for rapidly progressive hydrocephalus, usually due to fourth ventricle tumors. Some patients will require permanent ventriculoperitoneal shunting once the tumor is removed.
- RADIATION THERAPY:
  - Grade I and many completely resected supratentorial grade II ependymomas are observed without radiation.
  - 45 to 54 Gy to the tumor plus a margin for all grade III, infratentorial grade II, and some incompletely resected supratentorial grade II ependymomas.
  - Radiation is avoided in infants and young children <3 years (1)[B].
  - Concurrent chemotherapy is not routinely used.
  - Craniospinal radiation is used when CSF metastases are found on neuraxis staging.
- CHEMOTHERAPY:
  - A large number of chemotherapy agents have been used in ependymomas, usually in multiagent combinations, for *recurrent* disease. The best response rate (31–67%) is seen with platinum-based regimens containing either cisplatin or carboplatin. Alkylating agents, including the nitrosoureas carmustine (BCNU) and lomustine (CCNU) demonstrate response rates in the 25% range. Non platinum containing regimens with cyclophosphamide, vincristine, or etoposide are commonly used but response rates are 11–13%. Temozolomide is not frequently used. Epidermal growth factor receptor (EGFR) inhibitors such as erlotinib and gefitinib are considered experimental.
  - In very young children, multiagent chemotherapy is used, and radiation treatment is deferred to avoid the profound neurotoxicities and associated developmental complications in this age group (1)[B].
  - Chemotherapy is contraindicated in patients with persistent leucopenia (WBC <2,000) or thrombocytopenia (PLT <100,000)

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Admit to neurosurgical or neurology unit for close monitoring. MRI is recommended if patient is stable.

Admission Criteria

- Admit for signs of elevated intracranial pressure or rapidly progressive neurologic deficits.

IV Fluids

- Avoid hypotonic solutions if cerebral edema is significant.

Nursing

- Special care is required for sedation and pain control in patients suspected of having elevated intracranial pressure, especially if related to a posterior fossa mass where respiratory depression and loss or airway protection may rapidly develop.

Discharge Criteria

- Discharge when neurologic symptoms have stabilized, and neurosurgery has evaluated patient.

ONGOING CARE

PATIENT MONITORING

- For children, MRI scans to be done every 2 to 4 months during therapy and for the first year afterwards, every 6 months for 5 years, and annually thereafter. For adults, MRI every 6–12 months is appropriate for histologically benign ependymomas.
  - MRI scanning of entire neuraxis may be required for some patients.
  - Clinical assessment for subarachnod metastases, particularly spinal "drop mets". CSF for cytology may be indicated in some patients.

PROGNOSIS

- Children: High likelihood of local recurrence in ~90% of patients. Some patients develop concurrent sub-arachnoid metastases. Recurrence in the subarachnoid space without local recurrence is much less common.
- Metastases outside the neuraxis are exceedingly rare.
- 5-year progression-free survival (PFS) estimates from 50 to 70%; 10-year overall survival (OS) after gross total resection is 70%. Decreases to 33% after subtotal resection.
  - ADULTS: 5-year PFS/OS rates 43–63%/86%; 10 year PFS/OS rates 24-53%/81%.

REFERENCE

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ADDITIONAL READING

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- http://www.cbtrus.org/reports//2007-2008/2007report.pdf.

CODES

ICD9

- 191.9 Malignant neoplasm of brain, unspecified site
- 192.2 Malignant neoplasm of spinal cord

CLINICAL PEARLS

- Ependymomas are usually low-grade tumors that are amenable to complete resection.

BRAIN TUMOR: HIGH-GRADE ASTROCYTOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

- High-grade astrocytomas (HGA) are a group of malignant neoplasms that typically occur in middle-age and older adults; they have a high growth potential and are more infiltrative than low-grade gliomas; survival is limited in most patients and ranges between 1 and 5 years.

EPIDEMIOLOGY

Incidence/Prevalence

- HGA comprise approximately 33–45% of primary brain tumors in adults. This corresponds to roughly 7,500 new cases of HGA each year in North America. 50–80% of HGA are glioblastoma multiforme (GBM), 20–40% are anaplastic astrocytoma (AA); gliosarcoma and mixed anaplastic oligoastrocytoma (AOA) occur less frequently.
- All races and ethnic groups affected. Caucasians are affected more commonly than blacks, Latinos, and Asians. Typical presentation is between 50 and 65 years of age for GBM and gliosarcoma patients and between 30 and 50 years of age for AA and mixed AOA patients. Incidence is slightly higher in males than females (1.5:1).

RISK FACTORS

- The only known risk factors for HGA are prior cranial radiation exposure and genetic diseases with a predilection for astrocytomas, such as Turcot's syndrome, neurofibromatosis (NF) types I and II, and Li-Fraumeni syndrome; rarely, HGA can be familial.

Genetics

- HGA are usually sporadic and do not have an underlying genetic predilection; rarely, HGA can manifest as part of a genetically mediated syndrome (i.e., NF).

GENERAL PREVENTION

- No preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

- The World Health Organization classifies AA as grade III, GBM as grade IV, gliosarcoma as grade IV, and mixed AOA as grade III.
- HGA are derived from transformed astrocytes. Molecular genetic studies of HGA reveal frequent loss or mutation of the tumor suppressor gene, p53. Amplification of MDM2 or CDK2 and deletion or mutation of the tumor suppressor genes p16 and retinoblastoma may be present. Primary GBM have amplification of epidermal growth factor receptors and/or deletion of the PTEN tumor suppressor gene. Deletion of 1p and 19q may be noted in mixed AOA and is associated with improved survival.

COMMONLY ASSOCIATED CONDITIONS

- NF type I, NF type II, Turcot's syndrome, Li-Fraumeni syndrome.

DIAGNOSIS

HISTORY

- The median duration from onset of symptoms to diagnosis ranges from less than 6 months in GBM to 6 to 8 months for AA. The most common symptoms at presentation include headache (70%), seizure activity (54% overall; partial motor, 23%; generalized tonic-clonic, 20%; partial complex, 9%), cognitive and personality changes (52%), focal weakness (43%), nausea and emesis (31%), speech disturbances (27%), and alterations of consciousness (25%).

PHYSICAL EXAM

- The common findings on neurological examination include hemiparesis (57%), cranial nerve palsies (54%), papilledema (53%), cognitive deficits and confusion (45%), depressed sensorium (37%), hemianopsia (29%), and dysphasia (25%).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Routine labs are not helpful except for in the setting of pre-surgical screening.

Follow-up & special considerations

- Molecular analysis of chromosome 1p and/or 19q loss may be of prognostic significance in patients with mixed AOA.

Imaging

Initial approach

- MRI, with and without gadolinium contrast, is the most sensitive diagnostic test; MRI is more sensitive than CT for HGA that are small or within the posterior fossa. On T1 images, the tumor is usually infiltrative and appears hypo- or isointense compared to brain. On T2 images, the mass is hyperintense. With gadolinium administration, most HGA show either diffuse or ring-like enhancement. Peritumoral edema and mass effect are usually moderate to severe. Hemorrhage and regions consistent with necrosis may be noted. CT demonstrates an ill-defined region of hypodensity with moderate to severe enhancement, edema, and mass effect.

Diagnostic Procedures/Other

- Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of HGA to differentiate from non-neoplastic lesions and to maximize targeting for biopsy. HGA typically appear hypermetabolic on PET imaging. Magnetic resonance spectroscopy (MRS) can also be used for metabolic screening to differentiate HGA from other lesions. MRS of HGA often reveals an elevated choline peak, severely reduced N-acetyl aspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.

Pathological Findings

- Pathological evaluation reveals significant heterogeneity, with high cellularity, cellular and nuclear atypia, moderate to high mitotic rate, endothelial proliferation, and necrosis (GBM and gliosarcoma only); gliosarcomas show regions of sarcomatous differentiation admixed with separate areas of neoplastic glial cells; staining for glial fibrillary acidic protein is more variable in HGA and typically less than that of low-grade gliomas.

DIFFERENTIAL DIAGNOSIS

- Other mass lesions that enhance should be considered, including mature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

TREATMENT

MEDICATION

First Line

- Seizures are a common problem in patients with HGA; appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical. Dexamethasone is used at the lowest dose able to control symptoms related to intracranial pressure.

ADDITIONAL TREATMENT

General Measures

- The management of HGA requires a multi-modality approach to cytoreduction that includes surgery, radiotherapy, and chemotherapy; input from neurosurgeons, neuro-oncologists, and radiation oncologists is necessary for optimal treatment.

Additional Therapies

- External beam radiation therapy (RT) should be considered for all HGA after surgical resection. Phase III trials demonstrate that time-to-progression and overall survival are significantly improved with RT (overall survival 36 weeks with RT versus 16 weeks with surgery alone); the recommended RT dose is 60 Gy over 6 weeks, in 180 to 200 cGy daily fractions. Focal three-dimensional treatment planning and conformal techniques should be used whenever possible to minimize radiation exposure to normal brain, especially in younger patients. For elderly patients (>65 years) and those with poor Karnofsky performance status, a protracted course of RT may be appropriate—30 to 40 Gy in 10 fractions over 3 weeks.
- Stereotactic radiosurgery (SRS) has been used for HGA, as a boost after initial RT and at recurrence, for tumors up to 4 cm in size. Larger tumors will not benefit from SRS due to infiltration beyond the treatment field. Median doses range from 15 to 17 Gy in one fraction. SRS may improve survival in carefully selected patients with small HGA.
- Chemotherapy should be considered for all patients with HGA after RT and at recurrence. Clinical trials and meta-analyses suggest a modest survival benefit after RT (10–15% extension in 1-year survival), especially in patients with AA and mixed AOA. For AA and GBM, the most active drugs and combinations include temozolomide, bevacizumab, BCNU, procarbazine, PCV (procarbazine, CCNU, vincristine), cisplatin, carboplatin, and etoposide. Mixed AOA may respond well to chemotherapy with PCV or temozolomide if chromosome 1p and 19q deletions are noted. At recurrence, local chemotherapy with BCNU impregnated wafers may add a modest survival benefit, as suggested in several phase III trials.

SURGERY/OTHER PROCEDURES

- Surgery should be considered in all patients to make a histological diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms. Maximal surgical resection is the treatment of choice for accessible HGA, preferably by computer-assisted volumetric resection techniques (e.g., stealth apparatus). For patients with deep, inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Some studies suggest that overall and 1-year survival are improved with complete or sub-total resection versus biopsy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Dexamethasone (4–16 mg/d; intravenous, IV) may be of benefit to reduce peritumoral edema and swelling; in some patients, IV mannitol (12.5 to 25 g, q3-6h) may also be necessary to control severe edema, mass effect, and midline shift.

Admission Criteria

- Patients with HGA are often admitted for seizure control or neurological deterioration due to elevated intracranial pressure and tumor growth. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure will be required before discharge.

Discharge Criteria

- Will be appropriate after stabilization of acute issues such as modifying anticonvulsant medications, reducing intracranial pressure, and recovery from surgical procedures.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Will be variable depending on the acute issues during the admission, and the plan for further active treatment.

Patient Monitoring

- Patients are followed with serial MRI scans and neurological examinations every 4 to 8 weeks. Patients receiving chemotherapy may require more frequent follow-up; anticonvulsant levels need to be monitored carefully.

PATIENT EDUCATION

- National Brain Tumor Foundation: www.braintumor.org
- American Brain Tumor Association: www.abta.org
- The Brain Tumor Society: www.tbts.org

PROGNOSIS

- The median survival after diagnosis of patients with HGA is 30 to 42 months for AA, 8 to 16 months for GBM and gliosarcoma, and 42 to 52 months for mixed AOA.
- Prognosis is improved with young age (<40 years), AOA or AA histology, and high Karnofsky performance status; prognosis is worse with age >50 years, poor Karnofsky performance status, and GBM or gliosarcoma histology.

COMPLICATIONS

- Will be variable but often include continued seizure activity and neurological dysfunction, such as weakness, difficulty with speech, and imbalance.

ADDITIONAL READING

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- Newton HB. Bevacizumab. Review of development, pharmacology, and application to brain tumors. *Clin Med Therapeut* 2009;1:1577–1597.
- Sathornsumetee S, Rich JN, Reardon DA. Diagnosis and treatment of high-grade astrocytoma. *Neurol Clin* 2007;25:1111–1139.

See Also (Topic, Algorithm, Electronic Media Element)

- Brain Tumor—Oligodendroglioma

CODES

ICD9

191.9 Malignant neoplasm of brain, unspecified site

CLINICAL PEARLS

- AA and GBM are malignant tumors that will require a multifaceted treatment approach, including surgical resection, RT, and chemotherapy.
- Chemotherapy can be helpful for controlling tumor growth, when used in combination with RT and as adjuvant therapy afterwards.

BRAIN TUMOR: LOW-GRADE GLIOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Low-grade gliomas (LGG) are a diverse group of pathologically distinct neoplasms that usually occur in children and young adults. The most common LGG are of astrocytic and oligodendroglial origin. These tumors have a reduced growth potential and are often less infiltrative when compared to malignant gliomas. Survival is typically prolonged, greater than 5 years in most patients.

EPIDEMIOLOGY

Incidence/Prevalence

- LGG comprise approximately 10–15% of primary brain tumors in adults. This corresponds to roughly 1,900 new cases of LGG each year in North America. The majority of LGG consist of grade II astrocytomas, oligodendrogliomas, and mixed tumors.
- All races and ethnic groups equally affected. Typical presentation is between 30 and 45 years of age, with a mean of 37 years. Incidence is slightly higher in males than females.

RISK FACTORS

- The only known risk factors for LGG are prior cranial radiation exposure and genetic diseases with a predilection for gliomas, such as Turcot's syndrome, neurofibromatosis (NF) types I and II, Li-Fraumeni syndrome, basal cell nevus syndrome, and tuberous sclerosis. Rarely, LGG can be familial.

Genetics

- LGG are usually sporadic and do not have an underlying genetic predilection. Rarely, LGG can manifest as part of a genetically mediated syndrome (i.e., NF).

GENERAL PREVENTION

- There are no preventive measures against LGG.

PATHOPHYSIOLOGY/ETIOLOGY

- LGG are a heterogeneous group of neoplasms that include pilocytic astrocytoma (PCA; WHO grade I), diffuse astrocytoma (WHO grade II), WHO grade II oligodendroglioma, WHO grade II mixed oligoastrocytoma, subependymoma, subependymal giant cell astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, central neurocytoma, and dysembryoblastic neuroepithelial tumors.
  - Cells of origin of LGG are variable depending on tumor type. Pathological evaluation of LGG reveals mild to moderate cellularity without anaplasia or severe nuclear atypia, minimal mitotic activity and endothelial proliferation, no necrosis. Tumor cells often stain for glial fibrillary acidic protein. Diffuse astrocytomas can undergo anaplastic degeneration in up to 75% of cases.
  - Molecular genetic studies of LGG reveal frequent allelic deletions of chromosome 17p, often with loss or mutation of the tumor suppressor gene, p53. The presence of abnormal p53 protein in LGG is associated with shorter survival. Amplification of MDM2 or CDK2 and deletion of the tumor suppressors p16 and retinoblastoma may be present in some tumors. Deletion of 1p and 19q may be noted in oligodendrogliomas and is associated with chemosensitivity and extended survival.

COMMONLY ASSOCIATED CONDITIONS

- NF type I, NF type II, Turcot's syndrome, Li-Fraumeni syndrome, basal cell nevus syndrome, tuberous sclerosis.

DIAGNOSIS

HISTORY

- The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months. The most common symptom at presentation is seizure, which occurs in 60–65% of patients. Focal seizures are more likely than generalized seizures. Headache and focal weakness each occur in approximately one quarter of patients. Cognitive changes, speech deficits, and visual abnormalities are noted in less than 15% of patients.

PHYSICAL EXAM

- The neurological examination is normal in about 50% of patients; neurological abnormalities that may be noted include focal motor deficits (45%), sensory alterations (40%), mental status alterations (25%), papilledema (20%), dysphasia (20%), and memory deficits (18%).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Lab testing is generally not helpful, except to measure anticonvulsant levels and for pre-operative screening.

Imaging

Initial approach

- MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for tumors that are small or within the posterior fossa. On T1 images, the tumor is usually somewhat circumscribed and appears hypo- or isointense compared to brain. On T2 images, the mass is hyperintense. Cystic regions are often present in PCA. With gadolinium administration, most LGG show minimal or no enhancement. PCA can show variable enhancement, often within a cyst-associated mural nodule. Peritumoral edema and mass effect are usually mild to moderate. Calcification may be noted. CT demonstrates an ill-defined region of hypodensity with minimal enhancement. More than one-third of tumors that appear to be LGG by MRI/CT criteria are higher grade tumors, usually anaplastic astrocytoma.

Diagnostic Procedures/Other

- Molecular analysis of chromosome 1p and/or 19q loss may be of prognostic significance in patients with oligodendroglioma. Electroencephalography should be considered in patients with atypical or unusual seizures.

Pathological Findings

- LGG will demonstrate low cellularity, minimal cellular or nuclear atypia, minimal vascularity, no necrosis, and a lack of mitotic activity.

DIFFERENTIAL DIAGNOSIS

- Other mass lesions that may or may not enhance should be considered, including immature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

TREATMENT

MEDICATION

First Line

- Seizures are a common problem in patients with LGG; appropriate anticonvulsant choices and management will be critical. Dexamethasone is used at the lowest dose able to control symptoms related to intracranial pressure.
- All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

ADDITIONAL TREATMENT

General Measures

- The management of LGG remains controversial. Some authors recommend observation and serial MRI scans for proof of growth potential before initiation of treatment (i.e., surgery, irradiation). Other authors suggest immediate tissue diagnosis with biopsy or resection, followed by irradiation or chemotherapy. Observation is most appropriate for small, deep tumors that are asymptomatic except for seizure activity.

Additional Therapies

- External beam radiation therapy (RT) should be considered for all non-pilocytic LGG after incomplete surgical resection. Post-operative RT can be postponed for patients with PCA until growth potential is demonstrated. Retrospective studies suggest that time-to-progression and overall survival are improved with RT (5-year survival 32% with RT versus 10% with surgery alone). Timing of RT remains controversial, some authors advocate immediate post-operative treatment while others suggest waiting till tumor progression; however, the timing of RT does not appear to be critical, since overall survival is similar in the immediate and delayed treatment groups. RT for LGG is more beneficial for older patients (40 years or older). Conformal techniques should be used whenever possible to minimize radiation exposure to normal brain. Recommended RT doses are 50 to 55 Gy over 6 weeks. Irradiation should be delayed post-operatively in young children until proof of growth by MRI and/or neurological examination.
  - Stereotactic radiosurgery is a more recent RT option. Several studies have used doses of 15 to 50 Gy, for LGG up to 40 mm in size. Objective responses have been noted in over 50% of patients, although follow-up has been brief.
  - Chemotherapy does not have a clear role in most patients with LGG. Young children may respond to cisplatin-based regimens in order to delay the need for RT. A Southwest Oncology Group phase III trial of LGG in adults did not demonstrate a survival benefit for lomustine in combination with RT. Phase II studies suggest nitrosoureas (lomustine, carmustine), alone or in combination with platinum (cisplatin, carboplatin) drugs, may have benefit for patients with LGG. PCV (procarbazine, lomustine, vincristine) has demonstrated activity against LGG, especially oligodendrogliomas. Objective responses range from 30 to 45% in some studies. Temozolomide has demonstrated activity similar to PCV against LGG in recent phase II studies. Progressive or recurrent PCA may respond to cisplatin-based multiagent chemotherapy regimens.

SURGERY/OTHER PROCEDURES

- Surgery should be considered in all patients to make a histological diagnosis and alleviate symptoms; maximal surgical resection is the treatment of choice for accessible LGG, preferably by computer-assisted volumetric resection techniques (e.g., stealth apparatus). For patients with deep, inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Some studies suggest that overall and 5-year survival are improved with complete or sub-total resection versus biopsy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Usually related to seizure control and adjustment of anticonvulsants.

Admission Criteria

- Patients with LGG are most often admitted for seizure control or to reduce elevated intracranial pressure; maximizing anticonvulsant doses and resolving metabolic disturbances will be required before discharge.

Discharge Criteria

- Appropriate after stabilization of seizure activity or raised intracranial pressure; or after recovery from surgical resection.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Will be variable, depending on the type of LGG and the need for further active treatment (e.g., RT, chemotherapy).

PATIENT MONITORING

- Patients are followed with serial MRI scans and neurological examinations every 4 to 6 months. Patients receiving chemotherapy will require more frequent follow-up. Anticonvulsant levels will need to be monitored, if appropriate.

PATIENT EDUCATION

- National Brain Tumor Foundation: www.braintumor.org
- American Brain Tumor Association: www.abta.org
- The Brain Tumor Society: www.tbts.org

PROGNOSIS

- The median survival after diagnosis of patients with LGG is 4.7 years for diffuse astrocytomas, 7.1 years for mixed oligoastrocytomas, and 9.8 years for oligodendrogliomas; the 10-year survival in these cohorts is 17, 33, and 49%, respectively.
- Prognosis is improved with oligodendroglial or pilocytic histology, young age, and seizures at presentation. Prognosis is worse with age >40 years, poor performance status, and diffuse astrocytic histology.

COMPLICATIONS

- Most likely related to continued seizure activity or focal neurological deficits secondary to tumor growth or surgical intervention.

ADDITIONAL READING

- Brandes AA, Vastola F, Basso U. Controversies in the therapy of low-grade glioma: when and how to treat. *Expert Rev Anticancer Ther* 2002;2:529–536.
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- Duffau H. Surgery of low-grade gliomas: towards a "functional neurooncology." *Curr Opin Oncol* 2009;21:543–549.

See Also (Topic, Algorithm, Electronic Media Element)

Brain Tumor—Oligodendroglioma.

CODES

ICD9

191.9 Malignant neoplasm of brain, unspecified site

CLINICAL PEARLS

- LGG are a diverse group of slow-growing brain tumors that often present with seizures.
- Long-term stabilization and growth control is possible with early diagnosis and appropriate treatment.

BRAIN TUMOR: MEDULLOBLASTOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

- Medulloblastoma (medullo) is the most common malignant primary brain tumor of childhood, it is an invasive embryonal neoplasm that arises in the midline cerebellum; recent advances in multimodality treatment have led to significant improvements in local tumor control and survival.

EPIDEMIOLOGY

Incidence/Prevalence

- Medulloblastoma comprises approximately 20–25% of all malignant primary brain tumors in children; the overall incidence in the USA is approximately 5 cases per million persons, which corresponds to roughly 350 new cases each year; medullo is uncommon in adults, with an incidence of 1%; adults account for 15–20% of medullo cases.
- All races and ethnic groups affected; Caucasians are affected more commonly than blacks, Latinos, and Asians. Typical presentation is between 7 and 9 years of age; 80% of patients present before the age of 20 years; a secondary peak occurs in adults, between 26 and 30 years. Incidence in childhood is slightly higher in males than females (1.4:1 to 2.3:1); males and females are equally affected in adulthood.

RISK FACTORS

- The only known risk factors for medullo are the heritable syndromes noted below and rare familial predilections.

Genetics

- Medulloblastomas are usually sporadic; medullo can arise as a manifestation of heritable disorders such as Turcot's syndrome, Li-Fraumeni syndrome, ataxia-telangiectasia, nevoid basal cell carcinoma syndrome, and Gorlin's syndrome; rarely, medullo can be familial.

GENERAL PREVENTION

- There are no preventive measures available.

PATHOPHYSIOLOGY/ETIOLOGY

- The cell of origin of medullo remains controversial; they are derived from transformation of pluripotent cells that reside either in the external granular layer of the cerebellum or the subependymal matrix; in children they typically occur in the midline cerebellum, with variable extension into the brainstem; in adults, they are eccentrically located, with extension into one of the cerebellar hemispheres.
- Molecular genetic studies of medullo have noted frequent deletions of chromosomes 17p, 1q, and 10q; three separate pathways have been implicated in the transformation process: amplification of the N- and C-myc genes, mutation of the PTCH gene and dysfunction of the sonic hedgehog/PTCH signaling pathway, and dysregulation of the Wnt/APC/β-catenin signaling pathway; high expression of TrkC is associated with extended survival.

DIAGNOSIS

HISTORY

- The median duration from onset of symptoms to diagnosis ranges from 3 to 6 months; initial symptoms include irritability, loss of appetite, progressive headache, lethargy, and nausea and emesis (often in the morning); later onset symptoms include double vision, truncal and/or limb ataxia, gait imbalance, neck stiffness, and dizziness.
- The common findings on neurological examination include lethargy, papilledema, gait ataxia, nystagmus, and sixth nerve palsy; less common findings include hemiparesis, internuclear ophthalmoplegia, dysphagia, and myelopathy.
- Unusual signs and symptoms such as seizure activity, radicular pain, back pain, hemiparesis, internuclear ophthalmoplegia, dysphagia, and myelopathy are suggestive of brainstem infiltration and/or leptomeningeal dissemination.
- Patients with persistent pain in the extremities or pelvis, or unexplained lymphadenopathy of the neck or axillae should be suspected of extraneural metastases.

PHYSICAL EXAM

- The neurological exam will often reveal coarse nystagmus, gait ataxia, and mild dysarthria; upper motor neuron (UMN) signs may also be present.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- An evaluation of the CSF may be necessary in selected patients during the "extent of disease" work-up (EODWU); CSF parameters should include cell count and differential, routine chemistries, lactate, β-2-microglobulin, and cytology.

Imaging

Initial approach

- MRI, with and without contrast, is the most sensitive diagnostic test; MRI is more sensitive than CT for tumors within the posterior fossa and has the advantage of midsagittal formatting; on T1 images, the tumor is mildly to moderately infiltrative and appears hypo- or isointense compared to brain; on T2 images, the mass is hyperintense; with gadolinium, medullo demonstrate patchy or dense enhancement (90%); edema and mass effect are mild to moderate, with frequent compression of the fourth ventricle; leptomeningeal metastases are noted in one-third of patients; CT demonstrates an ill-defined region of hypodensity that has variable enhancement, mild edema, and mass effect; hydrocephalus is common (75–85%).

Diagnostic Procedures/Other

- All patients require an EODWU to screen for leptomeningeal metastases and allow stratification into low- and high-risk groups; the EODWU involves a contrast-enhanced MRI scan of the spine; patients with normal or equivocal MRI results require a lumbar puncture to evaluate CSF; patients suspected of extraneural metastases require a skeletal survey and nuclear medicine scan.

Pathological Findings

- The World Health Organization classifies medullo as grade IV, and is a highly cellular tumor consisting of densely packed, small, poorly differentiated cells with hyperchromatic nuclei and scant cytoplasm, Homer-Wright rosettes, occasional ganglion cells, regions of necrosis, and frequent mitoses; histological variants include the desmoplastic, nodular, and large cell forms.

DIFFERENTIAL DIAGNOSIS

- Other mass lesions of the cerebellum that may or may not enhance should be considered, including abscess, subacute infarct, tumefactive regions of demyelination, evolving hematoma, other primary brain tumors (e.g., astrocytoma), and metastasis.

TREATMENT

MEDICATION

First Line

- Seizures can occasionally be a problem; appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management are critical.
- All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

Second Line

- Patients on chemotherapy must meet appropriate hematological parameters before proceeding with the next cycle; WBC >2.0, hemoglobin >10.0, and platelets >100,000.

ADDITIONAL TREATMENT

General Measures

- The management of medullo involves a multi-modality approach to cytoreduction that requires surgery, radiotherapy and, in selected patients, chemotherapy.
- Dexamethasone (4–16 mg/d) is usually necessary to reduce peritumoral edema, swelling, and mass effect.

Additional Therapies

- External beam radiation therapy (RT) is recommended for all medullo patients; standard RT involves treatment of the entire intracranial cavity and spine; RT to the posterior fossa consists of 50 to 55 Gy over 6 to 7 weeks, in daily fractions of 180 to 200 cGy; RT to the brain and spinal neuraxis is administered concomitantly; dosing for the brain ranges from 40 to 45 Gy; dosing for the spine ranges from 33 to 36 Gy; patients receiving less than 30 Gy to the spine are at increased risk of early relapse and shorter survival time; RT is the sole initial treatment for low-risk patients; recent attempts to reduce RT toxicity in pediatric patients have included using reduced doses in combination with multi-agent chemotherapy; focal RT may be necessary for patients with extraneural metastases (e.g., bone lesions); the role of radiosurgery remains unclear.
- Chemotherapy (Chemo) should not be used for low-risk medullo patients; phase III trials have only demonstrated a survival advantage for chemo in the high-risk patient cohorts when used during and after RT; chemo should be considered for all high-risk patients and for any patient with recurrent disease; the most active single agents include cisplatin, carboplatin, CCNU, etoposide, and cyclophosphamide; the most active combination regimens include CCNU [lomustine] and vincristine, MOPP (mustard, vincristine, prednisone, procarbazine), cyclophosphamide and vincristine, and platinum-based regimens (e.g., cisplatin, CCNU, vincristine); adult medullo patients have similar chemo response profiles to pediatric patients.

SURGERY/OTHER PROCEDURES

- Surgery should be considered in all patients to make a histological diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms; maximal surgical resection is the treatment of choice for medullo, preferably by computer-assisted volumetric resection techniques; for patients with extensive infiltration of tumor into the brainstem or cerebellar hemispheres, an extensive subtotal resection should be performed; a ventriculoperitoneal shunt may be necessary if hydrocephalus persists after maximal tumor resection (35–40%); several studies suggest that overall and 5-year survival are improved with complete or sub-total resection versus biopsy; a post-operative CT or MRI should be performed within 24 to 72 hours to screen for residual tumor.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Initial treatment will usually involve reduction of intracranial pressure, with or without hydrocephalus.

Admission Criteria

- Patients with medullo are often admitted for neurological deterioration due to elevated intracranial pressure, tumor growth, seizures, leptomeningeal metastases, or infections; maximizing anticonvulsant doses, reducing intracranial pressure, and treating infections will be required before discharge; some patients may require the initiation of new cytotoxic treatment (e.g., intrathecal chemotherapy).

Discharge Criteria

- Will be variable depending on the acute problem related to the admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Will depend on whether or not the patient is low or high risk, and if further treatment is required after the completion of RT (i.e., chemo).

Patient Monitoring

- Patients are followed with serial MRI scans and neurological examinations every 4 to 8 weeks; patients receiving chemotherapy may require more frequent follow-up.

PATIENT EDUCATION

- American Brain Tumor Association: www.abta.org
- The Brain Tumor Society: www.tbts.org
- National Cancer Institute: Childhood Medulloblastoma: www.cancernet.nci.nih.gov/clinpdg/pif/Childhood_medulloblastoma_Patient.htm

PROGNOSIS

- Low-risk patients (complete resection, intact neurological function, negative EODWU) have 5- and 10-year survival rates of 85% and 50%, respectively; high-risk patients (subtotal resection, brainstem infiltration, focal neurological dysfunction, positive EODWU) have 5- and 10-year survival rates of 50 and 30%, respectively; long-term survivors often develop impairment of memory and cognition.
- Prognosis is improved with adult onset, complete surgical resection, negative EODWU, intact neurological function, and the presence of high TrkC expression; prognosis is worse with young age, incomplete surgical resection, positive EODWU, and focal neurological dysfunction.

COMPLICATIONS

- Are quite variable, but may involve permanent cranial nerve and motor dysfunction.

ADDITIONAL READING

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- Schmidt AL, Brunetto AL, Schwartsmann G, et al. Recent therapeutic advances for treating medulloblastoma: Focus on molecular targets. *CNS Neurol Disord Drug Targets* 2010;9:335–348.

CODES

ICD9

191.6 Malignant neoplasm of cerebellum nos

CLINICAL PEARLS

- Medulloblastoma is a malignant tumor that develops in the midline of the cerebellum, that usually affects children, but can occur in adults.
- Treatment requires surgical resection and RT of the brain and spinal axis, as well as chemotherapy in high-risk patients.

BRAIN TUMOR: MENINGIOMA

Herbert B. Newton, MD, FAAN
Jacob J. Mandel, MD

BASICS

DESCRIPTION
Meningiomas are extra-axial tumors that arise from the meninges of the intracranial dura mater. They can develop in any location that has continuity with the meninges. Of all meningiomas, 90% occur in the supratentorial compartment. The most common locations are the parasagittal region (25%), cerebral convexities (20%), sphenoid wing (17%), posterior fossa (8.7%), olfactory groove (8%), and middle fossa (4%); less common locations include the optic nerve or chiasmal region, cerebellopontine angle, and within the ventricles.

EPIDEMIOLOGY
Incidence
Meningiomas are one of the most common primary brain tumors in adults, comprising 18–20%, but only 2% in children; the incidence is 2 to 7/100,000 in women and 1 to 5 per 100,000 in men; this corresponds to approximately 3,500 to 4,500 newly diagnosed meningiomas in the US each year.

Prevalence
The prevalence of pathologically confirmed meningioma is estimated to be approximately 97.5/100,000 in the US, with over 170,000 individuals currently diagnosed with this tumor.

RISK FACTORS
Risk factors that increase the risk of meningioma include cranial radiation (≥10 Gy), focal head trauma (especially with dural penetration), breast cancer, the use of hormone replacement therapy, inheritable disorders (e.g., neurofibromatosis (NF), and rare familial clusters.

Genetics
Meningiomas are usually sporadic tumors; less frequently, they can arise as part of a heritable syndrome such as NF. In rare cases, they can be familial.

GENERAL PREVENTION
There are no preventive measures for the development of meningiomas.

PATHOPHYSIOLOGY/ETIOLOGY
- The cells of origin of meningiomas are transformed arachnoidal cap cells from the outer layer of the arachnoid membrane. Typical low-grade tumors demonstrate uniform sheets of spindle-shaped cells, minimal cellular and nuclear atypia, whirl formation, psammoma bodies, and no evidence for mitotic activity or brain infiltration. Higher-grade tumors have higher cellularity, more prominent nucleoli, high mitotic activity, necrosis, and brain invasion.
- Molecular genetic studies reveal frequent deletions of chromosomes 22q and 1p. The NF2 gene (located at 22q12.3) is mutated in up to 60% of meningiomas, with dysfunction of the merlin protein. Additional genomic regions which are recurrently lost in meningiomas include 14q, 1p, 6q, and 18q. The majority of meningiomas are positive for estrogen and progesterone receptors. Other receptors of importance include the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors, both of which stimulate secretion of vascular endothelial growth factor. The RAS signaling pathway is activated by stimulation by EGF and PDGF. Somatostatin receptors, especially the sst2A subtype, are also expressed in nearly 90% of meningiomas.

COMMONLY ASSOCIATED CONDITIONS
NF type I, NF type II

Pregnancy Considerations
In some women, pregnancy can accelerate the growth and increase the clinical symptoms of meningiomas.

DIAGNOSIS

HISTORY
Meningiomas are slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., months to years). The presentation will vary with tumor location, rate of growth, and amount of peritumoral edema. Common symptoms at presentation include headache, seizure activity (often focal), personality changes, speech abnormalities, cranial nerve dysfunction (e.g., double vision, facial numbness), visual field defects, and focal motor deficits. In some patients, meningiomas are asymptomatic at diagnosis.

PHYSICAL EXAM
Common neurological signs include monoparesis or hemiparesis, asymmetric reflexes, impairment of memory and cognition, visual loss (monocular or hemianopic), aphasia, and cranial nerve palsies (i.e., V, VI, VII).

DIAGNOSTIC TESTS AND INTERPRETATION
Imaging
Initial approach
MRI, with and without gadolinium contrast, is the most critical diagnostic test. Axial, coronal, and midsagittal enhanced images should be obtained. MRI is more sensitive than CT for small tumors and associated vascular structures, although both modalities properly visualize large masses. On T1 images, the tumor is usually isointense to brain while on T2 images it is hyperintense. Meningiomas enhance densely after administration of gadolinium. On CT, meningiomas are isodense compared to brain and enhance densely with contrast; MRI and CT often demonstrate a site of dural attachment or a dural tail, as well as hyperostotic changes in nearby bone.

Follow-up & special considerations
MR spectroscopy has also been found useful in diagnosing patients unable to undergo surgery. Creatine containing peaks in meningiomas are often reduced in comparison to normal brain.

Diagnostic Procedures/Other
Angiography is performed in selected patients to assess vascular anatomy and collateral blood supply prior to surgery. It may also be useful as a prelude to pre-surgical embolization (to minimize intra-operative bleeding) or postoperative vascular reconstruction.

Pathological Findings
The World Health Organization (WHO) grades typical low-grade meningiomas (e.g., meningothelial, fibrous, transitional, psammomatous, angiomatous) as WHO grade I; intermediate tumors (e.g., atypical, clear cell, chordoid) are WHO grade II; malignant tumors (e.g., rhabdoid, papillary, anaplastic) are WHO grade III; the majority of meningiomas are WHO grade I; grades II and III tumors are uncommon.

DIFFERENTIAL DIAGNOSIS
Includes other extra-axial enhancing masses such as schwannoma, metastasis, choroid plexus papillomas, and abscess.

TREATMENT

MEDICATION
First Line
- Dexamethasone (2–8 mg/day) may be of benefit to reduce edema and swelling for patients with brain compression; it may also improve transient symptoms of pressure and swelling after radiotherapy (RT) or radiosurgery. All patients should be on an H2 blocking drug while receiving chronic dexamethasone.
- Currently, chemotherapy has a limited role in the treatment of meningiomas. It should be considered for patients that cannot undergo surgical resection and for tumors that recur despite surgery and/or RT. Traditional cytotoxic chemotherapy has limited activity against meningiomas. Drugs with modest activity in phase II trials include mifepristone (RU 486; antagonist to progesterone receptors), hydroxyurea (induces apoptosis in meningioma cells), and interferon-α-2b. When active, chemotherapy usually induces tumor stabilization, shrinkage is uncommon. However, a prospective randomized multicenter study on hydroxyurea failed to demonstrate any benefit. Somatostatin receptor agonists have shown some benefit in pilot studies and pasireotide is currently undergoing a multicenter phase II trial.
- Additionally, inhibitors of the cell cycle, angiogenesis, and a multitude of growth factor signaling pathways (including the PDGF receptor, EGF receptor, mitogen-activated protein kinase, PI3K/Akt, and TGF-b-SMAD pathways) are currently under investigation and the subject of much research.

ADDITIONAL TREATMENT

General Measures

In certain patient cohorts, meningiomas are followed conservatively after diagnosis, including those with poor health, elderly patients with small lesions or who are reluctant to proceed to surgery, and patients with small tumors that do not correlate with symptoms. Observation should include an enhanced CT or MRI every 4 to 6 months to monitor for growth. Tumors may remain quiescent if they are stable during the initial observation period. Conservative approaches are unjustified in symptomatic patients and most young patients, especially if growth potential is demonstrated.

Additional Therapies

- Conventional external beam RT is of benefit for selected patients after subtotal removal, for recurrent or progressive tumors, and for all patients with malignant pathology (WHO grade III). Clinical trials demonstrate a survival advantage for patients given RT after subtotal removal versus surgery alone. Recommended RT doses for typical low-grade tumors are 50 to 55 Gy over 6 weeks, with 180 to 200 cGy/day fractions. More aggressive RT doses of 55 to 60 Gy may be appropriate for malignant meningiomas. Three-dimensional conformal treatment planning or intensity-modulated techniques should be used to minimize irradiation of normal brain. RT is not necessary for completely resected meningiomas with low-grade pathology.
- Stereotactic radiosurgery (linear accelerator, Gamma Knife) can be an adjunctive form of treatment in selected patients. Patients most appropriate for radiosurgery include those that are medically unstable, elderly (greater than 65 years of age), have failed previous surgery, or refuse surgical intervention. Tumors less than 3 cm in diameter are most suitable. Dosing is usually between 16 and 18 Gy in a single fraction to the 50% isodense line. Local control rates range from 90 to 95%, with variable amounts of tumor shrinkage. Standard single-dose radiosurgery may be unsuitable for tumors in close proximity to the optic chiasm or the brainstem. Fractionated radiosurgery (linear accelerator) may be a safer option for tumors near the optic apparatus or brainstem. The role of heavy particle irradiation (proton beam, carbon ion) is also currently being investigated but has yet to be shown to superior to contemporary conformal techniques.

SURGERY/OTHER PROCEDURES

Surgical resection is the treatment of choice for most symptomatic patients. The surgical approach will vary depending on the location of the tumor. Complete surgical extirpation is the goal whenever possible. Only subtotal removal is possible for tumors intimately associated with cranial nerves and/or vessels. In addition, it is usually difficult to completely resect atypical and malignant meningiomas due to extensive infiltration along the dura mater and invasion of the underlying cortex or major venous sinuses. After removal of the tumor, involved bone and dural attachments should also be resected, with a wide margin. Dural defects should be repaired with pericranium, temporalis fascia, or fascia lata grafts.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

May consist of dexamethasone to control symptoms of intracranial pressure and anticonvulsants as required to control seizures depending on the patients' symptoms and neurological exam.

Admission Criteria

Admission is generally reserved for pre-surgical evaluation and surgical resection; angiography may be included in the work-up to assess regional vascular anatomy; patients with severe brain or brainstem compression might benefit from admission for intravenous dexamethasone.

Nursing

Perioperative management in patients undergoing surgical resection requires careful attention to prevent complications from cerebral edema, deep venous thrombosis, and seizures

Discharge Criteria

Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure as needed are required before discharge.

ONGOING CARE

PATIENT MONITORING

Patients are followed with serial MRI scans and assessment of neurological function every 6 to 12 months.

PROGNOSIS

- Prognostic variables predictive for survival in patients with meningiomas include the extent of resection, histological grade, patient's age, and tumor location. The recurrence rate for completely resected tumors is 20% at 10 years; for incompletely resected tumors the rate is 55% at 10 years; the 5- and 10-year progression-free survival rates are 88 and 75%, respectively, for completely resected tumors; for tumors that have undergone surgery plus RT, the 5- and 15-year progression-free survival rates are 95 and 86%, respectively; survival is more limited for patients with malignant meningioma, with a 5-year rate of 63%.
- Factors that increase the probability for recurrence include incomplete removal of all dural attachments, invasion of bone, soft tumor consistency, and malignant histology.

COMPLICATIONS

Possible complications depend on the size and location of the meningioma, and include seizures, lower extremity weakness and urinary incontinence. The pressure of the tumor may cause papilledema and result in loss of vision.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

NF types I and II

CODES

ICD9

- 192.1 Malignant neoplasm of cerebral meninges
- 225.2 Benign neoplasm of cerebral meninges
- 239.6 Neoplasm of unspecified nature of brain

CLINICAL PEARLS

- Meningiomas are extra-axial tumors that can arise anywhere within the intracranial cavity.
- They are often resectable, but in some cases will require treatment with radiotherapy or chemotherapy.

BRAIN TUMOR: METASTASES

Herbert B. Newton, MD, FAAN
Jacob J. Mandel, MD

BASICS

DESCRIPTION

- Metastatic brain tumors (MBT) are the most common complication of systemic cancer (affecting 10% of patients with cancer); MBT most often arise from tumors of the lung (50–60%), breast (15–20%), melanoma (5–10%), and GI tract (4–6%); however, they can develop from any systemic malignancy, including primary tumors of the prostate, ovary and female reproductive system, kidney, esophagus, soft tissue sarcoma, bladder, and thyroid. In children and young adults, MBT most often arise from sarcomas (e.g., osteogenic, Ewing's), germ cell tumors, and neuroblastoma. Postmortem studies suggest that melanoma, renal carcinoma, and testicular carcinoma have the greatest propensity for spread to the brain. Histological subtype can also impact the incidence of metastases, for instance Small Cell Lung cancer is more frequently found to metastasize to the brain than Non-Small Cell Lung Cancer. In 65–75% of patients, MBT will present as multiple lesions; multiple MBT are most common with lung carcinoma and melanoma; single MBT are most often noted in patients with breast, colon, and renal cell carcinoma.

EPIDEMIOLOGY

Incidence/Prevalence

- Annual incidence is 3.4 to 8.3 per 100,000 population (currently as high as 150,000 cases estimated in the USA alone). Males have a higher incidence than females—1.36:1. Incidence is on the rise and thought most likely to be due to improved imaging techniques, earlier diagnosis and better therapeutic treatment of systemic cancers. Brain metastases develop in 20–40% of adult and 6–10% of children with systemic cancer.

RISK FACTORS

- Risk factors that increase the probability of MBT include lung carcinoma and other primary malignancies with a predilection for the brain (i.e., melanoma, renal carcinoma, testicular carcinoma) and widespread aggressive disease, especially lung metastases.

Genetics

- Brain metastases are sporadic tumors without any specific genetic influence.

GENERAL PREVENTION

- Prophylactic cranial irradiation in patients with limited stage Small Cell Lung Cancer has become accepted treatment for prevention of metastases.

PATHOPHYSIOLOGY/ETIOLOGY

- Systemic tumor cells usually travel to the brain by hematogenous spread through the arterial circulation, most often originating from the lungs (primary or lung metastasis); the distribution of MBT follows the relative volume of blood flow to each area, so that 80% of tumors arise in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem; tumor cells typically lodge in small vessels at the gray–white junction and then spread into the brain parenchyma, where the cells proliferate and induce their own blood supply; MBT are histologically similar to the primary tumor of origin.
- Neurological function is disrupted by MBT through several mechanisms, including direct displacement of brain structures, perilesional edema, irritation of overlying gray matter, and compression of arterial and venous vasculature.
- Tumor cells more likely to metastasize to the brain have a more aggressive phenotype, with increased cell motility and angiogenic capacity; these changes are mediated by scatter factor, autocrine motility factor, activation of the RAS signal transduction pathway, amplification of oncogenes, and loss or mutation of metastasis-suppressor genes (e.g., nm23, KiSS1).

COMMONLY ASSOCIATED CONDITIONS

- Include other common general and neurological complications of patients with cancer such as infection and sepsis, metabolic encephalopathy, carcinomatous meningitis, and epidural spinal cord compression.

Pregnancy Considerations

Pregnancy does not affect the clinical behavior of MBT.

DIAGNOSIS

HISTORY

- Typical presentation is between 45 and 70 years in adults and 8 and 14 years in children; 40–45% of MBT present in patients 65 years or older. Symptoms caused by MBT are usually progressive over days to weeks; any symptom can arise from MBT, depending on tumor location; the most frequent symptoms include headache (25–40%), alterations of thinking and memory (20–25%), focal weakness (20–30%), and seizure activity (15–20%); less common symptoms consist of gait difficulty, visual loss, speech abnormalities, and sensory loss.

PHYSICAL EXAM

- Common neurological signs include hemiparesis (55–60%), impaired cognition (55%), papilledema (20%), dysphasia (15–20%), gait disturbance (10–20%), hemianopsia (5%), and hemisensory loss (5%).

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

Initial approach

- MRI, with and without gadolinium contrast, is the most critical diagnostic test; axial, coronal, and midsagittal enhanced images should be obtained; MBT present as rounded, well-circumscribed, non-infiltrative masses surrounded by a large amount of edema; MRI is more sensitive than CT for small tumors and tumors in the posterior fossa and brainstem, although both modalities properly visualize large MBT; on T1 images, the tumor is usually hypointense or isointense compared to brain while on T2 images it is hyperintense; MBT enhance densely after administration of gadolinium; on CT MBT are hypodense or isodense compared to brain and enhance densely with contrast.

Follow-up & special considerations

- Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of the suspected MBT to differentiate it from non-neoplastic lesions; MBT typically appear hypermetabolic on PET imaging; magnetic resonance spectroscopy (MRS) can also be used for metabolic screening to differentiate MBT from other lesions; MRS of MBT often reveals an elevated choline peak, reduced N-acetyl aspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.
- Patients with brain metastases of unknown primary origin may need to undergo a chest x-ray, chest CT, abdominal CT, and bone scan to attempt to identify the primary disease and try to determine the extent of metastatic disease.

Diagnostic Procedures/Other

- Biopsy should be undertaken in patients with a single lesion for whom the diagnosis of metastasis is in question.

Pathological Findings

- Will vary depending on the primary source of brain metastasis.

DIFFERENTIAL DIAGNOSIS

- Includes other enhancing solitary or multifocal masses such as mature abscess or abscesses, primary brain tumor, acute infarct, and hemorrhage.

TREATMENT

MEDICATION

First Line

- Dexamethasone (4 to 16 mg/d) is of benefit to reduce edema and swelling; it may also improve transient symptoms of pressure and swelling after radiotherapy (RT) or radiosurgery. All patients should be on an H2 blocking drug while receiving chronic dexamethasone. Seizures are a common problem in patients with MBT. However, anticonvulsants should not be used prophylactically; they should be implemented only after documented seizure activity; appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical. Patients with known systemic cancer receiving chemotherapy should use newer antiepileptic drugs such as lamictal or levetiracetam for seizures, which do not affect the p450 enzymes in the liver that induce the metabolism of many chemotherapeutic agents.
- Chemotherapy has a limited role in the majority of patients with MBT; it is most beneficial for patients with stable systemic disease that have progressive MBT after RT or radiosurgery; several approaches have been used (e.g., multi-agent intravenous, intra-arterial, oral) and demonstrated modest efficacy in phase II trials; the most active intravenous drugs are cisplatin, etoposide, and cyclophosphamide; intra-arterial carboplatin and oral temozolomide have also been effective in some patients.
- New molecular targeted therapies are also currently under investigation. These include tyrosine kinase inhibitors and monoclonal antibodies targeting epidermal growth factor (EGF) such as Lapatinib, Gefitinib, Erlotinib or angiogenesis pathways like Bevacizumab and sunitinib.

Second Line

- Bevacizumab and other Inhibitors of vascular endothelial growth factor may be beneficial in reducing amount of corticosteroids needed.

ADDITIONAL TREATMENT

General Measures

- Conventional external beam RT to the whole brain is the most commonly used mode of treatment for patients with MBT; RT increases median survival to 12 to 24 weeks in most patients. RT is effective at palliation of neurological symptoms (70–80% rate of symptomatic improvement) and reduces the risk of death due to progression of the MBT; the addition of RT after surgical resection will prolong time to neurological recurrence and reduce the risk of death from the MBT; recommended RT doses are 30 to 45 Gy administered over 3–4 weeks, in 180 to 200 cGy fractions. Radiosensitizers such as efaproxiral, topotecan or motexafin gadolinium, designed to increase the effect of radiation therapy in tumors, are currently being investigated.
- Stereotactic radiosurgery (SRS) (linear accelerator, Gamma Knife) can also be an adjunctive form of treatment in selected MBT patients; SRS offers the potential for treating patients with surgical comorbidities that preclude surgery or with inaccessible lesions. Metastases in the eloquent cortex, basal ganglia, thalamus and brainstem can be treated with relatively low risk in a minimally invasive way without requiring an extensive hospitalization. Appropriate patients have a good prognostic profile, including minimal neurological dysfunction, three or fewer MBT that are less than 3 cm in size, stable systemic disease, and relatively young age; recommended doses are 18 to 25 Gy in a single fraction. SRS can also be used at times as salvage treatment for local recurrence and new distant lesions after surgery or Whole-brain radiotherapy (WBRT).

Issues for Referral

- Based on the number and location of the brain metastases, a decision needs to be made on which treatments to utilize, including surgery, whole brain radiation, radiosurgery, or chemotherapy.

Additional Therapies

- Patients may benefit from occupational and physical therapy for weakness or speech therapy for aphasia, depending on their symptoms and location of metastases.

SURGERY/OTHER PROCEDURES

- Surgical resection is used for carefully selected patients with symptomatic, accessible MBT and limited systemic disease; it is most frequently applied to patients with solitary MBT. Phase III trials have demonstrated a survival advantage for surgical resection plus irradiation versus irradiation alone (40 vs. 15 weeks) for patients with solitary lesions; patients with multiple MBT can also be considered for resection if one or two accessible tumors are responsible for the majority of symptoms.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Consists of dexamethasone to control symptoms of intracranial pressure and anticonvulsants as required to control seizures.

Admission Criteria

- Admission is usually for exacerbation of cerebral edema and intracranial pressure or for excessive seizure activity.

Nursing

- Patients should be monitored every few hours with frequent neurological examinations to monitor for seizures or the development of any new focal neurological signs.

Discharge Criteria

- Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure will be required before discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients are followed with serial MRI scans and assessment of neurological function every 2 to 4 months; patients receiving chemotherapy may need more frequent monitoring of clinical and hematological status.

Patient Monitoring

- Patients on chemotherapy must meet appropriate hematological parameters before proceeding with the next cycle; WBC >2.0, hemoglobin >10.0, and platelets > 100,000; Anticonvulsant levels need to be monitored carefully, if indicated.

PATIENT EDUCATION

- Patients and their families should be educated about the signs of and how to treat seizures. They also should be instructed on the possible side effects of various chemotherapy protocols and the risks of surgery, if applicable.

PROGNOSIS/COMPLICATION

- Overall prognosis depends on the histological tumor type, number and size of MBT, severity of neurological dysfunction, and amount of systemic involvement. If left untreated, the expected survival of most patients with MBT is 4 weeks; survival is improved to 8 weeks with the addition of dexamethasone; surgical resection and/or RT can extend survival another 8–20 weeks for most patients.
- The most important factors for extended survival are age less than 65 years, intact neurological function, with a Karnofsky Performance Status greater than 70, and well-controlled systemic disease (for whom median survival is around 7 months); patients with multiple MBT have a reduced survival.
- Complications include other common general and neurological complications of patients with cancer such as infection and sepsis, metabolic encephalopathy, carcinomatous meningitis, and epidural spinal cord compression.

ADDITIONAL READING

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CODES

ICD9

198.3 Secondary malignant neoplasm of brain and spinal cord

CLINICAL PEARLS

- MBT are common complications of systemic cancer, and often respond well to treatment with surgical resection and RT.

BRAIN TUMOR: OLIGODENDROGLIOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

- Oligodendrogliomas (oligos) are an uncommon group of glial neoplasms that typically occur in young and middle-age adults. They have variable growth potential and can be quite infiltrative, depending on whether they are typical low-grade oligodendrogliomas (LGO) or the more aggressive anaplastic oligodendrogliomas (AO). Survival is prolonged in most patients and ranges between 4 and 10 years.

EPIDEMIOLOGY

Incidence/Prevalence

- Oligodendrogliomas comprise approximately 4–5% of primary brain tumors in adults; this corresponds to roughly 700 new cases each year in North America. The incidence of LGO and AO are relatively equal, similar to the incidence of pure and mixed oligos.
- All races and ethnic groups affected. Caucasians are affected more commonly than Blacks, Latinos, and Asians. Typical presentation is between 40 and 50 years of age for all forms of oligo. Incidence is slightly higher in males than females (1.5:1).

RISK FACTORS

- The only known risk factors for oligos are prior cranial radiation exposure and those rare families in which oligos are genetically transmitted.

Genetics

- Oligodendrogliomas are usually sporadic and do not have an underlying genetic predilection; rarely, oligos can be familial.

GENERAL PREVENTION

- No preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

- The World Health Organization classifies LGO as grade II, AO as grade III, and mixed anaplastic oligoastrocytoma (AOA) as grade III.
- Oligodendrogliomas are most likely derived from transformed oligodendrocytes. They have a predilection for the subcortical white matter of the cerebral hemispheres. Molecular genetic studies of oligos have noted that the two most common abnormalities are deletion of chromosomes 19q (50–80%) and 1p (40–65%). Loss of 1p and 19q are associated with chemosensitivity and prolonged survival of LGO and AO. Overexpression (without amplification) of epidermal growth factor receptors (EGFR) and platelet-derived growth factor receptors (PDGFR) is present in over 50% of oligos. Other abnormalities include loss of chromosomal material on 9p and 10q, mutation or deletion of the tumor suppressor genes p53 and p16, and overexpression of vascular endothelial growth factor (VEGF).

DIAGNOSIS

HISTORY

- The median duration from onset of symptoms to diagnosis ranges from 6 to 12 months in AO to 18 to 30 months for LGO. The most common symptom at presentation is seizure activity (50–70%). Seizures can be simple partial, complex partial, generalized tonic-clonic, or a combination. Other presenting symptoms include headache and other signs of increased intracranial pressure (e.g., nausea, emesis, diplopia), focal weakness, speech dysfunction, cognitive decline, and behavioral changes; rarely, patients can have acute symptoms from intra-tumoral hemorrhage.

PHYSICAL EXAM

- The common findings on neurological examination include hemiparesis, papilledema, dysphasia, impaired memory and cognition, hemianopsia, and sensory loss. Many patients with LGO have non-focal neurological examinations.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- General lab tests are not helpful except for pre-surgical screening and to check anticonvulsant levels.

Imaging

Initial approach

- MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. MRI is more sensitive than CT for oligos that are small or within the posterior fossa. On T1 images, the tumor is usually infiltrative and appears hypo- or isointense compared to brain. On T2 images, the mass is hyperintense. Foci of hemorrhage or calcification may be noted. With gadolinium administration, most LGO do not enhance while AO/AOA show either patchy or ring-like enhancement. Peritumoral edema and mass effect are usually mild to moderate. CT demonstrates an ill-defined region of hypodensity with variable enhancement; edema and mass effect are mild. CT may show calcification of some oligos but this is not a specific finding.

Diagnostic Procedures/Other

- Fluorodeoxyglucose-positron emission tomography (FDG-PET) may be of benefit to assess the metabolism of oligos to differentiate from non-neoplastic lesions and to maximize targeting for biopsy; on PET imaging, LGO appear hypometabolic and AO appear hypermetabolic; magnetic resonance spectroscopy (MRS) can also be used for metabolic screening to differentiate oligos from other lesions; MRS reveals an elevated choline peak, moderately reduced N-acetyl aspartate (NAA) peak, the presence of a lactate peak, and a reduced NAA/choline ratio.

Pathological Findings

- Pathological evaluation of LGO reveals a moderately cellular tumor with rounded, homogeneous cells that have a "fried-egg appearance" on paraffin sections. Other features include microcalcifications, dense branching capillaries, mild nuclear atypia, and low-level mitotic activity; AO will have similar features with the addition of higher cellular density, cellular and nuclear atypia, high mitotic rate, endothelial proliferation, and necrosis.
- Molecular analysis of chromosome 1p and/or 19q loss is of prognostic significance in patients with AO and LGO.

DIFFERENTIAL DIAGNOSIS

- Other mass lesions that may or may not enhance should be considered, including abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

TREATMENT

MEDICATION

First Line

- Seizures are a common problem in patients with LGO and AO; appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical. Dexamethasone is used at the lowest dose able to control symptoms related to intracranial pressure.

ADDITIONAL TREATMENT

General Measures

- The management of LGO and AO requires a multi-modality approach to cytoreduction that may require surgery, radiotherapy, and chemotherapy (chemo). Treatment must be individualized, and input from neurosurgeons, neuro-oncologists, and radiation oncologists is necessary for optimal therapy. Patients with small, indolent tumors (i.e., presentation with seizures, normal neurological examination, no evidence on CT/MRI of increased intracranial pressure) may be followed without treatment for evidence of growth.

Additional Therapies

- External beam radiation therapy (RT) should be considered for carefully selected oligo patients after subtotal resection or at progression; it is appropriate to consider delaying RT for patients with clean post-operative margins on follow-up MRI.

- Most patients with AO should be considered for RT after surgery, although it may be delayed until after chemotherapy (chemo) in patients with deletion of 1p and 19q. The majority of phase II clinical trial data suggest an extension of median and 5-year survival by RT after subtotal resection and at recurrence. The recommended RT dose is 50 to 60 Gy over six weeks, in 180 to 200 cGy daily fractions; focal three-dimensional treatment planning and conformal techniques should be used whenever possible to minimize radiation exposure to normal brain.
  - Stereotactic radiosurgery (SRS) has recently been used for recurrent oligos that were less than 4 cm in size. Larger tumors will not benefit from SRS due to infiltration beyond the treatment field. Median doses range from 15 to 17 Gy in one fraction. SRS may improve survival in carefully selected patients with small oligos.
  - Oligodendrogliomas are the most chemosensitive type of primary brain tumor. The use of chemo should be delayed after complete surgical resection. Chemo should be considered first-line treatment for subtotally resected LGO or AO with 1p/19q deletion status (100% response rate, survival >120 months) or 1p deletion/p53 mutation (100% response rate, survival >71 months). Patients with oligos that retain 1p and/or 19q may still respond to chemo, but with lower response rates and shorter median survival. The most active regimens are temozolomide, PCV (procarbazine, CCNU [lomustine] vincristine), BCNU [carmustine], and melphalan.

SURGERY/OTHER PROCEDURES

- Surgery should be considered in all patients to make a histological diagnosis, reduce tumor bulk and intracranial pressure, and alleviate symptoms. Maximal surgical resection is the treatment of choice for accessible LGO and AO, preferably by computer-assisted volumetric resection techniques (e.g., stealth apparatus). For patients with deep, inaccessible lesions or tumors in eloquent cortex, stereotactic biopsy should be performed. Several studies suggest that median and 5-year survival of LGO and AO are improved with complete or sub-total resection versus biopsy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Will often be for seizure control or raised intracranial pressure, or for pre-surgical evaluation. Dexamethasone (4–16 mg/d) may be of benefit to reduce peritumoral edema and swelling.

Admission Criteria

- Patients with LGO and AO are often admitted for seizure control or neurological deterioration due to elevated intracranial pressure and tumor growth; maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure will be required before discharge.

Discharge Criteria

- After stabilization of seizures or intracranial pressure, or recovery from surgical intervention.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Will be variable depending on the status of seizure control and the need for further active treatment.

Patient Monitoring

- Patients are followed with serial MRI scans and neurological examinations every 4 to 6 months. Patients receiving chemotherapy may require more frequent follow-up; anticonvulsant levels need to be monitored carefully.

PATIENT EDUCATION

- National Brain Tumor Foundation: www.braintumor.org
- American Brain Tumor Association: www.abta.org
- The Brain Tumor Society: www.tbts.org

PROGNOSIS

- The median survival of patients with LGO is 6 to 10 years, with a 5-year survival rate of 75%; median survival of patients with AO is 3 to 4 years; survival of AO patients is affected by 1p and 19q status; tumors with deletion of both 1p and 19q are very chemosensitive, with patient survival of 8 to 10 years; tumors which maintain both 1p and 19q are treatment resistant, with patient survival of 2 to 5 years.
- Prognosis is improved with young age (<40 years), LGO histology, high Karnofsky performance status, and deletion of 1p and/or 19q; prognosis is worse with age >50 years, poor Karnofsky performance status, AO histology, and presence of 1p and 19q.

COMPLICATIONS

- Most often include continued seizure activity, and neurological deficits caused by the tumor and/or active treatment.

ADDITIONAL READING

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- Lwin Z, Gan HK, Mason WP. Low-grade oligodendroglioma: Current treatments and future hopes. *Expert Rev Anticancer Ther* 2009;9:1651–1661.
- Rodriguez FJ, Giannini C. Oligodendroglial tumors: Diagnostic and molecular pathology. *Semin Diagn Pathol* 2010;27:136–145.

See Also (Topic, Algorithm, Electronic Media Element)

- Brain Tumor—High-grade Astrocytomas; Brain Tumor - Low-grade Gliomas.

CODES

ICD9

191.9 Malignant neoplasm of brain, unspecified site

CLINICAL PEARLS

- Oligodendrogliomas often arise in the cerebral hemispheres and present with seizures.
- They have a better prognosis than astrocytomas and are often chemosensitive

BRAIN TUMOR: PITUITARY

Nicholas F. Marko, MD
Robert J. Weil, MD

BASICS

DESCRIPTION
- Pituitary adenomas are benign neoplasms that most commonly originate from the adenohypophysis (anterior pituitary gland). Classified as functional (endocrine active hormones) or nonfunctional (nonsecretors). Microadenomas (≤10 mm in greatest diameter) or macroadenomas (≥10 mm).
- Pituitary carcinomas are rare. Evidence of distant metastasis(es) is the defining feature.
- Other sellar lesions, particularly craniopharyngioma and Rathke's cleft cysts, are not true histologic pituitary tumors.

EPIDEMIOLOGY
Incidence
~2.7–3.0 per 100,000 person-years.

Prevalence
- 4/100,000 to 1/1,000 in various studies.
- Microadenomas >macroadenomas.
- 14.3% of CNS tumors by location.

Age Distribution
- Most common in the third to the fifth decade.
- In young adults and children, they comprise 28.5% of primary brain and CNS tumors.

Sex
- Overall M = F occurrence.
- Prolactin-secreting and adrenocorticotrophic hormone (ACTH-secreting) tumors are more in females, growth hormone (GH) secreting and nonfunctional adenomas more in men.

Pregnancy Considerations
Symptomatic enlargement during pregnancy microadenoma 2–4.5%, macroadenoma 15–25%.

RISK FACTORS
- Most not associated with specific risk factors
- The Multiple Endocrine Neoplasia syndromes (Types 1 and 4) and the Carney Complex are increased risk of pituitary adenomas.

Genetics
- Most sporadic, 5% familial. Familial may have aryl hydrocarbon receptor interacting protein (AIP) mutations.
- *GNAS* mutations in some GH adenomas.
- Pituitary adenomas in MEN-1 *(MEN1 gene)* and MEN-4 (*CDKN1B gene)*.

PATHOPHYSIOLOGY
- Precise pathophysiology unknown.
- Excess hormone production results in symptoms.

ETIOLOGY
Etiology remains unknown.

COMMONLY ASSOCIATED CONDITIONS
Cushing's disease, Acromegaly, Infertility, Amenorrhea, and Visual field loss.

DIAGNOSIS

HISTORY
- Pituitary adenomas may be asymptomatic.
- Many patients report headaches, but their true association with pituitary tumors is unknown.
- Visual disturbances, particularly bilateral superior quadrantanopsias or bitemporal hemianopsias (often noted first by the patient's ophthalmologist) result from mass effect on the antero-inferior aspect of the optic chiasm.
- Microadenomas often cause symptoms related to hormonal hypersecretion. Common complaints include:
  - *Prolactinoma:* Amenorrhea, galactorrhea
  - *GH-secreting tumors:* Excessive sweating, joint pain, obstructive sleep apnea, menstrual irregularity, and rare gigantism.
  - *ACTH-secreting tumors:* Easy bruising, back pain, emotional labiality, fatigue, memory problems, muscle weakness, and menstrual irregularity.
  - *Thyroid stimulating hormone (TSH)-secreting tumors:* Anxiety, palpitations, and heat intolerance.

PHYSICAL EXAM
- Visual field examination often reveals a bilateral superior quadrantanopsia or bitemporal hemianopsia.
- Signs related to specific hormonal hypersecretion syndromes may include:
  - *Prolactinoma:* Galactorrhea
  - *GH-secreting tumors* (Acromegaly)*:* Hypertension, acral enlargement, skin thickening, coarse facies, soft tissue swelling, carpal tunnel syndrome
  - *ACTH-secreting tumors* (Cushing's syndrome): Moon facies, buffalo hump, abdominal striae, hypertension, diabetes, hirsutism, skin thinning, and easy bruising
  - *TSH-secreting tumors:* Tachycardia, hypertension, and goiter

ALERT
Pituitary apoplexy is a syndrome that occurs as a result of hemorrhage and/or infarction within a pituitary adenoma. Signs and symptoms: Acute and severe headache, acute visual loss, nausea/vomiting, ocular paresis, meningeal signs, and altered sensorium. Suspicion of pituitary apoplexy should prompt neurosurgical consultation as it may be a surgical emergency.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
- A basic electrolyte panel is indicated, as is a hormonal workup, including serum prolactin level, GH level, insulin-like growth factor type I, serum TSH, T_4/T_3 levels, serum luteinizing hormone, follicular stimulating hormone, and estradiol and testosterone serum levels.
- Screen the hypothalamic-pituitary-adrenal axis with an AM cortisol level and/or an ACTH stimulation test.
- When checking the prolactin serum levels, falsely low levels may be measured due to saturation of the detection assay. This is known as the "hook effect" and represents a laboratory error that will correct with dilution of the serum sample.

Follow-up & special considerations
Specialized follow-up laboratory testing may be indicated. Such tests may include oral glucose tolerance testing, insulin tolerance testing, metyrapone stimulation testing, and/or inferior petrosal sinus sampling. These tests are generally ordered by pituitary tumor specialists.

Imaging
Initial approach
- MRI is the radiologic study of choice, protocols for the sellar and parasellar regions.
- Pituitary microadenomas typically are hypointense to surrounding tissue on T1-weighted images, and isointense or hyperintense on T2-weighted images, and enhance with gadolinium.
- These tumors typically enhance more slowly than normal pituitary tissue.
- Cavernous sinus invasion may be suspected when the tumor coats the wall of the cavernous sinus(es) or encases the cavernous portion of the internal carotid artery.
- Pituitary macroadenomas may show heterogeneity due to necrosis, hemorrhage, or cyst formation.
- CT may be used to delineate the bony structures of skull base or sella.

Follow-up & special considerations
- MRI imaging is often obtained at regular intervals to follow patients with asymptomatic microadenomas, in patients being treated with medical therapy, or in postoperative patients.

Diagnostic Procedures/Other
Invasive sampling of hormone levels from the inferior petrosal sinus(es) may be required for diagnostic confirmation.

Pathological Findings
- Anterior pituitary hyperplasia is typically apparent on standard Hematoxilin and Eosin preparation.
- Classification based on immunostaining

DIFFERENTIAL DIAGNOSIS
Pituitary hyperplasia, Craniopharyngioma, Empty sella syndrome, Rathke cleft cyst, Meningioma, Germ cell tumors (germinoma), Chiasmatic/hypothalamic glioma, Metastasis (lung, breast, prostate), Juxtasellar aneurysm, Lymphocytic hypophysitis, Hamartomas, Chordomas, Granulomas, Langerhans' cell histiocytosis, and Sarcoidosis

TREATMENT

MEDICATION

First Line

- Early surgery often indicated for symptomatic pituitary adenomas. In some circumstances, medications may be tried before surgery. Medical management strategies vary by tumor type.
- *Prolactinomas:* Bromocriptine suppresses prolactin secretion, binds to D2 receptors of prolactin-producing cells. Therapy is started 0.625–1.25 mg qhs gradually increased to 2.5 mg three times a day. This gradual increase may avoid possible side effects (headaches, nausea). Somatostatin analogues (SSAs) can also be used.
- *GH-secreting adenomas:* A somatostatin analog (octreotide, lanreotide) and/or a GH receptor blocker (pegvisomant) can be used as adjuvant therapy for patients with GH-secreting pituitary adenomas.
- *ACTH-secreting adenomas:* Drugs that inhibit steroidogenesis, such as ketoconazole and metyrapone, have been used in the perioperative period in Cushing's disease. These drugs are relevant before surgical intervention or in cases of recurrences that have been treated with radiation therapy, but are not long-term options.

Second Line

Combination therapy if failing monotherapy.

ADDITIONAL TREATMENT

General Measures

- Primary goals of treatment: Reduction in mass effect, decompression of optic apparatus, reduce/correct endocrinopathy, and preserve residual normal pituitary function.
- Prolactin-secreting pituitary adenomas are often treated initially with medical therapy using dopamine agonists or SSAs.
- Surgical therapy is the first-line treatment for ACTH-producing pituitary microadenomas, many GH-secreting tumors, prolactinomas in women desirous of pregnancy, and nonfunctional pituitary tumors.
- If surgery fails to achieve biochemical remission, post-surgical adjuvant pharmacotherapy and/or radiotherapy are considered.

Issues for Referral

- Patients with suspected pituitary lesions should undergo prompt biochemical workup, particularly to investigate potential adrenal hypofunction. They should also undergo MRI imaging of sellar and parasellar region.
- Referral if positive to a neuro-endocrinologist.
- Patients with incidentally identified pituitary lesions ("pituitary incidentalomas") should undergo a complete biochemical and radiographic workup. Will need continued followup.

Additional Therapies

- Radiation is effective in treating pituitary adenomas, and can be delivered either conformally or stereotactically. Risks include damage to the optic nerve/chiasm, hypothalamus, and adjacent temporal lobe. Radiation therapy may lead to hypopituitarism.
- Radiation is usually reserved as an adjuvant modality if failing standard therapy.

SURGERY/OTHER PROCEDURES

- Most pituitary adenomas can be approached via a transsphenoidal approach. The sphenoid sinus is accessed via an endonasal, transnasal, or sublabial approach and is followed by trans-sellar removal of the tumor.
- Surgical removal of pituitary lesions is associated with low morbidity and mortality and typically results in biochemical remission.
- Surgical complications: CSF rhinorrhea, hypopituitarism, and diabetes insipidus, usually transient. Rare serious complications possible.
- A cranial approach may be indicated for patients with tumor extension into the anterior and/or middle cranial fossa, for patients with recurrent tumors, or for patients with complex tumor anatomy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- With the exception of the peri-operative period, pituitary adenomas are generally diagnosed and managed in the outpatient setting.
- The exception to this would be either patients presenting in Addisonian crisis or patients presenting with pituitary apoplexy. Initial stabilization in these patients may require administration of intravenous steroids.

Admission Criteria

Suspected Addisonian crisis or pituitary apoplexy

IV Fluids

- Iso-osmotic maintenance fluids are indicated in patients unable to tolerate PO intake.
- In general, patients who can drink should be allowed to do so. Even patients with pituitary lesions who develop diabetes insipidus can usually replace their volume losses enterally.
- Hypotonic fluids are indicated when patients with diabetes insipidus are unable to match enterally their volume losses, resulting in hypernatremia secondary to volume depletion.

Nursing

- Appropriate training in ACTH stimulation test.
- Nurses caring for post-surgical patients should be specifically instructed to insert nothing into the nose without physician's supervision.
- Patients at risk of diabetes insipidus (e.g. postoperative patients) should always have water readily available so that they can drink.

Discharge Criteria

Out-of-bed ambulating, performing basic personal care maneuvers, pain controlled, tolerating oral intake, cortisol controlled, normal salt-water balance

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Follow-up testing of the hypothalamic-pituitary-adrenal axis is typically performed in the postoperative period (6 weeks– 3 months).
- Patients are informed to call about any clear nasal drainage, fever, headaches, neck stiffness, or other signs of CSF leak or meningitis.

DIET

Resume regular or appropriate diet.

PATIENT EDUCATION

http://www.pituitary.org

PROGNOSIS

- *Prolactinomas:* Both medical and surgical treatment of a prolactin-secreting microadenoma can achieve biochemical remission. Surgical cure rates in excess of 70–90% are reported. Macroadenomas lower cure rate.
- *GH-secreting adenomas:* Up to 70% of patients with acromegaly are expected to achieve remission with surgical treatment (more common with microadenomas).
- *ACTH-secreting adenomas:* Approximately 70% or more of patients with a distinct adenoma on MRI achieve remission, although ACTH-secreting adenomas may recur.

COMPLICATIONS

Selective or panhypopituitarism

ADDITIONAL READING

- Central Brain Tumor Registry of the United States. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004–2007. Available: http://www.cbtrus.org/2011-NPCR-SEER/WEB-0407-Report-3-3-2011.pdf. Accessed 14 July 2011.
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CODES

ICD9

227.3 Benign neoplasm of pituitary gland and craniopharyngeal duct

BRAIN TUMOR: PRIMARY CNS LYMPHOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Primary CNS lymphoma (PCNSL) is a malignant non-Hodgkin's lymphoma that is limited to the cranial-spinal axis, without systemic involvement. It originates in the brain and must be distinguished from metastatic systemic lymphoma. At the time of diagnosis, the leptomeninges (30 to 35%) and eyes (25%) are also frequently involved. PCNSL occurs most often in patients with an immunological disorder but can also arise in patients with intact immune function.

EPIDEMIOLOGY

Incidence/Prevalence

- The incidence of PCNSL is rising in patients with immunocompetence and in those with HIV, with a 10-fold increase over the past 25 years. PCNSL now accounts for 2 to 3% of all primary brain tumors in patients with immunocompetence. For patients with HIV, the lifetime incidence is in the range of 5 to 10%. The annual incidence is currently 30 cases per 10 million persons.
- All races and ethnic groups affected; Caucasians are affected more commonly than blacks, Latinos, and Asians. Typical presentation is between 50 and 55 years of age in patients with immunocompetence and between 30 and 35 years in patients with HIV. Incidence is slightly higher in males than females (3:2). Patients with HIV and PCNSL are predominantly male (7.3:1).

RISK FACTORS

The most important risk factor for PCNSL is immunosuppression, usually in patients with HIV or after organ transplantation. Less often in congenital immunodeficiency states such as ataxia-telangiectasia and Wiskott–Aldrich syndrome; Epstein–Barr virus (EBV) is involved in the pathogenesis of more than 95% of PCNSL from patients with HIV; EBV is implicated in less than 5% of PCNSL from patients with immunocompetence.

Genetics

PCNSL are sporadic and do not have an underlying genetic predilection, except for genetically mediated immunodeficiency states.

GENERAL PREVENTION

There are no preventive measures for PCNSL.

PATHOPHYSIOLOGY/ETIOLOGY

- PCNSL is classified as a Stage I_E non-Hodgkin's lymphoma because the involvement is restricted to a single extranodal site—the brain. It is a clonal expansion of B cells in over 97% of cases, and T-cell PCNSL is uncommon (2 to 3%). The World Health Organization does not have a specific classification scheme for PCNSL. Histological sub-typing of PCNSL suggests that diffuse large cell and diffuse large cell immunoblastic types are most common; however, sub-typing has not been shown to have clinical relevance.
- It remains unclear how PCNSL arises in the brain, since the CNS is devoid of lymphoid tissue or lymphatics. Histological evaluation reveals an angiocentric, diffusely infiltrative mass of neoplastic lymphoid cells, with extension into surrounding brain parenchyma. Isolated nodules of lymphoma cells can be observed at remote sites; reactive astrocytosis and necrosis may be noted.
- Molecular genetic studies of PCNSL demonstrate clonal abnormalities of several chromosomes (1, 6, 7, 14) and translocations (e.g., 1;14, 6;14); clonal rearrangements of the immunoglobulin and TcR genes are typically noted; the most common genetic alterations are mutations of the CDKN2A/p16 and CDKN2B/p15 tumor suppressor genes.

DIAGNOSIS

HISTORY

PCNSL is a highly aggressive tumor with a rapidly progressive course; median time from onset of symptoms to diagnosis is only 4 to 12 weeks. The most common signs and symptoms at presentation include focal neurological deficits (e.g., hemiparesis, dysphasia, cranial neuropathy; 50 to 55%), mental status changes (e.g., reduced mentation, lethargy, confusion; 34 to 50%), seizures (10 to 25%), and evidence of increased intracranial pressure (e.g., headache, nausea, emesis, papilledema; 14 to 30%). Patients with ocular involvement complain of blurred vision or floaters; patients with spinal and/or leptomeningeal disease complain of neck or back pain, myelopathic weakness, and/or bowel and bladder dysfunction.

PHYSICAL EXAM

Focal neurological deficits are noted in 50–55% of patients, including hemiparesis, dysphasia, and cranial neuropathies. Mental status changes are also common, affecting 35–50% of patients.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Routine tests are not helpful, except in the setting of pre-surgical evaluation.

Follow-up & special considerations

Patients with suspected PCNSL require a lumbar puncture to assess CSF for cytology; HIV screening; CSF EBV DNA testing should be obtained in patients with AIDS; bone marrow evaluation for lymphomatous involvement.

Imaging

Initial approach

PCNSL usually presents in the periventricular region or among the deep nuclear structures. The tumor nodules are multifocal in 40% of cases (more so in patients with HIV). MRI, with and without gadolinium contrast, is the most sensitive diagnostic test. On T1 images, the tumor is usually infiltrative and appears hypo- or isointense compared to brain. On T2 images, the mass is hyperintense. With gadolinium administration, most PCNSL show either diffuse or ring-like enhancement. Peritumoral edema and mass effect are usually mild to moderate. Hemorrhage and regions consistent with necrosis are occasionally noted. CT demonstrates an ill-defined region of hypodensity with variable enhancement, and mild to moderate edema and mass effect. Spinal MRI is indicated in patients with spinal symptoms, to screen for involvement of the spinal cord or leptomeninges.

Follow-up & special considerations

Chest x-ray and CT of the abdomen and pelvis are necessary to screen for systemic lymphoma.

Diagnostic Procedures/Other

Fluorodeoxyglucose–positron emission tomography (PET) may be of benefit to assess the metabolism of PCNSL to differentiate it from non-neoplastic lesions. PCNSL typically appears hypermetabolic on PET imaging; flurodeoxyglucose (FDG)-PET is especially helpful in patients with HIV to differentiate PCNSL from infection (i.e., toxoplasmosis). CSF evaluation reveals mild pleocytosis in 35 to 60% of patients, with positive cytology in up to 30% of cases. Ophthalmological evaluation (including slit-lamp testing) is necessary to screen for ocular lymphoma.

Pathological Findings

Pathological features include perivascular location of dense sheets of neoplastic lymphoid cells, with numerous mitotic figures and extensive apoptosis, and extensive staining for CD20 and CD79a.

DIFFERENTIAL DIAGNOSIS

Other mass lesions that enhance should be considered, including other malignant brain tumors, mature abscess, subacute infarct, tumefactive regions of demyelination, and evolving hematoma.

TREATMENT

MEDICATION

First Line

Seizures are a common problem in patients with PCNSL; appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical; dexamethasone should be avoided if possible, or used at the lowest dose able to control pressure-related symptoms.

ADDITIONAL TREATMENT

General Measures

- The management of PCNSL requires a multi-modality approach that involves input from neurosurgeons, neuro-oncologists, and radiation oncologists.
- Symptomatic treatment consists of reducing intracranial pressure, controlling seizures, and pain control; corticosteroids should be used as sparingly as possible, since PCNSL may shrink transiently and make biopsy more difficult.

Additional Therapies

- External beam radiation therapy (RT) should be considered, since PCNSL is radiosensitive in patients with immunocompetence and HIV. Complete and partial responses can be noted. However, the responses are not durable, with relapse within 8 to 14 months. The recommended approach for patients with immunocompetence patients is whole-brain RT, 45 to 50 Gy over five weeks in 180 to 200 cGy/d fractions. Patients with HIV receive 40 to 45 Gy; patients with ocular PCNSL may require RT to both orbits (40 Gy). Median survival with RT alone is 17 months in patients with immunocompetence patients and 3 months in patients with HIV. Lower-dose RT is sometimes combined with chemotherapy.
- Chemotherapy should be considered for all patients with PCNSL. The most active regimens use high-dose methotrexate (MTX) (intravenous or intra-arterial; IA) in combination with other drugs (e.g., cyclophosphamide, etoposide, procarbazine, cytarabine). IA chemotherapy is combined with mannitol-induced blood-brain barrier disruption in some patients. Chemotherapy can be used alone (i.e., neoadjuvant) or in combination with RT. Younger patients with intact neurological function and good performance status are the best candidates for neoadjuvant approaches. Median survival ranges from 40 to 45 months in patients treated with chemotherapy alone or in combination with RT. Intra-thecal chemotherapy (MTX, cytarabine, cytarabine depofoam), preferably via an ommaya reservoir, improves survival in PCNSL patients in combination with systemic chemotherapy; intra-ocular chemotherapy (MTX) may be of benefit in selected patients with ocular PCNSL.

SURGERY/OTHER PROCEDURES

Surgery should be considered in all patients to make a histological diagnosis. Since extent of surgical resection has not been found to correlate with survival in patients with PCNSL and most lesions are located deep in the brain, stereotactic biopsy is the recommended approach. Intra-ocular biopsy may be necessary to demonstrate lymphoma cells and justify ocular therapy; ocular biopsy may be diagnostic of PCNSL in some patients.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Usually involves reduction of raised intracranial pressure, controlling seizures, and pain control.

Admission Criteria

Patients with PCNSL are often admitted for seizure control, neurological deterioration due to elevated intracranial pressure and tumor growth, or leptomeningeal metastases. Maximizing anticonvulsant doses, resolving metabolic disturbances, and reducing intracranial pressure will be required before discharge. New therapeutic interventions may be necessary (e.g., intrathecal chemotherapy).

IV Fluids

Aggressive IV hydration may be important for patients undergoing high-dose IV or IA MTX chemotherapy.

Nursing

Will need to follow hydration status and urinary pH status during inpatient stays for high-dose MTX chemotherapy.

Discharge Criteria

Will be variable depending on the specific issue involved in the admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Will depend on what phase of treatment the patient is in—RT or chemotherapy—and whether there are plans for continued treatment.

Patient Monitoring

Patients are followed with serial MRI scans and neurological examinations every 4 to 8 weeks; patients receiving chemotherapy may require more frequent follow-up; anticonvulsant levels need to be monitored carefully.

PATIENT EDUCATION

- National Brain Tumor Foundation: www.braintumor.org
- American Brain Tumor Association: www.abta.org
- The Brain Tumor Society: www.tbts.org

PROGNOSIS

- The natural history of PCNSL is death within 8 to 14 weeks without treatment; with RT plus chemotherapy or chemotherapy alone, median survival ranges from 25 to 45 months in patients with immunocompetence patients; for patients with HIV, median survival is 6 to 18 months with treatment.
- Prognosis is improved with young age (<60 years), intact neurological function and good performance status, and male sex; prognosis is worse with age greater than 60 years, poor neurological function, female sex, and tumor involvement of the corpus callosum and/or brainstem.

COMPLICATIONS

Mainly involve the potential for continued seizure activity and neurological dysfunction, such as reduced mental status and focal deficits.

ADDITIONAL READING

- Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. *Arch Neurol* 2010;67:291–297.
- Jahnke K, Thiel E. Treatment options for central nervous system lymphomas in immunocompetent patients. *Expert Rev Neurother* 2009;9:1497–1509.
- Morris PG, Abrey LE. Therapeutic challenges in primary CNS lymphoma. *Lancet Neurol* 2009;8:581–592.

See Also (Topic, Algorithm, Electronic Media Element)

AIDS: Management of Focal Brain Lesions

CODES

ICD9

- 191.9 Malignant neoplasm of brain, unspecified
- 200.50 Primary central nervous system lymphoma, unspecified site, extranodal and solid organ sites
- 202.80 Other malignant lymphomas, unspecified site, extranodal and solid organ sites

CLINICAL PEARLS

- Diagnosis of PCNSL will usually require a brain biopsy; further surgery is generally not helpful.
- Treatment will require either RT or chemotherapy with a MTX-based regimen.

CARCINOMATOUS MENINGITIS

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BASICS

DESCRIPTION

Carcinomatous meningitis (CAM) is a common neurological complication of systemic cancer that is associated with a high mortality and morbidity. CAM is caused by the spread of cancer cells into the subarachnoid space and CSF, with subsequent access to the entire neuraxis. CAM has the capacity to affect every component of the CNS, including the brain, cranial nerves, spinal cord, spinal nerve roots, and cauda equine. It can develop in virtually any malignancy, but is most common in leukemia, lymphoma, and solid tumors such as melanoma, breast carcinoma, and small cell lung carcinoma.

EPIDEMIOLOGY

Incidence/Prevalence

- The estimated incidence of CAM is 4–15% of patients with solid tumors, 7–15% of patients with lymphoma, 5–15% of patients with leukemia, and 1–2% of patients with primary brain tumors.
- All races and ethnic groups equally affected. Typical presentation is between 45 and 60 years of age. Females have a higher incidence than males—1.6:1.

RISK FACTORS

Risk factors that increase the probability of CAM include tumor type (e.g., melanoma) and aggressive, wide-spread systemic disease.

Genetics

CAM is a sporadic process without any specific genetic influence.

GENERAL PREVENTION

No preventive measures are known.

PATHOPHYSIOLOGY/ETIOLOGY

- Systemic tumor cells gain access to the subarachnoid space and CSF through hematogenous spread to arachnoidal vessels, choroid plexus, or Batson's vertebral venous plexus; by direct extension from superficial regions of brain parenchyma, periventricular, or epidural metastases; and by perineural spread along spinal or cranial nerves. CAM is histologically similar to the primary neoplasm.
- Neurological function is disrupted by CAM through several mechanisms, including elevation of intracranial pressure by the presence of diffuse tumor burden, direct invasion of neural tissues (brain, spinal cord, cranial and spinal nerves), ischemia due to obstruction of arterial blood flow, and regional metabolic alterations (e.g., lactic acidosis, low glucose concentration).
- Tumor cells most likely to metastasize to the CNS have a more aggressive and motile phenotype. These changes are mediated by scatter factor, autocrine motility factor, amplification of oncogenes, and mutation of metastasis-suppressor genes (e.g., nm23).

COMMONLY ASSOCIATED CONDITIONS

Commonly associated conditions include other common, general, and neurological complications of cancer patients such as infection and sepsis, metabolic encephalopathy, brain metastasis, and epidural spinal cord compression.

DIAGNOSIS

HISTORY

Symptoms and signs of CAM can involve any region of the neuraxis, including the brain, cranial nerves, and spine. The symptoms are usually progressive over days to weeks. In 30–40% of patients, more than one region of the neuraxis will be involved. Cerebral signs and symptoms include headache (60%), mental status changes (50%), gait alterations (25%), nausea and emesis (22%), seizures (11%), and hemiparesis (3%). Cranial nerve signs and symptoms include diplopia and ocular motor pareses of III, IV, and VI (30%), facial weakness (27%), impaired hearing (13%), facial numbness (8%), visual loss and optic neuropathy (8%), and tongue weakness (8%); spinal signs and symptoms include reflex asymmetry (85%), leg weakness (70%), paresthesias (40%), sensory loss (30%), back/neck pain (30%), radicular pain (26%), and bowel/bladder dysfunction (15%).

PHYSICAL EXAM

Stepwise loss of function affecting some or all levels of the neuraxis, as noted above.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

The single most useful diagnostic test is examination of the CSF by lumbar puncture (LP); the CSF is always abnormal, even when the cytology is negative; in most patients, there is a mild to moderate pleocytosis, elevated protein, reduced glucose level, and elevated lactate level; tumor markers (e.g., β-glucuronidase, β-2-microglobulin, carcinoembryonic antigen) are adjunctive tests that can improve diagnostic accuracy if elevated; 50% of patients with CAM will have a positive cytology after one LP and 90% will be positive after the third LP; CSF cytology can remain negative in some patients.

Follow-up & special considerations

Brain imaging should occur before LP to rule out focal mass lesion and potential risk of herniation.

Imaging

Initial approach

Magnetic resonance imaging of the brain and/or spinal cord, with or without gadolinium contrast, is the most sensitive imaging test. Axial, coronal, and midsagittal-enhanced images should be obtained. Abnormal enhancement is noted in 70% of patients with CAM, along the surface of the brain, ventricular ependyma, cranial nerves, spinal cord, and cauda equina. Nodules of enhancement and hydrocephalus are noted in 38% and 7% of patients, respectively. CT reveals similar enhancement patterns, but in only 40% of patients with CAM. MRI or CT evidence of CAM can be diagnostic if CSF cytology is negative; however, a negative MRI or CT does not rule out CAM. Myelography, with or without CT follow-through, can also be diagnostic if MRI is unavailable.

Diagnostic Procedures/Other

Flow cytometry of the CSF may be diagnostic of CAM from leukemia and lymphoma if able to demonstrate a monoclonal population of cells; it may also demonstrate the presence of neoplastic aneuploid DNA populations. For CAM patients with diffuse, bulky disease, a radionuclide CSF flow study may be necessary to demonstrate patency of the CSF pathways before intrathecal (IT) chemotherapy is administered through an Ommaya reservoir.

Pathological Findings
Patches and nodules of tumor cells, with same histology as the primary tumor, along the surface of the cranial meninges, cranial nerves, spinal cord, and spinal nerve roots.

DIFFERENTIAL DIAGNOSIS
Differential diagnosis includes other diseases that can involve the subarachnoid space, induce CSF inflammation, and cause enhancement of the leptomeninges on MRI, such as chronic bacterial or fungal meningitis, neurosarcoidosis, Guillain–Barre syndrome, and vasculitis.

TREATMENT

MEDICATION
First Line
Dexamethasone (2–8 mg/day) may be of benefit to reduce edema and swelling, or to improve transient symptoms of pressure and swelling after RT. Seizures may be a problem in patients with CAM. Appropriate anticonvulsant choices (e.g., phenytoin, carbamazepine, levetiracetam) and management will be critical. Narcotic analgesics may be necessary for adequate amelioration of pain.

ADDITIONAL TREATMENT
General Measures
General measures should include symptomatic treatment and consultation by radiation oncology, neuro-oncology, and neurosurgery for treatment evaluation.

Additional Therapies
- Conventional radiotherapy (RT) is of benefit to stabilize or palliate symptomatic regions of CAM. It is most often administered to the whole brain or to involved regions of the spinal axis with bulky disease. RT is more effective than IT chemotherapy for bulky disease, due to poor penetration of drug deeper than 2–3 mm. Pain-related symptoms are often improved with RT. Spinal neuraxis RT is generally avoided due to severe myelosuppression. The recommended dose to the brain or involved spine is 30 Gy in 10 fractions over 2 weeks. Patients with leukemic or lymphomatous CAM may improve neurologically after RT. Improvement is uncommon with CAM from solid tumors.
- Chemotherapy is the only therapeutic modality that can treat the whole neuraxis. It is best administered by the IT route, either by LP or Ommaya reservoir. Drug distribution is more even throughout the neuraxis when using the intraventricular route. Drugs that are approved for IT chemotherapy (usually once or twice weekly) include methotrexate, cytarabine, thiotepa, and depofoam cytarabine. Systemic chemotherapy has not been as effective as IT, due to poor CSF penetration and low drug concentrations. High-dose intravenous methotrexate, cytarabine, and thiotepa have had modest efficacy in some patients.

SURGERY/OTHER PROCEDURES
Surgical intervention is rarely necessary for treatment of CAM. Leptomeningeal biopsy may be of benefit in clinically suspicious patients with negative CSF and MRI testing. Ommaya reservoir placement should be considered for all patients receiving IT chemotherapy. Patients that develop hydrocephalus will require placement of a ventriculoperitoneal shunt. The shunt should contain an on–off valve to allow IT chemotherapy.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Initial stabilization consists of dexamethasone to control symptoms of intracranial pressure, anticonvulsants as required to control seizures, and pain control.

Admission Criteria
Admission is usually for progression of neurological dysfunction and/or seizure activity.

Discharge Criteria
Maximizing anticonvulsant doses and resolving metabolic disturbances will be required before discharge; new modes of treatment may be required (e.g., RT, IT chemotherapy).

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Follow-up recommendations will vary depending on the acute issues involved, and on the extent of further active treatment.

Patient Monitoring
Patients are followed with assessment of neurological function and CSF evaluation every 4–8 weeks. MRI follow-up is required every 2–4 months; patients receiving chemotherapy may need more frequent monitoring of clinical and hematological status. Anticonvulsant levels need to be monitored carefully.

PATIENT EDUCATION
- Carcinomatous/neoplastic meningitis. www.neuro-oncology.org/neomen1.htm
- Carcinomatous/neoplastic meningitis. www.bt-treatment.com/neomen1.htm

PROGNOSIS
- CAM is a virulent complication of cancer with a natural history of death in 4–8 weeks without treatment. Median overall survival is poor and ranges from 4 to 6 months with treatment. Survival is most limited for patients with solid tumors, except for those with breast cancer, who may survive 6–12 months. Patients with leukemia and lymphoma may respond well to therapy.
- The most important factors for extended survival are early diagnosis with low subarachnoid tumor burden, good performance status, mild neurological dysfunction, female sex, longer duration of symptoms, and treatment with IT chemotherapy; factors contributing to brief survival include high CSF protein levels, severe neurological dysfunction, male sex, poor performance status, and clinical involvement of the supratentorial leptomeninges.

COMPLICATIONS
Complications involve the potential loss of neurological function if leptomeningeal tumor is allowed to damage the brain, cranial nerves, spinal cord, or spinal nerve roots.

ADDITIONAL READING

- Chamberlain MC. Neoplastic meningitis. *Oncologist* 2008;13:967–977.
- Newton HB. Neurologic complications of systemic cancer. *Am Fam Phys* 1999;59:878–886.
- Shapiro WR, Johanson CE, Boogerd W. Treatment modalities for leptomeningeal metastases. *Semin Oncol* 2009;36[Suppl 2]:S55–68.

CODES
ICD9
- 198.3 Secondary malignant neoplasm of brain and spinal cord
- 198.4 Secondary malignant neoplasm of other parts of nervous system

CLINICAL PEARLS
- CAM can affect any level of the nervous system, but often causes mental status changes and cranial nerve palsies.
- Treatment with RT and IT chemotherapy can often improve symptoms and stabilize neurological function.

CARDIOEMBOLIC STROKE

Tamer Ammar, MD
Irene Katzan, MD

BASICS

DESCRIPTION
Cardioembolic stroke is defined as the sudden or rapid development of focal neurological symptoms or sometimes global disturbance of cerebral function caused by embolism to the brain from a cardiac source.

EPIDEMIOLOGY
Cardioembolic stroke is responsible for approximately 20% of all ischemic strokes.

- The annual incidence of cardioembolic strokes in the US is estimated at approximately 146,000 cases.
- *Age*: Affects all ages but incidence is higher with increased age.
- *Sex*: Both sexes equally affected.
- *Race*: More prevalent in whites than blacks or Hispanics.

RISK FACTORS
See Etiology.

Genetics
Some hypercoagulable states are inherited.

PATHOPHYSIOLOGY
- The mechanism is occlusion of cerebral arteries with emboli from a cardiac source, causing ischemia.
- Emboli can be composed of:
  - Thrombus
  - Platelets, cholesterol, calcium
  - Bacteria
  - Neoplastic cells
  - Air, fat
- The composition of embolic material depends on the specific cardiac source (see Etiology).

ETIOLOGY
- Cardiac disorders leading to formation of a cardiac source of emboli include:
  - *Arrythmias*: Atrial fibrillation, which is responsible for 50–70% of cardioembolic strokes, and for one-sixth of all ischemic strokes. Other arrhythmias include sick sinus syndrome and atrial flutter.
  - *Valvular disease*: It includes rheumatic, prosthetic mitral or aortic valve disease, infective and marantic endocarditis.
  - *Left ventricular thrombus*: It occurs in the setting of abnormal left ventricular function, especially anterior wall motion abnormalities which can occur with ischemic heart disease (especially with ejection fraction <30%). Thrombi can also form in the left ventricle in hypercoagulable states.
  - *Cardiac tumors*: Such as atrial myxoma and papillary fibroelastoma.
  - *Shunts*: Septal defects and patent foramen ovale (PFO) allow venous emboli formed in the peripheral veins to bypass the lungs (where the emboli would result in pulmonary emboli) and enter the arterial circulation causing paradoxical embolism.
  - *Atrial abnormalities*: Examples include dilated atria, atrial wall infarcts and thrombi, and atrial septal aneurysms.
  - *Hypercoagulable states* can trigger thrombus formation in the cardiac chambers or valves
- *Procedures*: Strokes can occur as a complication of open heart surgeries and cardiac endovascular procedures such as catheterization and stenting.

COMMONLY ASSOCIATED CONDITIONS
See Etiology.

DIAGNOSIS

HISTORY
The clinical features of the stroke can suggest embolism, although they are not sensitive or specific enough to definitively determine a cardiac source for stroke.

- Patients with embolism to the brain often have sudden onset of neurologic signs that are maximal at onset without warning episodes.
- Another characteristic clinical pattern has been called the *spectacular shrinking deficit*, which is described as sudden, complete or nearly complete clearing of the neurologic deficit, due to early lysis of the embolus.
- Emboli typically lodge in cortical vessels or larger intracranial vessels so clinical syndromes related to damage in these vascular distributions are typical.
- Symptoms suggesting lesions in multiple vascular territories should raise the suspicion of cardiogenic emboli.
- Transient ischemic attacks can occur. When multiple, symptoms differ for each.
- Headaches are common, seizures are uncommon.

PHYSICAL EXAM
- Findings on the neurological examination vary depending on the cerebral vessel(s) involved, and are not specific of the etiology.
- General examination may find:
  - Signs of cardiac disease causing the embolic stroke: Atrial arrhythmias, heart murmurs, congestive heart failure
  - Signs of systemic embolism such as ischemic fingers or toes

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
- Blood test should include serum glucose, lipid profile, BUN, creatinine, CBC with platelet, PT, PTT, and INR.
- A hypercoagulable profile can be considered in young patients, since hypercoagulable states may contribute to clot formation in cardioembolic stroke.
- Serial blood cultures should be obtained when infective endocarditis is suspected.

Imaging
- *Chest x-ray film* should be obtained to look for cardiomegaly.
- *Brain imaging* must be performed in all patients presenting with suspected stroke.
- *CT scan* is typically the first brain imaging test performed since it is very sensitive in detecting intracranial hemorrhage, is inexpensive, quick, and, importantly, is readily available. When CT shows strokes in multiple vascular distributions, then cardiac source of emboli must be suspected.
- *MRI* of the brain (especially diffusion weighted imaging and FLAIR) is more sensitive in detecting early infarction, and infarcts in the cerebellum, brainstem, and inferior temporal lobes.
- *Vascular imaging* should be performed in all patients and should include imaging of the carotid arteries if symptoms could be referable to the carotid circulation.
- *Carotid ultrasound* is safe, portable, and relatively inexpensive. It is an important test to evaluate for extracranial carotid disease, which is part of differential diagnosis for sources of embolic stroke.
- *Transcranial Doppler examination* can be used to look for the presence of intracranial disease, and to assess for right to left shunts ("TCD bubble study").
- *MR angiography* is a noninvasive test and is accurate for assessing the major extra- and intracranial arteries, but it may overestimate the severity of the stenosis.
- *CT angiography* although requires a dye load, this test has good accuracy in the detection of intracranial and extracranial disease.
- *Angiography* is the gold standard for an accurate assessment of both the extracranial and intracranial vasculature. However, it is an invasive procedure and should be reserved for use in patients in whom noninvasive testing is inconclusive or produces conflicting findings.
- *Cardiac testing*:
  - *ECG* and *cardiac monitoring* should be performed to evaluate for arrhythmias. There is an increasing interest in prolonged cardiac monitoring up to 2–4 weeks for the detection of intermittent arrhythmias.
  - *Transthoracic echocardiography (TTE)* is indicated in all patients suspected of having a potential cardiac source of ischemic stroke. If the TTE is negative and a cardiac source is still suspected, then transesophageal echocardiography (TEE) can be performed. TEE is more accurate than TTE in showing atrial thrombi, valvular vegetations, detecting shunts; and evaluating the proximal aorta, which can be another source of embolism.

DIFFERENTIAL DIAGNOSIS
- Large artery atherosclerosis with *in situ* thrombosis or artery-to-artery emboli
- Arterial dissection
- Vasculitis

TREATMENT

MEDICATION

- *Intravenous recombinant tissue plasminogen activator (r-tPA)* is indicated for acute ischemic strokes, including those with cardiac source of embolism. It must be given within 4.5 hours of time last known well.
- *Antiplatelet agents* are indicated for secondary stroke prevention in patients with native valvular heart disease without atrial fibrillation, patients with atherosclerosis, and patients who are not candidates for anticoagulation. Options include *aspirin* (50–325 mg daily), *clopidogrel* (*Plavix*) (75 mg daily) or *combination of aspirin* 25 mg/extended-release *dipyridamole* (200 mg one tablet twice daily) (*Aggrenox*). The combination of aspirin and clopidogrel might confer more protection than aspirin alone in cases of atrial fibrillation who are not candidates for anticoagulation, although this combination increases the risks of bleeding complications above antiplatelet monotherapy.
- *Anticoagulants* are indicated for atrial fibrillation. Their use is also reasonable for secondary stroke prevention in rheumatic mitral valve disease and dilated cardiomyopathy. The most used anticoagulant is warfarin. Dabigatran and rivaroxaban are newer alternatives to warfarin for patients with atrial fibrillation.
- Main contraindications:
  - *Intravenous r-tPA*:
    - Within 3-hour window: Patients with recent history of stroke or head trauma, major surgery, gastrointestinal bleeding. Additional contraindications include persistently elevated blood pressure, elevated INR, hypoglycemia, and minor or isolated neurologic signs (see references 1 and 2 for complete list).
    - In the 3- to 4.5-hour window: In addition to the above exclusion criteria, patients >80 years old, those taking oral anticoagulants (regardless of INR), those with a baseline NIH stroke scale >25, and those with a history of both stroke and diabetes.
  - *Aspirin/Aggrenox*: Known allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer.
  - *Clopidogrel*: Active systemic bleeding.
  - *Warfarin:* Active bleeding, bleeding tendency, noncompliance, and fall risk.
  - *Dabigatran:* Active bleeding, noncompliance, and fall risk.
  - *Rivaroxaban:* Active bleeding, noncompliance, and fall risk.
- Precautions:
  - *r-tPA:* Noncompressible arterial or venous punctures must be avoided. Blood pressure must be monitored closely during administration of the medicine and for 24 hours afterwards. Blood pressure should be treated if elevated. Watch for allergic reaction.
  - *Clopidogrel:* Monitor for any TTP symptoms at the beginning of treatment.
  - *Warfarin and dabigatran:* Watch for compliance, bleeding events, and falls.

ADDITIONAL TREATMENT

General Measures

General treatment of stroke includes acute supportive care, management of contributory cardiac lesions, and secondary stroke prevention.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Prevention and treatment of complications:
  - Includes treatment of hyperglycemia, fever, and infection; deep vein thrombosis prophylaxis; aspiration precautions adequate hydration and nutrition; judicious control of blood pressure with avoidance of excessive reduction in the acute setting and adequate control in the long run; avoidance of prolonged use of indwelling catheter to prevent urinary tract infection
- Symptomatic treatment:
  - Antidepressants for depression; muscle relaxants, such as baclofen or tizanidine for residual spasticity
- Adjunctive treatment:
  - Physical, occupational, speech and swallow therapy

SURGERY/OTHER PROCEDURES

- Patients with ischemic strokes due to large vessel occlusions may benefit from acute intra-arterial interventions including intra-arterial tPA, mechanical clot retrieval, angioplasty, and stenting. The treatment window for endovascular intervention is generally considered to be 8 hours from time last known well.
- Some cardiac lesions require procedural interventions, such as valve replacement for infected valve, resection of cardiac tumors (myxoma), pacemaker placement for sick sinus syndrome. PFO closure is not recommended in most cases.
- Hemicraniectomy may be needed for large strokes causing significant mass effect.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Any patient with acute ischemic stroke should be admitted to the hospital for evaluation and treatment, prevention of complications, early initiation of physical, occupational, and speech therapy, determination of additional rehabilitation and care needs, and patient and caretaker education.

IV Fluids

Stroke patients should generally be started on a normal saline solution drip to maintain hydration and maximize cerebral perfusion.

Nursing

Admission to a stroke unit with nurses trained in the management of stroke patients improves outcome.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Close INR monitoring for patients on warfarin.
- Because atherosclerosis is often a factor leading to cardioembolic stroke, controlling vascular risk factors is especially important in this population. This includes monitoring blood pressure, glucose, weight, and cholesterol, as well as smoking cessation.

PATIENT EDUCATION

American Stroke Association, National Center 7272 Greenville Avenue, Dallas, TX, 75231.
www.strokeassociation.org

PROGNOSIS

- Important predictors of future functional status include initial severity of neurological impairment and presence and timing of vessel recanalization.
- Rate of recurrence varies, depending on exact source of cardiac embolism. Risk is reduced with adequate secondary prevention, including appropriate antithrombotic medications, and vascular risk factor control.

COMPLICATIONS

- *Neurological*: Recurrent cardiac embolism, stroke extension, hemorrhagic transformation of the ischemic stroke, herniation from mass effect, death, seizures.
- *Medical*: Infections, including aspiration pneumonia and urinary tract infection, deep venous thrombosis, pulmonary embolus, pressure ulcers, pain, depression.

REFERENCES

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2. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack. *Stroke* 2006;37(2):577–617.

CODES

ICD9

434.11 Cerebral embolism with cerebral infarction

CLINICAL PEARLS

- Atrial fibrillation is the most common cause of cardioembolic stroke and is treated with anticoagulation with warfarin or dabigatran.
- Cardioembolic stroke typically results in occlusions of large intracranial vessels or more distal intracranial vessels causing cortical strokes.

CARPAL TUNNEL SYNDROME

Steven J. Shook, MD

BASICS

DESCRIPTION
- Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy.
- It is caused by compression of the median nerve within the carpal tunnel.
- Symptoms include paresthesia, pain, weakness, and muscle atrophy in the median nerve distribution.

EPIDEMIOLOGY
Incidence
Up to 276:100,000/year.

Prevalence
Up to 9.2% in women and 6% in men.

RISK FACTORS
- Obesity
- Female gender
- Pregnancy
- Renal failure
- Acromegaly
- Glucose dysmetabolism (diabetes)
- Mechanical injury/trauma
- Amyloidosis
- Thyroid disorders
- Infectious disease
- Connective tissue disease
  - Rheumatoid arthritis

Pregnancy Considerations
- Most frequent mononeuropathy in pregnancy
- The cause is likely multifactorial, including fluid retention within the carpal tunnel
- Incidence of clinically diagnosed CTS in pregnancy ranges from 31% to 62%
- Symptoms persist in a substantial number of patients 1 or more years after delivery

Genetics
- Several inherited disorders affecting the peripheral nerve myelin sheath, or causing abnormal amyloid accumulation increase the risk of CTS:
  - Charcot–Marie–Tooth disease
  - Hereditary neuropathy with liability to pressure palsies
  - Familial amyloid polyneuropathy
- "Familial primary CTS" is a rare, but genetically distinct disorder

GENERAL PREVENTION
Avoidance or appropriate treatment of the above risk factors.

PATHOPHYSIOLOGY
- Incompletely understood, likely multifactorial
- Compression and/or inflammation damage the nerve, impairing axon function or causing ischemia (by compressing perineurial vessels)
- Demyelination and/or axon loss lead to symptoms within the distribution of the nerve

ETIOLOGY
- The carpal tunnel is formed by the transverse carpal ligament (a.k.a. flexor retinaculum) superiorly with the carpal bones inferiorly
- The median nerve passes through this space accompanied by the 9 forearm flexor tendons
- Reduced anatomic space (e.g., due to mass lesions, protein accumulation, scarring/fibrosis), edema, or inflammation may all play a role

COMMONLY ASSOCIATED CONDITIONS
See risk factors.

DIAGNOSIS

HISTORY
- Numbness and tingling (paresthesias) or a sensation of swelling in first 3 digits and the radial half of the fourth digit of the hand
- In the earliest stage, typically present at night and often awaken patients from sleep. Shaking the hands brings relief
- Later, symptoms persist during the day, particularly with sustained positions or repetitive movements
- Pain may radiate from the wrist to the hand or proximally to the forearm or shoulder
- Weakness and atrophy of the thenar eminence is a late finding

PHYSICAL EXAM
- Hand symptom diagrams (e.g., the Katz hand diagram) are useful self-administered tools which aid diagnosis of CTS
- Hypalgesia in the median nerve territory
- Weakness of thumb abduction
- *Phalen's sign* (placing the wrists in flexion for 60 seconds and reproducing symptoms), and *Tinel's sign* (tapping over the median nerve at the wrist and reproducing symptoms) are believed to have no reliable diagnostic value

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Nerve conduction studies (NCS) to assess for slowing (evidence of demyelination) across the wrist, and loss of response amplitude (evidence of axon loss)
  - Median sensory NCS across the wrist are most sensitive for CTS
  - Median motor NCS recording from the thenar eminence are less sensitive, but helpful when the sensory response is absent, and for rating severity
- Electromyography (EMG) utilizes a needle electrode to assess for changes in muscle suggestive of denervation
  - Normal in early, mild CTS
  - Active denervation, and eventually chronic motor axon loss changes may be identified later in the disease
  - Most useful for identifying CTS mimics

Imaging
Initial approach
- Neuromuscular ultrasound
  - Increased cross-sectional area of the median nerve at the level of the pisiform bone is a sensitive test for CTS
  - CTS etiologies including space-occupying lesions (e.g., cysts) and tenosynovitis may be identified, altering management
  - Identifying anatomic variants (e.g., persistent median artery), may alter surgical approach to treatment
- MRI/CT
  - Particularly useful in the setting of trauma (e.g., wrist fracture)
  - Similar benefits to ultrasound, but at a higher cost and with a less flexible field of view

DIFFERENTIAL DIAGNOSIS
- Cervical radiculopathy (particularly C6)
- True neurogenic thoracic outlet syndrome
- Brachial plexopathy
- Proximal median neuropathy
- Motor neuron disease
- Disorders of the central nervous system (stroke, multiple sclerosis, etc.)
- Arthritis/Tendonitis

TREATMENT

MEDICATION

- Anti-inflammatory medications
  - Oral steroids (prednisolone or prednisone) provide short-term relief
    - prolonged use is limited by side effects
    - rarely utilized for CTS in clinical practice
  - NSAIDs are less effective than steroids for symptom relief
- Diuretics do *not* improve short-term symptoms

ADDITIONAL TREATMENT

General Measures

- Conservative (nonsurgical) treatment is considered first line for patients with mild-to-moderate symptoms (no weakness or atrophy, and pain is not severe/intractable)
  - Splinting of the affected wrist(s) in a neutral position for at least 2 weeks provides short-term symptom relief
    - Limited evidence suggests night-only use is as effective as full-time splinting
  - Short-term benefits have been demonstrated with therapeutic ultrasound (after 7 weeks), carpal bone mobilization (physiotherapy)
  - Avoidance of symptom-provoking activities is also effective

Additional Therapies

- There is equivocal evidence regarding use of ergonomic keyboards for symptom relief

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Yoga treatment for 8 weeks provides short-term pain relief based on limited evidence
- Laser acupuncture, B6, and magnet therapy are *not* effective based on limited evidence

SURGERY/OTHER PROCEDURES

- Carpal tunnel release (CTR) surgery
  - Considered for patients who:
    - do not respond to conservative treatment
    - have evidence of denervation (on EMG, or clinical evidence of atrophy/weakness)
  - Surgery is more effective than conservative therapy for long-term symptom management
  - Complication rates of surgery are low (<0.5%)
  - Open (OCTR) and endoscopic (ECTR) release techniques are equally effective
  - ECTR may facilitate an earlier return to work
- Local corticosteroid injection
  - Provides temporary symptomatic relief for patients with severe symptoms
  - Two injections are no more effective than one
  - Local is superior to intramuscular injection
  - Relief is superior to the effect from oral steroids when compared at 3 months
  - Complications rates vary, but are similar to surgical complication rates

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Reassess patients attempting conservative therapy at 2 months in order to consider surgical options as needed.

PATIENT EDUCATION

Address risk factors for CTS, and suggest avoidance of activities which provoke symptoms.

PROGNOSIS

- Resolution of symptoms by 6 months in 34% without retreatment (one observational study)
- Most patients with mild-to-moderate symptoms improve with conservative therapy
- 71% of patients requiring CTR are improved significantly at 3 months, and long-term (12–18 month) symptom control is superior to conservative therapy in these patients

ADDITIONAL READING

- Alfonso C, Jann S, Massa R, et al. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. *Neurol Sci* 2010;31:243–252.
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- Scholten RJ, Mink van der Molen A, Uitdehaag BM, et al. Surgical treatment options for carpal tunnel syndrome. *Cochrane Database Syst Rev* 2007;(4): CD003905.
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CODES

ICD9

354.0 Carpal tunnel syndrome

CLINICAL PEARLS

- CTS is the most common entrapment neuropathy.
- The earliest symptom is typically numbness and tingling (or "swelling") in first 3 digits at night. Hand shaking classically brings relief.
- Patients with mild-to-moderate symptoms improve with conservative therapy, including night-time splinting of the wrist in a neutral position.
- Surgery is effective for patients with persistent, moderate–severe symptoms.

CAUDA EQUINA SYNDROME

Ryan Armour, DO

BASICS

DESCRIPTION

- Within the dural sac, the spinal cord ends between L1 and L2 (in adults). Below this point continues the conus medullaris and the bundle of lumbar and sacral nerve roots called the cauda equina (named due to its gross appearance similar to a horse's tail). These nerve roots continue inferiorly within the dural sac, exit the spinal canal through the respective neural foraminae, eventually forming the lumbosacral plexus. They ultimately supply the motor, sensory and autonomic nerves in the pelvis and lower extremities.
- Cauda equina syndrome is a disorder caused by a lesion of this bundle of nerve roots before they exit the spinal canal. Although not a true spinal cord injury, it is often placed into this category for discussion purposes due to similar presentation, symptoms, and management.

EPIDEMIOLOGY

Incidence

Incidence of cauda equine syndrome of all causes is estimated to be 3.4 per million. Incidence of cauda equine syndrome due to disc herniation is estimated to be 1.8 per million.

Prevalence

Prevalence is estimated to be 8.9 per 100,000 in the general population.

RISK FACTORS

- People with low back pain are more likely to develop cauda equina syndrome.
- Pregnant women.
- Patients with congenital lesions of the spinal cord such as spina bifida or vertebral body malformation.
- Patients with underlying malignancy that may spread to the spinal canal.
- Immunocompromised patients are at risk to develop infections affecting the spinal canal.

Genetics

There are no known direct genetic causes or risk factors associated with cauda equina syndrome. A variety of genetic disorders associated with spinal canal disorders may be associated with an increased risk to develop cauda equina syndrome.

GENERAL PREVENTION

Prevention for cauda equine syndrome focuses on identifying those patients at risk and education to inform their physicians if they develop early signs.

PATHOPHYSIOLOGY

Cauda equina syndrome is caused by direct compression on the proximal nerve roots by a mass lesion in the lumbar spinal canal, or by inflammatory disorders affecting these nerve roots. The compression may be due to a wide variety of reasons, including displaced intervertebral disc material, tumor, infection, hemorrhage, or trauma causing bony fracture. Direct compression on axons will cause delayed action potential propagation and ultimately axon loss. Motor axons are more prone to compressive injury than sensory axons. Thus patients will present more commonly with weakness and bowel/bladder dysfunction, with sensation being relatively preserved.

ETIOLOGY

- Any lesion causing direct mass effect and compression of the cauda equina may cause cauda equina syndrome.
- The most common cause of cauda equina syndrome is herniation of an intervertebral disc in the lumbar region.

COMMONLY ASSOCIATED CONDITIONS

- Lumbar disc herniation
- Trauma
- Bony collapse of the spinal column
- Metastatic tumor spread
- Epidural hematoma
- Carcinomatous meningitis
- Chronic meningitis (various etiologies)
- Epidural abscess
- Vertebral osteomyelitis and diskitis
- Trauma

DIAGNOSIS

HISTORY

Patients will present with complaints of weakness that is often asymmetric in the lower extremities. Asymmetric sensory disturbances in the lower extremities may be present. Spontaneous radicular pain is often present. Pain is asymmetric or may be unilateral in the lower back, lower extremities or pelvis. Patients may also have saddle anesthesia. Bowel and bladder dysfunction (retention/incontinence) and impaired sexual function such as the ability to have an erection is often present but may be less prominent than with a conus medullaris lesion. Onset of symptoms may be acute or more gradual in nature, depending on the underlying etiology.

PHYSICAL EXAM

Physical examination should include a full and detailed neurological examination. Patients may have weakness in the lower extremities. Sensory loss in the lower extremities may be patchy and asymmetric. Patients may have "saddle anesthesia," which is consisted of sensory loss in the buttocks, perineum, genitalia, and proximal posterior thigh area. A rectal examination should be performed as rectal tone is often decreased. Palpation of the abdomen may reveal an extended urinary bladder. Loss or reduced deep tendon reflexes at the patella and ankles is common in this condition. Asymmetric weakness in the legs reflecting patchy root injury is characteristic.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- A CBC, CMP, aPTT, PT, and INR should be obtained. Erythrocyte sedimentation rate and C-reactive protein may be useful to evaluate for underling infectious or inflammatory process. Three sets of blood cultures should be obtained.
- Cerebrospinal fluid, WBC, RBC, protein and glucose cultures, and cytology may be helpful to rule out conditions in the differential and to identify the underlying etiology.

Imaging

Initial approach

Plain lumbar films and an urgent MRI of the lumbar spine with or without contrast are essential for proper diagnosis. In cases where MRI is not possible, a myelogram can be obtained. Contrast-enhanced CT is not a sensitive modality for evaluation of cauda equina syndrome.

Diagnostic Procedures/Other

Nerve conduction studies and electromyography may be helpful in diagnosis, determining the extent of injury and prognosis for long-term recovery. They will not usually be helpful until about 3 weeks after onset of injury due to delay in Wallerian degeneration.

Pathological Findings

Pathological findings vary greatly depending on the underlying etiology. It is important to identify the underlying etiology to determine proper long-term treatment and prevention of worsening neurological symptoms.

DIFFERENTIAL DIAGNOSIS

- Conus medullaris syndrome
- Acute inflammatory demyelination polyradiculopathy (Guillain–Barre syndrome)
- Spinal cord compression
- Transverse myelitis
- Lumbosacral plexopathy
- Tethered cord syndrome

TREATMENT

MEDICATION

First Line

Treatment with intravenous steroids (dexamethasone 4 mg every 6 hours or methylprednisolone 1 g daily) may be initiated in an attempt to reduce mass effect from local inflammation (1)[C]. This is based on practice experience only as there are no studies to support the use of steroids for treatment of cauda equina syndrome.

Second Line

- Treatment will vary depending on the underlying etiology.
- Appropriate antibiotic therapy may be indicated in the case of infection.
- Chemotherapy may be indicated in cases secondary to malignancy.

ADDITIONAL TREATMENT

General Measures

Additional treatment varies greatly depending on the underlying etiology.

Issues for Referral

- Early referral to a neurosurgeon should be pursued if cauda equina syndrome is suspected.
- Referral to a physiatrist should be made early in the hospital course to determine the best therapy regimen and discharge disposition for the patient.
- Referral to an infectious diseases specialist or oncologist should be considered depending on the underlying etiology.
- Patients are at risk of developing symptoms of depressed mood and anxiety regarding residual symptoms, particularly bowel and bladder dysfunction. Referral to a psychiatrist should be considered.

Additional Therapies

Ongoing physical and occupational therapy is the mainstay of treatment to improve strength and long-term functional outcome.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Alternative therapies are not recommended in the acute phase, but may be considered to treat chronic pain and bladder/bowel dysfunction may be pursued after surgical intervention has been performed.

SURGERY/OTHER PROCEDURES

Surgical decompression of the cauda equina should be pursued as quickly as possible in suspected cases. Although the optimal timing of surgery is controversial, it is generally accepted that surgery early in the clinical course is associated with better clinical outcome (2,3)[B].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Cauda equina syndrome is considered to be a surgical emergency. If it is suspected, selection of the proper imaging modality should be pursued immediately.

Admission Criteria

Patients with rapidly progressing neurological deficits or bowel/bladder dysfunction should be evaluated in an emergency setting and admitted.

IV Fluids

Maintenance of IV fluid should be initiated. Patients should be made NPO in anticipation of urgent surgical intervention.

Nursing

- Patients should be turned in bed every 2 hours to prevent formation of pressure ulcers.
- Patients should be monitored for urinary retention by checking post-void residuals every 6 hours. If post-void residuals exceed 150 mL, the urinary bladders should be intermittently catheterized.
- Prevention of thrombosis of the deep veins in the lower extremities with intermittent pneumatic compression devices and low dose subcutaneous heparin or low-molecular-weight heparin should be considered.

Discharge Criteria

- The neurological examination should be stable or improving.
- Patients with bowel or bladder dysfunction should be educated or provided with home care regarding hygiene and intermittent urinary catheterization if necessary.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients should follow-up regularly with their neurosurgeon and neurologist to assess for worsening or return of symptoms

DIET

As the patient is being evaluated, they should be made NPO in anticipation of urgent surgical intervention. After a plan is made or surgery is performed, a regular diet can be resumed.

PATIENT EDUCATION

Patients at risk to develop cauda equina syndrome should be educated on the signs and symptoms of compromise of the spinal canal, so urgent evaluation is obtained when necessary.

PROGNOSIS

- Patients with slow progressive symptoms overall have better prognosis than those who present with acute onset of symptoms.
- Patients experiencing bowel and bladder dysfunction, typically, have a poor outcome and difficulty returning to a normal life as they deal with these symptoms.
- Weakness and sensory disturbance in the lower extremities generally improve.

COMPLICATIONS

- Urinary tract infection
- Deep venous thrombosis
- Pressure ulcers
- Chronic bowel and bladder retention or incontinence
- Depressed mood secondary to change in lifestyle and functional capacity

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ADDITIONAL READING

- Brown MD, Levi AD. Surgery for lumbar disc herniation during pregnancy. *Spine* 2001;26:440–443.
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CODES

ICD9

- 344.60 Cauda equina syndrome without mention of neurogenic bladder
- 344.61 Cauda equina syndrome with neurogenic bladder

CLINICAL PEARLS

- Cauda equina syndrome should be suspected in patients with the following:
  - Acute asymmetric lower extremity weakness particularly with radicular pain.
  - Acute bowel/bladder and sexual dysfunction.
  - "Saddle" anesthesia may be seen both in cauda equina syndrome and in conus medullaris syndrome.

CAVERNOUS SINUS THROMBOSIS

Aarti Sarwal, MD

BASICS

DESCRIPTION

- Cavernous sinus thrombosis (CST) is a rare disorder characterized by clot formation in the cavernous sinuses.
- Because of its complex neurovascular anatomic relationship, CST is the most important of any intracranial septic thrombosis.

EPIDEMIOLOGY

Incidence

- CST is generally a fulminant process with high rates of morbidity and mortality with only a few hundred case reports in the medical literature.
- Fortunately, the incidence has markedly decreased with the advent of effective antimicrobial agents.
- There is no known age, sex, or race predilection.

RISK FACTORS

- *Infection*: Middle third of the face, paranasal sinuses, pharynx, maxilla, middle ear, or mastoid process in otherwise healthy individual
- *Trauma*: Otolaryngologic surgery or trauma
- *Hypercoagulable states*: Malignancy, pregnancy, oral contraceptive use
- Diabetes mellitus
- Chronic sinusitis

Pregnancy Considerations

Pregnancy is a risk factor for the aseptic form of CST.

GENERAL PREVENTION

Furuncles or abscesses (pimples) in the central portion of the face should not be manipulated without prior antibiotic coverage.

PATHOPHYSIOLOGY

- The cavernous sinuses are paired, interconnected, trabeculated cavities located on either side of the sella turcica, superior to the sphenoid sinus and posterior to the optic chiasm.
- They receive venous drainage from face, orbits, sinuses, and brain through valveless veins.
- The internal carotid artery and sixth cranial nerve pass through the sinuses, whereas the third, fourth, ophthalmic, and maxillary branches of the fifth cranial nerve lie within the lateral wall of the sinuses.

ETIOLOGY

- Any infection in structures with venous drainage to the cavernous sinuses may propagate through valveless veins. Once the organisms are caught in the trabeculations of the sinuses, inflammation and secretion of coagulase may lead to clot formation and thrombosis.
- In the rare chronic form, slow thrombosis of the sinuses allows time for formation of venous collaterals.
- Coagulase-positive *Staphylococcus aureus* accounts for most infections. *Streptococcus pneumonie*, Gram-negative bacilli, *Rhizopus*, *Aspergillus*, and *Mucor* can also be seen.

COMMONLY ASSOCIATED CONDITIONS

- Infection of the central face or paranasal sinuses, bacteremia or infections of the ear or maxillary teeth.
- Surgical or blunt trauma or hypercoagulable state leads to thrombosis of the cavernous sinus and often to bacterial superinfection.

DIAGNOSIS

PHYSICAL EXAM

- Eye swelling that begins as a unilateral process and spreads to the other eye within 24–48 hours is pathognomonic for CST.
- Orbital swelling with cranial nerve involvement should raise suspicion of CST.
- Signs and symptoms of the primary infection, venous congestion and sepsis:
  - Fever and headache
  - Ptosis and pupillary dilation
  - Chemosis of bulbar conjunctiva
  - External or internal ophthalmoplegia
  - Proptosis and periorbital edema
  - Decreased visual acuity
  - Meningeal signs
  - Systemic signs indicative of sepsis including chills, fever, shock, delirium, and coma

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- CST is primarily a clinical diagnosis.
  - Polymorphonuclear leukocytosis on CBC and blood cultures can help confirms an infectious etiology.
  - CSF is consistent with either parameningeal inflammation or frank meningitis.

Imaging

Initial approach

Contrast-enhanced CT or MRI of the head is the most sensitive and specific imaging studies to confirm the diagnosis and differentiate its CST from alternatives like orbital cellulitis.

Follow-up & special considerations

Angiography and venography are considered when carotid-cavernous fistula or intracavernous aneurysm is suspected.

Diagnostic Procedures/Other

- *Lumbar puncture*: CSF is typically inflammatory but may not grow organisms
- Funduscopic examination

DIFFERENTIAL DIAGNOSIS

- Contralateral spread of signs and symptoms within 48 hours is virtually pathognomonic for CST.
- Differential to be considered include:
  - Orbital or periorbital cellulitis
  - Epidural or subdural infection
  - Sinusitis
  - Trauma at orbital apex or superior orbital fissure
  - Orbit or optic nerve tumor
  - Rhinocerebral mucormycosis
  - Intracavernous carotid artery aneurysm
  - Carotid-cavernous fistula
  - Intraorbital pseudotumor or Tolosa–Hunt syndrome
  - Exophthalmic goiter

TREATMENT

MEDICATION

First Line

- Antibiotics
  - Early and aggressive high-dose, broad-spectrum antibiotics
  - Coverage should include penicillinase producing Gram-positive, Gram-negative, and anaerobic organisms
  - Dosed for CNS penetration
  - Antifungals should be added in case patient has diabetes, neutropenia, or is otherwise immunosuppressed
- A regimen including intravenous oxacillin or nafcillin 2 g every 4 hours plus a third-generation antipseudomonal cephalosporin such as intravenous ceftazidime 2 g every 8 hours or IV imipenem 2 g every 6 hours should cover Gram-positive and Gram-negative organisms.
  - IV metronidazole 500 mg every 6 hours should be added for anaerobic coverage
  - If MRSA is suspected Vancomycin 1 g IV q12 or Linezolid may be added to the coverage
- IV antibiotics are recommended for a minimum of 3–4 weeks or at least 2 weeks beyond clinical resolution as the infection may be sequestered within the thrombus.

Second Line

- Anticoagulation
  - Some studies have shown prevention of propagation and septic embolization (2)[C].
  - Anticoagulation with heparin should be considered unless contraindications like presence of intracerebral hemorrhage or other bleeding diathesis exist.
  - The duration for anticoagulation is controversial and may be considered for 3 and 9 months depending on the severity of symptoms and the clinical course.
- Corticosteroids may help to reduce inflammation and edema and may be instituted after antibiotic coverage.
  - Pituitary insufficiency may develop necessitating steroid treatment.

ADDITIONAL TREATMENT

General Measures

- Eradicating the infection, halting progression of thrombosis, and reducing inflammation
- Rapid diagnosis and initiation of treatment are essential

Issues for Referral

- Infectious disease consultations for antibiotic choice
- Necessary surgical consultations should be sought

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
- Pain control

SURGERY/OTHER PROCEDURES

Locally administered thrombolytics may be considered for severe refractory cases on experimental basis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with diagnosed or suspected CST should be admitted to an intensive care unit.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Follow clinical course rather than normalization of imaging studies.

Patient Monitoring

Relapses and intracranial abscess have been reported weeks to months later due to sequestration of bacteria within thrombus. Thus, patients should be followed for several months after antibiotics are stopped.

PROGNOSIS

In the absence of treatment, meningitis, intracranial spread, septic shock, and death follow. Mortality rate is as high as 30%; the majority of survivors suffer permanent sequelae including blindness, visual impairment, diplopia, pituitary insufficiency, hemiparesis, seizure disorder, or vascular steal syndrome.

COMPLICATIONS

Complications and sequelae include

- Meningitis, encephalitis
- Brain abscess, subdural empyema, epidural abscess (consider if not responding to therapy)
- Progressive sinus thrombosis causing hemorrhagic venous infarction
- Hydrocephalus
- Carotid stenosis or occlusion causing ischemic stroke

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ADDITIONAL READING

- Aseptic thrombosis of the cavernous sinuses
- Cavernous sinus phlebitis
- Cavernous sinus thrombophlebitis
- Cavernous sinus phlebothrombosis
- Septic cavernous sinus thrombosis

CODES

ICD9

325 Phlebitis and thrombophlebitis of intracranial venous sinuses

CLINICAL PEARLS

Eye swelling that begins as a unilateral process and spreads to the other eye within 24–48 hours is pathognomonic for CST.

CENTRAL PONTINE MYELINOLYSIS

C. L. Hall, MD, MAT
Beth A. Leeman, MD

BASICS

DESCRIPTION

Central pontine myelinolysis (CPM) is an acute demyelination of the central basis pontis. The characteristic presentation includes spastic tetraparesis, pseudobulbar palsy, and alteration of consciousness, classically occurring 2–6 days after rapid correction of hyponatremia. Less commonly, demyelination occurs outside of the pons, in the cerebellum, lateral geniculate body/thalamus, putamen, cerebral cortex, and subcortical white matter, termed extrapontine myelinolysis (EPM). When CPM occurs with EPM, the term osmotic demyelination syndrome is used.

EPIDEMIOLOGY

Incidence

- CPM was evident in an estimated 0.5–10% of consecutive autopsies, and was symptomatic in up to 1/15 cases.
- CPM was also found in 29% of liver transplant patients upon autopsy.
- EPM occurs in 10–15% of patients with CPM.

RISK FACTORS

Almost all cases of CPM and EPM are associated with chronic disease states including alcoholism, malnourishment, cancer, liver disease, and transplantation.

ALERT

- CPM/EPM is commonly associated with rapid correction of hyponatremia in the setting of chronic medical conditions. Generally, sodium correction rates should not exceed 1–2 mEq/hour for the first few hours or when correcting levels below 125 mEq/L. Rates of correction should be limited to 8–12 mEq/L within the first 24 hours and 20 mEq/L within the first 48 hours. However, the varying susceptibility to myelinolysis makes establishment of guidelines difficult.
- CPM is more common with chronic hyponatremia. Some authors recommend slower rates of sodium correction in chronic compared with acute hyponatremia.
- Potassium, magnesium, and phosphorus deficiencies are additional risk factors for CPM and should be addressed concurrently.
- Case reports of CPM occurring with normal sodium levels suggest that derangements unrelated to hyponatremia can contribute to CPM.

GENERAL PREVENTION

General prevention comprises recognition of those at greatest risk for CPM/EPM, adequate attention to water, sodium, and serum osmolarity balance, and avoiding rapid correction of hyponatremia.

PATHOPHYSIOLOGY

- The pathogenesis underlying CPM/EPM remains unknown. They are most often associated with rapid correction of hyponatremia.
  - One hypothesis suggests that increases in sodium lead to endothelial injury and disruption of the blood–brain barrier, causing edema and leakage of myelinotoxic factors.
  - Mechanisms controlling osmotic balance may not respond quickly enough in rapid sodium repletion, leading to edema that destroys myelin and blood vessels, and dehydration of susceptible brain regions.
  - Some have argued for an autoimmune etiology. An inflammatory component has also been identified in laboratory studies.

ETIOLOGY

- Those with underlying medical illness are more susceptible to CPM/EPM due to a decreased ability to generate the necessary osmoles to protect against the above processes.
- Alternatively, those with medical conditions are more likely to be hospitalized where iatrogenic fluctuations in osmolarity can occur.

COMMONLY ASSOCIATED CONDITIONS

- Alcoholism (39.4–78% of CPM cases): Alcohol blocks antidiuretic hormone (ADH). During alcohol withdrawal, the ADH pathway may be overactive, resulting in hyponatremia
- Rapid correction of hyponatremia (21.5–61%)
- Liver transplants (17.4%): Onset is usually in the first 30 days after transplantation. Liver transplant-associated CPM occurs more commonly in children and those with cyclosporine use
- Other liver disease, including cirrhosis (4.8%) and Wilson's disease
- Burns (2.5%): CPM occurs in 7% of burn patients
- Diabetes (2%)
- AIDS (1.4%)
- Pregnancy (0.5%) and hyperemesis gravidarum (1.4%)
- Disturbances in electrolytes and osmolality (0.7%), including hypernatremia, hypokalemia, lithium toxicity, and correction of hypoglycemia
- Neoplasms (0.5%), particularly of lung or GI tract; Hodgkin's disease; stem cell transplantation
- CNS conditions including stroke (0.5%) and schizophrenia (0.5%)
- Acute porphyria (0.5%)
- Other associated conditions include eating disorders and malnutrition, sepsis, ADH deficiency, adrenal and pituitary insufficiency, heat stroke, hemorrhagic pancreatitis, trauma, ornithine carbamoyltransferase deficiency, arginine hydrochloride deficiency, and Sjögren's syndrome

DIAGNOSIS

HISTORY

- Symptoms of CPM vary widely and can range from no deficit to devastating neurologic injury. The symptoms typically develop over the 2–6 days after correction of sodium, and reflect damage to the pons and associated tracts of the brainstem.
- Classically, patients present with encephalopathy which improves with sodium correction, and then deteriorate after 48–72 hours.
- Symptoms depend upon the tracts affected.
- Pseudobulbar palsy, spastic tetraparesis, and coma are characteristic of CPM.

PHYSICAL EXAM

- Encephalopathy is present in 70% of CPM cases, ranging from lethargy to coma. Cognitive deficits affecting speech, judgment, insight, attention, and memory are common.
- Pseudobulbar palsy includes dysphagia, dysarthria, tongue weakness, and emotional lability, and occurs in 40% of cases.
- Tetraparesis, paraparesis, or a locked-in syndrome occurs in 33% of cases.
- Ocular findings may include miosis or sixth nerve palsies. Pontine lesions may cause horizontal gaze paralysis, while lesions extending to the midbrain may lead to vertical gaze paralysis.
- Seizures are evident in 25% of cases.
- 25% of cases present with psychiatric symptoms such as emotional lability, agitated delirium, akinetic mutism, or catatonia.
- Hyporeflexia, hypotension, respiratory depression, and bowel or bladder dysfunction are common. Alternative presentations include hemiparesis and bilateral upper extremity weakness.
- Ataxia and cerebellar signs can occur but are often masked by weakness.
- EPM may manifest as postural tremor, myoclonic jerks, Parkinsonian symptoms, catatonia, dystonia or pyramidal dysfunction.
- Sensory symptoms are notably absent.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Serum electrolytes including basic chemistry panel with magnesium and phosphorus.

Follow-up & special considerations

Repeat electrolytes as clinically indicated.

Imaging

Initial approach

Head CT scan, although less sensitive than MRI, is typically the initial imaging study. The CT finding in CPM is usually a symmetric central pontine hypodensity.

Follow-up & special considerations
- MRI is the imaging modality of choice. A symmetric, non–space-occupying lesion located in the central pons is characteristic of CPM.
- The lesion is hypointense on T1 and hyperintense on T2/FLAIR sequences.
- The lesion is often described as a "bat's wing" on coronal views, appearing triangular on axial cuts, and ovoid on sagittal images.
- Findings on neuroimaging lag behind clinical symptoms. Repeat imaging in suspicious cases 10–14 days later, if early scans are unrevealing, is recommended.
- Radiologic findings may persist for months or longer after neurologic recovery.
- The severity of clinical manifestations does not necessarily correlate with neuroimaging.

Diagnostic Procedures/Other
- Positron emission tomography (PET) studies have shown the demyelinated patches to have increased metabolic activity early, and decreased metabolic activity as CPM progresses. PET, however, is not routinely used in the evaluation of CPM/EPM.
- Auditory evoked potentials may be abnormal, with prolongation of the latency period between waves I and V, due to demyelination of auditory pathways in the pons. This finding is nonspecific and inconsistent.

Pathological Findings
- Autopsy studies of CPM demonstrate regions of demyelination in the central basis pontis, grossly seen as a triangular region of soft, discolored tissue.
- Microscopic examination reveals demyelination with loss of oligodendrocytes, myelin-filled phagocytes, astrocytic gliosis, and fat decomposition. Evidence of inflammation is notably absent. Axons, nuclei, and blood vessels are relatively spared.

DIFFERENTIAL DIAGNOSIS
Differential diagnosis includes acute neurologic processes (e.g., infarct, hemorrhage) localizing to the pons. Other demyelinating diseases, such as multiple sclerosis and acute disseminated encephalomyelitis should be considered. Comorbid conditions such as critical illness myopathy, Wernicke's encephalopathy and hepatic encephalopathy, as well as other causes of altered mental status (e.g., complex partial seizures, uremia), may have symptoms that overlap with CPM.

TREATMENT

MEDICATION
First Line
The primary treatment is prevention. No consensus guidelines have been established for the treatment of CPM or EPM. It remains unclear whether early initiation of treatment would improve prognosis.

Second Line
Case reports of successful treatments, not FDA approved for this indication, included:
- Varying regimens of corticosteroids, plasma exchange, and IVIG (1–2)
- Thyrotropin-releasing hormone (0.6 mg IV daily for 6 weeks) (3)
- Methylphenidate, titrated to 10 mg b.i.d., for treatment of neuropsychiatric symptoms (4)

ADDITIONAL TREATMENT
General Measures
General measures include symptomatic ICU and general medical care.

Issues for Referral
Rehabilitation programs including cognitive, speech, occupational therapy (OT), and physical therapy (PT) may be helpful.

Additional Therapies
Additional therapies comprise routine symptomatic treatment.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Stabilize electrolyte abnormalities.
- Monitor for swallowing and respiratory dysfunction.

Admission Criteria
ICU level care is warranted in all suspected cases of CPM due to the initial progressive nature of the condition, and potential need for intubation and aggressive fluid management.

IV Fluids
As determined by clinical state.

Nursing
Importance of electrolyte checks, strict I/Os, and serial neurologic examinations must be emphasized.

Discharge Criteria
As determined by clinical state and progress in PT, OT, and speech therapy. Discharge to an inpatient rehabilitation center is often necessary.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
As indicated by medical condition.

Patient Monitoring
As indicated by medical condition.

PROGNOSIS
- The course may range from death to nearly complete recovery. Symptoms typically worsen over the first week, then stabilize or improve over the following weeks to months.
- Neuroimaging and EMG/NCS do not aid in prognosis, nor does the presence of associated disease processes (i.e., alcoholism) predict outcome. Mortality depends on extent of initial injury and on prevention and treatment of ICU-related complications. Survivors of CPM typically have ongoing neurologic deficits such as ataxia and dysarthria. The cognitive effects of CPM may be most persistent.

COMPLICATIONS
Complications include myopathy, ventilator dependence, aspiration pneumonia, venous thrombosis, pulmonary embolism, contractures, muscle wasting, decubitus ulcers, urinary tract infections, and depression.

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See Also (Topic, Algorithm, Electronic Media Element)
- Hyponatremia

CODES

ICD9
341.8 Other demyelinating diseases of central nervous system

CLINICAL PEARLS
- CPM/EPM is commonly associated with rapid correction of hyponatremia in the setting of chronic medical conditions.
- Pseudobulbar palsy, spastic tetraparesis, and coma are characteristic of CPM, typically developing 2–6 days after correction of sodium.
- No consensus guidelines have been established for the treatment of CPM/EPM, but recognition of those at greatest risk, and adequate attention to water, electrolyte, and serum osmolarity balance, aid in its prevention.
- Symptoms may be masked by comorbid conditions (e.g., myopathy, seizures). In such cases, neuroimaging may be the key to diagnosis.

CEREBRAL PALSY

S. Anne Joseph, MD

BASICS

DESCRIPTION

Cerebral palsy is the term used to describe the neurological disorder of motor dysfunction that occurs as a direct result of injury to the developing brain. The insult is nonprogressive and occurs before the age of 3–5 years and manifests as abnormalities of tone, posture, or motion. Although the insult is nonprogressive, the manifestations of motor dysfunction may subtly change with time, as the injured brain matures. However, by definition, this condition does not involve true neurological regression.

EPIDEMIOLOGY

Prevalence

The prevalence of cerebral palsy among children at school entry is about 2 per 1,000 live births.

RISK FACTORS

The most common risk factors for cerebral palsy have varied over time because of advances in prenatal and neonatal care. Prematurity is a risk factor for cerebral palsy. The risk of cerebral palsy rises steadily as birth weight declines. The risk is approximately 3.4 per 1,000 in infants weighing 2,500 g and over, 13.9 per 1,000 in infants weighing 1,501–2,500 g, and 90.4 per 1,000 in infants less than or equal to 1,500 g. Infants of normal birth weight with a 5-minute Apgar score of 3 or less had a 5% probability of developing cerebral palsy. Similar scores at 10 minutes increased the risk to 17%, and scores of 3 or less at 20 minutes were associated with a 57% risk of cerebral palsy. In a term infant, risk factors include in-utero infections, maternal chorioamnionitis, genetic thrombophilic tendencies, meconium aspiration, breech presentation, placental abnormalities that include placental abruption and maternal factors such as hypertension.

ETIOLOGY

It is known that many conditions can injure the developing brain and lead to cerebral palsy. Yet, approximately one quarter of all cases have no definable cause.

- Causes of cerebral palsy
  - Prenatal
    - First trimester (44%): Teratogens, genetic syndromes, brain malformations, chromosomal abnormalities
    - Second and third trimesters: Intrauterine infections, fetal/placental dysfunction
  - Labor and delivery (19%): Pre-eclampsia/eclampsia, complications of labor and delivery
  - Perinatal (8%): Hypoxic-ischemia, sepsis/CNS infections, prematurity, stroke, traumatic brain injury
  - Childhood (5%): Meningitis/encephalitis, traumatic brain injury, toxins
  - No obvious cause (24%)
- *Note:* Cerebral palsy occurring repeatedly in a family that is not due to a definable genetic syndrome or chromosomal abnormality should raise the concern that the diagnosis of cerebral palsy is inaccurate. In these cases, an underlying neurometabolic or neurodegenerative disorder should be sought.

COMMONLY ASSOCIATED CONDITIONS

Many children with cerebral palsy have at least 1 additional disability associated with damage to the CNS. The most common associated deficits are:

- Cognitive impairment
- Sensory deficits
- Communication disorders
- Seizures
- Feeding problems
- Behavioral and emotional problems

DIAGNOSIS

Cerebral palsy is a clinical diagnosis. To make the diagnosis, there has to be motor dysfunction that localizes to the brain as opposed to the peripheral nervous system. Motor dysfunction can manifest as failure to attain motor milestones at the appropriate age or abnormalities in tone. Clinical examination should localize the lesion to the brain. Clues on physical examination, which raise the suspicion of peripheral nervous system dysfunction include difficult-to-elicit or absent reflexes. Neurological regression or loss of neurological skills either in the area of motor dysfunction or in other areas of development makes the diagnosis of cerebral palsy suspect.

- Multiple classifications have been proposed for cerebral palsy
  - Swedish classification of cerebral palsy
    - Spastic: Quadriparesis, hemiparesis, diparesis
    - Dyskinetic: Choreoathetosis, dystonia
    - Ataxic
    - Mixed type
    - Spastic cerebral palsy: Abnormalities of the pyramidal tract, increased tendon reflexes, increased muscle tone
    - Dyskinetic: Choreoathetosis or dystonia with variable tone and rigidity
    - Ataxic cerebral palsy: Truncal ataxia, limb dysmetria, and tremor

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Laboratory testing in patients suspected of having cerebral palsy is undertaken to delineate the extent of neurological impairment and the presence of other associated deficits, as well as in selected cases a thorough evaluation for progressive disorders mimicking cerebral palsy is undertaken. Testing that may be helpful includes:

- Hearing evaluation
- Eye examination including dilated eye examination
- Swallowing evaluation
- X-rays when scoliosis or dislocation of hips are suspected
- Serial developmental assessments
- EEG when spells suspicious of seizures are present

Imaging

- Imaging studies are helpful with regard to pattern recognition. Certain patterns are recognized as occurring in static disorders:
  - Developmental abnormalities such as migrational disorders.
  - Patterns of previous insult such as periventricular leukomalacia, multicystic encephalomalacia, and porencephalic cysts.
- Certain imaging abnormalities are specific in pointing away from cerebral palsy to a neurodegenerative disorder such as white matter changes indicative of leukodystrophy. In a portion of children with cerebral palsy, the MRI of the brain reveals no radiographic abnormality.
- In general, the MRI is a better tool for assessing brain parenchyma, whereas the CT is a better test for evaluation of the size of the ventricles.

Diagnostic Procedures/Other

Evaluation for a neurometabolic or neurodegenerative disease should be undertaken in any child with motor dysfunction and neurological regression.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes progressive brain diseases that initially manifest as delayed motor milestones. Aspects of the history and physical examination in a child with motor dysfunction that would steer the clinician away from the diagnosis of cerebral palsy toward a diagnosis of a progressive neurometabolic or neurodegenerative disorder would include:

- Regression of previously acquired skills
  - Strong family history of similar conditions
- Family history of sudden infant death
- Repetitive episodes of unexplained vomiting, shock, or metabolic acidosis
- Unusual body odors
- Hypotonia with absent or diminished reflexes
- Abnormal movements
- Ataxia
- Pigmentary retinopathy
  - Some of the mimickers of the various types of cerebral palsy are listed below.
- Spastic quadriparesis
  - Leukodystrophies occurring in infancy such as Krabbe's disease, congenital adrenoleukodystrophy, and Pelizaeus–Merzbacher disease
  - Other hereditary metabolic diseases
- Spastic diparesis
  - Arginase deficiency
  - Familial spastic paraparesis
  - Tethered cord syndrome
- Ataxic cerebral palsy
  - Vitamin E deficiency
  - Ataxia telangiectasia
  - Late infantile sphingolipidoses
  - Late infantile ceroid lipofuscinoses
  - Abetalipoproteinemia
  - Hypobetalipoproteinemia
  - Spinocerebellar ataxias

- Dyskinetic cerebral palsy
  - Mitochondrial disorder
  - Fahr's syndrome
  - Hallervorden–Spatz disease
  - Lesch–Nyhan disease
  - Segawa's syndrome or dopa-responsive dystonia
  - Dystonia musculorum deformans
  - Glutaric aciduria
  - Rett syndrome

TREATMENT

MEDICATION

There are no specific medications for cerebral palsy. Management should involve a multi-disciplinary approach aimed at addressing symptoms of spasticity, adventitious movements, and bulbar dysfunction; medications used for spasticity include baclofen (Lioresal), diazepam (Valium), or tizanidine (Zanaflex). Dosages depend on age and body weight.

- Contraindications: Baclofen, diazepam, or tizanidine is contraindicated if there is a history of prior hypersensitivity to these or similar agents.
- Precautions: Baclofen may in higher doses cause reversible muscular weakness or sedation. Diazepam may be habit forming and cause sedation and respiratory compromise in higher doses. Tizanidine may cause fatigue or hypotension.
- Alternative drugs
  - Danazol is occasionally used for syndromes of muscular spasticity.
  - Treatment modalities in older children for spasticity include utilization of baclofen via pump and focal botulinum injections.

ADDITIONAL TREATMENT

General Measures

Once the clinical diagnosis has been made, a comprehensive evaluation should be undertaken to define the extent of motor disability and to determine the presence of associated conditions. Early and aggressive physical and occupational therapy is recommended, with enrollment in an early intervention program. Speech therapy should be instituted if speech is delayed as well. Treatment, by medications and surgical measures, is aimed at maximizing motor function, treatment of associated conditions, and monitoring and treatment of complications.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - See Medications, given below
- Adjunctive treatment
  - N/A

SURGERY/OTHER PROCEDURES

- Dorsal rhizotomy to decrease spasticity
- Tendon lengthening and transplant measures to decrease impact of contractures
- Management of scoliosis
- Management of salivary pooling secondary to bulbar dysfunction

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patient monitoring should target the following:

- Efficacy and adequacy of therapies, e.g., physical therapy
- Monitoring of musculoskeletal system, e.g., bones/joints
- Adequacy of nutrition and growth
- Treatment of associated conditions such as seizures
- Adequacy of daily programs in the school or preschool systems, including utilization of communication devices
- Serial monitoring to determine that there is no true regression

PATIENT EDUCATION

Educating parents of children with cerebral palsy, demonstrating how positioning can be an effective way of helping the child with mobility, encouraging the parent–child interaction, and muscle stretching should be part of the information given to parents. Counseling on the need to monitor for associated conditions and complications is also an important aspect of treatment. Management should include education of all caretakers including teachers and therapists involved. Attempts should be targeted at maximizing function, including routes of communication, prevention of complications, and treatment of associated medical symptoms.

PROGNOSIS

Although cerebral palsy is a static condition, the clinical symptoms can subtly change with time. Usually infants who are hypotonic with increased reflexes eventually become hypertonic within a few years. Athetosis or chorea in dyskinetic cerebral palsy may gradually appear toward the end of the first year of life. Ataxia may be noted only when the child begins to sit or reach for objects. Contractures tend to develop over time in patients with spasticity. In general, a number of factors affect prognosis: The type of cerebral palsy, the degree of delay in motor milestones, and the degree of associated deficits in intelligence, sensation, and emotional adjustment. The following are general guidelines:

- Children with hemiplegia and no other problems have a good chance of walking at about the age of 2 years.
- More than 50% of children with spastic diplegia learn to walk by about the age of 3 years.
- Of children with quadriplegia, 25% require total care, approximately 33% walk – usually after the age of 3 years.
- Few children who do not sit by the age of 4 years learn to walk.
- Seizure disorder is seen in up to a third of individuals who have cerebral palsy.
- Cognitive deficits are seen in about 50% of people with cerebral palsy.
- Complications of motor dysfunction include muscle spasms, orthopedic issues, undetected dental caries, skin breakdown, constipation, and gastric reflux, which is commonly seen in nonambulatory patients.

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See Also (Topic, Algorithm, Electronic Media Element)

Static encephalopathy manifested by motor dysfunction.

CODES

ICD9

- 343.2 Congenital quadriplegia
- 343.8 Other specified infantile cerebral palsy
- 343.9 Cerebral palsy NOS

CEREBROVASCULAR DISEASE, ARTERIOVENOUS MALFORMATION

David S. Younger, MD
Christina Hadzitheodorou, BA

BASICS

DESCRIPTION

Arteriovenous malformations (AVMs) are congenital masses of arteries and veins with no intermediate capillaries. The direct connection results in high-pressure channels and abnormal arteriovenous shunting. AVMs appear as well-circumscribed tangles of vessels fed directly by arteries. Surrounding tissue may be slightly hypoxic as AVMs exert pressure on draining veins and prevent adequate extraction of nutrients and oxygen. Most are asymptomatic; but left untreated, AVMs may lead to hemorrhage, hypoperfusion, and mass effect, resulting focal neurological deficits and even catastrophic neurovascular injury. AVM can cause seizures by directly irritating the surrounding brain. The first description of an AVM is credited to Rudolf Virchow, who in 1863 wrote a 3-volume treatise on unrecognized vascular malformations including AVMs. Within 3 decades, neurosurgical attempts were reported in the literature; Giordano was credited with performing the first operation on a cerebral AVM in 1889, and in 1908 Krause attempted to eliminate an AVM by ligating a feeding artery. Twenty years later, Cushing and Bailey wrote that it would be unthinkable to remove these "aneurysmal angiomas" in their active state, but that same year Walter Dandy published a case series of 8 patients whose cerebral AVM had been surgically treated. Endovascular embolization was employed as a treatment in 1960 by Luessenhop and Spence, and stereotactic radiotherapy (SRS) was introduced in 1972. Surgical resection, endovascular embolization, and radiotherapy continue to be the main forms of AVM treatment today.

EPIDEMIOLOGY

- Several autopsy studies reflect a 0.01–0.50% prevalence of sporadic AVMs. About 300,000 Americans are believed to have intracranial or intraspinal AVMs; 85% are supratentorial, and 15% are infratentorial.
- The natural history is not well known, as most symptomatic lesions are treated and most asymptomatic lesions are undetected; however, it is estimated that 12% of patients harboring AVMs are symptomatic. Most patients present with hemorrhage.
- The yearly rate of AVM ruptures is 2–4%, although there are reports of up to 32.6%. A general guideline for estimating a patient's lifetime risk of hemorrhage = 105 minus the patient's age in years. The risk of re-hemorrhage is higher (6%) in the first year after the initial hemorrhage and then returns to baseline. Mortality rates for the first, second, and third hemorrhagic events are 10%, 15%, and 20%, respectively. There is a 30–50% chance of permanent or disabling neurological deficits associated with hemorrhages.
- About 2% of hemorrhagic strokes in adults and up to 40% in children are attributed to AVMs. Very rarely spontaneous obliteration has been reported.
- Age
  - Patients are generally 20–40 years of age; most are diagnosed before 30.
- Race/sex
  - Males and females of all races and ethnic groups are equally affected.

RISK FACTORS

The risk of hemorrhage cannot be accurately predicted. Irregular growth of AVMs complicates this further. Several factors may increase the risk of hemorrhage: Deep venous drainage, high feeding artery pressure, hypertension, prior hemorrhage, a single draining vein, related aneurysms, smaller size, and venous stasis.

Pregnancy Considerations

Evidence suggests an increased tendency of AVMs to rupture during pregnancy. Although treatment of unruptured AVMs is usually not recommended during pregnancy, the risk of re-hemorrhaging is higher in pregnant women; thus, treatment should be a consideration if a rupture does occur. Additionally, Cesarean section is generally recommended as a precaution during labor.

Genetics

Sporadic AVMs have no known genetic susceptibility. They have been associated with hereditary neurocutaneous angioma and hemorrhagic telangiectasia (Osler–Weber–Rendu disease) and other rare neurological syndromes (Wyburn–Mason syndrome, Sturge–Weber syndrome, von Hippel–Lindau disease). AVMs are not considered familial and an overwhelming majority is sporadic.

ETIOLOGY

Current evidence suggests that AVMs result from dysregulated angiogenesis producing persistent primitive arteriovenous connections or redevelopment of such connections after the initial closure. Trauma to developing vessels may also contribute. The lack of normal capillaries results in a high-flow, high-pressure arteriovenous shunt. High flow produces vascular steal, and high pressure promotes growth of the AVMs, formation of aneurysms, and rupture. Persistent high pressure also causes feeding arteries to swell and distort and draining veins to stenose. Vessels become progressively thinner and weaker. Multiple AVMs are very rare.

COMMONLY ASSOCIATED CONDITIONS

Aneurysms are found in up to 58% of patients with AVMs. They can be managed like regular intracranial aneurysms if they are not in an artery that feeds the AVM. Aneurysms in the feeding arteries can rupture and hemorrhage, thus microsurgical clipping or endovascular coiling of the aneurysm (especially if it is greater than 7 mm in diameter) may be performed before treatment of the AVM. Intranidal aneurysms are treated together with the AVM.

DIAGNOSIS

Most AVMs are asymptomatic. The most common symptom is hemorrhage (50%) with varying neurological deficits related to the location and extent of hemorrhage. Other common symptoms are seizures (25%) and headache (20%) of no characteristic pattern. Focal neurological deficits can also occur (15%), including aphasia, apraxia, ataxia, cognitive dysfunction, memory difficulties, papilledema, paresthesias, vertigo, visual disturbances, and weakness. Asymptomatic adult patients have a higher incidence of learning disabilities. A rare sign may be a cranial bruit.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- In an emergent setting, CT is the imaging procedure of choice to exclude hemorrhage; however, CT angiography (CTA), MRI, and MR angiography (MRA) provide more vascular detail and may be as readily available.
- MRI provides greater resolution and better visualization of the surrounding cerebral structures that can include characteristic honeycomb tangle of flow voids. Large arteries, arterialized veins, and the relation of AVMs to intracranial structures may be seen. Areas of hemorrhage, blood products of various ages, and local edema may also be present.
- MRI and MRA can noninvasively create 3D representations of AVMs.
- One of the aforementioned tests should be performed before cerebral angiography, which is invasive but provides a definitive diagnosis and allows for AVM grading according to the Spetzler and Martin system. Cerebral angiogram best demonstrates blood vessel architecture. Superselective angiogram is recommended to delineate the internal architecture of an AVM. Associated aneurysms should also be identified.
- MRI and cerebral angiography are recommended prior to surgery.

Diagnostic Procedures/Other

The Wada test and functional imaging techniques can be useful in localizing eloquent areas prior to treatment.

DIFFERENTIAL DIAGNOSIS

- Non-AVM-related intraparenchymal hemorrhage.
- Cavernous malformation—an abnormal collection of low-flow blood-filled channels with no intervening neural tissue. These can hemorrhage and are more likely to be multiple.
- Cerebral aneurysm.

- Venous angioma (developmental venous anomaly), the most common vascular malformation of the brain—multiple abnormally enlarged veins near a ventricular surface confluence into a larger vein toward the cortex forming a "caput medusa" appearance on angiography. These generally do not impair neural function and rarely, if ever, hemorrhage.
- Arteriovenous fistula—an abnormal acquired arteriovenous shunt sometimes resulting from trauma involving the external and internal cranial vasculature.
- Tumor—rarely, an AVM may resemble a tumor by its mass effect and edema.
- Amyloid angiopathy in older patients with a history of cognitive decline or seizures.

TREATMENT

MEDICATION

- Medications treat symptoms such as headache, seizures, and the side effects of treatment including hypertension, vomiting, and vasogenic edema.
- Precautions: Monitor blood glucose with steroids.

ADDITIONAL TREATMENT

General Measures

- Indications for treatment include prevention of hemorrhage, treatment of seizures, enhancement of local perfusion, and treatment of hemorrhage. Complete obliteration is the goal of treatment, as partial obliteration offers no protection from hemorrhage and may in fact increase the risk.
- There are 4 treatment options: Observation, surgery, radiosurgery, and endovascular therapy. Treatment planning considers the lowest risk of injury with the highest chance of lesion obliteration. Randomized trials have not compared available interventional AVM treatments in adults. A Randomized Trial of Unruptured Brain AVM (ARUBA) is an ongoing trial attempting to ascertain this data. Many centers treat AVMs with a combination of interventions.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Adjunctive treatment
  - Embolization: Endovascular neurosurgery is often used in conjunction with surgical resection or radiosurgery. In preparation for surgery, embolization can be used to reduce blood flow to an AVM, reducing the risks associated with surgery. Additionally, it can be used to reduce the size of the AVM making it small enough for effective treatment by stereotactic radiosurgery. While endovascular embolization is usually used as an adjunctive treatment, curative embolization rates of about 20% have been reported using the embolic agent Onyx. Complications have been detailed in 6–14% of cases.
- Symptomatic treatment
  - No medical management can completely mitigate AVM hemorrhage risk. Acute hemorrhage should be treated like any intracranial hemorrhage. Seizures can be treated with surgery. Focal neurological deficits may or may not improve with treatment. Surgery should be strongly considered for low surgical risk lesions that are easily accessible. Small lesions that cannot be easily accessed may be treated with radiosurgery. A combined embolization and surgery approach may be suggested for moderate surgical risk lesions. High-grade AVMs offer a challenge as neither surgical resection nor SRS is recommended. A recent study utilized endovascular embolization followed by SRS on lesions with diameters >3 cm. This allowed for 81% obliteration of AVMs that were initially too large for radiosurgery.

SURGERY/OTHER PROCEDURES

Surgery: Surgical removal of the entire AVM while limiting brain injury is the treatment of choice. The Spetzler–Martin scale (I–V) is used to rate AVMs on the basis of maximum diameter, eloquence of location, and venous drainage pattern—3 characteristics shown to be predictive of surgical outcomes. The higher the grade, the riskier the surgical treatment. Surgical resection is usually recommended for grade I and II lesions; grade III may require endovascular embolization before surgery; surgery is not recommended for grade IV or V lesions. Mortality rates are close to 0 for surgery on grade I–III lesions. Spetzler and Ponce have suggested a new 3-tier classification system that simplifies the Spetzler–Martin system wherein grades I and II become class A, grade III becomes class B, and grades IV and V become class C. The revised classification simplifies treatment recommendations and is similarly predictive of outcome.

- Radiosurgery: Radiosurgery is recommended for patients with small lesions (diameter <3 cm) especially when located in surgically inaccessible or eloquent areas. Complete obliteration occurs in 80% of patients within 2–3 years; however, during this time the risk of hemorrhage remains at 2–4% per year. Reports of obliteration have been as high as 90% for lesions <3 cm. There is radiation exposure and a small risk of recurrence. Still, treatment-related risks are low, and outpatient treatment is employed.

IN-PATIENT CONSIDERATIONS

Admission Criteria

The decision to treat an AVM is based on age, neurological status, hemorrhage risk factors, medical condition, and the architecture of the lesion. Carefully planned treatment with multiple preoperative visits for testing and counseling affords the best possible outcome. Due to the lifetime risk of hemorrhage, more aggressive treatment is warranted in younger patients.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- After surgery, standard postcraniotomy care, including control of intracranial pressure and blood pressure, is warranted. Rapid neurological decline after AVM resection due to the increased perfusion to previously hypoperfused tissue (normal perfusion pressure breakthrough) may occur.
- Angiography should be performed after surgery to confirm AVM obliteration. Serial angiography should be performed in patients selecting observation or radiosurgery. Some centers may employ MRA and CTA in serial follow-up of treated and untreated lesions.

PATIENT EDUCATION

- No restrictions on activity or diet are recommended to prevent hemorrhage. Aspirin and other NSAIDs may promote a more serious hemorrhage.
- Website: National Institute of Neurological Disorders and Stroke, http://www.ninds.nih.gov/disorders/avms/avms.htm

PROGNOSIS

A surgically excised AVM can be considered cured with no further risk of hemorrhage and recurrence. Rarely, recurrence has been described in radiosurgically obliterated AVMs. Incompletely treated lesions do not reduce the risk of hemorrhage.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Vascular malformation
- Cerebrovascular disease, intracerebral hemorrhage

CODES

ICD9

747.81 Anomalies of cerebrovascular system

CEREBROVASCULAR DISEASE, DISSECTIONS

Yuebing Li, MD, PhD

BASICS

DESCRIPTION

Arterial dissection denotes the separation of arterial wall by a mural hematoma. Cervical (carotid and vertebral) arterial dissections (CAD) are increasingly recognized owing to improved awareness and detection methods. Cerebral infarction is the most frequent and severe manifestation of CAD.

EPIDEMIOLOGY

Incidence

Typically occurs in young adults with a mean age of 45 years. It accounts for up to one-fourth of ischemic strokes before 50 years of age. Excluding traumatic cases, the average annual incidence of CAD is 2.6–2.9 per 100,000. Carotid dissections are more common than vertebral. Multiple CADs are seen in 13–16% of cases.

Prevalence

Assuming a life expectancy of 30 years after dissection, the prevalence of CAD survivors is about 1/1,000.

RISK FACTORS

- Connective tissue disorders:
  - A minority of patients (5%) shows evidences of a connective tissue disorder such as fibromuscular dysplasia, Marfan's syndrome, Ehlers–Danlos syndrome or osteogenesis imperfecta
  - Half of patients with evidences of connective tissue disorders on skin biopsy: Disordered elastic fibers, increased cystic medial degeneration, and fibrosis
- Trauma, severe or minor (see Etiology)
- Recent respiratory infection
- Season: Peak incidence in the fall
- Migraine headache

Genetics

Genetic predisposition: Not convincingly proven despite of many reported familial cases and several genetic studies. Possible association with ICAM1, COL3A1, and MTHFR genes.

PATHOPHYSIOLOGY

- An intimal tear or a vasa vasorum rupture allows blood to enter between layers of the vessel wall. An intramural hematoma develops, resulting in luminal stenosis, luminal occlusion, intraluminal thrombus formation, aneurysmal dilatation or extravascular hemorrhage.
- Pathogenesis of ischemic stroke: Embolic in approximately 92% and hemodynamic (hypoperfusion) in 8% of cases.
- Most common sites of spontaneous dissections: 2–3 cm distal to carotid bulb, V2 (segment within transverse foramen) and V3 (segment surrounding C1 and C2 vertebra) segments of the vertebral artery.
- Carotid dissecting aneurysm: Mostly located immediately below cranial base.

ETIOLOGY

- Traumatic CAD:
  - Incidence of 1% or less following significant blunt or penetrating trauma. Motor vehicle accidents accounting for half of the cases. Vertebral artery dissection seen in 10% of patients with cervical spine fracture.
  - Traumatic CAD should be considered under following circumstances: Expanding cervical hematoma, evidence of infarction on brain imaging, Horner's syndrome with neck pain or headache, unexplained neurological deficit, transverse process fracture of the cervical spine.
- Spontaneous dissection: Much more common
  - Spontaneous CAD: Without above significant trauma history but may be provoked by minor trauma.
  - Trivial trauma in about one-third of cases: Vomiting, sneezing, coughing, falling or rapid head turning.
  - Sports and recreational activities.
  - Cervical spine manipulation, particularly causing vertebral artery dissection.
  - Iatrogenic: Chiropractic maneuvers, endotracheal intubation, carotid procedures, cervical spine surgery.

DIAGNOSIS

HISTORY

- 6% of CAD can be asymptomatic
- Unusual ipsilateral neck pain, headache or eye pain seen in 70% patients
- Pain followed by transient or long-lasting symptoms of cerebral, retinal or spinal ischemia (weakness, numbness, ataxia, speech disturbance, diplopia or visual loss)
- Pulsatile tinnitus
- Radicular pain in arm

PHYSICAL EXAM

- Horner's sign: Ptosis and aniscoria in approximately half of patients
- Audible bruits
- Cranial nerve palsies (mostly IX–XII)
- Signs of ischemia as above

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

A CBC, electrolyte, serum glucose, serum creatinine, PT, PTT should be obtained.

Follow-up & special considerations

- Sedimentation rate, C-reactive protein, lipid panel to rule out other diagnoses (see Differential Diagnosis section)
- Electrocardiogram and echocardiogram to evaluate cardiac function and rule out cardioembolism

Imaging

Initial approach

- Non-contrast head CT to rule out intracranial hemorrhage.
- MRI/MRA of head with fat-suppressed T1-axial image of cervical spine: MRI of brain may show scattered embolic infarctions and less likely a watershed pattern secondary to hypoperfusion. Axial MRI of cervical spine may show an enlarged artery with a crescent-shaped rim of hyperintense signal surrounding a lumen of reduced size. Sensitivity of 90–99% for carotid and 60% for vertebral dissections when comparing to digital subtraction angiography (DSA).
- Computed tomography angiography: Equally accurate to MRI/MRA for carotid but superior to MRI/MRA in vertebral dissections. It can be performed quickly but with increased radiation exposure.

Follow-up & special considerations

DSA: Typical findings—tapered stenosis, intimal flap with false lumen, dissecting aneurysm, flame-shaped occlusion, intra-luminal thrombus. Also helpful in providing information of collateral circulation. However, there is associated risk and it does not provide adequate information about mural hematoma in vessel wall.

Diagnostic Procedures/Other

Duplex ultrasonography: Limited role is defined.

Pathological Findings

In addition to the separation of vessel wall by hematoma, other findings may include irregular intima with thickening and interruptions, disorganization of the elastic fibers, and vacuolization of myocytes.

DIFFERENTIAL DIAGNOSIS

- Migraine or cluster headache: Lack of vessel or brain parenchyma abnormalities
- Cardioembolism: Stroke in multi-vessel territories and presence of cardiac diseases
- Atherosclerotic arterial disease: Lack of typical imaging appearance and presence of risk factors such as smoking, hypertension, diabetes, etc.
- Fibromuscular dysplasia: Multi-focal stenosis with adjacent dilatations, so-called "string of beads" sign
- Takayasu's arteritis: Large vessel arteriopathy affecting aorta and its main branches
- Giant cell arteritis: Seen in older population with elevation of sedimentation rate
- Behçet's disease: Multi-system inflammatory disease characterized by uveitis, oral and genital ulceration, occlusion or thrombophlebitis of major veins

TREATMENT

MEDICATION

First Line

- Thrombolytic agent: Efficacy and complication rate comparable to stroke by other etiologies. However, contraindicated in traumatic CADs.
- Antiplatelet (aspirin, clopidogrel, combination of aspirin, and dipyridamole) versus anticoagulation (warfarin with a targeted international normalized ratio of 2.0–3.0). No advantage of either regime. No randomized trial for comparison.
- Probable indication for anticoagulation: Arterial occlusion, presence of free-floating thrombus, high-intensity transient signals on transcranial Doppler indicating embolism, presence of pseudoaneurysm, recurrent events while on antiplatelet therapy.
- Probable contraindication for anticoagulation: Severe stroke with NIH stroke scale of more than 15, accompanying intracranial dissection (possible co-existing subarachnoid hemorrhage), and local compressive syndrome.
- Anticoagulation is maintained for no longer than 6 months, but long-term usage of antiplatelets may be appropriate.

ADDITIONAL TREATMENT

Issues for Referral

Follow-up with a neurologist in 1 week, then 1 month, then 3 months, then 6 months' post discharge.

Additional Therapies

Physical, occupational and speech therapies are needed for those with significant neurological deficits.

SURGERY/OTHER PROCEDURES

- Surgical repair of a spontaneous dissection is generally not required.
- Surgical repair of a traumatic dissection may include vessel ligation, thrombectomy, bypass grafting or direct repair of injured arteries.
- Endovascular therapy such as stenting is still controversial. It seems appropriate for patients with continuing ischemic symptoms despite antithrombotic therapy, hemodynamic instability due to hypoperfusion and significant enlargement of a dissecting aneurysm.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Watch for signs of respiratory compromise
- Cervical spine stabilization in traumatic patients

Admission Criteria

- Acute dissection with significant neurological deficits
- All traumatic patients with clinical suspicion of arterial dissection
- Recurrent ischemic event with a known diagnosis of dissection
- Significant complication of treatment such as hemorrhage

IV Fluids

- IV fluids required for patients with dysphagia or risk of aspiration
- Intravenous heparin might be needed for bridging warfarin treatment

Nursing

- Monitoring symptoms of ischemia
- Treat pain as needed
- Monitoring signs of bleeding

Discharge Criteria

- Neurologically stable and antithrombotic treatment option made
- Preferably when INR reach or close to therapeutic range (2–3) prior to discharge

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Follow-up with neurology as described above.

Patient Monitoring

- Most patients can be admitted to regular floor.
- Watch for signs of deep venous thrombosis in non-mobile patients.
- When on Coumadin, check INR weekly, more frequently if on multiple medications or unstable.

DIET

A regular diet without restrictions in most patients can be given.

PATIENT EDUCATION

- Educate patient about signs of ischemia and signs of bleeding (skin, GI tract)
- Educate patient about avoidance of major trauma including fall when on anticoagulation

PROGNOSIS

- Traumatic CADs have worse outcomes (10% mortality, 40% permanent neurological deficit)
- Spontaneous CADs:
  - Excellent outcome in 70–80% patients
  - Mortality rate of 3–7%
  - Subsequent ischemic stroke risk of 1% per year, with the greatest risk in the first month after diagnosis
  - Image appearance: Most healing occurring within the first 3–6 months. Improvement of stenosis or occlusion in 40–70% patients. Complete resolution of arterial abnormalities in 46% of stenosis, 33% of occlusions, and 12% of dissecting aneurysms
  - A 0.3% annual risk of symptomatic recurrent dissections
  - No study has documented an increase in the size of spontaneous dissecting aneurysms

COMPLICATIONS

- Ischemia due to hemodynamic insufficiency or embolism
- Lower cranial nerve palsy due to the expansion of arterial wall
- Subarachnoid hemorrhage when dissection extending to intracranial portion
- Dissection of other arteries (aortic, renal, abdominal)
- Deep venous thrombosis and/or pulmonary embolism in non-mobile patient

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebrovascular diseases, ischemic infarction
- Cerebrovascular diseases, TIA

CODES

ICD9

- 443.21 Dissection of carotid artery
- 443.24 Dissection of vertebral artery
- 443.29 Dissection of other artery

CLINICAL PEARLS

- Most CADs are spontaneous albeit provoked, and non-traumatic.
- Painful Horner's syndrome is highly suggestive of a carotid dissection.
- No overall difference between antiplatelet and anticoagulation treatment.
- Interventional treatment should be reserved for patients with recurrent ischemia while on antithrombotic therapy.
- In the acute setting, spontaneous dissection is not a contraindication for thrombolytic therapy.

CEREBROVASCULAR DISEASE, INTRACEREBRAL HEMORRHAGE

Aarti Sarwal, MD

BASICS

DESCRIPTION
- Intracerebral hemorrhage (ICH) is direct bleeding into the brain.

EPIDEMIOLOGY
- Incidence
  - ICH accounts for 10% of all strokes in North America with an incidence of 12–15 per 100,000.
  - No sex predilection.
  - African American and Asian populations have higher rates of ICH.

GENERAL PREVENTION
- Control of risk factors—hypertension
- Close monitoring of anticoagulation

PATHOPHYSIOLOGY
- Non-traumatic ICH may occur from hypertensive damage to blood vessel walls, autoregulatory dysfunction in cerebral blood flow, rupture of a vascular malformation, arteriopathy, or altered hemostasis.

ETIOLOGY
Depends on patient age and hemorrhage location
- Hypertension: classic location of bleed is in basal ganglia, thalamus, deep subcortical white matter, pons, or cerebellum
- Vascular malformation: arteriovenous malformations, cavernomas, venous angiomas account for higher incidence in younger patients
- Aneurysm usually causes subarachnoid hemorrhage but can rupture into brain parenchyma
- Amyloid angiopathy may cause lobar hemorrhages in elderly patients
- Bleeding diathesis from therapeutic anticoagulation, antiplatelet therapy, or thrombolytic therapy. Disseminated intravascular anticoagulation, thrombocytopenia, coagulation deficiency disorders, and hematologic disease may also cause ICH
- Tumors such as malignant melanoma and renal cell carcinoma may metastasize to the brain, producing lesions that have high risk of bleeding
- Drugs such as cocaine and amphetamine and alcohol can cause vasculopathy
- Penetrating or non-penetrating head trauma

DIAGNOSIS

HISTORY
- Abrupt onset of headache, nausea, and vomiting
- Focal neurologic deficit
- Seizures
- Decreased level of consciousness
- History of hypertension, trauma, illicit drug abuse or a bleeding diathesis may be elicited

PHYSICAL EXAM
- Severe hypertension
- Focal neurologic deficits corresponding to the location of the bleed
- Signs of increased intracranial pressure Signs of herniation
- Systemic signs of bleeding diathesis

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests
- Complete blood count with platelets
- Coagulation studies—PT/INR, aPTT
- Urine drug screen
- Type and screen for cross-match
- Etiology-specific tests, e.g., liver function tests, vasculitis panel

Follow-up & special considerations
- Abnormal coagulation factors should be aggressively corrected or replaced

Imaging

Initial approach
- Abrupt onset of focal neurologic symptoms is presumed to be vascular in origin until proven otherwise. Neuroimaging is thus mandatory to rule out intracranial hemorrhage (1)[A]
- CT is very sensitive for identifying acute hemorrhage and is considered the gold standard
- CT angiography and contrast-enhanced CT may identify patients at high risk of ICH expansion based on the presence of contrast extravasation within the hematoma

Follow-up & special considerations
- Active bleeding may proceed for hours after symptom onset. About 30% of patients have hematoma expansion of greater than one third on follow-up CT.
- Hematoma expansion is predictive of clinical deterioration and increased morbidity and mortality.

Diagnostic Procedures/Other
- Cerebral angiogram to rule out underlying aneurysm or vascular malformation
- Continuous EEG monitoring should be considered in patients with depressed mental status disproportionate to the degree of brain injury (1)[B]

Pathological Findings
- Depends on the etiology of the ICH
- Charcot–Bouchard microaneurysms may be seen at bifurcations of distal lateral lenticulostriate vessels in hypertensive ICH
- Lobar hemorrhages of cerebral amyloid angiopathy may reveal pathologic deposition of β-amyloid protein within the media of small cortical and meningeal vessels.

Pregnancy Considerations
- There is increased risk of hemorrhage from vascular malformation or aneurysm during pregnancy and labor.
- Hemorrhage from veno-occlusive disease is also more frequent

DIFFERENTIAL DIAGNOSIS
- Hemorrhagic transformation of ischemic stroke
- Intraventricular hemorrhage or subarachnoid hemorrhage
- Cerebral venous sinus thrombosis
- Seizures or migraine

TREATMENT
- The risk for early neurologic deterioration and the high rate of poor long-term outcomes underscores the need for aggressive early management
- Aggressive early management aims to prevent rebleeding, minimize hematoma expansion, and prevent cerebral ischemia.

MEDICATION

First Line
- Correct coagulopathy by reversing anticoagulation or antiplatelet therapy using protamine, Vitamin K, or fresh frozen plasma
- Treat hypertension meticulously. After the acute ICH period, a goal target of a normal BP of $<$140/90 mm Hg ($<$130/80 mm Hg if diabetes or chronic kidney disease) is reasonable

Second Line
- Initiate measures to reduce intracranial pressure in case of rapid deterioration, signs of hydrocephalus, or herniation.
- Keep head of bed elevated
- Establish airway to induce hyperventilation.
- Use mannitol boluses or hypertonic saline infusion as osmotic therapy.
- Consider external ventricular drainage for draining CSF and monitoring ICP.

ADDITIONAL TREATMENT

General Measures

- Airway management to prevent hypoxia and aspiration
- Maintain strict normoglycemia and normothermia
- Avoid NSAIDs for pain control. Use short-acting opoids
  – GI and deep vein thrombosis prophylaxis

Issues for Referral

- Following prehospital and emergent stabilization, all patient s with ICH should be transferred to a medical facility with neurosurgical expertise (2).
- Neurosurgery for hematoma evacuation, external ventricular drainage placement, or decompressive hemicraniotomy
- Patients with cerebellar hemorrhage who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage as soon as possible (1)[B]. Initial treatment of these patients with ventricular drainage alone, rather than surgical evacuation, is not recommended.
- Traumatic bleeds or contusions may blossom and should be monitored closely.

Additional Therapies

- Seizure should be aggressively treated.
- Prophylaxis with antiepileptics may be considered in patients with altered mental status.
- Aggressive maintenance of normothermia and normoglycemia

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Consider factor VII for warfarin-related intracranial hemorrhage in case of hematoma expansion (2)
- Aggressive physical, occupational, and speech therapy

SURGERY/OTHER PROCEDURES

- External ventricular drainage for patient s with depressed mental status and hydrocephalus
- Decompressive hemicraniotomy for refractory cerebral edema
- Hematoma evacuation for lobar bleeds >30 mL and <1 cm from the surface

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Because of the high risk of hematoma expansion, aggressive control of BP and measures to reduce cerebral edema should begin as soon as ICH is suspected

Admission Criteria

- All patients with significant ICH should be monitored in the ICU to check for acute deterioration

IV Fluids

- Avoid dextrose-containing fluids
- Maintain euvolemia

Nursing

- Head of bed should be elevated at 30 degrees to reduce cerebral edema while maintaining cerebral perfusion
- Pneumatic compression devices
- Aspiration precautions but cautious early refeeding

Discharge Criteria

- Depending on neurologic status after stabilization, patient should be evaluated for acute stroke rehabilitation

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Any patient with unclear etiology for bleeding should be followed up for testing after acute stabilization
- Physical, occupational, and speech therapies may require to be administered on outpatient basis
- Aggressive control of risk factors with outpatient follow-up

Patient Monitoring

- Frequent clinical neurochecks.
- 73% of patients have demonstrable hematoma growth during first 24 hours.
- Early noncontrast CT scan for neurologic deterioration to look for hematoma expansion, intracranial hypertension, or hydrocephalus
- Frequent vital sign checks, neurologic assessments, and continuous cardiopulmonary monitoring including a cycled, automated BP cuff, ECG telemetry, and O_2 saturation probe should be standard.
- Continuous intra-arterial BP monitoring should be considered in patients receiving intravenous vasoactive medications
- Intracranial pressure monitoring

DIET

- Screen for dysphagia
- Aspiration precautions
- Early feeding

PATIENT EDUCATION

- Aggressive full care early after ICH onset and postponement of new do-not-resuscitate orders, until at least the second full day of hospitalization, is probably recommended (1)[B]
- Physical, occupational, and speech therapies

PROGNOSIS

- 40% mortality overall.
- 10–15% shall remain fully dependent
- 25% will be fully independent at 6 months
- Predictors of poor outcome include early reduction in level of consciousness, large hematomas, intraventricular hemorrhage, and hydrocephalus

COMPLICATIONS

- Prolonged neurologic deficit
- Seizures
- Hydrocephalus
- Thromboembolic disease
- Aspiration pneumonia

REFERENCES

1. Morgenstern LB, Hemphill JC 3rd et al; American Heart Association Stroke Council and Council on Cardiovascular Nursing. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke* 2010;41(9): 2108–2129.
2. Flower O, Smith M. The acute management of intracerebral hemorrhage. *Curr Opin Crit Care* 2011;17(2):106–114.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebral hemorrhage
- Intraparenchymal Hemorrhage

CODES

ICD9

- 431 Intracerebral hemorrhage
- 853.00 Other and unspecified intracranial hemorrhage following injury, without mention of open intracranial wound, with state of consciousness unspecified

CLINICAL PEARLS

- Early aggressive treatment including meticulous control of blood pressure, measures to reduce hematoma expansion and prevent cerebral ischemia are crucial to improving mortality
- Neurosurgery should be consulted for possibility of hematoma evacuation, external ventricular drainage placement, or decompressive hemicraniotomy.
- Patients with cerebellar ICH >3 cm or signs of deterioration should undergo surgical removal of the hemorrhage as soon as possible.
- Traumatic bleeds or contusions may blossom and should be monitored closely

CEREBROVASCULAR DISEASE, ISCHEMIC INFARCTS

James Gebel, MD, MSc
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BASICS

DESCRIPTION

Ischemic stroke is defined as a partially irreversible focal ischemic injury (or injuries) to the brain, retina, or spinal cord that produces clinical symptoms lasting at least 10 minutes. Cerebral infarction is defined as an area of focal brain ischemia sufficient to produce radiologically or pathologically evident infarction. Not all cerebral infarctions produce clinical symptoms.

EPIDEMIOLOGY

There are approximately 731,000 new or recurrent strokes every year in the US; 80–85% of these are ischemic.

- Age: 75% of strokes occur in persons ≥65
- Sex: Lifetime risk females 1 in 5, males 1 in 6
- Race/ethnicity: More common in African Americans, Asians, and Hispanics.

RISK FACTORS

Risk factors include hypertension, diabetes mellitus, elevated C-reactive protein, hyperlipidemia, tobacco, sedentary life, obesity, family history of stroke, and prior history of stroke or TIA, and known coronary artery or peripheral vascular disease.

Pregnancy Considerations

Pregnancy increases the risk of ischemic stroke. Conditions peculiar to pregnancy that lead to stroke include paradoxical emboli from the legs or pelvic veins, cardiomyopathy of pregnancy, cervical arterial dissection during labor and delivery, hypercoagulable state, amniotic fluid embolism, and vasoconstrictive medications like ergotamines.

Genetics

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, prothrombin variant, and infrequently (in young patients) Leiden factor V mutation, are all genetic conditions that can present with stroke.

ETIOLOGY

- Cardiac emboli: Conditions that predispose to the formation of cardiac emboli include persistent or paroxysmal atrial fibrillation/flutter, mitral valve stenosis, sick sinus syndrome, prosthetic heart valve, infective or marantic endocarditis, congestive heart failure with EF of 35% or less, dilated cardiomyopathy, myxomas, left atrial enlargement, and spontaneous echo contrast.
- Large artery disease: Stenosis of the extracranial internal carotid and vertebral arteries, and large intracranial vessels of the Circle of Willis and posterior circulation (intracranial vertebral and basilar arteries, usually due to atherosclerosis. Other diseases include dissection, vasculitis, moyamoya, and fibromuscular dysplasia.
- Small vessel disease: Lacunar infarction.
- Hypercoagulable states, both inherited such as prothrombin II variant mutation; and acquired such as antiphospholipid antibody syndrome, lupus anticoagulant, sickle cell anemia, and paraneoplastic (especially mucin-secreting carcinomas with elevated CA-125 levels).
- Cerebral vasculitis, moyamoya disease, vasospasm, fibromuscular dysplasia, carotid or vertebral artery dissection, and reversible cerebral vasoconstrictive syndrome (uncommon).

COMMONLY ASSOCIATED CONDITIONS

The commonly associated conditions comprise TIA, coronary artery disease, and peripheral arterial disease.

DIAGNOSIS

The clinical features depend on the brain area affected. Common symptoms include hemiparesis, hemisensory loss, visual field defects, ataxia, aphasia, dysarthria, dysphagia, diplopia, and vertigo.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- All patients with stroke should have blood drawn for fasting lipid profile, BUN, creatinine, CBC and platelets, PT with international normalized ratio (INR), and PTT.
- Hypercoagulable profile including factor V mutation, factor II mutation, lupus anticoagulant, antiphospholipid antibodies, and homocysteine should be requested in young patients. Protein S, C, and antithrombin II deficiencies rarely cause TIA or stroke and much more often cause venous, not arterial, thromboembolic events.
- Serial blood cultures for endocarditis prn.

Imaging

- CT scan of the brain non-contrast must be performed in all patients with suspected stroke because it is very sensitive in detecting intracerebral hemorrhage or subdural hematoma, which can mimic ischemic stroke clinically. CT angiography of the neck and brain can also be simultaneously or subsequently performed to detect stenosis or occlusion of the large neck or brain vessels.
- MRI of brain is much more sensitive than CT scan in detecting small or early cerebral infarction. MR angiography of the neck and brain is another noninvasive testing option for assessing the major extracranial and intracranial arteries for stenosis, though it may overestimate the degree of stenosis.
- Transthoracic echocardiogram (TTE) is indicated in most patients with stroke. If the TTE is negative and a cardiac source of embolism is still suspected, the transesophageal echocardiogram (TEE) should be performed. TEE is also indicated in almost all young stroke patients (unless an explanation for the stroke is found on TTE), in whom half of all ischemic strokes are of cardioembolic origin.
- TEE is more accurate than TTE in showing atrial and ventricular thrombi, vegetations, and left atrial enlargement, detecting shunts, and aortic arch atheroma.
- Angiography is the gold standard for an accurate assessment of both the extra- and intracranial vasculature. However, it is an invasive expensive procedure with greater risk than CTA, MRA, or ultrasound, and should be reserved for patients in whom noninvasive testing has not definitely shown the source of stroke or gives conflicting estimation of degree of stenosis of the large neck or brain vessels.
- Ultrasound is a safe, portable, and inexpensive. It includes transcranial Doppler to look for intracranial disease and carotid duplex to assess for extracranial carotid disease. Carotid duplex insensitive in extracranial vertebral disease.

Diagnostic Procedures/Other

ECG and cardiac monitoring, either inpatient telemetry or 24-hour Holter monitoring to evaluate for arrhythmias.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes migraine aura/status, migrainosus, multiple sclerosis, seizures (Todd's paralysis), vertigo, syncope, metabolic disorders, intracerebral hemorrhage, subdural hematoma, conversion disorder, and cerebral venous sinus thrombosis.

TREATMENT

MEDICATION

- Recombinant tissue plasminogen activator (rt-PA) is the only FDA-approved medication for acute ischemic stroke and must be given within 3–4.5 hours from the onset of symptoms. Dose 0.9 mg/kg to maximum of 90 mg; 10% of the dose given IV bolus over 1 minute and the rest as an IV drip over 1 hour. Only alteplase is FDA approved for use in ischemic stroke patients. *Retevase and other (non-alteplase) thrombolytic medications should NOT be administered for acute ischemic stroke treatment under any circumstances.*
- Antiplatelet agents: Indicated for stroke prevention in small vessel disease, intracranial large artery disease, mild (<50%) extracranial carotid artery disease, extracranial vertebral artery disease, aortic arch disease without mobile plaque, irregular nonstenotic valve surfaces, and in patients who are not Coumadin candidates.
  - Aspirin: 50–325 mg/day
  - Clopidogrel (Plavix): 75 mg/day
  - Aspirin 25 mg/extended release dipyridamole 200 mg (Aggrenox) po b.i.d.
- Anticoagulants
  - Warfarin (Coumadin): Indicated in hypercoagulable states; cardiac sources like atrial fibrillation, intracardiac thrombi, and intracranial large artery stenosis
  - Dabigatran (Pradaxa): Indicated in patients with persistent or paroxysmal nonvalvular atrial fibrillation and is preferred over warfarin due to superior efficacy and at least comparable safety

- Contraindications
  - IV rTPA given within 3 hours: Suspicion of subarachnoid hemorrhage; recent (within 3 months) intracerebral or intraspinal surgery; recent head trauma; recent major (abdominal or thoracic) surgery; previous stroke within 3 months; history of intracerebral hemorrhage; history of uncontrolled hypertension; uncontrolled hypertension at time of treatment (SBP >185 mm Hg or DBP >110 mm Hg); seizure at the onset of stroke; active internal bleeding; GI bleeding within 30 days; known or suspected intracranial neoplasm, arteriovenous malformation, or aneurysm; known bleeding diathesis including but not limited to current use of oral anticoagulants (e.g., warfarin sodium), or an INR >1.7; administration of heparin in the preceding 48 hours and an elevated aPTT at presentation; platelet count <100,000/mm^3; blood glucose <70 or >400; presence of low attenuation on head CT in >1/3rd of the middle cerebral artery; presence of any blood on head CT
  - IV rTPA given within 4.5 hours: *In addition to all of the above*; age >80, history of BOTH previous stroke AND diabetes mellitus, warfarin use *no matter what the PT INR is*, NIH Stroke Scale Score >25
  - Aspirin/Aggrenox: Mainly known allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer
  - Clopidogrel: Mainly active systemic bleeding
  - Warfarin: Mainly active bleeding, bleeding tendency, noncompliance, drug interactions and dietary (vitamin K containing foods) interactions. Rarely warfarin skin necrosis
  - Dabigatran: Known history of active/recent GI bleeding; other active bleeding
- Precautions
  - rtPA: Noncompressible arterial or venous punctures must be avoided. Blood pressure must be monitored closely during administration of the medicine and treated if elevated. If serious bleeding is suspected, then it must be stopped immediately. Watch for allergic reaction
  - Clopidogrel: Monitor for TTP
  - Warfarin: Watch for compliance, bleeding events, and falling events
  - Dabigatran: Watch for bleeding events (especially GI bleeding)

ADDITIONAL TREATMENT

General Measures

General treatment of stroke includes acute supportive care and stroke, e.g., screening for dysphagia prior to administering any diet or medication by mouth, oxygen administration, DVT risk assessment and prophylaxis, fall risk and pressure sore risk assessment and prevention, evaluation for rehabilitation, administration of statins to atherosclerosis-related stroke patients with LDL >70, Stroke education, management of coexisting medical illnesses, secondary stroke prevention. Physical, occupational, speech, and cognitive therapy may be needed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Rx hyperglycemia, fever, and infection; aspiration precautions when indicated; adequate hydration and nutrition; *judicious control of blood pressure with avoidance of excessive reduction in the acute setting* and adequate control (SBP <120 and DBP <80) in the long run, and avoidance of prolonged use of indwelling catheter to prevent urinary tract infection.
  - Amitriptyline or gabapentin for pain related to thalamic strokes; antidepressants for the depression that may accompany some cortical strokes; muscle relaxants such as Lioresal for residual spasticity; and stool softeners for constipation.

SURGERY/OTHER PROCEDURES

- Carotid endarterectomy (CEA) or carotid artery stenting (CAS) is indicated for most patients with significant (>50%) symptomatic extracranial carotid artery stenosis and for almost all patients with >70% symptomatic extracranial carotid stenosis. Patients with known concomitant coronary artery disease are generally better CAS candidates, and patients over the age of 72 are generally better CEA candidates. CAS associated with higher rate of periprocedural stroke than CEA but lower incidence of periprocedural MI and minimal risk of cranial nerve palsies (5% of CEA cases). Recent preliminary clinical trial data suggests that angioplasty and stenting of symptomatic large intracranial stenosis may be inferior to maximal medical management with antiplatelet medication + aggressive modifiable risk factor management. Angioplasty and stenting of symptomatic large intracranial stenosis at this time is reserved only for patients in clinical trials, or last resort for recurrent strokes on maximal medical therapy.
- Neurointerventional therapies: These are utilized mostly for patients with large vessel occlusions presenting within 6–8 hours of symptoms onset. They may be considered for patients ineligible for IV tPA, with contraindications to IV tPA, or refractory to conventional medical therapy. Further randomized trials are needed to establish improved efficacy compared to medical therapy
  - Intra-arterial therapies:
    - Chemical thrombolysis: tPA, pro-urokinase, glycoprotein IIb/IIIa inhibitors, etc.
    - Mechanical clot disruption
    - Thrombectomy and clot retrieval: Merci and Penumbra device
    - Angioplasty and stenting
    - Retrievable stents: Trevo, Solitaire, Revasc, etc.
    - Multimodal therapy: Combination of the above

IN-PATIENT CONSIDERATIONS

Admission Criteria

In general, any patient presenting with acute ischemic stroke should be admitted to the hospital for the evaluation of etiology and appropriate prevention measures; prevention and management of stroke complications; early initiation of physical, occupational, and speech therapy; evaluation for eligibility for inpatient rehabilitation; assistance with appropriate placement; and patient and caregiver education.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Frequent follow-up visits are important to assess patients for recurrent events, compliance with treatment and recommendations, and adverse reactions from the treatment medications.
- Monitor INR for treatment with Coumadin.

PATIENT EDUCATION

American Stroke Association, National Center, 7272 Greenville Avenue, Dallas, TX, 75231, 1-888-478-7653. www.strokeassociation.org

PROGNOSIS

Appropriate preventive secondary measures significantly decrease the risk of recurrent stroke. However, despite these measures patients continue to be at increased risk.

ADDITIONAL READING

- Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke. *Stroke* 2007;38:1655–1711.
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- Gregory J, del Zoppo MD, Faha MS, et al. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator. *Stroke* 2009;40:2945–2948.
- Michaels MD, Spinler SA, Leeper B, et al. Medication errors in acute cardiovascular and stroke patients. *Circulation* 2010;121:1664–1682.
- National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581–1587.

CODES

ICD9

- 433.81 Occlusion and stenosis of other specified precerebral artery with cerebral infarction
- 434.11 Cerebral embolism with cerebral infarction
- 434.91 Cerebral artery occlusion, unspecified with cerebral infarction

CEREBROVASCULAR DISEASE, SUBARACHNOID HEMORRHAGE AND INTRACRANIAL ANEURYSMS

Shaye I. Moskowitz, MD, PhD

BASICS

DESCRIPTION

An intracerebral bleed in which blood is primarily between the arachnoid and pial layers. This is not necessarily limited to this space and can be associated with subdural, intraparenchymal, or intraventricular blood. This type of nontraumatic bleed is most classically and most commonly associated with a ruptured cerebral aneurysm.

EPIDEMIOLOGY

Incidence

Incidence: Subarachnoid hemorrhage (SAH) occurs in an estimated 6–16 per 100,000 people. Approximately 30,000 cases occur in the USA per year.

Prevalence

Cerebral aneurysms occur in an estimated 1–9% of the population on the basis of limited autopsy and imaging studies. Most, however, do not become clinical significant.

RISK FACTORS

- Both controllable and uncontrollable factors exist.
  - Smoking, heavy alcohol use, and certain street drugs contribute. Poorly controlled hypertension is a risk factor as well.
  - Family and personal history of SAH, female gender, aneurysm details including size, location, and morphology.

Genetics

Aneurysms themselves have a familial link as do their rupture. This is an active area of research. Specific genes are not well understood at this time.

PATHOPHYSIOLOGY

The rupture of an aneurysm results in the release of blood into the subarachnoid space temporarily. Continuous bleeding is ultimately not possible in a confined space and as such results in rapid death. Should the bleeding be brief, potentially stemmed by the sudden rise in intracranial pressure, the patient may survive to present for medical attention. Rerupture is possible and often fatal.

ETIOLOGY

The etiology of aneurysms in general is not completely well known. Most do not rupture and most likely never are identified. It remains unknown why some ultimately progress to rupture, though considerations may be flow dynamics into the aneurysm and stress on the vascular wall.

COMMONLY ASSOCIATED CONDITIONS

Aneurysms are associated with certain collagen vascular diseases, including Ehlers–Danlos and Marfans, and with polycystic kidney disease. Rupture specifically has not yet been associated with any diseases.

DIAGNOSIS

HISTORY

- The classic presentation for a SAH is headache. This is often described as the "worst headache in my life." Headaches can be varying in intensity however and may be a reflection of the patient and size of the hemorrhage.
- Seizure, loss of consciousness, and focal findings are possible as well, though should be differentiated from many other neurological disorders.

PHYSICAL EXAM

- Neurological findings often include meningismus, as a result of the irritation from the blood in the subarachnoid space.
- Findings are varied and range from normal to comatose with focal findings.
- A normal exam with an acute cranial nerve 3 palsy is potentially a sign for a posterior communicating artery aneurysm.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Routine lab work including serology and chemistries and coagulation profiles are standard. No specific finding is pathognomonic.
- Lumbar puncture when performed should reveal xanthochromia on spun samples. Additionally, continued high red cell counts through multiple tubes may be a reflection of a SAH as well.

Follow-up & special considerations

- Monitoring for serum sodium levels is important in the care of these patients as cerebral salt wasting is common, resulting in hyponatremia.
- Additional hospital-acquired infections and medical complications are common, and surveillance is critical.

Imaging

Initial approach

- A non-contrast enhanced CT scan is usually definitive with a clear pattern of blood in the basal cisterns. An MRI may similarly be definitive, though is not the usual first image mode considered.
- Hydrocephalus should be a focus on these tests as well, as this is common.
- Vascular imaging to evaluate for an aneurysm follows. This can include a CT-, an MR-, or a formal catheter angiogram.

Follow-up & special considerations

- Serial CT scans to monitor for delayed or progressive hydrocephalus are routine. This may be performed with or without clinical symptoms.
- Transcranial Doppler ultrasonography is performed to detect or monitor for cerebral vasospasm, usually occurring between 4 and 14 days post-ictus. Imaging tests including catheter angiography, CT, or MR angiography may be considered as well.

Diagnostic Procedures/Other

Catheter angiography may be needed for aneurysm evaluation and for consideration of treatment options. With improving noninvasive imaging modes, this is not necessarily required.

DIFFERENTIAL DIAGNOSIS

- Many headaches can present with acute severe headache, including most commonly thunderclap headaches. Evaluation however may not reveal a SAH or aneurysm on imaging or xanthochromia on lumbar puncture.
- The severity of the diagnosis of SAH often prompts very extensive evaluations of other headaches.

TREATMENT

MEDICATION

First Line

- Initial management is directed at neurological and hemodynamic stabilization. Critical care is standard. Reversal of any coagulopathy and antiplatelet regimen is standard.
- Aggressive blood pressure control into a normal range is standard.

Second Line

- Nimodipine is routinely used in the care of SAH patients continuously in the management of cerebral vasospasm.

ADDITIONAL TREATMENT

General Measures

Supportive care in a critical care unit is appropriate for the many systemic complications possible during their care.

Issues for Referral

A neurosurgeon should be immediately consulted.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Alternative therapies are not appropriate for SAH.
- Placing patients in a relaxing and quiet environment is considered standard. It is not known whether this reduces the risk of rerupture.

SURGERY/OTHER PROCEDURES

- Early definitive treatment is standard. Options include craniotomy for surgical clipping and endovascular coil embolization.
- Many considerations impact the treatment mode of choice, and decisions should be made with a neurosurgeon and endovascular interventionalist in concert.
- Monitoring of intracranial pressure with a ventriculostomy or bolt may be needed.
- Many additional modes of brain monitoring may be applied, including tissue oxygenation, though are less common and require specialized neurological units.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Blood pressure and hemodynamic control are standard. Cardiac stunning is common as well and may result in significant hemodynamic variability. Hypertension as a result of intracranial hypertension may occur as well and should be controlled.
- Respiratory support with ventilator assistance is appropriate for the patient with a depressed level of consciousness and lost airway control.
- Placement of a ventriculostomy for treatment of hydrocephalus is important and should be performed early if possible.

Admission Criteria

Patients with the diagnosis or presumed diagnosis should be admitted to the hospital for evaluation and management.

IV Fluids

- Adequate hydration is less important at the initial phase of management.
- However, delayed cerebral vasospasm is worsened by inadequate hydration. It is therefore common to maintain adequate hydration for all patients.

Nursing

- Many aspects of the patient require monitoring, and a skilled nursing team is needed. Frequent neurological exams are critical for detecting subtle changes suggestive of problems is standard, and often relies on well-trained neurological nurses.
- Systemic and intracranial catheters and intravascular monitors are routine and require standard precautions and care. Intracranial monitors similarly require specialized training and handling.

Discharge Criteria

- Discharge occurs when the patient is no longer at risk for the development of cerebral vasospasm and systemic and neurological issues have stabilized.
- Individual patients may be discharged home or to a longer care or rehabilitation facility depending upon their physical and neurological condition.
- Hospital courses routinely at 1–3 weeks.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Follow-up for the aneurysm is routine to evaluate for recurrence or development of additional aneurysms. This is not well understood and many practice patterns exist.
- Aneurysms treated with coil embolization should be followed more aggressively than clipped aneurysms for recurrence, though no standard exists.

DIET

No special diet is required, though formal swallow evaluations are reasonable and should be performed for all stroke patients.

PATIENT EDUCATION

- Importance of smoking cessation should be emphasized.
- Follow-up care and aneurysm reimaging are important to prevent missing a recurrence.

PROGNOSIS

- SAH is fatal in 1/3 of all patients at the time of the ictus, never presenting to medical attention for care.
- Of those who present, 1/3 die during the hospital course, 1/3 survive with significant neurological injury, and 1/3 return to full function.
- Rerupture is fatal in the majority of the time.

COMPLICATIONS

- Systemic and neurological complications are common.
- Delayed hydrocephalus is common as well.

ADDITIONAL READING

- Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association, Stroke. 2009;40:994–1025.

CODES

ICD9

- 430 Subarachnoid hemorrhage
- 437.3 Cerebral aneurysm, nonruptured

CLINICAL PEARLS

- SAH is a significant neurological injury requiring aggressive and comprehensive care.
- Surgical and endovascular options are both accepted for the management of the underlying aneurysm to prevent rerupture.

CEREBROVASCULAR DISEASE, TRANSIENT ISCHEMIC ATTACK

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BASICS

DESCRIPTION

Transient ischemic attack (TIA) is a transient episode of 10 minutes or less of clinical symptoms indicating neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Recent TIA is considered a neurological emergency.

EPIDEMIOLOGY

The annual incidence of TIA in the US is estimated to vary from 1 in 200,000 to 1 in 500,000. However, the actual incidence may be higher because many of these attacks are not reported by the patients since their symptoms by definition resolve.

- Age
  - – It is more common in the elderly, as is stroke.
- Sex
  - – It is more common in females, as is stroke.
- Race
  - – It is probably more common in African Americans, Asians, and Hispanics, given the increased incidence of stroke in these populations.

RISK FACTORS

Risk factors include age, hypertension, diabetes mellitus, elevated C-reactive protein, hyperlipidemia, tobacco, sedentary life, obesity, family history of stroke, and prior history of stroke or TIA, and known coronary artery or peripheral vascular disease.

Pregnancy Considerations

There is an increased incidence of TIA and stroke in pregnancy.

Genetics

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, prothrombin variant, and Leiden factor V mutations are all genetic conditions that can present with TIA.

ETIOLOGY

- *Cardiac emboli*: Conditions that predispose to the formation of cardiac emboli include persistent or paroxysmal atrial fibrillation/flutter, mitral valve stenosis, sick sinus syndrome, prosthetic heart valve, infective endocarditis, marantic endocarditis, congestive heart failure with ejection fraction (EF) of 35% or less, dilated cardiomyopathy, myxomas, left atrial enlargement, and spontaneous echo contrast.
- *Large artery disease*: Stenosis of the extracranial internal carotid and vertebral arteries, and large intracranial vessels of the Circle of Willis and posterior circulation (intracranial vertebral and basilar arteries), usually due to atherosclerosis. Other diseases include dissection, vasculitis, moyamoya, and fibromuscular dysplasia.
- *Small vessel disease*: These TIAs can present as multiple, increasing frequency, stereotypical events termed crescendo TIAs or stuttering lacune and are often associated with completed lacunar cerebral infract radiologically even though the clinical symptoms are temporary.
- Hypercoagulable states, both inherited such as prothrombin variant mutation, and acquired such as antiphospholipid antibody syndrome, lupus anticoagulant, sickle cell anemia, and paraneoplastic (especially mucin-secreting carcinomas with elevated CA-125 levels).

COMMONLY ASSOCIATED CONDITIONS

Stroke, coronary artery disease, and peripheral arterial disease.

DIAGNOSIS

By the new definition, a TIA should resolve within 10 minutes; otherwise it is more likely to be a radiological stroke (cerebral infarct) than a TIA. As in ischemic stroke, the symptoms are typically sudden and abrupt. The clinical features depend on the brain area affected. Common symptoms include:

- Hemiparesis
- Hemisensory loss
- Visual field defects
- Ataxia and incoordination
- Aphasia
- Dysarthria
- Dysphagia
- Diplopia
- Vertigo

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- All patients with TIA should have blood drawn for fasting lipid profile, chemistry panel, BUN, creatinine, CBC and platelets, PT with INR, and PTT.
- Hypercoagulable profile including factor V mutation, factor II mutation, lupus anticoagulant, antiphospholipid antibodies, and homocysteine should be requested in young patients. Protein S, C, and antithrombin II deficiencies rarely cause TIA or stroke and much more often cause venous, not arterial, thromboembolic events.
- Serial blood cultures should be done when infective endocarditis is suspected. *Anticoagulation should generally be avoided in patients with suspected infective endocarditis*.

Imaging

- CT scan must be performed in all patients with suspected TIA because it is very sensitive in detecting intracerebral hemorrhage or subdural hematoma, which can mimic TIA.
- CT angiography of the neck and brain can also be simultaneously or subsequently performed to detect stenosis of the large neck or brain vessels. Both can often be performed quickly and relatively inexpensively.
- MRI of brain is much more sensitive than CT scan in detecting small or early infarction. The infarction is sometimes shown despite the resolution of the symptoms within 10 minutes.
- MR angiography of the neck and brain is another noninvasive testing option for assessing the major extracranial and intracranial arteries for stenosis, though it may overestimate the degree of stenosis.
- Transthoracic echocardiogram (TTE) is indicated in most patients with TIA. If the TTE is negative and a cardiac source of embolism is still suspected, the transesophageal echocardiogram (TEE) should be performed. TEE is also indicated in almost all young patients, in whom half of all strokes and TIAs are of cardioembolic origin.
- TEE is more accurate than TTE in showing atrial and ventricular thrombi, vegetations, and left atrial enlargement, detecting shunts, and evaluating the proximal aorta.
- Angiography is the gold standard for an accurate assessment of both the extra- and intracranial vasculature. However, it is an invasive expensive procedure with greater risk than CTA, MRA, or ultrasound, and should be reserved for patients in whom noninvasive testing has not definitely shown the source of TIA or gives conflicting estimation of degree of stenosis of the large neck or brain vessels.
- Ultrasound is a safe, portable, and less expensive. It includes transcranial Doppler to look for intracranial disease and carotid duplex to assess for extracranial carotid disease. It should be noted that carotid duplex is fairly insensitive for detecting extracranial vertebral artery stenosis and when possible should not be exclusively relied upon for this purpose.

Diagnostic Procedures/Other

ECG and cardiac monitoring, either inpatient telemetry or extended (48 hours to 3 weeks) Holter monitoring in select patients to evaluate for arrhythmias.

DIFFERENTIAL DIAGNOSIS

- Ischemic stroke
- Migraine aura
- Multiple sclerosis related transient neurological events (last seconds, may occur hundreds of times a day)
- Seizures (Todd's paralysis) (may last up to 1 day simulating stroke)
- Labyrinthine disorders (paroxysmal vertigo)
- Syncope
- Metabolic disorders
- Intracerebral hemorrhage
- Subdural hematoma
- Somatization disorders

TREATMENT

MEDICATION

- *Antiplatelet agents*: Indicated for stroke prevention in small vessel disease, intracranial large artery disease, mild (<50%) extracranial carotid artery disease, extracranial vertebral artery disease, aortic arch disease without mobile plaque, irregular nonstenotic valve surfaces, and in patients who are not warfarin or dabigatran candidates whom would otherwise be anticoagulated.
  - Aspirin: 50–325 mg/day
  - Clopidogrel (Plavix): 75 mg/day
  - Aspirin + extended-release dipyridamole (Aggrenox): Combination of aspirin 25 mg/extended-release dipyridamole 200 mg one capsule swallowed whole bid
- Anticoagulants
  - Warfarin (Coumadin): Indicated in hypercoagulable states, cardiac sources like atrial fibrillation, intracardiac thrombi
  - Dabigatran (Pradaxa): Indicated in patients with persistent or paroxysmal nonvalvular atrial fibrillation and is an alternative to warfarin therapy
  - Contraindications
  - Aspirin/Aggrenox: Mainly known allergic reaction to salicylic acid, active systemic bleeding, or active gastric ulcer
  - Clopidogrel: Mainly active systemic bleeding, very rarely TTP
  - Warfarin: Mainly active bleeding, bleeding tendency, noncompliance, drug interactions and dietary (vitamin K containing foods) interactions. Rarely warfarin skin necrosis
  - Dabigatran: Known history of active/recent GI bleeding; other active bleeding, dyspepsia
- Precautions
  - Clopidogrel: Monitor for any TTP symptoms at the beginning of treatment
  - Warfarin: Watch for compliance, bleeding events, and falls
  - Dabigatran: Watch for bleeding events (especially GI bleeding)

ADDITIONAL TREATMENT

General Measures

Management of coexisting medical illnesses and secondary stroke prevention.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Judicious control of blood pressure with avoidance of excessive reduction in the acute setting and adequate control in the long run
- Adjunctive treatment
  - Management of underlying hyperlipidemia, diabetes and other medical problems
  - Smoking cessation, if applicable

SURGERY/OTHER PROCEDURES

- Carotid endarterectomy (CEA) or carotid artery stenting (CAS) is indicated for most patients with significant (>50%) symptomatic extracranial carotid artery stenosis and for almost all patients with >70% symptomatic extracranial carotid stenosis. Patients with known concomitant coronary artery disease are generally better CAS candidates, and patients over the age of 72 are generally better CEA candidates. However, surgical risk is also affected by concomitant medical problems, which have to be taken into consideration in all age groups. CAS is associated with a higher rate of periprocedural stroke than CEA but a lower incidence of periprocedural MI and minimal risk of cranial nerve palsies which complicate up to 5–6% of CEA cases. Recent preliminary clinical trial data suggests that angioplasty and stenting of symptomatic large intracranial stenosis may be inferior to maximal medical management with antiplatelet medication + aggressive modifiable risk factor management. Therefore, angioplasty and stenting of symptomatic large intracranial stenosis at this time is reserved only for patients in clinical trials, or as a last resort for recurrent strokes on maximal medical therapy.

IN-PATIENT CONSIDERATIONS

Admission Criteria

In general any patient presenting with TIA, within 1 week from the onset of symptoms should be admitted to the hospital for the evaluation of etiology, frequent neurological check monitoring to promptly identify and treat stroke, and for appropriate empiric and then secondary stroke prevention measures. There is an approximately 5.1% risk of full blown stroke within 48 hours of TIA in patients presenting to the emergency room with a diagnosis of TIA. The ABCD2 TIA score and its recent modified renditions can help identify high risk (for stroke and other vascular events) TIA patients, but is not widely used in clinical practice at present time. Recent TIA should be considered a medical emergency like acute stroke. Specialized TIA observation units where a rapid initial workup for stroke mechanism is completed represent an innovative and growing care option which combines efficiency and quality care and can be categorized as observation stays rather than full-blown admissions if the work-up is completed and appropriate definitive secondary prevention treatment are initiated prior to discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Frequent follow-up visits are important to assess patients for recurrent ischemic events, modifiable risk factor assessment, compliance with treatment and recommendations, and adverse reactions from the treatment medications.
- Close monitoring of INR is crucial for the patients maintained on warfarin.

PATIENT EDUCATION

- American Stroke Association, National Center, 7272 Greenville Avenue, Dallas, TX, 75231, 1-888-478-7653. www.strokeassociation.org

PROGNOSIS

- Although by definition TIA patients promptly and fully resolve their neurological deficits and symptoms, TIA is often a precursor for a stroke, and is also associated with elevated risk of MI and vascular death. The risk of stroke, MI or vascular death in untreated patients, after a TIA, is about 10% in the first year and at least 25% over 5 years. The risk of stroke is highest within the first 48 hours to 1 month after the TIA, but remains elevated for at least 5 years.
- Appropriate secondary preventive measures significantly decrease the risk of stroke.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebrovascular disease
- Ischemic infarct

CODES

ICD9

435.9 Transcerebral ischemia NOS

CEREBROVASCULAR DISEASE, VENOUS THROMBOSIS

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BASICS

DESCRIPTION

Cerebral venous sinus thrombosis (CVST) is an uncommon cause of stroke. It represents approximately 0.5–1% of all strokes. Despite being rare, it is a very important diagnosis to consider, because treatment may be dramatically different from that of ischemic or hemorrhagic arterial strokes.

EPIDEMIOLOGY

Incidence

- Estimated annual incidence: 3–5 cases per 1 million
- Age: Approximately 78% of patients younger than 50 years of age
- Sex: More common in females in population <60 years of age

Pregnancy Considerations

- Approximately 12 cases per 100,000 deliveries
- Approximately 2% of pregnancy-related strokes are CVST
- As high as 50% of CVST cases may occur in pregnancy and puerperium

Prevalence

No large population-based data is available. A previous pathological study showed a 9.3% prevalence of CVST in 182 autopsies

RISK FACTORS AND ETIOLOGY

- Prothrombotic/hypercoagulable conditions (see list in "Initial lab tests")
- Pregnancy and puerperium
- Hormonal changes
- Drugs and antineoplastic medications
  - Intravenous immunoglobulin, vitamin A, Ecstasy, Lithium, Danazol, androgens, tamoxifen, L-asparaginase
- Oral contraceptives
- Cancer
- Infection
  - Ear–nose–throat, face and neck
  - Mastoiditis and sinusitis
- Mechanical factors
  - Lumbar puncture
  - Spontaneous intracranial hypotension
  - Epidural blood patch
  - Surgery
  - Trauma
- Hematologic disorders
  - Polycythemia
  - Thrombocythemia
  - Paroxysmal nocturnal hemoglobinuria
  - Nephrotic syndrome
  - Iron deficiency anemia
  - Sickle cell disease
- Systemic and autoimmune diseases
  - Systemic lupus erythematosus
  - Behçet's disease
  - Inflammatory bowel disease
  - Thyroid disease
  - Sarcoidosis
  - Wegener's granulomatosis
  - Liver disease
- Severe dehydration
- Idiopathic/unknown

PATHOPHYSIOLOGY

Due to a congenital and/or acquired prothrombotic condition, there is change in the composition of the blood, vessel wall, and/or venous stasis occurs followed by venous thrombosis. Obstruction of the venous outflow may lead to venous hypertension, increased intracranial pressure, venous infarct, hemorrhage, and seizures.

COMMONLY ASSOCIATED CONDITIONS

- Deep venous and pelvic vein thrombosis
- Pulmonary embolism
- Increased intracranial pressure
- Cerebral edema
- Brain infarct and hemorrhage
- Seizures
- Visual loss/deficit

DIAGNOSIS

HISTORY AND PRESENTING SYMPTOMS

- Headache (present in 90% of cases)
- Nausea, vomiting
- Seizure
- Altered mental status, somnolence, coma
- Focal deficits: Double/blurred vision and other visual changes, weakness, speech changes, sensory deficits

PHYSICAL EXAM

- Altered level of consciousness, encephalopathy, somnolence, coma
- Speech and/or language deficits
- Cranial nerve deficits, diplopia, visual field problems
- Hemiparesis and/or hemisensory loss
- Papilledema on fundoscopic exam
- Dilated scalp veins and scalp edema possible
- Proptosis, chemosis, retinal hemorrhages and painful ophthalmoplegia may be seen in cavernous sinus thrombosis

Special Considerations

Bilateral clinical deficits may be seen with thrombosis of midline venous structures.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Complete blood count, complete metabolic panel, prothrombin time, partial thromboplastin time, INR, serum β-HCG
- Screening for prothrombotic and/or inflammatory conditions if indicated: Activated protein C resistance, factor V Leiden deficiency, protein S and C deficiencies, prothrombin 20210 gene mutation, anticardiolipin antibodies, antiphospholipid antibodies, lupus anticoagulant, antithrombin III deficiency, homocysteine, ESR, CRP, ANA, rheumatoid factor, c-ANCA, p-ANCA
- Sickle cell preparation or hemoglobin electrophoresis in patients with African descent
- Infectious workup, including blood cultures
- Urine protein
- Normal D-dimer level may suggest low risk of CVST, but it should not exclude further testing if CVST is strongly suspected

Follow-up & special considerations

Hypercoagulable panel testing in the acute setting or in patients on warfarin may have limited value. Testing should be performed 6–12 weeks after the initial event and/or 2–4 weeks after discontinuation of anticoagulation if possible.

Imaging

Initial approach

- CT and CTV:
  - Shows thrombus in cortical veins and/or venous sinuses (delta sign, empty delta sign, cord sign)
  - Venous infarct and hemorrhage
  - Rapidly obtainable and widely available
  - Risk of radiation and contrast exposure
- MRI and MRV:
  - Sensitive for small lesions and early ischemia
  - Good visualization of deep and superficial venous structures
  - Slow flow may affect interpretation
  - Time consuming and less available
  - Not obtainable in patients with pacemaker
- Cerebral angiogram and venogram:
  - "Gold standard" for detection
  - Shows venous congestion, increased arteriovenous transit times, filling defects or occlusions
  - Good visualization of deep and superficial venous structures
  - Possibility to directly measure venous pressure during procedure
  - More invasive than CT and MR
  - Radiation and contrast exposure

Special Considerations

- Transcranial ultrasound may support the diagnosis in pediatric patients
- Anatomic variants, altered flow dynamics, arachnoid granulations, congenital sinus hypoplasia or atresia, signal variability and artifacts may affect imaging interpretation

Diagnostic Procedures/Other

- Lumbar puncture: Reserved for suspected meningitis or intracranial infection. It should be deferred if mass effect is seen on brain imaging due to increased risk of herniation
- Routine EEG if seizures are suspected. Continuous EEG monitoring may be used in patients with subclinical status epilepticus or frequent seizures
- Lower and/or upper extremity ultrasound in patients with concern for concurrent DVT

DIFFERENTIAL DIAGNOSIS
- Migraine
- Arterial stroke
- Intracranial hemorrhage for other reasons
- Pseudotumor cerebri
- Encephalitis, meningitis
- Brain abscess
- Cerebral vasculitis
- Preeclampsia and eclampsia

TREATMENT

MEDICATION
First Line
- Anticoagulants: To prevent clot progression and further thrombosis. Low molecular weight heparin or unfractionated heparin used in the acute phase. Recommended even in the presence of venous hemorrhage, as benefits appear to outweigh risks. Recanalization may be achieved in 47–100%
- Adequate intravenous hydration in all patients

Second Line
Fibrinolytics: Approximately 9–13% of patients on anticoagulation therapy have poor outcomes. Recanalization rates may be higher with fibrinolytic therapy. Used in endovascular procedures (see details below)

SURGERY/OTHER PROCEDURES
- Endovascular therapies: Direct clot disruption, removal and/or lysis in venous sinuses. No randomized controlled trials available. Currently recommended as last resort if medical therapy fails and clinical deterioration occurs despite anticoagulation
  - Direct catheter chemical thrombolysis with fibrinolytics
  - Mechanical thrombectomy: Angiojet, Penumbra and Merci devices
  - Mechanical thrombolysis: Clot disruption; possible angioplasty and stent
- Decompression craniectomy: Used in cases of significant cerebral edema leading to herniation
- Hematoma evacuation: Should be considered for large, space occupying hemorrhages
- Surgical drainage of infectious source

ADDITIONAL TREATMENT
General Measures
- Addressing primary cause, if known (e.g., antibiotics for CNS infection, fluids for severe dehydration, discontinuation of causative medication, etc.)
- Supportive ICU care and management of coexisting illnesses. Respiratory, nutritional and hemodynamic support. Prevention of infections, DVTs and other possible in-hospital complications

Prevention & Management of Comorbidities & Potential Complications
- Seizures: Antiepileptics used only if seizures are present; EEG monitoring
- Elevated ICP: ICP monitoring, CSF drainage, elevation of head, hyperventilation, hyperosmolar therapy, cooling, medication-induced coma
- Hydrocephalus: Ventriculostomy, lumbar drain, ventriculoperitoneal shunt
- Acetazolamide may be considered for elevated ICP
- Vision loss: Optic nerve sheath fenestration
- Dural arteriovenous fistulas: Appropriate surgical and/or endovascular treatment
- Infections: Appropriate precautions and preventative measures, meticulous nursing and respiratory care, antibiotics as necessary
- Headache: Cautious pain control without excessive sedation
- Other: DVT and GI prophylaxis

Additional Therapies
- Early initiation of physical, occupational, cognitive, and speech therapies as necessary
- Prenatal and postpartum care in pregnant patients

IN-PATIENT CONSIDERATIONS
Admission Criteria
All patients presenting with established or suspected CVT should be admitted for evaluation and treatment.

ONGOING CARE

Follow-Up Medications
- After the acute stage, oral anticoagulation is recommended:
  - Unprovoked CVST: For 6–12 months
  - Provoked CVST: For 3–6 months
  - Recurrent CVST, VTE after CVST, or first CVST with prothrombotic condition: indefinite therapy

Pregnancy Considerations
- Pregnancy without other cause:
  - Complete full dose anticoagulation for 6 months total
  - Consider LMHW prophylaxis during future pregnancies

FOLLOW-UP RECOMMENDATIONS
- Evaluation for inpatient rehabilitation and assistance with appropriate placement
- Patient and caregiver education

Patient Monitoring
- Frequent follow-up visits for new symptoms or recurrence, compliance with treatment, control of the underlying etiology, and potential adverse reactions from medications
- Reimaging in 3–6 months, or if new symptoms develop
- Close INR monitoring on warfarin

PROGNOSIS
- Mortality: Estimated 6–30%
- Poor outcome associated with: Age >37, male gender, seizures, involvement of deep cerebral veins, coma, large ICH, sepsis, cancer, underlying prothrombotic condition
- Annual risk of recurrence of any thrombotic event is approximately 6.5%

PATIENT EDUCATION
American Stroke Association.
www.strokeassociation.org

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Venous thrombosis of the brain
- Cerebral vein thrombosis

CODES

ICD9
- 325 Cerebral venous sinus thrombosis

CEREBROVASCULAR DISEASE, YOUNG PATIENT EVALUATION FOR ISCHEMIC STROKE

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BASICS

DESCRIPTION
- Abrupt onset of focal neurological deficits attributable to cerebral infarction due to ischemia (arterial occlusion, hypoperfusion) or hemorrhage.
- Defined as stroke occurring before the age of 45 years.

EPIDEMIOLOGY
Incidence
- Neonatal stroke: 1 in 2,300 live births
- Childhood stroke: 2–3/100,000 per year
- Young adult stroke: 8–19/100,000 per year; highest incidence in the age group of 35–45 years

Prevalence
US prevalence of stroke in persons aged 18–44 years is 0.8%; accounts for ~5% of all strokes.

RISK FACTORS
- *Classic vascular risk factors*: Hypertension, diabetes, hyperlipidemia, smoking and family history of stroke, or myocardial infarction
- *Other*: Migraine, oral contraceptive use, sympathomimetic drug use, prothrombotic state including pregnancy, cardiac disease, HIV infection, trauma, and family history of young stroke

Pediatric Considerations
- *Neonatal stroke risks*: Primiparity, infertility, perinatal complications (pre-eclampsia chorioamnionitis, asphyxia, neonatal sepsis), cardiac disease, and infection
- *Childhood stroke risks*: Varicella or other infection, trauma, cardiac disease, iron deficiency anemia, prothrombotic state, and sickle cell disease

Genetics
- *Inherited thrombophilias*: Factor V Leiden, prothrombin gene mutation (G20210A), protein C deficiency, and antithrombin III deficiency are all autosomal dominant
- *Inherited arteriopathies*: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; Notch 3 mutation on chromosome 19), Fabry's disease (X-linked dominant), homocystinuria with methyltetrahydrofolate reductase (MTHFR) deficiency (autosomal recessive)
- *Other*: Sickle cell disease (autosomal recessive), Osler–Weber–Rendu syndrome (autosomal dominant)

GENERAL PREVENTION
- Secondary prevention related to etiology with risk factor modification (diabetes, hypertension, dyslipidemia treatment; smoking cessation)
- Avoid estrogen-containing oral contraception
- Antiplatelet therapy
- Anticoagulation in hypercoagulable conditions, cardiac disease or arterial dissection
- Removal of a cardiac source of embolism
- Patients with large patent foramen ovale (PFO) or with an interatrial septal aneurysm (IASA) should be considered for clinical trials of anticoagulation vs. closure if negative work-up

PATHOPHYSIOLOGY
Ischemic Strokes
- *Arteriopathies*: Endothelial abnormalities cause vessel stenosis and constitute a prothrombotic surface for thrombus formation causing occlusion or artery-to-artery embolization.
- *Cardiac disease*: Cardiopathy, valvular disease, intracardiac tumors and cardiac or arteriovenous right-to-left shunts can constitute a source of emboli to the cerebral circulation.
- *Prothrombotic conditions*: Risk of thrombus formation in cerebral vessels or the heart which can embolize to the brain.

Hemorrhagic Strokes
Intraparenchymal, subarachnoid, or intraventricular hemorrhages due to rupture of normal or abnormal cerebral vessels (aneurysm, vascular malformation).

ETIOLOGY
Ischemic Stroke
- Early onset atherosclerosis
- Arterial dissection
- Cardioembolism
- Small and large vessel stenosis or occlusion
- Vasoconstrictor drugs (antihistamines, pseudoephedrine, cocaine, LSD, and amphetamines)
- Prothombotic state
- Infection
- Idiopathic

Hemorrhagic Stroke
- Cerebral venous sinus thrombosis
- Vascular malformations: Arteriovenous malformation, cavernous malformation, aneurysm
- Hypertension
- Head trauma
- Bleeding diathesis

COMMONLY ASSOCIATED CONDITIONS
Cardioembolism
- *Valvular disease*: Mitral valve prolapse and mechanical prosthetic valve
- *Cardiopathy*: Intracardiac tumors, infectious or marantic endocarditis, myocardial infarction, congenital heart disease, and cardiomyopathies
- *Atrial fibrillation* associated with valvular disease or cardiopathy
- *Paradoxical embolism* from large PFO or PFO with IASA, ventricular or atrial septal defect, or pulmonary arteriovenous malformation
- *Cardiac procedures*: Cardiac surgery and cardiac interventional catheterizations

Small Vessel Disease
- *CADASIL*: Notch 3 gene mutation

Large Vessel Disease
- *Arterial dissection* (cervical or intracranial)
- *Moyamoya syndrome*
- *Fibromuscular dysplasia*
- *Primary angiitis of the central nervous system*
- *Vasculitis* secondary to systemic inflammatory disorders
- *Infection*
  – Bacterial: Syphilis, tuberculosis, and Lyme
  – Viral: HIV and herpes zoster
- *Radiation vasculopathy*
- *Reversible cerebral vasoconstriction syndrome*

Hematological Diseases
- *Inherited thrombophilia*
- *Thrombotic thrombocytopenic purpura*
- *Nocturnal paroxysmal hemoglobinuria*
- *Antiphospholipid antibody syndrome*
- *Hyperviscosity* from polycythemia, thrombocythemia, and malignancy.

Metabolic Disorders
- *Fabry's disease*: Endothelial vasculopathy due to defective lysosomal storage
- *MELAS*: Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
- *Homocystinuria*: Elevated plasma homocysteine due to MTHFR gene mutation

DIAGNOSIS

HISTORY
- Confirm acute onset of focal neurological deficits localizable to a vascular territory
- Cervical neck pain, headache, pulsatile tinnitus or history of recent head trauma
- Recreational drug use
- Cardiac disease or arrhythmias
- Pregnancy, malignancy, and prothrombotic state
- Vascular risk factors: Previous stroke, diabetes, hypertension, hyperlipidemia, and smoking
- Family history of young stroke
- See *Risk Factors*

PHYSICAL EXAM
- *Hyperacute period <4.5 hours of symptom onset:* Vital signs, short neurological examination based on National Institutes of Health Stroke Scale
- *General*: Neurocutaneous stigmata, carotid and cardiac auscultation, complete neurological examination

Pediatric Considerations

Neonatal stroke: Level of alertness, growth parameters, fontanelle, antigravity movement, response to sensory stimuli, and primitive reflexes.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- CBC, electrolytes, creatinine, INR, PTT, Ca^{2+}, Mg^{2+}, PO_4, glucose, troponin, and toxicology screen
- Fasting lipid profile, fasting glucose, and HbA1c

Follow-up & special considerations

- *Prothrombotic workup*: Proteins C and S, activated protein C resistance, antiphospholipid antibodies, antithrombin, homocysteine, mutation for Factor V Leiden, prothrombin G20210A, and MTHFR
- *Childhood stroke*: Also add lipoprotein-A, sickle cell screen, D-dimer, Factors VIII, IX, and XI

Imaging

Initial approach

- *CT brain*: In hyperacute period to rule out hemorrhage (for possible thrombolysis) (1)[A]
- *MRI brain*: For characterization of the infarct. Early MRI brain preferred over CT for children
- *CT or MR angiography*: For assessment of possible arteriopathy

Follow-up & special considerations

Direct subtraction angiography: In cases of suspected small vessel arteriopathy or for further assessment of arterial dissection or moyamoya.

Diagnostic Procedures/Other

- *ECG*
- *Transthoracic echocardiography + bubble study* to rule out right-to-left shunt & embolic sources
- *Transesophageal echocardiography* to look for PFO and IASA
- *48-hour Holter monitoring* for atrial fibrillation

DIFFERENTIAL DIAGNOSIS

Stroke mimics: Migraine (with aura or hemiplegic), focal seizures, post-ictal Todd's paresis, mass lesion, acute demyelination, hypo/hyperglycemia, hypo/hypernatremia, conversion disorder.

TREATMENT

MEDICATION

First Line

- *IV tissue plasminogen activator (tPA)* in young adult >18 years within 4.5 hours of symptom onset:
  - 0.9 mg/kg (max. 90 mg) IV over 60 minutes with 10% of total dose administered first as bolus over 1 minute. Keep sBP <185, dBP <110 (1)[A] NNT = 7.
- *IV heparin*: In *adults* routine use *not* recommended (1)[B]. Can be considered for *arterial dissection* or other specific situations.

Pediatric Considerations

- Neonatal strokes without cardiac lesion do not require treatment.
- Initial heparin in first 5–7 days following stroke is an option until dissection, cardiogenic embolism, prothrombotic state ruled out (2)[C].
  - *LMWH*: Enoxaparin 1.0 mg/kg q12h for >2 months, 1.5 mg/kg q12h for <2 months old. Target anti-Xa level 0.5–1.0 U/mL. Monitor platelets (2)[C], *or*
  - *Unfractionated heparin*: 20 U/kg/hour for >1 year or 28 U/kg/hour <1 year old. Target anti-factor Xa level 0.35–0.7 U/mL, *without* loading (2)[C].
- Alternatively *ASA* 3–5 mg/kg/day initially, and long-term if no risk factors identified (2)[C].
- *Transfusion therapy* in sickle cell disease to keep HbS <30% (3)[C].

Second Line

- *Antiplatelet agents* for secondary prevention of ischemic stroke (hold within 24 hours of tPA) (1)[A].
  - ASA 81 mg OD, clopidogrel 75 mg OD, ASA/dypiramidole 25/200 mg b.i.d.
- *Warfarin* for long-term anticoagulation of selected cardiac conditions and prothrombotic states, and medium term (3–6 months) for dissection. Keep INR at 2–3 (1,2)[C].

ADDITIONAL TREATMENT

General Measures

- *Contraindications to thrombolysis or antithrombotic therapy*: Recent systemic or intracranial hemorrhage, recent stroke or surgery, known bleeding diathesis, sBP >185 or dBP >110.
- *Blood pressure*: Treat sBP >220 or dBP >120, with IV Labetalol drip or nitropaste (non-tPA patients) (1)[B] aiming for a 15% reduction.
- *Neuroprotection*: Maintain normothermia, normoglycemia, normovolemia. Manage seizures.
- *For children on heparin*: Head CT on Day 3 of therapeutic heparin to rule out hemorrhage.

Issues for Referral

- *Neurosurgery* for decompressive procedures or ventricular shunting.
- *Hematology* for prothrombotic conditions.

SURGERY/OTHER PROCEDURES

- *Decompressive craniectomy*: For malignant cerebral edema secondary to infarction
- *Hematoma evacuation*: For intracerebral hemorrhages with significant mass effect
- *Ventricular shunting*: For reduction of ICP in patients with obstructive hydrocephalus

IN-PATIENT CONSIDERATIONS

Initial Stabilization

ABCs, vital signs, secure IV access, treat seizures, correct metabolic derangements, NPO.

Admission Criteria

All patients with confirmed stroke for work-up of etiology and treatment.

IV Fluids

- Young adults: IV 0.9% saline at 75 mL/hour
- Children: Weight-based maintenance with 5% dextrose in 0.45% saline

Nursing

- NPO until swallowing assessed, bedrest to activity as tolerated, neurovitals q6h
- Occupational therapy, physical therapy, and speech and language assessments

Discharge Criteria

Discharge after investigations complete, treatment started, rehabilitation needs, and home support in place.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- *Young adult*: Follow-up in stroke prevention clinic 6–8 weeks after discharge
- *Neonate and child*: Neurologist follow-up at 3 months, then yearly

Patient Monitoring

Monitor neurological status and vitals q6h.

DIET

Avoid high fat (atherogenic) diet.

PATIENT EDUCATION

For stroke risk factor modification.

PROGNOSIS

- *Young adult*: Low mortality (4.5%) and recurrence (1.4%) in first year, especially if idiopathic. Risk of seizures 5–7% at 3 years.
- *Neonate*: Low recurrence risk, unless underlying cardiac disease, or thrombophilia.
- *Child*: Mortality rates 6% (arterial ischemic stroke), 20% (hemorrhagic stroke). Recurrence rate 15%, highest with arteriopathy and cardiac disease. Long-term neurodevelopmental deficits in 50–80% and seizures in up to 40% poststroke.

COMPLICATIONS

Malignant cerebral edema, hemorrhagic transformation, recurrent stroke, seizures, and hydrocephalus.

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3. Adams R, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusion in children with abnormal results of transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5–11.

CODES

ICD9

- 434.91 Cerebral artery occlusion, unspecified with cerebral infarction
- 436 Acute, but ill-defined, cerebrovascular disease
- 437.9 Unspecified cerebrovascular disease

CLINICAL PEARLS

- Cervical artery dissection is the most common cause of young stroke.
- Pediatric stroke may present with vague symptoms of seizures, headache, and fluctuating weakness.
- Initial CT scan is normal in 40–60% of children with arterial ischemic stroke: MRI preferred initial test.

CERVICAL STENOSIS/SPONDYLOSIS/SPONDYLOTIC MYELOPATHY

P. Mark Li, MD, PhD

BASICS

DESCRIPTION

Cervical spondylosis refers to intervertebral disk degeneration, disk space narrowing, and osteophyte formation associated with age-related changes of the cervical spine. Cervical stenosis is the narrowing of the cervical spinal canal. Cervical spondylotic myelopathy (CSM) refers to the clinical symptom set resulting from spinal cord compression resulting in turn from degenerative changes of the cervical spine. CSM is the most common cause of spinal cord dysfunction in adults over the age of 55 years.

EPIDEMIOLOGY

Degenerative changes of cervical spine have been observed in up to 95% of asymptomatic individuals over 65 years old. Up to 20% of individuals with evidence of spondylosis are thought to progress to myelopathy.

- Race
  - There is no known racial or ethnic predilection.
- Age
  - The disease process is associated with natural aging. Individuals over 65 years old have a much higher rate of spondylosis and therefore a higher rate of CSM.
- Gender
  - Males are more commonly affected. Some Scandinavian studies estimate that males may be affected twice as often as females. Most investigators believe there is at least a 1.5:1 male-to-female ratio.

RISK FACTORS

Male gender, age >55 years, repetitive neck trauma, congenitally narrow cervical canal (less than 12-mm diameter).

Pregnancy Considerations

There is no additional risk with pregnancy.

Genetics

The disease is sporadic with no known genetic factors involved. Rarely, disseminated idiopathic skeletal hyperostosis or ankylosing spondylitis may cause cervical stenosis.

ETIOLOGY

The pathophysiological hallmark is spinal cord dysfunction brought on by a combination of mechanical compression and degenerative instability. With aging, the intervertebral disk degenerates and collapses, leading to osteophyte formation, most prominently at the uncovertebral processes. This process tends to begin at C5-6 and C6-7. There is a relative decrease in spinal motion at these levels with a concomitant increase in spinal motion at C3-4 and C4-5. At these higher levels, the resultant degeneration and motion leads to instability with antero- or retrolisthesis (subluxation of vertebral bodies out of the normal cervical alignment). Therefore, at C5-6 and C6-7, the cord tends to be compressed from osteophyte formation and at C3-4 and C4-5 from listhesis. Anterior cord compression from degenerated disks and osteophytes is often accompanied by posterior compression from ligamentum flavum hypertrophy. In addition to the static compressive forces, the cord is subject to further injury from repetitive dynamic injury during normal neck movements. These static and dynamic compressive forces on the spinal cord lead to spinal cord injury and the clinical myelopathic syndrome.

DIAGNOSIS

- Initial symptoms may be subtle. Loss of hand dexterity, painless weakness of the upper extremities, and ambulatory difficulty may be present. There is often a history of progressive difficulty with the hands. Pain may or may not be a significant complaint. If pain is present, it is usually neck pain with or without some radicular component down the arm. Loss of fine motor control in the hands, such as difficulty with writing, buttoning, or painting, is a usual complaint. Walking difficulty is usually present but may initially be subtle.
- The exam usually shows bilateral (or initially unilateral) weakness of the hands and arms with varying degrees of lower extremity weakness. Long tract signs resembling an anterior cord syndrome may be present. Initially, the strength may not be affected, but spastic quadriparesis is seen as patients experience clinical progression. Disturbances of bowel and bladder are rarely caused by CSM, although these symptoms are common in the elderly. Hyperreflexia in all 4 extremities and pathologic reflexes such as bilateral Hoffmann's, clonus, and even Babinski's may be present.
- Paresthesias in the fingertips signaling posterior column dysfunction are less common than anterior cord signs. Rarely patients may present with Brown-Séquard syndrome with the development of a crossed motor and sensory deficits presumably arising from unilateral cord compression. Some patients also complain of Lhermitte's phenomenon with electric shocks going down the spine or into the arms. This may be most apparent in certain neck positions, especially extension, which decreases the width of the spinal canal.
- Of the 5 clinical syndromes characterized by (1), the most common are brachialgia cord syndrome (upper extremity radiculopathy from nerve root compression combined with myelopathy) and motor system syndrome (corticospinal tract compromise by anterior compressive pathology producing spastic quadriparesis with minimal sensory complaints).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

No specific laboratory tests have been identified.

Imaging

MRI is the most useful diagnostic tool in evaluating cord compression, canal diameter, and most of the other causes of myelopathy. Plain x-ray films may demonstrate disk degeneration, loss of vertebral height, subluxation, and loss of lordotic curvature. CT with myelography is recommended in cases where MRI is contraindicated or unavailable.

Diagnostic Procedures/Other

Electrophysiologic studies may be useful in confirming dysfunction at the root or cord level. A majority of patients with CSM have abnormal findings on EMG and nerve conduction velocity testing. These studies also offer a useful method to follow the progression of CSM in the absence of obvious changes on MRI or the neurological examination.

DIFFERENTIAL DIAGNOSIS

Alternative diagnoses should be considered in patients without risk factors (young, female, no history, or cervical stenosis) or if there is findings on the exam that are inconsistent with CSM (e.g., cranial nerve palsy). However, many of the following present with similar clinical findings:

- Tumor
- Amyotrophic lateral sclerosis
- Syringomyelia
- Multiple sclerosis
- Transverse myelitis
- Herniated disk
- Ossified posterior longitudinal ligament
- Spinal arteriovenous malformation
- Subacute combined degeneration
- Neurosyphilis
- Rheumatoid arthritis with subluxation

TREATMENT

MEDICATION

- NSAIDs: Must be used with caution in patients over 65 years of age and in patients with history of gastrointestinal problems or renal insufficiency.
- Oral steroids: Very short course (a few days) only and must consider the additional risk imposed by their use in patients with diabetes mellitus, immunocompromised patients, or those with history of infection. This seems to be effective only in the treatment of radiculopathic pain. Steroids may exacerbate NSAIDs' gastrointestinal side effects and should not be routinely used in conjunction with other antiinflammatory medications.
- Muscle relaxants: No benefit seen for use longer than 3 weeks.

ADDITIONAL TREATMENT

General Measures

- Immobilization with a rigid neck brace: There is no well-recognized nonsurgical therapy for CSM other than this.
- Cervical traction under the supervision of a physician and physical therapist for severe pain (radiculopathy). This may have associated risks in patients with narrow cervical canal and should be used with caution in patients with myelopathy.
- Ultrasound with electronic stimulation for severe neck/shoulder pain.
- Discriminate use of antiinflammatory medication and analgesics.
- Avoidance of excessive neck motion and trauma

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  – Refer to "General measures."
- Adjunctive treatment
- Body mechanics emphasizing optimal posture (easier with rigid collar) with avoidance of neck twisting and excessive flexion and extension are recommended. Rest, isometric exercise, and application of ice or heat for symptomatic relief can be prescribed.

SURGERY/OTHER PROCEDURES

- Because the condition of the patients with CSM may deteriorate, surgery to alleviate the compression and instability has been the primary treatment of this condition. Laminectomy alone has been used extensively and is excellent at spinal cord decompression, but it does not address the dynamic forces in CSM. Its use is limited to spines with normal cervical lordosis, and there is associated risk of postoperative instability and late deterioration.
- Anterior discectomies and corpectomies combined with fusion and fixation can be performed on kyphotic spines and address the compressive and dynamic forces leading to CSM. However, they can be associated with high morbidity and complications, especially when deployed over a long segment (3 or more vertebral levels). Laminoplasty had been performed in different fashions to decompress the cord and minimize instability from loss of the posterior tension band. Recent studies of laminectomy with fusion appear to have promising results and low morbidity in straight or lordotic cervical spines. A lordotic spine can be treated with a decompressive laminectomy alone in a patient with advanced age (>75 years).

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with new neurological deficit, progressive myelopathy, new gait or bowel/bladder disturbance, or uncontrollable pain should be admitted for serial evaluations. Significant neck trauma in a patient with known CSM also warrants an evaluation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Frequent evaluation of patients with overt myelopathy is recommended due to the probability of deterioration. All patients should undergo complete radiological evaluation. In the most severe cases, MRI will reveal evidence of cord injury. After serial examinations depicting a stable neurological status, the frequency of clinical monitoring may be gradually decreased. All patients with CSM should undergo a neurosurgical evaluation for the consideration of surgical intervention.
- Patients who opt for nonsurgical therapy should be followed by periodic MRIs to evaluate the extent of spinal cord deformation and spinal alignment. Patients with clear CSM who do not undergo surgery should wear a cervical collar at all times to minimize further injury associated with normal motion.

PATIENT EDUCATION

- The Congress of Neurological Surgeons has ample educational material on this subject on the web at Neurosurgery-On-Call (*www.neurosurgery.org*).
- The Cervical Spine Research Society provides useful educational material as well as in-depth research on the pathophysiology and management of CSM (*www.csrs.org*).

PROGNOSIS

The natural history of CSM is difficult to elucidate, because early investigations combined patients with cervical stenosis, cervical spondylosis, and CSM. Up to 75% of patients with myelopathy show episodic deterioration; 20% are thought to show steady deterioration. Spontaneous, rapid progression is seen in only 5% of patients. Useful indicators of poor prognosis are duration of symptoms, severity of myelopathy, presence of high-intensity cord lesion on MRI, and multilevel compression. These patients should be strongly considered for surgery. It is important to note that patients with cervical stenosis and early CSM are at high risk for significant spinal cord injury (central cord syndrome) during high force flexion/extension injuries. Patients should be cautioned to avoid activities that may predispose to this type of injury.

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CODES

ICD9

- 721.0 Cervical spondylosis without myelopathy
- 721.1 Cervical spondylosis with myelopathy
- 723.0 Spinal stenosis in cervical region

CERVICAL TRAUMA

Raju S.V. Balabhadra, MD
Russell J. Andrews, MD
P. Mark Li, MD, PhD

BASICS

DESCRIPTION
Cervical trauma constitutes the broad spectrum of soft tissue, bony, and spinal cord injury (SCI) involving the cervical spine. Cervical trauma includes:
- Musculoligamentous injuries: Strain/sprain
- Bony injuries: Flexion/extension/vertical compression/distractive flexion/distractive extension/lateral flexion injuries
- SCI (transient or permanent)
- SCI without radiologic abnormality (SCIWORA)

EPIDEMIOLOGY
- Incidence
  - Incidence of SCI is 10,000 cases per year in the US. Cervical spine injuries constitute 50% of all SCIs, i.e., the incidence of cervical SCI is 5,000 cases per year. Midcervical spine – levels C4 to C6 – are the most commonly involved levels.
- Age
  - Young adults (less than age 40) are most commonly affected.
- Sex
  - Males (80%) are more commonly affected than females.

RISK FACTORS
Patients with osteoporosis or ankylosing spondylitis are at high risk of spinal fractures even with minor trauma. Patients with pre-existing spinal stenosis (congenital or acquired) are at increased risk of neurologic deficits with minor trauma. Children younger than 10 years of age are at risk of SCIWORA, although recent use of high-field MRI has shown soft tissue injury in many cases previously thought to be SCIWORA.

ETIOLOGY
- Motor vehicular injuries are the most common cause.
- Sports injuries, e.g., horseback riding, gymnastics, diving injuries
- Falls
- Penetrating spinal injuries – missile (gunshot) or non-missile (stabbing) injuries constitute 12% of all traumatic SCIs.
- Industrial and domestic injuries

COMMONLY ASSOCIATED CONDITIONS
Cervical canal stenosis

DIAGNOSIS

- Pain: Neck pain, radicular arm pain, occipital headache
- Neurologic deficits due to SCI, which can be complete or incomplete
- Complete injury: No motor or sensory function below the level of injury
- Incomplete injury: Partial preservation of motor or sensory function below the level of injury. It may present as:
  - Central cord syndrome: Upper extremity more than lower extremity weakness, with sacral sparing
  - Anterior cord syndrome: Motor paralysis, hypesthesia, loss of pain and temperature, preservation of posterior columns (position, proprioception, and vibration)
  - Brown-Séquard syndrome: Ipsilateral loss of motor function and posterior column sensation, contralateral loss of pain and temperature sensation
  - Mixed syndromes: Combination of the above syndromes
- Spinal shock may be seen immediately after injury. Total loss of neurologic function (sensory, motor, reflexes) plus hypotension without tachycardia.
- Persisting hypotension and bradycardia after cervical SCI indicate a poor prognosis.
- High cervical spine injuries (at or above C4) often present with respiratory insufficiency due to phrenic nerve involvement.
- Neurologic status is often assessed by Frankel grading or the American Spinal Injury Association (ASIA) scale.
- Frankel grading:
  - Type A: No motor or sensory function below the injury level
  - Type B: Sensory preservation without motor function
  - Type C: Motor function useless
  - Type D: Motor function useful
  - Type E: Normal motor and sensory function
- ASIA scale:
  - Total motor score (normal = 100). Strength is graded from 0 to 5 in (a) 5 upper extremity muscles groups (elbow flexors and extensors, wrist extensors, finger flexors of middle phalanx, finger abductors of the little finger), and (b) 5 lower extremity muscle groups (hip flexors, knee extensors, ankle dorsiflexors and plantar flexors, long toe extensors) bilaterally.
  - Total sensory score (normal = 224). Sensation (pain + light touch) is graded from 0 to 2 (0 = absent, 1 = impaired, 2 = normal) by testing 28 dermatomes (C2 to S5) bilaterally.
- The ASIA score more accurately predicts neurologic recovery than Frankel grading.
- Ascending neurologic deficits can occur a few days after injury, likely due to vascular compromise.
- Autonomic dysreflexia may result in headache, sweating, nasal congestion, etc.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging
- Plain radiographs may show an increase in prevertebral soft tissue (normal soft tissue less than 5 mm at C2 to C4, and up to 15 mm at C4 to C7). Dynamic radiographs (flexion and extension) can identify instability due to ligamentous injuries. Open-mouth view and swimmer's views are important to evaluate odontoid fractures and the cervicothoracic junction, respectively.
- CT often detects fractures not evident on plain radiographs or MRI. It can delineate the fracture geometry and the extent of spinal canal encroachment. CT with coronal and sagittal reconstructions is recommended to rule out cervical spine injuries in all unconscious trauma patients. It is useful in the evaluation of penetrating spinal injuries due to gunshot wounds (the metallic bullet fragments prevent evaluation by MRI).
- MRI is the imaging modality of choice for direct SCI and cord compression. It can detect soft tissue and ligamentous injuries as well as traumatic disc lesions. Because it can differentiate cord edema from cord contusion, it can provide prognostic information. Dynamic MRI may demonstrate instability due to ligamentous injuries (e.g., atlantoaxial dislocations).
- In practice a combination of CT and MRI is indicated in patients who present with neurologic deficits, and allows the correlation of bony injury (CT scan) with ligamentous/disc/soft tissue injury (MRI scan) and frank SCI (MRI scan).

Diagnostic Procedures/Other
Neurophysiological studies – somatosensory evoked potential recording – can be of prognostic value after SCI.

DIFFERENTIAL DIAGNOSIS
- Polytrauma with head injuries
- Missed lesions are common: (a) intoxicated or comatose patients, (b) multilevel noncontiguous spinal injuries, and (c) upper cervical injuries (e.g., odontoid fractures), where neurologic deficits are frequently absent.

TREATMENT

MEDICATION

Methylprednisolone has been shown to be of some benefit in improving neurologic outcome when given within 8 hours after SCI. It is given as an intravenous bolus of 30 mg/kg followed by 5.4 mg/kg/h for 23 hours when begun within 3 hours (or for 48 hours when begun 3–8 hours) after SCI. However, recent literature has suggested that the potential benefit of high-dose steroid therapy may be outweighed by the risks.

- Contraindications:
  - Known history of GI bleeding
- Precautions
  - History of peptic ulcer/immunosuppression
- Alternative drugs
  - There is evidence suggesting that antioxidants (e.g., tirilazad mesylate, G_{M1} ganglioside) may be of some benefit in improving neurologic outcome after SCI in human studies.

ADDITIONAL TREATMENT

General Measures

As in all trauma cases, assessment of patient's airway, breathing, and circulation are the initial priority. All comatose and polytrauma patients should be considered to have a cervical spine injury until ruled out by radiologic evaluation, and kept in cervical immobilization (back board, hard cervical collar). In-line emergency intubation or tracheostomy should be performed if the patient presents with respiratory distress. Cervical SCI is often complicated by hypotension and bradycardia due to sympathetic insufficiency. Maintenance of normal to high-normal blood pressure is essential to avoid worsening of SCI. Soft tissue injuries can be managed with rest, cervical collar, physical therapy, analgesics, and muscle relaxants.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Pain control by judicious bracing with nonsteroidal anti-inflammatory drugs, narcotics, and/or muscle relaxants is often required.
- Adjunctive treatment
  - Cervical traction may be used to reduce dislocations, restore normal alignment, and stabilize the spine. In the presence of respiratory insufficiency, ventilatory support by endotracheal intubation or tracheostomy is mandatory. Patients with permanent respiratory insufficiency can be treated by phrenic nerve pacemaker implantation or domiciliary mechanical ventilatory support. Patients with SCI benefit from comprehensive multidisciplinary rehabilitation. This is best achieved in a SCI unit. Patients with SCI require appropriate bladder, bowel, and skin care. Psychological counseling and support are essential to make necessary mental adjustments to the residual disability.

SURGERY/OTHER PROCEDURES

Surgery is clearly indicated in the presence of spinal cord compression, spinal instability, neurologic deficits (especially incomplete SCI), and certain cases of penetrating SCI. The goals of surgery include: (a) correction of deformity and restoration of normal spinal alignment, (b) decompression of spinal cord and nerve roots, and (c) rigid internal fixation for early mobilization and rehabilitation with minimal orthotic supports. Though the timing of surgery is controversial, early surgery may afford greater neurologic recovery. Halo fixation may be an alternative to surgical stabilization, especially in upper cervical spine injuries and high-risk surgical patients, or as an adjunct to surgery where the strength of the internal stabilization is questionable in the early healing period.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission should be considered in all patients with neurologic deficits, and severe trauma with suspected spinal instability.

Discharge Criteria

It is imperative to rule out unequivocally any cervical spine injury before discharge. Because spinal instability may be masked by muscle spasm and "splinting" in the acute phase, patients with severe neck pain should be considered for follow-up as an outpatient to rule out delayed instability.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Follow-up neurologic assessment with the ASIA scale provides objective evidence of neurologic improvement. Radiologic assessment is required for evaluation of fusion progression and to rule out delayed spinal deformity, instability, or a post-traumatic syrinx. Delayed neurologic deterioration should prompt an MRI of the cervical spine to rule out a post-traumatic syrinx – a treatable cause of delayed neurologic deterioration (e.g., by syringosubarachnoid or syringoperitoneal shunting).

PATIENT EDUCATION

- Patients with SCI and their families require education and psychological support to facilitate rehabilitation and for reintegration into the social environment.
- National Spinal Cord Injury Association:
  8701 Georgin Avenue-Suite 500
  Silver Spring, MD 20910
  1-800-962-9629
  www.spinalcord.org
- Paralyzed Veterans of America:
  801 18th Street NW
  Washington, DC 20006
  1-800-424-8200
  www.pva.org

PROGNOSIS

Neck pain usually resolves, or decreases significantly, in the initial weeks to months postinjury. Patients with complete SCI usually remain complete except for 1 or 2 cervical root level recovery. Incomplete cord injuries (especially Brown-Séquard or central cord syndromes) may show significant recovery, especially with surgical decompression of the cord. Patients with penetrating wounds usually experience limited recovery, unless the spinal canal has not been violated (e.g., ricochet gunshot injury).

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See Also (Topic, Algorithm, Electronic Media Element)

- Cervical spine injuries
- Cervical spinal cord injuries

CODES

ICD9

- 805.00 Cervical fracture
- 847.0 Cervical strain

CHIARI MALFORMATION

P. Mark Li, MD, PhD

BASICS

DESCRIPTION

Chiari malformations consist of 4 congenital hindbrain malformations, probably mechanistically unrelated to each other. These malformations involve only the mesenchymal elements of the posterior fossa (bone, dura, muscle, and skin) or include the cerebellum and brainstem. Patients with Chiari malformation can exhibit symptoms of headache, fatigue, cerebellar or brainstem dysfunction, and sometimes hydrocephalus and syringomyelia depending on the type. The vast majority of Chiari malformations are types I or II, and only a small subset of cases represent the other Chiari types.

- Chiari type I: Abnormal development of the posterior fossa resulting in ectopic "descent" of the cerebellar tonsils and medial inferior cerebellar lobes into the upper cervical spinal canal. The basis for diagnosis is dependent on evaluation of the posterior fossa and identification of the foramen magnum. Chiari type I malformations are the cause of approximately 70% of adult syringomyelia.
- Chiari type II: An anomaly of the hindbrain, is possibly a failure of pontine flexure during embryogenesis, resulting in elongation of the 4th ventricle. Type II has type I features, along with displacement of the inferior vermis, and caudal displacement of the pons and medulla. These patients also have an elongated 4th ventricle and often an associated lumbar meningomyelocele.
- Chiari type III: The suggested mechanism for type III is defective closure of the roof plate resulting in displacement of the entire cerebellum and medulla into an infratentorial meningoencephalocele. This is usually incompatible with life.
- Chiari type IV: Complete cerebellar hypoplasia is referred to as type IV Chiari, also known as Dandy–Walker malformation. This type consists of a cystic expansion of the 4th ventricle in the posterior fossa, due to a developmental failure of the 4th ventricle roof.

EPIDEMIOLOGY

- Chiari type I: Average age at presentation is 41 years, with a slight female predilection.
- Chiari type II: Most common serious malformation of the posterior fossa, with a frequency of approximately 1 case per 1,000 population in the US.
- Chiari types III and IV: Very rare

RISK FACTORS

Myelomeningocele has been associated with folic acid deficiency during early pregnancy. Chiari type II is commonly associated with myelomeningocele.

Pregnancy Considerations

Patients with headache associated with Chiari malformations may experience more headache during the active stage of labor. Otherwise, there are no major issues related to pregnancy and Chiari malformations.

ETIOLOGY

Chiari malformations are congenital anomalies of the hindbrain and associated tissues.

COMMONLY ASSOCIATED CONDITIONS

- Chiari type I is associated with syringomyelia.
- Chiari type II is associated with myelomeningocele.
- Chiari type IV is associated with hydrocephalus.

DIAGNOSIS

- Chiari type I: The most common initial presenting symptoms are headaches, gradual dysphagia, cervical pain, vertigo, weakness, paresthesias, and ataxia. Symptoms of Chiari type I are divided into early and late symptoms. Early symptoms consist of headache, fatigue, vertigo, intermittent nausea, dysphagia, and tinnitus. Headache may occur with exercise or coughing. Late symptoms are generally associated with syringomyelia, and consist of a dissociated sensory examination with a cape-like distribution of hypesthesia over the shoulders and upper back. In addition, patients can become myelopathic, with prominent upper extremity dysfunction. Signs may include ataxia, spastic quadriparesis, syringomyelic signs, and downbeating nystagmus. Lower cranial nerve palsies are often seen (absent gag, tongue wasting, etc.).
  - Chiari type I patients present in late childhood to early adulthood and commonly have multiple and variable clinical manifestations. This often results in delay or incorrect diagnosis until imaging is obtained. The systems involved include, but are not limited to, the lower brainstem, lower cranial nerves, and the otologic, cerebellar, sensory, and motor systems.
- Chiari type II: Patients are usually diagnosed in early childhood along with the diagnosis of myelomeningocele. Symptoms of Chiari type II can be mild or severe, and can include head lag, apnea, respiratory distress, stridor, and dysphagia. Patients may develop progressive hydrocephalus.
  - Chiari type II patients present as neonates and infants. When symptomatic, these patients most often have an associated myelomeningocele and exhibit signs of neurogenic dysphagia, stridor, apneic spells, and opisthotonus.
- Chiari type III: These malformations are usually incompatible with life.
  - Chiari type III patients present as neonates on the basis of their meningomyelocele.
- Chiari type IV: Patients with Dandy–Walker syndrome can present with headaches and symptoms of raised intracranial pressure due to hydrocephalus.
  - Chiari type IV patients often present with symptoms of hydrocephalus. Most patients with this type of Chiari malformation have normal development and normal intelligence.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

No specific laboratory studies are helpful in the diagnosis and treatment of the Chiari malformations.

Imaging

- Chiari type I: MRI is used to diagnose Chiari type I. The hallmark imaging finding is pointed cerebellar tonsils that lie greater than 5 mm below the foramen magnum. Lack of CSF flow posterior to the cerebellum can also be useful in diagnosing this condition.
- Chiari type II: MRI is the imaging study of choice and will show displacement of the inferior vermis, and caudal displacement of the pons and medulla causing descent of the cerebellar tonsils below the foramen magnum. These patients also have an elongated 4th ventricle and may have other abnormalities of the hindbrain and brainstem including beaked tectum, absence of the septum pellucidum, poorly myelinated cerebellar folia, hydrocephalus, heterotopias, hypoplasia of falx, microgyria, and degeneration of lower cranial nerve nuclei.
- Chiari type III: MRI imaging shows a high cervical or occipitocervical meningomyelocele with cerebellar herniation.
- Chiari type IV: MRI imaging classically shows hypoplasia or absence of the cerebellar vermis, extension of the 4th ventricle into the posterior fossa, and cerebellar hypoplasia.

DIFFERENTIAL DIAGNOSIS

A variety of chronic conditions affecting the cerebellum, brainstem, and foramen magnum region may mimic the findings of Chiari malformations. Cerebellar degenerations or mass lesions may cause slowly progressive ataxia with gait disorder. Brainstem gliomas and other brainstem tumors may present with nystagmus, vertigo, ataxia, and headache. Mass lesions at the foramen magnum may cause downbeat nystagmus with four-limb weakness, spasticity, and headache.

TREATMENT

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Headache may be treated in a similar fashion to migraine. Beta-blockers, tricyclic antidepressants, or nonsteroidals may be useful in therapy for headache related to Chiari type I malformations.
- Adjunctive treatment
  - N/A

SURGERY/OTHER PROCEDURES

- Surgery is the only treatment for symptomatic Chiari type I malformations. Surgical therapy is usually reserved for progressive and debilitating symptoms. The surgery involves a craniectomy to remove the suboccipital bone and foramen magnum along with an upper cervical laminectomy of C1, C2, and sometimes C3. The decompression is further augmented by a duraplasty, which is patched using a dural substitute. If there is an associated syrinx, serial MRIs are used to assess the progression of syringomyelia. In most cases, an adequate posterior fossa decompression will halt the progression of syringomyelia. If the syrinx persists and becomes more symptomatic, a syringo-subarachnoid shunt may be placed.
- For Chiari type II, correction of associated malformations is performed first, with the closure of a myelomeningocele and ventriculoperitoneal shunting if hydrocephalus is present. Surgical therapy for type II Chiari malformations is reserved for patients with critical warning signs of neurogenic dysphagia, stridor, and apnea. The operative results for posterior fossa decompression in type II Chiari malformation are poor, partly due to inherent uncorrectable brainstem and cerebellar abnormalities.
- Chiari type IV patients who develop hydrocephalus must be treated with conventional ventricular shunting procedures. Often, there is little communication of the lateral ventricular system with the Dandy–Walker cyst. In these patients, it may be necessary to place a shunt to decompress the posterior fossa cyst as well.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients usually require admission for surgery, often on the day of surgery.

Discharge Criteria

Discharge depends on postoperative status and course in hospital.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients with Chiari type I and associated syringomyelia must be monitored on a yearly basis for progression of the syrinx. For Chiari type II patients, close follow-up by a pediatric neurologist is critical in identifying progressive symptoms and the need for operative or reoperative therapy.

PATIENT EDUCATION

Patients should be made aware of the congenital nature of these abnormalities, the usual symptoms, the potential for progression, and the options for treatment. They should inform their doctor about any progression of symptoms.

PROGNOSIS

Surgical management may stabilize progressive symptoms of Chiari type I malformation, and improve headache symptoms. Patients may continue to have neurologic symptoms of gait disorders and dysphagia depending on the extent of prior injury.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Arnold–Chiari malformation
- Syringomyelia

CODES

ICD9

- 348.4 Compression of brain
- 741.00 Spina bifida with hydrocephalus, unspecified region
- 742.0 Encephalocele

CHOREA

Anwar Ahmed, MD

BASICS

DESCRIPTION

Chorea is characterized by involuntary, rapid, brief, irregular movements that seemingly flow from one body part to another, thus giving the appearance of dancing. Chorea may be a manifestation of a neurodegenerative disease or a complication of systemic, toxic or metabolic diseases.

EPIDEMIOLOGY

Incidence/Prevalence

Incidence and prevalence is variable, depending on etiology.

RISK FACTORS

- Family history of chorea
- Exposure to certain medications
- Immunological factors

Genetics

Chorea can be seen with a number of hereditary conditions. Classic examples are Huntington's disease (HD) chorea, neuroacanthocytosis, and benign hereditary chorea.

GENERAL PREVENTION

Drug-induced chorea can be prevented by avoiding dopamine blocking drugs.

PATHOPHYSIOLOGY

Chorea is a hyperkinetic movement disorder caused by excessive dopaminergic activity may be associated with dopamine receptors super sensitivity.

ETIOLOGY

- Multiple etiologies of chorea:
  - *Genetic*: HD, HD-like illnesses, neuroacanthocytosis, McLeod's syndrome, Wilson's disease (WD), benign hereditary chorea (BHC), spinocerebellar atrophy type 2, 3, and 17), Dentatorubropallidoluysian degeneration (DRPLA), ataxia-telangiectasia, ataxia associated with oculomotor apraxia, neuroferritinopathy, pantothenate kinase-associated degeneration, Leigh's disease and other mitochondriopathies and Lesch–Nyhan disease
  - *Immunologic*: Sydenham's chorea (SC), systemic lupus erythematosus, antiphospholipid antibody syndrome and paraneoplastic syndromes
  - *Drug/toxins*: Amphetamine, anticonvulsants (Phenytoin), carbon monoxide, CNS stimulants (methylphenidate, pemoline, cyproheptadine), cocaine, dopamine agonists, dopamine-receptor blockers (Metoclopramide), ethanol, levodopa, levofloxacin, lithium, manganese, and mercury toxicity, sympathomimetics, theophylline, tricyclic antidepressants
  - *Infectious*: HIV encephalitis, diphtheria, Scarlet fever, measles, mumps, West Nile encephalitis, neurocysticercosis, neurosyphilis, Lyme's disease, and toxoplasmosis
  - *Endocrine/metabolic dysfunction*: Hyperthyroidism, chorea gravidarum, hypo- and hyperparathyroidism and Addison's disease. Renal or hepatic encephalopathy and other electrolyte abnormalities
  - *Vascular*: Post-pump chorea (cardiac surgery), basal ganglia infarctions/ hemorrhage, subdural hematoma
  - *Miscellaneous*: Anoxic encephalopathy, cerebral palsy, Kernicterus, multiple sclerosis, nutritional (e.g., B12 deficiency), posttraumatic (brain injury)

COMMONLY ASSOCIATED CONDITIONS

- Benign hereditary chorea: Characterized by the onset of chorea in childhood, which is nonprogressive and self-limiting in most cases. Patient may have slight motor delay, ataxia and handwriting changes. Autosomal dominant illness, with a mutation in the TITF-1 gene.
- Essential/senile chorea: Adult onset chorea presents after age 60 nonprogressive and without dementia, psychiatric disturbance, or a family history of chorea and no other identifiable cause.
- HD: Autosomal dominant disease related to expansion of unstable stretch of CAG trinucleotide repeats in the huntington gene on chromosome 4p. It is characterized by chorea, ataxia, cognitive changes and psychiatric disturbances.
- Dentatorubropallidoluysian atrophy: Autosomal dominant trinucleotide (CAG) repeat disorder most prevalent in Japan. Manifested by variable combination of myoclonus, epilepsy, mental retardation in early onset before age 20 and in late onset manifested by ataxia, choreoathetosis, dystonia, and tremor
- WD: Autosomal recessive disease. The underlying defect is impaired biliary excretion of copper due to a defect in the WD gene, *Wc1*, on chromosome 13q, which encodes for a copper transporting adenosine triphosphatase (ATPase). Copper toxicity results in the deposition of copper initially in the liver and then the brain. Neurologic manifestations include tremor, chorea, dystonia, tics, myoclonus, ataxia, and Parkinsonism.
- Neuroacanthocytosis: It refers to a group of neurological disorders in which acanthocytes are seen on peripheral blood films: Several conditions can cause the combination of chorea and acanthocytosis.
  - Choreoacanthocytosis: Patients have autosomal recessive inheritance showing linkage to chromosome 9q21. Symptoms first begin in 3rd–4th decade of life with lip and tongue biting followed by orolingual dystonia, generalized chorea, and motor tics. Other features include cognitive and personality changes, seizures, dysphagia, dysarthria, parkinsonism, areflexia with evidence of axonal neuropathy.
  - McLeod phenotype is an X-linked recessive form of acanthocytosis associated with chorea, personality disorder, seizures, depression but do not exhibit lip biting or dysphagia.
- Sydenham chorea: Most common form of autoimmune chorea worldwide, is a major feature of acute rheumatic fever (ARF), a complication of group A β-hemolytic *Streptococcus* infection. Clinically, it is characterized by a combination of chorea, behavioral abnormalities, and cognitive changes. The usual age at onset of SC is 8–9 years. Typically, patients develop this disease 4–8 weeks after an episode of group A β-hemolytic streptococcal pharyngitis. It does not occur after streptococcal infection of the skin. Pathogenesis of SC is related to circulating cross-reactive antibodies.
- Other autoimmune choreas: Other immunologic causes of chorea are systemic lupus erythematosus (SLE), primary antiphospholipid antibody syndrome (PAPS), and vasculitis. Autoimmune chorea has rarely been reported in the context of paraneoplastic syndromes associated with CV2/CRMP5 antibodies in patients with small-cell lung carcinoma or malignant thymoma.
- Vascular choreas: Chorea is an unusual complication of acute vascular lesions, seen in less than 1% of patients with acute stroke. Vascular hemichorea, or hemiballism, is usually related to ischemic or hemorrhagic lesions of the basal ganglia and adjacent white matter in the territory of the middle or the posterior cerebral artery. Another rare form of vascular chorea is "postpump chorea," a complication of extracorporeal circulation.

Pregnancy Considerations

Chorea can occur during pregnancy, i.e., chorea gravidarum (CG), and typically resolves following delivery. However, the occurrence of CG may be the initial manifestation of systemic lupus erythematosus, HD, and the antiphospholipid antibody syndrome.

DIAGNOSIS

Diagnosis of chorea is based on history, physical examination, and diagnostic testing.

HISTORY

The clinical manifestations of chorea exist along a wide spectrum of diseases. History should include time of onset of chorea (acute, subacute or chronic). Exposure to drug and toxins should be excluded. Family or genetic history should be explored in detail. History of fever, infections and weight loss should be checked as well.

PHYSICAL EXAM

- In its mild form, patient may simply appear to be fidgety or restless; in its most extreme fashion, chorea can exist as large amplitude flinging movements of the proximal extremities, i.e., ballistic movements. Athetosis is a slow form of chorea and consists of slow writhing movements
- Memory: Usually is abnormal in HD
- Eye movements: Slow saccades is an early sign in HD
- Speech dysarthria can be seen in HD, SC and neuroacanthcytosis

- Patients with chorea exhibit motor impersistence (i.e., they cannot maintain a sustained posture). When attempting to grip an object, they alternately squeeze and release ("milkmaid's grip"). When they attempt to protrude the tongue, the tongue often pops in and out ("harlequin's tongue")
- The muscle tone is usually decreased
- Deep tendon reflex may be delayed (hang up)
- Gait may be ataxic (HD and SC)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Serum and urine for drug/medication screen
- Serum glucose, sodium, calcium, phosphate, magnesium
- CBC and peripheral smear for acanthocytes
- Lipid profile (including lipoproteins)
- Endocrine studies: Thyroid function studies; PTH level
- For suspected WD: serum ceruloplasmin level; 24-hour urine collection for copper
- For suspected SLE: ANA, anti–double-stranded DNA antibodies, anti–Smith antibodies
- For suspected rheumatic chorea: Antistreptolysin O titer, ESR, nose/throat culture, ECG, or echocardiogram
- For suspected APAS: VDRL (false-positive); platelet count (thrombocytopenia); aPTT (prolonged by at least 5 seconds and that does not correct with 1:1 dilution of the patient's plasma with normal or control plasma); lupus anticoagulant; and anticardiolipin antibody
- Paraneoplastic profile including CV2/CRMP5 antibodies in patients with small-cell lung

Imaging

Brain MRI may show

- Caudate atrophy in HD
- Caudate atrophy and white matter changes in neuroacanthocytosis
- T2 hyperintensity of the basal ganglia in WD
- T1 hyperintensity in putamen in hypermagnesemia

Diagnostic Procedures/Other

- Genetic testing for suspected HD and DRPLA; both are CAG repeat expansion disorders
- Slit-lamp examination for Kayser–Fleischer rings in WD

Pathological Findings

- Cavitary necrosis of basal ganglia seen in WD
- Loss of medium spiny neurons in the striatum seen in HD
- Peripheral smear show acanthocytes in neuroacanthocytosis

DIFFERENTIAL DIAGNOSIS

- Other hyperkinetic movement disorders:
  - Tics—rapid, nonrhythmic movements or suppressible for a short time
  - Myoclonus—random, irregular movements caused by rapid muscle contractions
  - Dystonia—characterized by sustained muscle contractions, resulting in twisting, repetitive, and patterned movements, or abnormal postures
  - Tremor—regular, rhythmic movement
  - A pseudo-choreoathetosis—due to proprioceptive sensory loss
  - Paroxysmal kinesigenic choreoathetosis

TREATMENT

General Measures

Management of the patient with chorea is dependent on the etiology. In all patients, any underlying treatable or reversible condition should be ruled out, e.g., metabolic or endocrine disturbance, adverse effect of medications, structural lesion, stroke, multiple sclerosis. If female, the possibility of pregnancy should be investigated. WD should be ruled out in every child, adolescent, or young adult presenting with chorea or other movement disorder for which no cause can be found. Immunologic and paraneoplastic etiologies should be identified and treated as indicated.

MEDICATION

- Dopamine-receptor antagonists—antipsychotic medications
  - Mechanism: Blockade of the D2 dopamine receptor; these include haloperidol, fluphenazine, perphenazine, trifluoperazine, and pimozide
  - Dose: Initially with a small nightly dose (0.5–2 mg); titrate as needed for symptom control
  - Adverse effects: Extrapyramidal side effects—acute dystonic reaction, neuroleptic malignant syndrome, Parkinsonism, tardive dyskinesia, and akathisia
  - Precautions: An ECG should be obtained prior to the use of pimozide
- Dopamine depletors
  - Tetrabenazine; Approved for HD chorea
    - Mechanism: Reversible depletion of dopamine.
    - Dose: 12.5–100 mg/day
    - Only rarely associated with acute dystonic reaction; tardive dyskinesia has not been seen. Monitor for depression, parkinsonism and orthostatic hypotension
  - Reserpine: Can be used if Tetrabenzine is not available
- Methylprednisolone is an effective and well-tolerated treatment regimen for patients with SC refractory to conventional treatment with antichoreic drugs and penicillin
- Other medications: Use of Clonazepam, Clozaril, Amantadine, and Keppra has been shown to be beneficial in selected cases

SURGERY/OTHER PROCEDURES

Deep brain stimulation may provide benefit, in selected cases. There are case reports showing bilateral globus pallidus internus may be helpful for choreic movements.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

A comprehensive resource for movement disorder information. *www.wemove.org*

PATIENT EDUCATION

***Genetic counseling*:** HD is inherited as an autosomal dominant fashion. Therefore, if there is a couple planning to conceive and one of the pair has HD, they should be educated that there is a 1-in-2 chance that each child they have could be affected.

PROGNOSIS

- Dependent on etiology:
  - BHC and senile chorea—benign course, life span is not threatened
  - Inherited neurologic disorders—typically a more progressive disease course with shortened life span
  - Chorea secondary to medications may be transient or persistent
  - Chorea can recur in Sydenham's chorea, SLE, and APAS

COMPLICATIONS

- The severity of the abnormal involuntary movements may cause rhabdomyolysis or local trauma in some patients.
- The swallowing difficulties and tongue chorea usually present in neuroacanthocytosis patients may cause aspiration pneumonia and early death in some patients

ADDITIONAL READING

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CODES

ICD9

- 333.0 Other degenerative diseases of the basal ganglia
- 333.4 Huntington's chorea
- 333.5 Other choreas

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Douglas W. Zochodne, MD

BASICS

DESCRIPTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired disorder of the peripheral nervous system with a chronic, subacute, or relapsing course.

EPIDEMIOLOGY

CIDP has a prevalence of approximately 1 per 100,000.

- Age
  - Maximum age-specific prevalence is 70- to 79-year olds. The mean age of onset is 46. CIDP may occur in children.
- Sex
  - The male/female ratio is 1.3:1.

RISK FACTORS

Pregnancy Considerations

CIDP may have onset or worsen during pregnancy or postpartum.

ETIOLOGY

CIDP is an autoimmune demyelinating low-grade inflammatory polyneuropathy, but its triggers are unknown. Unlike its acute cousin, Guillain–Barré syndrome (GBS; acute inflammatory demyelinating polyneuropathy), it generally does not follow a flu-like illness or vaccination. While the primary pathologic change in CIDP is that of segmental and paranodal demyelination, loss of axons may also occur. Repeated bouts of demyelination and remyelination may lead to the formation of concentric whorls of Schwann cells and fibroblasts surrounding fibers, resulting in structures known as "onion bulbs."

COMMONLY ASSOCIATED CONDITIONS

CIDP is not generally associated with other disorders but demyelinating polyneuropathies have been associated in some patients with benign monoclonal gammopathy. Monoclonal immunoglobulin M (IgM) κ subtype, associated with an autoantibody directed to myelin-associated glycoprotein (anti-MAG), has more prominent distal motor nerve fiber demyelination (very prolonged distal motor latencies on nerve conduction studies), and inappropriate separation and widening between myelin spaces (widened myelin lamellae) with abnormal deposition of the monoclonal protein in these widened spaces. This neuropathy responds to treatment differently than CIDP. There are sporadic reports of CIDP-like polyneuropathies associated with malignancy with or without gammopathy. Overall, uncommon associations with CIDP are Charcot–Marie–Tooth disease, lymphoma, melanoma, carcinoma, diabetes mellitus, collagen vascular disease, thyrotoxicosis, chronic hepatitis, inflammatory bowel disease, HIV infection, hepatic transplantation, glomerulonephritis, alopecia universalis, and the medication procainamide.

DIAGNOSIS

CIDP presents with symmetric motor weakness and incoordination especially of the hands, impaired walking, and foot drop. There may be muscle cramps and fasciculations. Sensory symptoms may include loss of sensation (numbness), paresthesias (tingling, prickling, "pins and needles," "asleep" sensations), and pain. Tremor may be prominent during recovery from an exacerbation. Cranial nerves, respiration, and autonomic function usually are not involved. In long-standing untreated CIDP there may be intrinsic hand or foot wasting, but usually there is an absence of wasting in the setting of prominent weakness. Some patients may be quadriparetic. Deep tendon reflexes are frequently absent or reduced. Sensory loss may be minimal or there may be stocking and glove distribution loss to various modalities. In many patients, however, the sensory loss to light touch, vibration, and position is more prominent, reflecting the greater involvement of large myelinated sensory fibers. Additional features are gait ataxia and Rombergism. The peripheral nerves are sometimes palpably enlarged. The EFNS/PNS consensus guidelines define typical CIDP as a "*chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; absent or reduced tendon reflexes in all extremities.*" Atypical versions include more distal involvement, rapid onset resembling GBS, asymmetry, focal involvement, pure motor or sensory variants. Exclusion criteria include other causes of demyelinating polyneuropathy (anti-MAG, POEMS, MMN and others), prominent sphincter involvement or a hereditary cause. Note that guidelines for diagnosis and management have recently been updated.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- On nerve conduction studies features of demyelination include prolonged distal latencies, motor and sensory conduction velocity slowing, temporal dispersion of compound muscle action potentials (CMAPs), and conduction block in motor nerve territories. Sensory nerve action potentials are reduced or absent although the sural nerve may be less involved. Needle EMG of weak muscles may identify abnormal recruitment of motor unit potentials, but infrequent fibrillations. Some patients with CIDP have axonal damage with reduced distal CMAP amplitudes and fibrillations. Specific EFNS/PNS criteria for demyelinating neuropathy are (reprinted with permission):
  - *Criterion 1, Definite*: At least one of the following (a) Motor distal latency prolongation 50% above ULN (upper limit of normal) in 2 nerves (excluding carpal tunnel syndrome), or (b) Reduction of motor conduction velocity 30% below LLN (lower limit of normal) in 2 nerves, or (c) Prolongation of F-wave latency 30% above ULN in 2 nerves (50% if amplitude of distal negative peak CMAP is $<$80% of LLN values), or (d) Absence of F-waves in 2 nerves if these nerves have distal negative peak CMAP amplitudes $\geq$20% of LLN plus 1 other demyelinating parameter in 1 other nerve, or (e) Partial motor conduction block: 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP $\geq$20% of LLN, in 2 nerves, or in 1 nerve plus 1 other demyelinating parameter in 1 other nerve, or (f) Abnormal temporal dispersion ($>$30% duration increase between the proximal and distal negative peak CMAP) in 2 nerves, or (g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in 1 nerve 1 other demyelinating parameter in 1 other nerve
  - *Criterion 2, Probable*: 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding the posterior tibial nerve, if distal negative peak CMAP 20% of LLN, in 2 nerves, or in 1 nerve plus 1 other demyelinating parameter in 1 other nerve
  - *Citerion 3, Possible*: As in criterion 1, but in only 1 nerve

    CSF protein is usually elevated without pleocytosis. If present, pleocytosis may suggest associated HIV infection. Serum protein electrophoresis, immunoelectrophoresis, and immunofixation may identify a monoclonal spike. Patients with IgMκ monoclonal gammopathy may have elevated anti-MAG antibodies. Nerve biopsy is not routinely required to make the diagnosis. IgA deficiency may be associated with anaphylaxis after IVIG. Inquiring about a history of TB or a TB skin test is important if prednisone is to be offered (see below).
- Other investigations are important in the diagnosis: Fasting glucose, HIV, serum protein electrophoresis, CBC, creatinine, hepatic function, thyroid function, ESR and CRP, others.

Imaging

Nerve root hypertrophy and enhancement may occur on spinal MRI studies. Rarely, brain MRI has identified concurrent CNS demyelination.

Diagnostic Procedures/Other

Sural nerve or deep and superficial peroneal nerve biopsies are reserved for "atypical" instances of CIDP, for example patients who do not fulfill its strict electrodiagnostic criteria or have normal CSF protein. See nerve biopsy section.

DIFFERENTIAL DIAGNOSIS

In examining patients with prominent upper limb weakness, the clinician should consider motor neuron disease, multifocal motor neuropathy, hand wasting from a high cervical myelopathy, cervical radiculopathy, paraneoplastic motor and sensory polyneuropathy, plexopathy from infiltrative tumor or radiation, and others. Some polyneuropathies that do not fulfill CIDP criteria may be milder versions of CIDP, while others are axonal polyneuropathies with superimposed demyelinating change. In diabetes, for example, there may be segmental demyelination especially at sites of entrapment, but sensory loss is more prominent than the motor weakness of CIDP. Hereditary neuropathy with sensitivity to pressure palsy may be mistaken for CIDP but shows focal entrapments at typical locations.

TREATMENT

MEDICATION

- From the EFNS/PNS guidelines recommendations are intravenous gamma globulin for initial or for ongoing treatment (Level A recommendation), corticosteroids (Level C recommendation) or plasma exchange (Level A recommendation but less well tolerated). Level A evidence also supports the use of intravenous gamma globulin. In addition it may be used together with prednisone. The dose is approximately 2.0 g/kg given as 2 g/kg over 2–5 consecutive days, traditionally 0.4 g/kg/day for 5 days monthly, although higher doses over fewer numbers of days (e.g., 2 g/kg over 2 days) has evidence of efficacy; maintenance therapy can be given at 1 g/kg over 1–2 days every 3 weeks. This is an expensive therapy. Anaphylaxis is a contraindication. In a recent randomized trial, IVIG was associated with headache (32%), pyrexia (13%), hypertension (9%), asthenia (8%), chills (8%), back pain (8%), rash (7%), nausea (6%), and dizziness (6%). Aseptic meningitis, hyperviscosity, susceptibility to thrombosis, hemolytic anemia, and transmission of viral infections have been reported rarely. Patients may require ongoing treatments over years. Serious side effects to IVIG occur in 0.9% of patients.
- High-dose chronic prednisone in CIDP starting at 60 mg daily although higher initial doses have also been recommended or alternating doses, e.g., 120 mg alternating with 7.5 mg. High doses are required for the first 1–3 months followed by very slow tapering, depending on the clinical response. Patients should receive osteoporosis prophylaxis (e.g., etidronate and calcium). Complications can include hypertension, diabetes, susceptibility to infection, peptic ulceration, cataracts, weight gain, edema, osteoporosis, and hip necrosis. All are relative contraindications.
- Plasma exchange is of benefit in CIDP but less commonly used now because of the difficulties obtaining venous access and less common availability of appropriate facilities.
- Alternative drugs: Other immunosuppressive agents have shown variable benefits but evidence is not considered greater than Class IV [azathioprine, alemtuzumab, cyclophosphamide, interferons; a trial of methotrexate was negative].

ADDITIONAL TREATMENT

General Measures

Patients with CIDP may be unable to work, may need the input of an occupational therapist to help prevent falls at their homes and to provide other types of assistance with activities of daily living.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Pain may be treated with simple analgesics; more severe pain may be treated with medications for neuropathic pain including pregabalin, gabapentin, duloxetine, amitryptilene, and others as described in recent AAN/AANEM guidelines. Patients with foot drop should be prescribed a custom-fitted ankle-foot orthosis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Quadriparetic and rapidly deteriorating patients can require hospitalization for investigation and therapy. Most management, however, is carried out in an outpatient setting.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients require follow-up by primary care physicians to monitor steroid or intravenous gamma globulin side effects and by their neurologist to monitor the need for and dose of therapy. Periodic electrophysiologic monitoring may add to the precision of clinical monitoring.

PATIENT EDUCATION

Excellent educational and support services are offered through the GBS/CIDP Foundation International (*www.gbs-cidp.org*) and the Neuropathy Association patient group (*www.neuropathy.org*).

PROGNOSIS

Patients may experience long-term remissions after a prolonged course of prednisone, or may require ongoing IVIG to maintain their functional status. There may be relatively rapid downhill relapses in CIDP that require urgent therapy.

ADDITIONAL READING

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- Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study. *Lancet Neurol* 2009;8:158–164.

See Also (Topic, Algorithm, Electronic Media Element)

- Chronic relapsing polyneuropathy
- Chronic inflammatory radiculoplexus neuropathy
- Chronic inflammatory demyelinating radiculoneuropathy
- Chronic GBS syndrome (this term is discouraged)

CODES

ICD9

357.81 Chronic inflammatory demyelinating polyneuritis

CLINICAL PEARLS

- CIDP is a reversible motor and sensory polyneuropathy.
- Electrophysiological features of demyelination are critical to the diagnosis.

COMPLEX REGIONAL PAIN SYNDROME

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BASICS

DESCRIPTION

- Complex regional pain syndrome (CRPS) is a painful and often debilitating condition that usually follows physical injury to an extremity (e.g., trauma, surgery). The clinical course of the original injury and expected duration and intensity of pain are prolonged. A broad array of signs and symptoms manifest, including allodynia/hyperalgesia, impaired motor function, altered vasomotor features, and sudomotor dysfunction. CRPS is characterized by variable progression over time.
- CRPS Type I, formally known as reflex sympathetic dystrophy (RSD), manifests without an obvious nerve lesion. Conversely, CRPS Type II, formally known as causalgia, follows a recognized nerve lesion. Diagnostic criteria and treatment regimens are identical for both types.

EPIDEMIOLOGY

The reported incidence of CRPS varies. Recent population studies range from 5.5–26.2 per 100,000 person years. The incidence rate in women is approximately 3.5 times higher. CRPS can manifest at any age, with the highest incidence reported in the 6th decade. The upper extremities are more commonly affected. The incidence of CRPS following a precipitating event (e.g., trauma, surgery, stroke) varies widely.

RISK FACTORS

Immobilization is the most common major risk factor, followed by trauma or operation, fracture, nerve injury (defining type 2), and stroke with significant paresis. Prior occurrence of CRPS increases the probability of the disorder's recurrence, or occurrence in another limb. Phenobarbital and isoniazid are drugs associated with the production of CRPS, refractory to any standard treatment until the offending agent is removed. ACE inhibitors have also shown an association with CRPS onset.

Pregnancy Considerations

Therapies selected in the management of CRPS must be carefully tailored in the pregnant patient to minimize fetal harm.

ETIOLOGY

The etiology of CRPS is still emerging. Earlier explanations of the onset and maintenance of CRPS weighed heavily on dysfunction in the peripheral and spinal segmental sympathetic nervous system. While paramount in a large subset of patients, SNS dysfunction alone does not account for the pathophysiology in many cases. It is now known that the entire neuraxis plus regional autonomic and somatic functions are disrupted. Areas of evolving research include (a) the somatic nervous system (sensory and motor), (b) inflammation (classic and neurogenic; peripheral and central), (c) hypoxia, and (d) psychological dysfunction. Finally, a genetic predisposition may exist.

COMMONLY ASSOCIATED CONDITIONS

Disease states with increased association of developing CRPS include the following: pre-existing neuropathies, osteoporosis, asthma, migraine, cyclic vomiting syndrome, and menstrual cycle dysfunction. Most of these disorders share a similar pathophysiological mechanism to those understood for CRPS.

DIAGNOSIS

Just as the understanding of this complex disorder has evolved with time, so have the paradigms for optimal diagnosis. The first diagnostic criteria adopted by the IASP were the product of a conference among experts in 1993 (Orlando Criteria). These efforts provided a standardized set of criteria that improved patient selection, and clinical communication. Further understanding of CRPS, with more stringent evidence validation yielded updated criteria in 2003 (Budapest Criteria; see below). The 2003 criteria have improved diagnostic sensitivity and specificity. The following criteria must be met for a *clinical* diagnosis:

- Continuing pain, which is disproportionate to any inciting event
- Must report at least one symptom in three of the four following categories:
  - Sensory: Reports of hyperesthesia and/or allodynia
  - Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
  - Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry
  - Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- Must display at least one sign at time of evaluation in two or more of the following categories:
  - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
  - Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
  - Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
  - Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- There is no other diagnosis that better explains the signs and symptoms.
  - 3 Stages of CRPS were previously described and used by clinicians. Stage selection was made by observing differences in the above categorical signs. Recent evidence suggests that these delineations may actually represent subtypes of the disease. Outcomes may theoretically improve by selecting treatments directed at counteracting the suspected pathophysiological mechanism for each sign, though evidence is limited.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

No specific diagnostic test exists. However, it is important to exclude other potential etiologies such as infectious, rheumatological, vascular, or other neuropathic pathologies. Diagnostic labs used for these other conditions are normal in CRPS (e.g., ESR, CRP, CBC).

Imaging

Imaging modalities are not required for the diagnosis of CRPS, but can assist in excluding other etiologies, as well as identifying components of disease progression.

- 3-Phase bone scanning—evaluate for disuse osteopenia
- X-ray or MRI—identify osteoporosis or fracture
- Duplex or ultrasound—exclude a vascular process

Diagnostic Procedures/Other

- Skin temperature measurement—useful for identifying asymmetry and effects of sympatholytic procedures
- EMG/NCV diagnose mononeuropathy
- Quantitative sensory testing
- Sweat output (e.g., resting, QSART)
- Pain and functional questionnaires
- fMRI—reorganization of central somatosensory and motor networks as well as atrophy can be visualized

DIFFERENTIAL DIAGNOSIS

CRPS is usually a complication of tissue injury rather than a primary disorder. All the conditions that could mimic CRPS could also underlie CRPS, and should be considered. Such diseases include vascular disorders such as deep venous thrombosis, arterial occlusion, and stenosis; inflammatory disorders such as cellulitis and osteomyelitis; anterior compartment syndrome; and occult stress fracture.

TREATMENT

The primary focus of treatment is early rehabilitation through active physical therapy. Other therapies, pharmacological and interventional, should be tailored toward symptom control to allow advancement of rehabilitation. Though unproven, it is logical to target the predominant physiological derangement in each patient.

REHABILITATION

Rehabilitation should be tailored for each patient, and communication with the therapist is crucial. Initial therapies should focus on desensitization. The focus then shifts to isometrics, flexibility, and edema control. With further progress, therapy is directed to improving range-of-motion and isotonic strengthening. These involve stress loading, aerobic conditioning, and postural normalization. It is now known that cortical reorganization and atrophy develop with CRPS. Recent evidence reveals that incorporating mirror therapy and motor imagery programs into rehabilitation can help reverse these cortical changes.

MEDICATION

- *Corticosteroids:* The only treatment that emerges as effective in a meta-analysis, a trial of prednisone 60 mg for 5–7 days should be extended to 3–4 weeks if effective. It is most effective for early disease of the lower extremity.
- *Tricyclic antidepressants:* Most of the tricyclic antidepressants have some impact on CRPS pain. Typically a nonsedating tricyclic is administered during the day such as imipramine or desipramine (in the elderly), with a sedating tricyclic agent such as amitriptyline or nortriptyline at night to aid sleep. The total tricyclic dosage usually begins at 20–30 mg and becomes maximally effective between 75 and 150 mg. Patients should not receive these medications if they have active suicidal ideation. Patients with tachy- or bradycardia, conduction block, Q-T interval prolongation, hypertension or hypotension, agitation, disorientation, hallucinations, dystonia, seizures, decreased secretions, urinary retention, mydriasis, and hyperthermia should be treated with caution.
- *Serotonin-norepinephrinereuptake inhibitors (SNRI):* The effectiveness of SNRI agents in other neuropathic pain states has been demonstrated. In addition to addressing depression, a common component of debilitating pain states such as CRPS, these agents modulate the descending pain pathway by enhancing serotonin and norepinephrine levels.
- *Antiepileptic agents:* Nearly all agents have been tried, with intermittent success. Gabapentin, carbamazepine, topiramate, tiagabine, clonazepam, levetiracetam, oxcarbazepine, and mexiletine have been beneficial in individual patients. Drugs should be started at the lowest available dose and advanced slowly. The only contraindication is allergy to the drug.
- *Nonsteroidal antiinflammatory drugs:* These are marginally helpful. When combined with other agents they can produce some added pain relief. They are seldom helpful in isolation. Maximal doses are usually necessary. Gastrointestinal, cardiovascular, and renal precautions are always imperative.
- *Adrenergic agents:* Clonidine decreases adrenergic transmission by activating presynaptic α_2-receptors. A dosage of 0.1–0.3 mg b.i.d. may be effective; higher doses may be needed for improved control. Clonidine can be particularly effective when applied as a patch over an area of scar suspected to harbor an underlying neuroma demonstrated by a Tinel's sign. Terazosin, another adrenergic agent, selectively blocks α_1-adrenergic receptors, producing systemic sympathetic blockade through the oral route. Dosage must be advanced slowly to avoid significant orthostatic hypotension. A typical regimen begins with 1 mg each evening, advancing by 1 mg every week to a goal of 5–10 mg per dose. This drug appears most effective when sympathetic blocks have produced pain relief. It can be used to prolong the effect of sympathetic blocks.
- *Bone homeostasis:* Equivocal evidence exists for both calcitonin and bisphosphonates in CRPS. These agents decrease bone turnover rates.
- *Antispastic agents:* Baclofen, methocarbamol, tizanidine, Artane, and Sinemet can be helpful for particular movement disturbances.
- *Free radical scavengers:* Supportive evidence exists for oral *N*-acetylcysteine, and topical dimethyl sulfoxide 50% (DMSO-50%) for improving pain and function.
- *Capsaicin*: By interrupting the activity of TRPV-1, capsaicin is believed to create a state of desensitization. Evidence is supportive for its use in neuropathic pain. It is available in low-dose creams and a high-dose patch.
- *NMDA antagonists:* Functional improvement and pain reduction have been demonstrated with ketamine infusions for CRPS; however, the best outcomes required several days of continuous infusion, incurring significant costs, and potential adverse effects.

INTERVENTIONAL

- *Sympatholysis:* Interrupting the sympathetic signal in CRPS via sympathetic blocks has been shown to hasten the recovery of function in CRPS, in addition to providing significant symptom reduction. This is typically achieved through a stellate ganglion block (upper extremities) or lumbar sympathetic block (lower extremities).
- *Neuromodulation:* Spinal cord stimulation (SCS) has demonstrated efficacy in the treatment of CRPS. Despite the initial costs, the overall cost burden of SCS therapy for this condition is favorable. The efficacy of peripheral nerve stimulation has growing evidence, particularly in CRPS Type II. Motor cortex stimulation has also demonstrated favorable results in severe, refractory cases of CRPS.

General Measures

Management is most successful when carried out early, in the first 5 months of the disorder. Since presentations are quite diverse, management must be tailored to the main obstacles preventing return to normal function. A rehabilitation program with training and education at its core is the cornerstone of successful management. The program should include psychological intervention to address pacing strategies, coping issues, and approaches to chronic pain.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Transcutaneous electrical nerve stimulation: The greatest benefit is derived when they are used in the context of a pain management program.
- Acupuncture can be of benefit in selected cases.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Once patients are taught self-management and are on a stable treatment regimen (which may take several months), they may continue regular follow-up with their primary care physician, with support from the pain specialist as needed.

PATIENT EDUCATION

- Proper education for the patient and caregiver is essential. Web-based information sources:
- International RSD Foundation: www.rsdinfo.com
- RSD Syndrome of America: www.rsds.org
- International Research Foundation for RSD/CRPS: www.rsdfoundation.usf.edu

PROGNOSIS

Patients with CRPS may develop complications including infection (cellulitis), ulcers, chronic edema, dystonia, atrophy of muscles in the affected area, and deep venous thrombosis (if immobile). Prognosis is generally worse with an increased duration of symptoms.

ADDITIONAL READING

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CODES

ICD9

- 337.20 Reflex sympathetic dystrophy, unspecified
- 337.21 Reflex sympathetic dystrophy of the upper limb
- 337.22 Reflex sympathetic dystrophy of the lower limb

CONVERSION DISORDER

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BASICS

DESCRIPTION

- Conversion disorder is a somatoform disorder defined as a condition characterized by symptoms or deficits affecting voluntary motor or sensory function in which there is a loss or alteration in physical functioning. These symptoms are suggestive of a physical disorder but, following investigation, are not found to have an identifiable medical explanation.
  - By definition, the symptoms are not voluntarily produced, and are conceptualized as the physical expression of an underlying psychological conflict.

EPIDEMIOLOGY

Incidence

- The incidence of conversion symptoms varies widely depending on the population being studied; most estimates range from 5–10 per 100,000 in the general population, and 20–120 per 100,000 among hospital inpatients.
- It is estimated that 1–14% of patients treated in psychiatric or neurologic settings have experienced conversion symptoms.

Prevalence

Prevalence estimates are around 40 per 100,000.

RISK FACTORS

- Conversion symptoms are more common in rural areas, and lower socioeconomic groups (less psychologically sophisticated populations). These symptoms are also more common in military personnel exposed to combat situations.
- Age
  - Conversion symptoms may present at any age, although onset is rare before age 5 or after age 35. Typically conversion symptoms are first seen in adolescence or early adulthood.
- Sex
  - Conversion symptoms are more frequently diagnosed in women, although some authorities suggest that the disorder is probably gender-equal.

Genetics

No clear genetic link has been established.

GENERAL PREVENTION

Reducing or addressing factors that may lead to psychological conflict.

PATHOPHYSIOLOGY

- Recently some studies have indicated that there may be cerebral dysfunction in the motor and limbic regions in patients with conversion disorder. According to this hypothesis, conversion may reflect certain neurophysiologic vulnerabilities in these patients.
  - Proposed abnormalities include inhibition of the motor and sensory processing by the prefrontal cortex and anterior cingulate cortex.

ETIOLOGY

- Until recently, historical explanations for conversion symptoms were limited to psychological models suggesting the subconscious conversion of mental distress or conflict into somatic symptoms.
- Now, modern advances in neuroimaging (PET, fMRI) have identified some of the possible correlating structural pathophysiologic changes in conversion patients.
- Psychodynamic conceptualizations include several explanations of conversion phenomenon, with symptoms potentially reflecting:
  - An intrapsychic conflict: The patient may experience conflict over an unconscious, unacceptable, sexual, aggressive, or dependency wish. The somatic symptom maintains the unacceptable wish out of awareness and often resolves the conflict by "punishing or not rewarding" the wish (primary gain).
  - An interpersonal communication motivated by obtaining gratification from the environment. In this model, patients who have great dependency needs use their conversion symptoms to obtain attention and to influence their environment (secondary gain). The patient's disability and "helplessness" can become powerful tools in controlling friends, family, or physicians.

COMMONLY ASSOCIATED CONDITIONS

- Conversion is probably multidetermined and represents a common pathway for a variety of etiologic factors. High rates of concomitant psychopathology have been found in patients with conversion symptoms. Depression and antisocial personality disorder are the most commonly reported. Patients with dissociative disorders have relatively high rates of conversion symptoms. Hysterical personality features are found in less than half of patients with conversion symptoms.
- A number of studies have found that patients with conversion symptoms also have high rates of medical and neurologic illness. Physical trauma, temporal lobe abnormalities, and multiple sclerosis may predispose to the development of conversion symptoms.
- Analyses of long-term follow-up studies report that <10% of patients initially diagnosed with conversion disorder are later found to have a medical or neurologic condition that explained their initial symptoms.
  - The false-positive diagnosis rate may have declined over time due to advances in diagnostic technology. It is extremely important to keep an open mind regarding the possibility of an organic etiology when making a diagnosis of conversion disorder and to seek appropriate consultations in order to rule out an organic etiology.

DIAGNOSIS

HISTORY

- Weakness, paralysis, sensory disturbances, pseudoseizures, blindness, deafness, and aphonia are the most frequent complaints.
- Patients often show a puzzling lack of concern about their deficits. This characteristic lack of concern has been termed "la belle indifference."
- History should include information about the patient's family, work, other possible stressors, as well as the possibility of secondary gain.

PHYSICAL EXAM

- Neurologic abnormalities are inconsistent and often lack a possible anatomic distribution on physical exam.
- Exam findings do not correlate or are out of proportion with other diagnostic findings or possible medical explanations.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Laboratory testing should be considered to rule out an organic etiology. There are no specific tests to diagnose or rule out conversion disorder. Laboratory studies that are inconsistent with the presenting symptom(s) may help with diagnosis of conversion disorder.

Follow-up & special considerations

LP to rule out an infection or a neurologic illness should be considered when appropriate.

Imaging

Initial approach

A CT scan or MRI of the head or spinal cord should be considered to rule out a lesion in these areas.

Follow-up & special considerations

- An EEG or prolonged EEG monitoring may be helpful in differentiating a true seizure disorder from pseudo seizures.
- Evoked potentials should be considered in the case of conversion blindness.

Diagnostic Procedures/Other

No psychological test can provide a definitive diagnosis of conversion disorder.

DIFFERENTIAL DIAGNOSIS

- The list of differential diagnoses may cover a good portion of a neurologic textbook. Diagnoses that may be more problematic to exclude are as follows:
  - Multiple sclerosis
  - Myasthenia gravis
  - Periodic paralysis
  - Polymyositis
  - Guillain–Barré syndrome
  - Transient ischemic attack
  - Stroke
  - Mercury toxicity
- The diagnosis of a conversion symptom can be made only when the symptom in question cannot be adequately explained on the basis of a medical condition. What complicates the diagnosis is the fact that conversion symptoms and physical illness frequently coexist.

TREATMENT

MEDICATION

First Line

- Medication has not been found to be generally effective for conversion disorder (1)[A].
- Adjunctive treatment of comorbid psychiatric disorders, for example, using antidepressants to treat co-occurring depression or anxiety, may be helpful.

Second Line

- Case reports have outlined the use of narcoanalysis, in which the patient is given amobarbital IV to the point of calm relaxation. The patient, who is in a relaxed state, is encouraged to discuss recent stresses or conflicts (2)[C].
- Amobarbital IV is given at a rate no faster than 50 mg/min. Infusion is continued until drowsiness, slurring of speech, or sustained lateral nystagmus occur. It is very uncommon to need to use 500 mg or more of Amytal.
- Contraindications:
  - Any condition in which pharmacologic respiratory depression would be likely to cause respiratory failure.
  - A history of porphyria.
- Precautions:
  - Narcoanalysis must be administered with close monitoring for respiratory depression.
- Short acting benzodiazepines have also been recently described in facilitating hypnosis or psychotherapy, possibly due to a more favorable side effect profile (2)[C].

ADDITIONAL TREATMENT

General Measures

Treatment planning should focus on regaining function. Direct confrontation of the patient regarding the psychological nature of the symptom is not recommended. A simple approach of reassurance, relaxation, and suggestion is indicated. Patients are reassured that their symptoms will disappear and are encouraged to discuss any stressful events or feelings that most likely have been on their mind. Education surrounding the mind–body connection may be useful (2)[B].

- Withdrawal of medical and social attention toward the symptoms, while encouraging physical rehabilitation with physical and occupational therapists may be useful for conversion motor and gait disturbances (3)[B].
- Many conversion symptoms are fleeting, may remit by the time of hospital discharge. Prompt resolution is important since a number of studies have shown that there is a direct relationship between duration of conversion symptoms and chronic disability.

Issues for Referral

- Most patients respond to a course of brief supportive psychotherapy. The focus is on developing a solid working alliance in an environment of mutual trust, respect, and acceptance. The aim of this treatment is to help patients explore various areas of conflict or stress and to help them develop better coping mechanisms. The focus generally shifts from the conversion symptoms to the psychological makeup of the individual (2)[C].
- Cognitive behavioral therapy, aimed at focusing on identifying and changing beliefs and thinking patterns linked to the pathologic symptoms, as well as the development of adaptive behaviors at the expense of maladaptive conversion reactions, may also be helpful (2)[C].

Additional Therapies

Hypnotherapy is thought to offer some benefit in patients with acute symptoms, but needs further study. While patients are under hypnosis, it is suggested to them that their symptoms will gradually improve posthypnotically. Patients are also encouraged to discuss areas of conflict or stress. Other psychosocial interventions warrant further study (4)[C].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Standard of care medical evaluation for the presenting complaint.

Admission Criteria

Admission should be considered to rule out any serious medical condition and when the severity of the conversion disorder prevents patients from caring for themselves.

Discharge Criteria

Recovery of function and ability to care for basic needs and activities of daily living.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Following discharge, patients may be referred to a psychiatrist for individual treatment.

Patient Monitoring

As prognosis is variable, follow-up for their neurologic complaints is warranted until symptoms resolve.

PATIENT EDUCATION

Patients should be educated about the possibility of recurrent symptoms under stress.

PROGNOSIS

- Good prognostic indicators include:
  - Acute symptoms (<30 days)
  - Fewer symptoms
  - Absence of psychiatric comorbid conditions
  - An identifiable stressor
  - Good premorbid health
  - Good intelligence
- Individual prognosis varies widely; although conversion symptoms are often self-limited and remit quickly, relapse is possible. One study found that symptoms relapse within 1 year in 20–25% of patients.
- Aphonia, blindness, and paralysis are associated with a better prognosis than pseudoseizures and conversion tremor.

COMPLICATIONS

Chronic conversion symptoms (>1 year) have a much poorer prognosis and may require long-term psychotherapy.

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Conversion hysteria

CODES

ICD9

- 300.11 Conversion disorder
- 300.15 Dissociative disorder or reaction, unspecified
- 300.82 Undifferentiated somatoform disorder

CLINICAL PEARLS

- Conversion disorder leads to non-medically explained neurologic deficits that are not consciously produced by the patient.
- Underlying psychological conflict, combined with possible biologic vulnerability, leads to the expressed symptoms.
- Prognosis is variable; treatment is focused on achieving improved functional outcomes and treating any comorbid mental illness.

CREUTZFELDT–JAKOB DISEASE

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BASICS

DESCRIPTION
Creutzfeldt–Jakob disease (CJD) is a rare, fatal disorder characterized by a rapidly progressive dementia that is caused by the accumulation of a misfolded isoform of the prion protein (PrP), a normal constituent of the neuronal membrane resulting in neuronal loss, gliosis, and spongiform changes in the subcortical gray matter. CJD is the most common form of the prion diseases (1), which are also known as transmissible spongiform encephalopathies.

EPIDEMIOLOGY
Incidence
- One in 1,000,000 per year worldwide
- ~200 cases per year in the US
- ~80 cases per year in the UK

Prevalence
One in 1,000,000 (90% patients die within 1 year of symptom onset; i.e., mortality rate is equal to the diagnosis rate).

RISK FACTORS
- Men and women affected equally
- Consumption of tissues contaminated with transmissible prions
- Butchers and farmers handling contaminated meat have a higher incidence

Genetics
- Autosomal dominant with incomplete penetrance transmission in familial forms (10–15% of cases)
- PrP gene mutation on chromosome 20
- PrP encodes a membrane-bound glycoprotein with an unknown function to date

GENERAL PREVENTION
- Avoidance of contaminated tissues
- Sterilization of surfaces and neurosurgical instruments with specialized agents such as copper and hydrogen peroxide is reducing iatrogenic cases

PATHOPHYSIOLOGY
CJD is caused by a change in structure or conformation of the normal (cellular isoform) prion protein (PrP-C) converted post-translationally from an α-helix to an abnormal β-pleated sheet conformation (PrP-SC) that is insoluble and tends to aggregate. The abnormal conformation of PrP-SC induces other normal PrP-C to change their conformation to the PrP-SC form. Accumulation of these PrP-SC to sufficient levels causes toxicity to cell membranes which leads to apoptosis of cells, vacuolization of brain tissue, and gliosis in an autophagic process resulting in the progressive neurodegenerative disease CJD. In sporadic cases (85–90%), what causes the initial conformational change is unknown but somatic cell mutations are considered. In inherited cases, mutations in the PrP gene cause PrP-C to be more likely to change conformation to the PrP-SC isoform. Introducing PrP-SC directly into the blood stream, CSF, or brain of humans causes rare transmitted cases. The incubation time before developing the clinical features of CJD is several years.

ETIOLOGY
- Sporadic: 85–90% of cases. There are 6 clinical phenotypes in sporadic CJD. The prion protein gene (PRNP) codon genotype is homozygous or heterozygous for methionine (M) or valine (V) at codon 129 (2).
- Familial: 10–15% CJD of cases. Of these cases however, 60% do not have a positive family history. Clusters of CJD cases are usually familial.
- Transmitted (iatrogenic) can occur via the transfer of human tissues, CSF, or blood contaminated with prion proteins (e.g., corneal transplant, neurosurgical equipment without sufficient sterilization, administration of contaminated growth hormone, or blood).
- Variant CJD (vCJD) is a rare form caused by dietary consumption of beef that contains brain or spinal cord tissue infected with the prion responsible for bovine spongiform encephalopathy.

COMMONLY ASSOCIATED CONDITIONS
- Variant CJD (vCJD)
- Kuru
- Gerstmann–Straüssler–Scheinker syndrome
- Familial fatal insomnia
- Anti-voltage gated potassium channel encephalopathy (anti-VGKC)
- Panencephalitis

DIAGNOSIS

HISTORY
- Usual age of onset 50–70 years old
- Clinical course: Rapid with death after several months to 1 year
- Early symptoms: Fatigue, anxiety/depression, insomnia, anorexia, forgetfulness
- Middle stage symptoms: Progressive dementia with developing language and memory impairments, visual disturbances, impaired judgment and reasoning
- Abnormal movement and motor symptoms: Startle, myoclonus, tremors, incoordination, gait disturbance, weakness
- Seizures
- Behavioral symptoms: Depression, anxiety, hallucinations, insomnia
- Late stage symptoms: Severe dementia, akinetic mutism

Geriatric Considerations
Peak age of onset is 65 years old.

Pediatric Considerations
This disease is rare in children.

PHYSICAL EXAM
- Rapidly progressive dementia with aphasia, amnesia, apraxia, constructional impairments, executive dysfunction (1)
- Movement abnormalities: Startle, myoclonus (awake and can persist in sleep), tremors, chorea
- Motor signs: Rigidity, spasticity, incoordination, ataxia, focal weakness, muscle atrophy, fasciculations
- Late features: Akinesia, mutism, cortical release signs

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- CSF biomarkers: Elevation in the level of these proteins represents rapid neuronal death with leakage of cell contents into the spinal fluid (3)
  - 14-3-3 brain protein (in patients with disease duration <2 years); specificity is 92%, sensitivity 96%
  - Total tau; specificity is 95%, sensitivity 92%
  - Neuron-specific enolase or S-100β do not have sufficient sensitivity or specificity to be useful for CJD

Follow-up & special considerations
- Neuronal injury from other conditions may cause spurious results
- Rule out positive paraneoplastic antibody panel especially for anti-voltage-gated potassium channel antibodies (anti-VGKC) which may present with similar symptoms as CJD

Imaging
Initial approach
- MRI with or without contrast
- Diffusion-weighted (DWI) and Fluid attenuated inversion recovery (FLAIR) MRI imaging: Multifocal cortical > subcortical hyperintensities in gray matter (4)
- Positron emission tomography: Multiple diffuse regions of cortical and subcortical hypometabolism

Follow-up & special considerations
Only initial MRI requires contrast.

Diagnostic Procedures/Other
- EEG, early disease stages: Often normal
- EEG, later disease stages: Background slowing and bilateral periodic high-voltage sharply contoured discharges is only 65% sensitive
- EEG serial testing often required
- Brain biopsy for atypical cases
- Biopsies may be negative if area sampled is not diseased
- Autopsy confirmation if requested by family

Pathological Findings
- Neuronal loss (apoptosis)
- Vacuolization of gray matter (spongiform appearance)
- Gliosis
- Minimal inflammation

DIFFERENTIAL DIAGNOSIS
- Many other pathologies can be confused with CJD but can typically be ruled out with knowledge of a long clinical course, specific lab tests, CSF and/or diagnostic imaging; conversely, many non-CJD diseases can have a positive 14-3-3 in CSF
  - Herpes simplex encephalitis
  - Infectious encephalitis
  - Alzheimer's disease
  - Frontotemporal dementia
  - Dementia with Lewy bodies
  - Non-CJD rapidly progressing dementias (fatal familial insomnia; Gerstmann–Straüssler–Scheinker syndrome)
  - Paraneoplastic disorders
  - Metabolic encephalopathy
  - Hashimoto's encephalitis
  - Vascular dementia
  - Vasculitis
  - Anti-GAD cerebellar ataxia
  - Amyotrophic lateral sclerosis
  - Parkinson's disease
  - AIDS dementia complex
  - Progressive multifocal leukoencephalopathy
  - Progressive supranuclear palsy
  - Tertiary syphilis
  - Malignancies
  - Carcinomatous meningitis
  - Diffuse or frontal brain tumors
  - Toxic encephalopathy
  - Adult-onset leukodystrophies

TREATMENT

MEDICATION
There is no known drug treatment for prion induced encephalopathies.

First Line
- Symptomatic relief/palliative care only:
  - Clonazepam or valproic acid for myoclonus
  - Anticonvulsants for seizures
  - Atypical antipsychotics for hallucinations
  - Opiates for pain

Second Line
No reports available.

Pregnancy Considerations
Insufficient data due to rarity of disease and incurable nature.

ADDITIONAL TREATMENT
General Measures
- Supportive care for patient and family
- Hospice resource education
- Education of family/contacts of noninfectious nature of disease

Issues for Referral
If doubtful of CJD (usually if duration >2 years or if paraclinical evidence suggests alternative diagnosis), then would refer for other workup

Additional Therapies
Artificial tube feeding for dysphagia if required.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
No reports available.

SURGERY/OTHER PROCEDURES
Patient requires brain biopsy.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Rule out other rapidly progressive dementias.

Admission Criteria
- Acute psychosis
- Outpatient diagnostic workup unrevealing, therefore patient requires brain biopsy

IV Fluids
As needed for any other co-morbidities.

Nursing
- Education of hospital staff to sterilize or discard any invasive instruments (5)
- Reassurance and counseling about non-infectious pattern

Discharge Criteria
Once appropriate supportive care plan is in place, patient may be discharged.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Autoclave or discard any invasive instruments used with suspected CJD cases to limit transmission (5)
- WHO protocols for decontamination of prions when incineration of instruments is not possible—immerse in 1 N NaOH and auroclave at 121°C for 30 min, followed by routine sterilization (5)
- Always notify pathologist of CJD suspicion prior to autopsy to ensure safe handling of tissue

Patient Monitoring
Observation and supportive care for patients.

DIET
As tolerated.

PATIENT EDUCATION
- Patients cannot be listed as tissue donors
- Planning end-of-life care should be encouraged while patient still has mental capacity to participate

PROGNOSIS
Poor—90% cases are fatal within 1 year of symptom onset.

COMPLICATIONS
Inadvertent transmission by contaminated instruments.

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4. Paolo Vitali, Elio Maccagnano, Eduardo Caverzasi, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011;76(20):1711–1719.
5. http://www.who.int/csr/resources/publications/bse/whocdscsraph2003.pdf

ADDITIONAL READING

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- Michael D. Geschwind, Huidy Shu, Aissa Haman, et al. The prion diseases. *Ann Neurol* 2008;64(1): 97–108.

See Also (Topic, Algorithm, Electronic Media Element)
- Transmissible spongiform encephalopathies
- Prion diseases
- Rapidly progressive dementias

CODES

ICD9
- 046.11 Variant Creutzfeldt-Jakob disease
- 046.19 Other and unspecified Creutzfeldt-Jakob disease

CLINICAL PEARLS
- Rapidly progressive dementias should raise suspicion for CJD
- An extensive evaluation to find treatable causes or alternative diagnoses is required prior to diagnosing CJD
- Great precautions must be observed to prevent inadvertent iatrogenic transmission of prion diseases (autoclave, proper discarding of invasive instruments)

DECOMPRESSION SICKNESS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Decompression sickness (DCS) develops when nitrogen gas, in solution at an elevated concentration within the bloodstream and tissues at depth, forms bubbles after rapid lowering of ambient pressure, with subsequent ischemia, inflammation, and mechanical disruption of the nervous system.

EPIDEMIOLOGY

Incidence

Exact figures are not available. Estimated incidence of DCS is 1 case per 5,000 to 10,000 dives for recreational scuba divers; 1 case per 500 to 1,000 dives for commercial divers.

Prevalence

Exact figures are not available.

RISK FACTORS

Rapid ascent rate, deep or sawtooth dive profile, hypothermia, older age, dehydration, alcohol intake, female sex, obesity, patent foramen ovale.

Genetics

Genetic factors have not been identified.

GENERAL PREVENTION

There are no preventive measures for DCS, other than not diving.

PATHOPHYSIOLOGY/ETIOLOGY

Exposure to elevated ambient pressure causes partial pressures of the gases in the breathing mixture to increase proportionately and reach a new equilibrium within the tissues. Although oxygen is actively metabolized within tissues, nitrogen is an inert gas that becomes dissolved in tissues and body fluids till saturation, proportional to the ambient pressure. The diver is at risk for DCS only if there is a sudden reduction of the ambient pressure. If the ambient pressure is released too quickly, nitrogen dissolved in tissues needs to reach a new equilibrium, such that excess gas that cannot remain in solution will form bubbles. Brain, spinal cord, cranial and peripheral nerves, and/or neural vasculature are affected by bubble formation. If the concentration of bubbles reaches a certain threshold, nervous system structures may be damaged by mechanical disruption, tissue compression, vascular stenosis or obstruction, and activation of inflammatory pathways (e.g., leukocyte cytokines, complement).

Cerebral DCS (30–40% of cases) most often involves the arterial circulation, while spinal cord DCS (50–60% of cases) more typically involves obstruction of venous drainage from the cord.

COMMONLY ASSOCIATED CONDITIONS

Air gas embolism (AGE): DCS and AGE can occur together and the combined syndrome is referred to as decompression illness.

Pregnancy Considerations

Pregnancy may increase the risk for developing DCS. If DCS were to occur in a pregnant diver, the fetus would be at risk for significant damage from bubble formation. It is recommended that pregnant women refrain from diving.

DIAGNOSIS

HISTORY

More than 50% of patients with neurological DCS have onset of symptoms within 1 hour of returning to atmospheric pressure. Within 6 hours, more than 90% of patients become symptomatic. The thoracic spinal cord is the most commonly affected region of the nervous system.

The most frequent symptoms are numbness and paresthesias of the trunk that often begin in a band-like pattern and then progressively worsen, ascending weakness of the lower extremities that may progress to paralysis, and bowel and bladder dysfunction. Less often, patients develop cervical cord involvement with quadraparesis or quadraplegia.

General cerebral symptoms can manifest as headache, confusion, fatigue, lethargy, change in personality, or poor concentration. Focal symptoms and signs are numerous and may include hemiparesis, hemisensory loss, ataxia, loss of vision or hemianopsia, dysphasia, and gait disturbance.

When DCS involves the inner ear, patients usually complain of vertigo, sensorineural hearing loss, nausea, emesis, and tinnitus.

PHYSICAL EXAM

On neurological examination, the most common findings are weakness (in legs more often than in arms), sensory deficits, gait disturbance, ataxia, visual dysfunction, and alterations of consciousness.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Initial laboratory testing should be comprehensive, because of the extensive differential diagnosis. All patients should undergo CBC, differential, platelet count, electrolytes, liver panel, renal panel, arterial blood gases, urine or serum toxicology screen, glucose, and creatine phosphokinase with isoenzymes. If contaminated breathing gas is in the differential diagnosis, then a blood carboxyhemoglobin level should be obtained.

Imaging

Initial approach

MRI T2-weighted and fluid-attenuated inversion recovery (FLAIR) images may show high-signal abnormalities within the brain or spinal cord. Regions of injury are often swollen and edematous but usually do not enhance with administration of contrast. MRI imaging of the brain correlates with the clinical symptoms in approximately 55% of neurological DCS patients, while imaging of the spinal cord correlates in one third of patients.

CT scans are relatively insensitive to the structural changes induced by DCS.

Follow-up & special considerations

Follow-up MRI scans of the brain and spinal cord may show improvement over time in areas of DCS-related injury. However, in some patients, permanent abnormalities may be seen on T2 and FLAIR images.

Electroencephalography, brainstem auditory-evoked potentials, visual-evoked potentials, and somatosensory-evoked potentials may be helpful to determine the extent of injury and follow recovery from neurological DCS. However, these tests are not sensitive enough to recommend routine use, especially in the acute setting. Neuropsychological testing may be helpful to screen for subtle cognitive and motor deficits that may not be detectable on the bedside neurological examination.

Audiography and electronystagmography may be helpful in cases of vestibular DCS.

Pathological Findings

The pathological features in spinal cord DCS include hemorrhagic infarction, edema, bubble defects, axonal degeneration, and regions of demyelination. In cerebral DCS, the pathological findings are similar but typically not as severe.

DIFFERENTIAL DIAGNOSIS

An alternative diagnosis to DCS should be considered if severe symptoms begin more than 6 hours after return to atmospheric pressure without altitude exposure or if any symptom develops more than 24 hours after surfacing. An alternative diagnosis should be considered in a diver who fails to improve despite prompt recompression treatment.

- Contaminated breathing gas (carbon monoxide)
- Near drowning and hypoxic brain injury
- Ingestion of toxic seafood—ciguatera, puffer fish, paralytic shellfish
- Envenomation—sea snake, cone shell
- Migraine
- Guillain–Barré syndrome
- Porphyria
- Multiple sclerosis
- Transverse myelitis

- Spinal cord compression
- Middle ear or sinus barotrauma with cranial nerve compression
- Inner ear barotrauma
- Oxygen toxicity with seizure
- Unrelated seizure
- Ischemic or hemorrhagic stroke
- Subarachnoid hemorrhage

TREATMENT

MEDICATION

First Line

There are no medications specific for DCS. Other than recompression therapy, oxygen is the only specific therapeutic intervention that expedites and enhances recovery.

ADDITIONAL TREATMENT

General Measures

Initial management of DCS occurs in the field, most often at some form of dive site (e.g., lake, dive boat, ocean beach). The patient should be assessed for adequacy of the airway, ventilation, pulse, and blood pressure. Cardiopulmonary resuscitation should be initiated in appropriate patients. In all cases, 100% oxygen should be started immediately. The patient should be placed in the supine position and prepared for transport to a medical facility with a recompression chamber.

During transport, patients should be monitored carefully for deterioration (e.g., shock). If the patient is unconscious or apneic, intubation and mechanical ventilation should be initiated. Proper ventilation with 100% oxygen should continue. Intravenous fluids should be started, since dehydration is common in DCS. In patients suspected of spinal cord DCS, the bladder should be catheterized and the urine output monitored.

Some form of prophylaxis against deep vein thrombosis is recommended in patients with spinal DCS or severe cerebral DCS in which there may be venous thrombosis and a risk for pulmonary embolism. Fevers should be treated aggressively, since hyperthermia may aggravate neurological injury.

Rehabilitation and physical therapy are helpful in DCS patients with residual neurological deficits. Function may slowly improve for several months to years after the effects of recompression therapy have plateaued.

Additional Therapies

The definitive treatment for DCS is recompression therapy, using algorithms established by the United States Navy (USN). The treatment algorithm used most often for patients with neurological DCS is USN Table 6. The patient is recompressed to 60 FsW (feet of sea water), breathing 100% oxygen, for a total of 60 minutes. Three brief periods of air breathing (5 minutes each) are interposed during this initial recompression to reduce the risk of oxygen toxicity. The patient is then decompressed to 30 FsW for 2 additional periods each of breathing pure oxygen (60 minute sessions) and air (15 minute sessions). The total treatment takes four 3/4 hours. For patients with incomplete resolution of symptoms and signs, treatment may be extended to as long as 12 hours. More complex treatment algorithms can be used for severely ill patients.

Recompression therapy induces off-gassing of excess nitrogen and reduces bubble volume in tissues and body fluids, thereby allowing easier reabsorption and dissipation of the bubbles.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Initial stabilization as an inpatient consists of hydration, evaluation, and treatment of breathing, airway patency, and vital signs as needed and administration of 100% oxygen, until the patient can undergo recompression therapy.

Admission Criteria

Patients are generally admitted for acute evaluation and recompression therapy as outlined above. Patients with significant residual neurological deficits following treatment should be considered for inpatient or aggressive outpatient rehabilitation.

IV Fluids

Aggressive hydration with isotonic fluids may accelerate off-gassing of nitrogen and is recommended for all patients. Because neurological injury can be exacerbated by hyperglycemia, intravenous solutions should not contain glucose. Blood glucose levels should be monitored and kept at or below 200 mg/dL.

Nursing

Nursing care is most important during recompression therapy, when the patient has to be closely monitored for any signs and/or symptoms of barotrauma, oxygen toxicity, or other complications of hyperbaric oxygen treatment.

Discharge Criteria

Discharge is usually appropriate when the patient has had complete resolution of neurological deficits following recompression therapy or has had stable neurological function for 2 or 3 days in a row during recompression therapy and is ready to transition to a rehabilitation unit.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Rehabilitation and outpatient physical therapy and occupational therapy as needed.

Patient Monitoring

Patient follow-up of neurological status is required.

PATIENT EDUCATION

The Divers Alert Network (DAN), at Duke University Medical Center in Durham, North Carolina, maintains a database of information related to diving injuries, including the location of recompression facilities around the world. They are able to provide instant referral for potentially injured divers to the nearest facility that can properly manage DCS. DAN also has a 24-hour hotline for consultation on suspected dive injuries—phone: 919-684-8111. DAN is also an educational resource for divers and diving educators regarding the diagnosis and treatment of diving-related injuries.

PROGNOSIS/COMPLICATION

Prognosis for complete recovery following neurological DCS is good for military and commercial divers, with relief of all symptoms reported in 95 and 70% of patients, respectively, after prompt recompression therapy.

For recreational divers, the prognosis is more guarded. Recent data indicate that residual symptoms exist after treatment in 75% of recreational divers with severe DCS and 46% of those with more mild-to-moderate cases of DCS. The poorer outcomes in recreational divers are likely related to delays in the initiation of recompression therapy and less frequent utilization of surface oxygen at the dive site.

ADDITIONAL READING

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- Newton HB. Neurological complications of scuba diving. *Amer Fam Phys* 2001;63:2211–2218.

CODES

ICD9

993.3 Caisson disease

CLINICAL PEARLS

- The patient should be started on 100% oxygen at the dive site, as soon as DCS is suspected.
- The patient should be transported as soon as possible, after initial treatment with 100% oxygen and stabilization, to the nearest hospital with a recompression chamber.
- Definitive treatment consists of recompression therapy, most likely using a USN Table 6 treatment algorithm.

DEMENTIA, GENERAL

Lorraine Spikol, MD

BASICS

DESCRIPTION

Dementia is a progressive impairment of memory and cognition that interferes with a patient's work and social relationships. Level of consciousness and attention are preserved.

EPIDEMIOLOGY

Varies from industrialized countries to low- and middle-income countries; prevalence greater in women due to greater longevity; little racial difference.

Incidence

- Varies with age
  - 0.3% age 65–69
  - 8.6% age 95 and over
  - Same in men and women

Prevalence

In industrialized countries, 5–10% of individuals 65 years old and older; doubles every 5 years thereafter. Low- and middle-income countries' prevalence is 1–3%.

Pediatric Considerations

Loss of developmental milestones could be indicative of a childhood onset dementia and should be evaluated by a pediatric neurologist.

RISK FACTORS

- Age
- Lifestyle
  - Level of education, history of head injury, dietary history, social contacts, physical activity, HIV risk factors, smoking, alcohol use
- Comorbid illnesses
  - Hypertension, diabetes, stroke, depression
  - Mild cognitive impairment (accelerated memory loss for age)

Genetics

- Genetics are applicable in some types
  - Alzheimer's disease has autosomal dominant and recessive forms; increased incidence in patients who carry 2 copies of the Apo E-3 allele
  - Frontotemporal dementia associated with mutations in the tau gene
  - Rare x-linked dementia, adrenoleukodystrophy
  - Rare mitochondrial mutations: Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS)

GENERAL PREVENTION

- No current, proven strategies for prevention
  - Suggested strategies are optimization of control of vascular risk factors, treatment of depression, exercise, balanced diet, social interaction, brain-stimulating activities

PATHOPHYSIOLOGY

- Brain cell damage with brain atrophy
  - Varied pathologies including accumulation of a toxic intracellular substance, impairment of neuronal transmission from damaged myelin, cell death from toxic exposure or lack of vital metabolites

ETIOLOGY

- Trauma
  - Dementia pugilistica; diffuse axonal injury, chronic subdural hematoma; postconcussion syndrome
- Inflammation/infection
  - Chronic meningitis (tuberculosis, cryptococcus), syphilis, post-herpes simplex encephalitis, focal cerebritis/abscess, HIV dementia and opportunistic infections, progressive multifocal leukoencephalopathy, Creutzfeldt–Jakob disease, Lyme encephalopathy, sarcoidosis, subacute sclerosing panencephalitis, Whipple's disease of the brain
- Neoplastic
  - Malignant, primary or metastatic; paraneoplastic limbic encephalitis
- Metabolic
  - Hypothyroidism; vitamin B12 deficiency; vitamin B_1 deficiency; vitamin E deficiency; nicotinic acid deficiency; uremia/dialysis dementia; chronic hepatic or hypoglycemia encephalopathy, hypercapnia/hyperviscosity/hypoxemia, Addison's/Cushing's diseases, inborn errors of metabolism, storage diseases
- Vascular
  - Multi-infarct dementia; Binswanger's encephalopathy; amyloid dementia; strokes in particular brain locations (thalamic, bifrontal, infratemporal); diffuse hypoxic/ischemic injury; MELAS; cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Autoimmune
  - Systemic lupus erythematosus; isolated angiitis of the CNS, Hashimoto's encephalitis
- Drugs/toxins
  - Medications (anxiolytics, neuroleptics, antidepressants, anticonvulsants); substance abuse (alcohol, marijuana, phencyclidine); toxins (lead, mercury, arsenic)
- Demyelinating
  - Multiple sclerosis, Schilder's, Balo's sclerosis, decompression sickness with demyelination, adrenoleukodystrophy, metachromatic leukodystrophy
- Structural
  - Normal pressure hydrocephalus; obstructive hydrocephalus
- Degenerative—adult
  - Alzheimer's disease; Pick's disease; Parkinson's disease; Huntington's disease; frontotemporal dementia; progressive supranuclear palsy; Lewy body disease; multisystem atrophy/spinocerebellar ataxias; primary progressive aphasia; corticobasal degeneration; Wilson's disease; Hallervorden–Spatz disease, amyotrophic lateral sclerosis dementia

DIAGNOSIS

HISTORY

Obtain history from the patient and a reliable informant regarding the patient's function and behavior. Confirm the decline over time and discern the speed of progression. Address the following specific topics to aid with the diagnosis.

- Memory
  - Misplacing items, forgetting appointments or to take medication, repeating themselves
- Cognitive abilities
  - Difficulties with language (word-finding difficulties, effortful speech); impaired math, spatial perception (getting lost), judgment, executive function (cannot plan meals), praxis
  - Prolonged time to answer questions or complete tasks, inability to multi-task
- Functional impairment
  - Cannot do something they could do before, errors in everyday function (car accidents, errors in finances, poor job reviews)
- Behavioral or neuropsychiatric symptoms
  - Changes in personality or comportment, visual hallucinations, delusions, paranoia, depression, agitation, apathy
- Associated physical symptoms
  - Incontinence, headache, focal neurological complaints, gait disorder

PHYSICAL EXAM

- Perform a thorough general and neurological exam with focus on mental status examination
  - General exam should include comments on vascular findings, skin, organomegaly
  - Neurological exam should evaluate for asymmetric findings, Parkinson-like features, gait disorders, extraocular movement abnormalities
  - Mental status exam should include assessment of orientation, attention, calculations, written and spoken language and comprehension, memory, praxis, spatial perception, speed of processing, comportment, judgment, abstractions. A brief standardized assessment such as the mini mental status exam or the Montreal cognitive assessment exam is very helpful

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Initial evaluation should include CBC, liver function tests, electrolytes, calcium, thyroid function, sedimentation rate, vitamin B12 level.
- If appropriate, consider HIV testing or Lyme serology (rapid plasma reagin rarely helpful).

- Presentations of rarer dementias may require 1 of the following: Ceruloplasmin and copper levels (Wilson's disease), plasma levels of very long-chain fatty acids (adrenoleukodystrophy), white blood cell arylsulfatase A (metachromatic leukodystrophy), vitamin E and B1 levels, porphyrins, blood gas, hemoglobin A_{1C}, paraneoplastic markers, antinuclear antibody/vasculitis workup, urine heavy metals, thyroid antibodies, toxicology screen.
- Genetic testing of blood usually not indicated out of the research setting.

Imaging

Initial approach

- Uncontrasted brain CT; brain MRI with and without gadolinium adds additional information, especially in atypical or vascular presentation
- Positron emission tomography/single-photon emission computed tomography useful in diagnosing Alzheimer's disease (new, specific isotopes not yet widely used)
- Systemic tumor screen if limbic encephalitis is considered

Diagnostic Procedures/Other

- Electroencephalography
- Computerized or conventional arteriography
- Formal neuropsychological testing
- Lumbar puncture should be considered in the following circumstances
  - Age <60, rapid progression, immunocompromised patient, cancer, reactive syphilis, or Lyme serology, unusual clinical presentation, suspected CNS infection or systemic infection, connective tissue diseases, CNS vasculitis, 14-3-3 protein (in Creutzfeld–Jakob disease), serology for viruses (Herpes simplex, John Cunningham virus), AD markers
- Brain biopsy should be considered in unusual cases as follows
  - Focal, relevant lesions of undetermined cause, suspected CNS vasculitis or where a treatable illness such as an unknown meningeal process or imaging consistent with lymphoma is present
- Muscle biopsy in suspected mitochondrial disorders

Pathological Findings

It depends on the type of dementia.

DIFFERENTIAL DIAGNOSIS

- Normal aging
- Mild cognitive impairment (memory loss excessive for the patient's age and educational attainment with preservation of daily function)
- Psychiatric disorders (mood predominantly)
- Toxic/confusional states or encephalopathy (level of attention and/or impaired consciousness present)
- Cognitive impairment has been stable (static encephalopathy)

TREATMENT

MEDICATION

First Line

Treatment is dependent on the cause of the dementia.

ADDITIONAL TREATMENT

General Measures

- Establish an etiologic diagnosis and institute therapy for specific cause
- Evaluate for superimposed illnesses or depression that may worsen dementia symptoms
- Symptomatic treatment
  - Medication or environmental manipulation for agitation, depression, delusions
- Determine if FDA-approved pharmacological intervention is available
- Suggest designating a family member who can help with future legal and financial decisions
- Assess patients' personal security (wandering, judgment, finances, medication administration) and public safety (driving), behavior, employment issues
- Address caregiver's physical, intellectual, emotional resources in caring for the patient

Issues for Referral

- Psychiatric referral
  - Severe depression, agitation, aggression, delusions may need specific expertise
- Neurosurgery—If biopsy or placement of an intraventricular shunt is contemplated
- Occupational therapy
  - Driving evaluation
- Neuropsychology
  - If diagnosis is in question, there are psychological comorbidities or formal documentation for employment issues is required
- Legal or financial planning advice
- Social work for advice on safe, appropriate living environment

Additional Therapies

Cognitive therapy can be considered, efficacy limited due to the progressive nature of these diseases

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Rarely admission is required for evaluation of rapid decline, advanced workup, caregiver's inability to care for the patient or severe, disruptive neuropsychiatric symptoms.

Nursing

Dementia is a risk factor for inpatient complications such as falls, hospital-acquired urinary tract infections, encephalopathy due to medications, concurrent illnesses, or sleep–wake cycle disturbances.

Discharge Criteria

Outpatient resources should be assessed as adequate for the level of care the patient requires prior to discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Serial examinations to monitor the rate of progression, response to interventions, assess for neuropsychiatric complications and safety issues

DIET

- Monitor weight
  - Anorexia can complicate dementia or be a side effect of medications.

PATIENT EDUCATION

- Discussion of diagnosis and prognosis
- Explain the necessity of changing routines and expectations in response to the disease
- Educate family about end-of-life issues, risk of caregiver stress, and necessity of respite
- Government-sponsored website: www.ninds.nih.gov//disorders/dementias

PROGNOSIS

Relentless decline; some have periods of stability. Fluctuations in severity and speed of progression vary depending on type.

COMPLICATIONS

Death results from inanition or aspiration pneumonia but varies depending on type.

ADDITIONAL READING

- NIH State of the Science Conference. Preventing Alzheimer's disease and cognitive decline. *April* 26–28, 2010. Available at http://consensus.nih.gov/2010/docs/alz/ALZ_Final_Statement.pdf.

CODES

ICD9

- 294.8 Other persistent mental disorders due to conditions classified elsewhere
- 294.11 Dementia in conditions classified elsewhere with behavioral disturbance
- 294.20 Dementia, unspecified, without behavioral disturbance

CLINICAL PEARLS

- Distinguish delirium from dementia by assessing level of consciousness
- Assess speed of progression
- Look for associated or atypical findings such as gait disorder, behavioral changes

DEMENTIA, ALZHEIMER'S DISEASE

Douglas W. Scharre, MD

BASICS

DESCRIPTION

Alzheimer's disease (AD) is the most common form of degenerative brain disorders leading to slowly progressive cognitive and functional loss.

EPIDEMIOLOGY

- Age: Typically >60 but some genetic cases as young as the late 30s
- Gender: Female/male ratio of 2:1
- Higher rates in African Americans, Hispanics

Incidence

Age-specific incidence of 0.5%, 2%, and 5% at age 70, 80, and 90, respectively

Prevalence

Age-specific prevalence of dementia is 3% at ages 65–74, 18% at ages 75–84, and 30–47% at ages 85 and about half due to AD

RISK FACTORS

- Definite risk factors: Increasing age, female sex, apolipoprotein E ε4 allele, and family history of AD, dementia, or Down syndrome
- Possible risk factors: Head trauma with loss of consciousness, cardiovascular/cerebrovascular risk factors (e.g., diabetes and hyperlipidemia)
- Possible protective factors: Higher educational achievement, apolipoprotein E ε2 allele, estrogen use, statin use, rheumatoid arthritis, NSAIDs use, and antioxidant use

Genetics

- Polygenic pattern is most common: 40–50%
- Autosomal dominant in 2% with mutations on chromosomes 21, 14, or 1; late 30s–50s onset
- Trisomy 21 (Down syndrome) develop AD pathology after age 35 and clinical AD by age 50
- Apolipoprotein E, cholesterol transport, and AD susceptibility gene (chromosome 19): ε4 allele is AD risk factor, ε2 allele is AD protective

GENERAL PREVENTION

Nothing yet proven

PATHOPHYSIOLOGY

- Extracellular accumulation of amyloid beta peptide followed by synaptic loss, neuronal injury, atrophy, and intraneuronal accumulation of tau protein resulting in progressive cognitive then functional decline over time (1)
- Stages of AD: Preclinical AD, mild cognitive impairment (MCI) due to AD, AD dementia
  - – Preclinical AD: Based on biomarkers of amyloidosis, neurodegeneration, and subtle cognitive decline (1)
  - – MCI due to AD: Cognitive decline, normal functioning, and no other conditions effecting cognition (2)
  - – AD dementia: Typical clinical characteristics
    - ○ Mild stage: Disorientation to date, low verbal fluency, mild anomia, impaired delayed recall, difficulties copying 3-D figures (cube), impaired problem solving, problems bill paying, diminished insight, irritability, apathy
    - ○ Moderate stage: Disorientation (time and place), comprehension difficulties, fluent aphasia, impaired recognition memory and delayed recall, getting lost in familiar areas, impaired calculations, concrete abstractions, trouble copying 2-D figures, poor judgment, difficulties with instrumental activities of daily living (ADLs) (cooking, shopping, handiwork), behavior symptoms (aggression, psychosis, sleep disturbances, restlessness, dysphoria)
    - ○ Severe stage: Unable to use language effectively, memory only for the moment, getting lost in the home, assistance with basic ADLs (bathing, dressing, and toileting), apraxia, urinary and fecal incontinence, and often troublesome behavioral symptoms

ETIOLOGY

- Polygenetic, sporadic, autosomal dominant
- Amyloid hypothesis: Either overproduction or decreased metabolism and misfolding of accumulated amyloid beta peptide resulting in neuritic plaque formation, neuronal toxicity, degeneration, and eventually clinical dementia
- Tau hypothesis: Abnormally phosphorylated tau proteins (tauopathy) accumulate in neurons as neurofibrillary tangles leading to neuronal death
- Other possible etiologies: Disorder of immune function, oxidative stress, excitatory amino acid toxicity, primary mitochondrial abnormality

COMMONLY ASSOCIATED CONDITIONS

- Vascular dementia (commonly mixed with AD)
- Dementia with Lewy bodies (up to 20% overlap with AD in autopsy series)

DIAGNOSIS

HISTORY

- Obtain patient and informant information regarding functional loss and cognitive changes
- Onset and course: Insidious onset, gradually progressive over months to years (3)[A]
- Inability to function at work or usual activities
- Cognitive and behavioral impairment in a minimum of 2 domains: Memory, executive, visuospatial, language, and behavior changes
- Probable AD: Without evidence of significant cerebrovascular disease, other degenerative dementia or condition greatly affecting cognition
- Possible AD dementia: With atypical course or evidence of other condition affecting cognition

PHYSICAL EXAM

- Elemental neurologic exam: Normal until late
- Apraxia develops by moderate-to-severe stages

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Lab tests are used to rule out other conditions.
- In all cases of cognitive impairment: Electrolytes, glucose, BUN, creatinine, liver function tests, CBC, lipid profile, TSH, B_{12}, folate, and FTA (or MHA-TP)
- Consider only if clinically indicated (usually for rapidly evolving dementias): Sedimentation rate, inflammatory markers, HIV, Lyme antibody, CXR, EKG, urinalysis, toxicology screen, EEG, LP
- Genetic markers only useful in those who are in early 50s or younger with significant dementia family history.
- CSF biomarkers for AD recommended only for atypical cases: Reduced beta amyloid 42 peptide and elevated tau protein with the combination providing 86% specificity and 85% sensitivity for AD compared to healthy controls (4)[A]

Follow-up & special considerations

Increase supervision to ensure proper medication use, safety, and functional capacity.

Imaging

Initial approach

- CT or MRI scans: Cortical atrophy in AD dementia; ordered to rule out other conditions.
- Functional imaging using fluorodeoxyglucose (FDG) positron emission tomography (PET), used when there is clinical uncertainty between AD and frontotemporal dementia, typically shows bilateral temporal and parietal hypometabolism and also predicts the risk of progression to AD dementia in MCI subjects in 94% after 3 years (4)[A].
- Volumetric MRI, amyloid PET, and functional MRI (fMRI) are not routinely recommended clinically at this time.
- MRI volumetric measurement of hippocampus and entorhinal cortex atrophy is 95% sensitive but only 40% specific for AD dementia (4)[A].
- Amyloid PET imaging (e.g., Florbetapir) to identify brain amyloid shows significantly more uptake in AD than MCI subjects or controls (4)[A].
- fMRI shows increased activation during memory tasks in individuals at high risk for AD (4)[C].

Follow-up & special considerations

Volumetric MRI, FDG, or amyloid PET could be repeated over time if diagnosis is questioned.

Diagnostic Procedures/Other

- Mental status examination [e.g., Mini-Mental Status Examination (MMSE), Self-Administered Gerocognitive Examination (SAGE), Montreal Cognitive Assessment (MoCA), others] or neuropsychological testing profiles a patient's cognitive functioning and should be done in every suspected AD case.
- Screening with mental status testing for early identification is suggested but needs validation.

Pathological Findings

- Amyloid beta peptide accumulation (neuritic plaques), neuronal loss, atrophy, tau protein accumulation (neurofibrillary tangles)
- Appears first in entorhinal cortex, hippocampus, then temporal/parietal association cortex before frontal association cortex

DIFFERENTIAL DIAGNOSIS

- MCI
- Acute confusional states and delirium
- Vascular dementia
- Frontotemporal lobar degenerations
- Primary progressive aphasia
- Dementia with Lewy bodies
- Parkinson plus syndromes
- Huntington's disease
- Traumatic dementias
- Neoplastic and paraneoplastic dementias
- Hydrocephalic dementias
- CNS vasculitis
- Toxic dementias
- Hepatic/uremic encephalopathy
- B_{12}, folate, or niacin deficiencies
- Thyroid, parathyroid, or adrenal conditions
- Hypoxic encephalopathy
- Infectious dementias
- Multiple sclerosis
- Depression

TREATMENT

MEDICATION

First Line

- Cognitive therapy (5)[A]
  - – Cholinesterase inhibitors (strive for highest recommended dose): Donepezil 5 mg/day for 6 weeks then 10 mg/day for 12 weeks then 23 mg/day; or galantamine ER 8 mg/day for 4 weeks then 16 mg/day for 4 weeks then 24 mg/day; or rivastigmine patch 4.6 mg/day for 4 weeks then 9.5 mg/day; avoid concurrent medications with anticholinergic effects
  - – NMDA antagonists (for moderate-to-severe stages of AD dementia): Memantine is titrated by 5 mg weekly to 10 mg b.i.d.
- Behavioral therapy
  - – Depression or anxiety: SSRIs (sertraline 50–200 mg/day, citalopram 10–40 mg/day)
  - – Psychosis: Quetiapine 25 mg qhs to 75 mg b.i.d. or risperidone 0.25 mg qd to 1.0 mg b.i.d. or ziprasidone 20 mg qd to 80 mg b.i.d.
  - – Sleep disturbance: Trazodone 50–150 mg/hs
  - – Restless behaviors: Citalopram 20–40 mg/day or divalproex sodium 125–500 mg b.i.d.
  - – Aggression: SSRIs or antipsychotics or mood stabilizers (divalproex sodium)
- Contraindications/Precautions
  - – Divalproex sodium: May cause hepatotoxicity, thrombocytopenia, pancreatitis, and hyperammonemia; monitor liver tests and platelets
  - – SSRIs: May cause hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone hypersecretion)
  - – Atypical antipsychotics: Weight gain, diabetes, hypertriglyceridemia, death, lower seizure threshold, orthostatic hypotension

Second Line

- Cognitive therapy
  - – Antioxidants: Vitamin E 200–2,000 IU/day
- Behavioral therapy
  - – Depression: Venlafaxine, bupropion, or mirtazapine
  - – Anxiety: Buspirone or propranolol
  - – Psychosis: Haloperidol or clozapine
  - – Sleep disturbances: Zolpidem
  - – Restless behaviors: Other SSRIs
  - – Aggression: Gabapentin or carbamazepine

ADDITIONAL TREATMENT

General Measures

- Constantly watch for non-reported medical illness, infection, dehydration, and pain conditions.
- Consider environmental adjustments prior to starting behavioral pharmacotherapies.
- Avoid benzodiazepines and anticholinergic medications as they cause cognitive impairment.
- Provide supervision for nutritional intake, medication compliance, and accident prevention.
- Minimize sensory deprivation by social stimulation, vision, and hearing care.
- Watch for overstimulation causing agitation.
- In early stages, limit driving and ride with patients monthly to monitor driving judgment.

Issues for Referral

- For atypical cognitive or behavioral symptoms, refer to a dementia specialist.
- Provide referrals as needed for social service, care services, legal services (Durable Power of Attorney for healthcare/finances, guardianship).

Additional Therapies

Caregivers often need emotional support through support groups and counseling services.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Use of estrogen, statins, NSAIDs, fish oil, nutraceuticals (e.g., ginkgo, lecithin, piracetam) may reduce the risk of AD but have shown no efficacy in clinical trials.
- Cognitive training has also shown no efficacy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Provide a sitter to ensure patient safety when delirium or acute confusional states occur.
- Low-dose antipsychotics are the most effective and tolerated agents for acute agitation.

Admission Criteria

Patients are occasionally admitted for wandering or aggressive behaviors.

Nursing

Close monitoring to care for all basic ADLs and ensure patient comfort.

Discharge Criteria

Discharge as soon as possible when stable.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Every 6 months measure cognitive status and ask about behavioral and functional abilities.
- MMSE declines 3 points per year on the average in untreated mild-to-moderate patients.

DIET

Maximize nutrition; may need to be fed.

PATIENT EDUCATION

Provide information about AD, Alzheimer's Association (*www.alz.org*), support groups, family counseling, social services, daycare, in-home health care, assisted living, long-term care, legal services, advanced directives, financial planning.

PROGNOSIS

Gradually progressive cognitive and functional decline with infections and lack of sufficient nutrition invariably leads to death in 8–12 years.

COMPLICATIONS

Incontinence, infections, gait disturbances, and inability to swallow at severe stages

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See Also (Topic, Algorithm, Electronic Media Element)

- Dementia

CODES

ICD9

- 294.20 Dementia, unspecified, without behavioral disturbance
- 294.8 Other persistent mental disorders due to conditions classified elsewhere
- 331.0 Alzheimer's disease

CLINICAL PEARLS

- AD spectrum includes asymptomatic, mild cognitive impairment, and dementia stages.
- Mental status testing should be done in every suspected AD dementia case.
- Ask informant about cognition and function.
- Cognitive treatments should be started at time of diagnosis and titrated to highest recommended dose tolerated.

DEMENTIA WITH LEWY BODIES

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BASICS

DESCRIPTION

Dementia with Lewy bodies (DLB) belongs to a family of disorders termed α-synucleinopathies which include idiopathic Parkinson's disease (IPD) and multiple system atrophy (MSA). In both DLB and PD, α-synuclein inclusions are found in the nucleus, axons, and dendrites of neurons; in MSA the inclusions are found within CNS glial cell cytoplasm. These disorders share common clinical features. However, neither PD nor MSA typically demonstrates significant cognitive abnormalities early in the disease course, while DLB is largely defined by early cognitive changes.

- DLB commonly presents with motor symptoms mimicking PD including bradykinesia and rigidity, as well as tremor and gait disturbances. DLB patients may also experience depression, anxiety, and REM sleep behavior disorder. Postmortem cases of DLB have shown coincident Alzheimer's disease (AD) pathology in over 70% of cases.
- Older literature described patients with dementia and parkinsonism as "Alzheimer's with extrapyramidal features" or diffuse Lewy body disease, consistent with a cortical, rather than brainstem, localization of Lewy bodies (LBs), differentiating DLB from IPD. These terms have been replaced by the current term "dementia with Lewy bodies."

EPIDEMIOLOGY

Incidence

The incidence, prevalence and other population features of DLB are unknown. DLB is likely the most common form of dementia with extrapyramidal features and may be the second most common dementia after AD.

Prevalence

Estimates suggest that DLB makes up approximately 10–30% of all cases of dementia.

RISK FACTORS

Age is the greatest risk factor for DLB.

Genetics

A number of mutations found in familial PD have also been associated with cases of DLB. Some of these mutations include genes encoding alpha-synuclein and leucine-rich repeat kinase 2.

PATHOPHYSIOLOGY

- 3 different pathological variants associated with a DLB clinical syndrome have been described. All 3 may overlap with pathological features of AD. The likelihood that DLB is the cause of the clinical symptoms is directly related to the severity and distribution of LB pathology and inversely related to the severity of concomitant AD pathology (neurofibrillary tangles)
  - Brainstem predominant –LB and Lewy neurite (LN) pathology seen predominantly in the 9th–10th cranial nerves, the locus coeruleus, and the substantia nigra. These findings are usually associated with IPD rather than DLB.
  - Limbic (transitional) – in addition to brainstem involvement, LB and LN pathology is seen in the nucleus basalis of Meynert, the amygdala, and transentorhinal and cingulate gyri. Mild AD pathology is generally associated with DLB, while severe AD changes are more commonly seen with clinical features of AD.
  - Diffuse neocortical – LB and LN pathology is seen throughout brainstem, limbic, as well as temporal, frontal, and parietal regions. Low or moderate concentrations of coexisting AD pathology correlate with a high chance of DLB clinical syndromes, while high concentrations of AD pathology along with diffuse LB disease may be seen in either AD or DLB.

ETIOLOGY

DLB is thought to be a disorder on a continuum between PD and AD.

DIAGNOSIS

HISTORY

- Consensus on diagnostic criteria for DLB includes 3 key features: Parkinsonism, visual hallucinations, and fluctuations/cognitive changes.
- Dramatic fluctuations in motor function and mentation unrelated to medication schedule.
- Patients may have syncope-like spells.
- Visual hallucinations are common in DLB.
- REM sleep behavior disorder is very common in DLB and may precede other features by years.
- Patients may also develop myoclonus.
- DLB and Parkinson's disease with dementia (PDD) have similar cognitive difficulties in attention, visuospatial processing, and executive function with lesser deficits in memory function and orientation early.

PHYSICAL EXAM

A combination of parkinsonian manifestations (bradykinesia, tremor, mask facies, gait disorder, rigidity) and early dementia, within the first year of motor symptom onset, suggest DLB.

Diagnostic Criteria – DLB Consortium 3rd Revision (1)

- *Central feature* (essential for the diagnosis of possible or probable DLB) – Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
  - Prominent or persistent memory impairment may not necessarily occur early on but is usually evident with progression. Deficits in attention, executive function, and visuospatial ability may be especially prominent.
- *Core features* (2 are sufficient for a diagnosis of probable DLB, 1 for possible DLB)
  - Fluctuating cognition with pronounced variations in attention and alertness
  - Recurrent visual hallucinations that are typically well formed and detailed
  - Spontaneous features of parkinsonism
- *Suggestive features*
  - REM sleep behavior disorder
  - Severe neuroleptic sensitivity
  - Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
- *Supportive features*
  - Repeated falls and syncope
  - Transient, unexplained loss of consciousness
  - Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence
  - Hallucinations in other modalities
  - Systematized delusions
  - Depression
  - Relative preservation of medial temporal lobe structures on CT/MRI scan
  - Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
  - Abnormal MIBG myocardial scintigraphy
  - Prominent slow wave activity on EEG with temporal lobe transient sharp waves

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Tests to identify potential underlying secondary causes of parkinsonism: Serum vitamin B12 level, thyroid function tests, ceruloplasmin, 24-hour urine copper excretion.

Imaging

Initial approach

- Structural imaging studies (CT, MRI) do not assist in the diagnosis of DLB; preservation of medial temporal structures may help differentiate DLB from AD. MRI imaging may reveal evidence of other causes of parkinsonism and/or dementia.
- PET or SPECT scanning is not specific for DLB, although some studies have suggested hypometabolism in parietal and occipital regions of DLB patients contrasts with the parietal and temporal hypometabolism in AD.

Diagnostic Procedures/Other

A therapeutic trial of Sinemet®, a combination of carbidopa and levodopa, at doses of up to 600–800 mg of levodopa equivalents in 24 hours, is sometimes considered diagnostic of true IPD when the patient responds with dramatic symptomatic improvement. Patients with DLB may have only partial response. They may also develop confusion and/or psychosis with this class of medications.

Pathological Findings

DLB consensus guidelines proposed pathological confirmation based on LB density by alpha-synuclein (AS) immunohistochemistry in brainstem, limbic, and 5 cortical regions. AS is a protein that forms the intraneuronal inclusions which, in part, make up LBs. DLB pathology is correlated with accumulation of LBs and apoptotic neurodegeneration. The severity of dementia correlates with the abundance of cortical LBs as well as varying degrees of AD pathology, typically seen in over 70% of DLB post-mortem cases. In contrast, LB deposits in IPD and PDD initially occur in brainstem and motor pathways with evidence suggesting a caudal to rostral accumulation.

DIFFERENTIAL DIAGNOSIS
Includes extrapyramidal and dementing illnesses:
- PDD
- Parkinson's disease (IPD)
- Drug-induced parkinsonism
- MSA
- Progressive supranuclear palsy (PSP)
- Wilson's disease
- Vascular parkinsonism
- Frontotemporal dementia with parkinsonism
- Alzheimer's with extrapyramidal features

TREATMENT

ADDITIONAL TREATMENT
General Measures
- The management of DLB is complicated by cognitive decline, behavioral changes, and frequent delusions and hallucinations.
- Parkinsonian manifestations may be managed with *anti-parkinsonian agents*, which may cause side effects, particularly confusion and visual hallucinations. Low doses of carbidopa/levodopa medications are best tolerated, with relatively increased toxicity from dopamine agonists.
- DLB patients are sensitive to confusion from many medications including anticholinergics, benzodiazepines, antihistamines, and narcotics.

Specific Therapies
- *Carbidopa/levodopa* (brand name Sinemet®): Doses vary, but patients are usually initiated with 25 mg carbidopa/100 mg L-Dopa t.i.d. and titrated to a total daily dose of dopamine of 300–800 mg. ***Cholinesterase inhibitors*** – these agents may benefit the cognitive and behavioral features in DLB. Oral forms need to be taken with food and titrated to minimize GI side effects.
- Donepezil (Aricept®, 5–10 mg daily). It can cause bradycardia when used with beta-blockers.
- Rivastigmine (Exelon®, 6–12 mg/day) is given twice daily and is also available as a topical skin patch (Exelon® patch 4.6 mg and 9.5 mg) applied daily to the skin for 24 hours. The patch has less GI side effects than the oral formulation.
- Galantamine (Razadyne®, 4, 8, 12 mg tablets and liquid 4 mg/ml) is given twice daily with food. Galantamine ER (Razadyne ER®, 8, 16 and 24 mg) is a daily extended-release formulation. ***NMDA receptor antagonists***—Memantine (5 mg and 10 mg twice daily).

ADDITIONAL TREATMENT
Psychiatric Measures
- *Atypical antipsychotics* are used in very low doses to treat associated hallucinations and behavioral disturbances. Judicious use is needed because of an increased risk of death in elderly, especially those with cardiovascular risk factors. Agents with no extrapyramidal side effects include:
  - Clozapine (Clozaril®, 12.5–25 mg/day) is the prototypic atypical antipsychotic. A rare, but life-threatening side effect is agranulocytosis. Weekly CBC is required for the first 6 months and every 2 weeks thereafter.
  - Quetiapine (Seroquel®, 25–100 mg/day) is another atypical antipsychotic that shows no dose-dependent extrapyramidal side effects.
- **ALERT –** Conventional neuroleptics are contraindicated in the treatment of DLB psychosis. DLB patients may experience severe, life-threatening rigidity and bradykinesia if administered medications with high affinity for dopamine receptors such as haloperidol.
- *Antidepressants* such as venlafaxine (75–225 mg/day) and paroxetine (10–20 mg/day) may be required for treatment of depression and/or anxiety but may worsen cognition.

Issues for Referral
Referral to geriatric psychiatry, cognitive or movement disorders neurology is warranted for assistance with medication management.

Additional Therapies
- Physical and occupational therapists to help with mobility issues and activities of daily living.
- Neuropsychologists may assess whether depression and/or anxiety are confounding components.
- Social workers assess caregiver stress and coordinate home health care services.

SURGERY/OTHER PROCEDURES
Deep brain stimulation is contraindicated in DLB due to risk of worsening dementia.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Not uncommonly, concomitant illnesses (e.g., pneumonia, UTI) may lead to an acute exacerbation of parkinsonian or cognitive symptoms, requiring hospitalization for dysphagia, airway management, confusion and issues of decreased mobility. Psychosis frequently precipitates hospitalization/institutionalization.

Nursing
Close observation is needed due to confusion and increased risk of falls from the extrapyramidal symptoms. Attention to sleep/wake cycles, hydration and nutritional status, as well as avoidance of heavily sedating agents is necessary. Treatment with carbidopa/levodopa needs to be dosed on a strict schedule to minimize motor and/or cognitive fluctuations.

Discharge Criteria
Evaluations from physical and occupational therapists, neuropsychologists, and social workers may be necessary to judge whether the patient will require home health care or a subacute rehab stay to return home safely. Persistent psychosis is a common cause of nursing home placement.

ONGOING CARE

PATIENT MONITORING
DLB requires steadily increasing doses of medications for the treatment of dopaminergic deficiency, side effects of dopaminergic therapy and the cognitive/behavioral abnormalities.

DIET
Separating carbidopa/levodopa from meals rich in protein may be required to obtain optimal clinical efficacy (levodopa absorption is impaired by the presence of neutral amino acids).

PATIENT EDUCATION
Support groups for parkinsonian disorders are available. There are several large national organizations that provide educational materials.

PROGNOSIS
DLB is typically more relentless than Parkinson's disease in its progression with significant disability – emotional, cognitive and physical – by 7–10 years after the onset of symptoms.

COMPLICATIONS
Drug-induced psychosis, falls, aspiration pneumonia, severe autonomic dysfunction including orthostatic hypotension and syncope.

REFERENCES

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See Also (Topic, Algorithm, Electronic Media Element)
- PDD
- Alzheimer's with extrapyramidal features
- MSA
- PSP

CODES

ICD9
331.82 Dementia with Lewy bodies

CLINICAL PEARLS

Cognitive deficits seen early in DLB include attention and concentration (serial 7's, spelling WORLD backwards) and visuospatial skills (intersecting pentagons, clock drawing test) while orientation and memory are largely preserved. This contrasts sharply to AD in which orientation and short-term memory are involved early or in equal proportion to attention/concentration and/or visuospatial skills.

DERMATOMYOSITIS

Bakri H. Elsheikh, MBBS, FRCP

BASICS

DESCRIPTION

- Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and characteristic cutaneous findings.
- DM is clinically, histologically, and pathogenically unique compared to the other subtypes of idiopathic inflammatory myopathies: Polymyositis (PM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (NM).

EPIDEMIOLOGY

Incidence

- Estimated to be less than 1 per 100,000.
- DM can occur at any age, but there is a peak in adults between 40 and 60 and children between 5 and 15 years of age.
- Incidence is higher in females than in males.
- There is no known racial predilection.

Prevalence

Estimated in a small US population-based study to be 21 per 100,000 persons.

RISK FACTORS

DM can occur in isolation or in association with connective tissue diseases (overlap syndromes) or malignancy.

Genetics

Association with specific HLA alleles is known to occur in some patients.

GENERAL PREVENTION

Exposure to the sun might lead to rash emergence or worsening.

PATHOPHYSIOLOGY

- DM was considered a humorally mediated microangiopathy with evidence of early immunoglobulins and C5b-9 membrane attack complex (MAC) deposition in the perifascicular capillaries causing ischemic damage to perifascicular muscle fibers with subsequent recruitment of CD4+ T helper cells, B cells, and macrophages. This secondary perimysial and perivascular infiltration by inflammatory cells causes further muscle damage.
- Recent evidence, however, suggests the majority of the reported CD4+ cells are actually plasmacytoid dendritic cells (PDC) rather than T helper cells. The PDC cells are part of the innate immune system. They secrete type 1 interferon (IFN) and act as antigen-presenting cells.
- Studies using gene microarray revealed increased expression of type 1 IFN inducible genes and proteins in the perivascular and perimysial regions. This precedes MAC deposition suggesting it is likely a secondary phenomenon.
- These findings led to the hypothesis that overproduction of type 1 IFN by dendritic cells might be toxic to the capillaries and the perifascicular muscle fibers.

ETIOLOGY

Autoimmune etiology as detailed under "Pathophysiology."

COMMONLY ASSOCIATED CONDITIONS

- Connective tissue disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma, mixed connective tissue disease, and Sjögren's syndrome.
- Malignancy including ovarian, lung, breast, non-Hodgkin's lymphoma, pancreatic, stomach, colorectal, and melanoma. The risk is greatest after the age of 50. Most are identified within 2 years but the risk remains elevated up to 5 years after the diagnosis.

DIAGNOSIS

HISTORY

- DM presents with subacute (over weeks) proximal leg and arm weakness and characteristic skin rash. Both insidious (over months) and fulminant (days) course can occur.
  - The rash usually precedes or accompanies the weakness. Some patients develop the rash but never develop weakness "DM sine myositis."
- Dysphagia is reported in up to 30% of patients due to oropharyngeal and esophageal muscle involvement. Chewing can be affected.
- Extramuscular manifestations include:
  - Joints: Arthralgia and joint contractures
  - Cardiac: Myocarditis, pericarditis, and congestive heart failure may occur but the majority of patients do not have cardiac symptoms.
  - Pulmonary: Aspiration pneumonia and interstitial lung disease (ILD) (10–20%)
- Necrotizing vasculitis: Skin, muscle, retina, GI tract, and kidney especially in juvenile DM

PHYSICAL EXAM

- Symmetric weakness predominantly involves the neck flexors, hip flexors/extensors, and trunk and shoulder girdle muscles.
- Rash
  - Heliotrope rash refers to purplish eyelids often associated with periorbital edema. It is the most specific rash for DM.
  - Macular erythematous rash can be seen on
    - Face, scalp, and anterior chest (V-sign)
    - Back and shoulders (shawl sign)
    - Knees, elbows, and knuckles (Gottron sign). This can evolve into scaly, papular erythematous lesions over the knuckles (Gottron papules).
  - Periungual erythema and dilated capillaries at the base of the fingernails.
  - Subcutaneous nodular calcifications over pressure points is more common in juvenile DM.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum creatine kinase is the most sensitive marker for muscle destruction but it can be normal in up to 10% of the patients.
- Alanine transaminase and aspartate transaminase may also be elevated. This might lead to unnecessary liver biopsy. Measurement of gamma-glutamyltransferase can be helpful.
  - Antinuclear antibodies are detected in 24–60%, mostly in those with overlap syndrome.
  - ESR is usually normal or mildly elevated.
  - Some patients have myositis-specific antibodies including anti-Jo-1 and anti-Mi2. Anti-Jo-1 is found in approximately 20% of the cases of PM and DM. Patients usually have ILD, Raynaud phenomena, and/or arthritic complications (anti-synthetase syndrome). Anti-Mi2 found in 15–20% of DM patients is associated with acute onset, florid rash, and good prognosis.
  - CBC, blood chemistries, urinalysis, and stool for occult blood may also be checked as part of underlying malignancy work-up.

Follow-up & special considerations

Breast and pelvic examination for women and testicular and prostate examination for men are performed for cancer screening.

Imaging

Initial approach

- Muscle MRI usually shows signal abnormalities in the affected muscles secondary to edema and inflammation and in chronic cases fatty replacement. Its current use is limited to identifying biopsy site in some patients.
- Chest, abdomen, and pelvis CT scans and mammography are obtained to screen for malignancy. Positron emission tomography scan can be considered if there is high clinical suspicion and the above are negative.

Follow-up & special considerations

N/A

Diagnostic Procedures/Other

- Electromyography is usually abnormal in active disease; however, the findings are nonspecific. Increased insertional activity and abnormal spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally complex repetitive discharges are found. The degree of abnormal spontaneous activity reflects disease activity. Motor unit potentials are polyphasic, of short duration, low amplitude with early recruitment.

Pathological Findings

- Muscle biopsy is invaluable for pathological confirmation of the disease and should be performed in all cases, preferably before starting treatment. The typical pathology is that of perifascicular muscle fiber atrophy. Inflammatory infiltrate composed of macrophages, B cells, and CD4+ cells is seen in the perimysial and perivascular regions. Increased expression of type 1 IFN inducible genes and protein and complement, C5b-9 (MAC) deposition are noted.

DIFFERENTIAL DIAGNOSIS
- Idiopathic inflammatory myopathies (PM, IBM, and NM)
- Connective tissue diseases, such as SLE, and mixed connective tissue disease
- Muscular dystrophies
- Drugs and toxins such as statins, hydroxychloroquine, colchicine, amiodarone, penicillamine, hydroxyurea, cocaine, and heroin
- Infectious myopathies related to viral, bacterial, fungal, and parasitic infections
- Endocrine disorders such as hypothyroidism, Cushing's syndrome, and hyperparathyroidism

TREATMENT

MEDICATION
First Line
- Prednisone is the first drug of choice despite the absence of randomized control trials.
- Prednisone: 0.75–1.5 mg/kg/day (maximum dose 100 mg) PO qam for 2–4 weeks then switch directly to qod regimen. Consider daily dosing in diabetics to avoid blood glucose fluctuations. Treat until strength normalizes, plateaus, or 3–6 months have passed, then slowly taper.
- Methylprednisolone is used for patients with severe weakness or non-ambulatory: 1 g IV qd × 3–5 doses followed by oral regimen as above.
- Prescribers should be familiar with side effects, contraindications, and monitoring needed.
- Tuberculin skin test is performed to screen for tuberculosis (TB). Isoniazid treatment is initiated for those with positive PPD (purified protein derivative) or history of TB.
- Corticosteroid is associated with weight gain, hypertension, diabetes, infections, peptic ulcer disease, cataracts, glaucoma, hypokalemia, osteoporosis, and avascular necrosis.
- Concurrent management includes baseline Dexa scan treatment, bone prophylaxis with calcium (1 g/day), and vitamin D supplements (400–800 IU/day). Bisphosphonate is considered in postmenopausal women or those with abnormal Dexa. Bactrim DS 3 times weekly is given for PCP prophylaxis. H2 blockers are prescribed for patients with GI discomfort or history of peptic ulcer disease.

Second Line
- Generally initiated early in those with severe weakness, other organ involvement, unable to tolerate steroids, or failed the steroid taper.
- IVIG: 2 g/kg over 2 days monthly for 3 months. Subsequently decrease or spread out the dose to 1 g/kg monthly or 2 g/kg every 2 months.
  - IVIG therapy is associated with renal failure, thromboembolic events, flu-like symptoms, skin rash, aseptic meningitis, and anaphylaxis.
- Methotrexate: 7.5–20 mg weekly
  - Avoid in ILD because of risk of pulmonary fibrosis. Leucopenia, anemia, infection, and hepatotoxicity are other side effects. Folic acid supplements (1–2 mg/day) are given to all patients. Bactrim increases the risk of myelosuppression.
- Mycophenolate: 1–1.5 g twice daily
  - Bone marrow suppression, infections, hypertension, and diarrhea are side effects.
- Azathioprine: 2–3 mg/kg/day
  - Flu-like symptoms, hepatotoxicity, pancreatitis, leucopenia, and infections are side effects. Screening for thiopurine methyltransferase deficiency prior to starting the drug helps predict toxicity risk.
- Other used immunosuppressive drugs include cyclosporine, tacrolimus, rituximab, cyclophosphamide, and etanercept.

ADDITIONAL TREATMENT
General Measures
N/A

Issues for Referral
- Dermatology for skin rash
- Ophthalmology for periodic eye examination

Additional Therapies
- Physical therapy to help with range of motions and to maintain strength.
- Assistive devices, such as cane, walker, or wheelchair, might be needed.
- Aspiration precautions and speech therapy evaluation for patients with dysphagia.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
N/A

SURGERY/OTHER PROCEDURES
Surgical excision is considered in some with cutaneous calcinosis as a last resort. Diltiazem, warfarin, colchicine, probenecid, and alendronate are used with variable success.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
N/A

Admission Criteria
Patients are admitted for severe weakness or for treatment of complications (infections, organ failure, etc.).

IV Fluids
N/A

Nursing
N/A

Discharge Criteria
N/A

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
While on high-dose prednisone patients are seen every 2–4 weeks.

Patient Monitoring
Patients are followed to monitor muscle strength, skin rash, extramuscular complications, and medication side effects.

DIET
- Low-salt, low-carbohydrate, and low-fat diet is recommended for patients on prednisone.

PATIENT EDUCATION
- Muscular Dystrophy Association. Website: www.mdausa.org
- Myositis Association of America. Website: www.myositis.org

PROGNOSIS
- Generally favorable; however, a number of patients do not respond adequately and remain disabled. Delay in starting therapy, ILD, cardiac involvement, old age, and associated malignancy are associated with poorer prognosis.

COMPLICATIONS
- Are usually related to the side effects of the immunosuppressive medications.

ADDITIONAL READING

- Amato AA, Barohn RJ. Evaluation and treatment of inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 2009;80:1060–1068.
- Choy EH, Hoogendijk JE, Lecky B, et al. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2005;3:CD003643.
- Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult inflammatory myopathies, with the exception of inclusion body myositis. *Neuromuscul Disord* 2004;14(5):337–345.

CODES

ICD9
710.3 Dermatomyositis

CLINICAL PEARLS
- DM is clinically, histologically, and pathogenically unique compared to the other subtypes of idiopathic inflammatory myopathies, i.e., DM is not polymyositis with a skin rash.
- A search for associated malignancy or connective tissue disease (overlap syndrome) as well as early detection of extramuscular manifestations has important therapeutic and prognostic implications.

DEVELOPMENTAL DELAY

Catalina Cleves Bayon, MD
Gary Hsich, MD

BASICS

DESCRIPTION

- Developmental delay is a common problem presenting to pediatricians and family physicians. Children with delayed development are usually identified in the preschool years. This review focuses on conditions that have symptoms affecting cognition and/or language development.
- Developmental delay is a *symptom complex* and by no means represents a specific diagnosis.
- The term global developmental delay is used when 2 or more domains (language, motor, cognition, social) are affected; it is usually reserved for small children.
- The terms mental retardation and intellectual disability require accurate assessment of intelligence and adaptive skills which may be difficult to accomplish in very young children. Better assessment can be made between 1 and 2 years, when children normally acquire language skills.
- Motor delay is usually noted early in the first year or two of life as a child fails to meet sitting, walking, or other motor milestones.
- Early identification of delay generally implies a more severe disorder of brain development.

EPIDEMIOLOGY

- Mental retardation has an incidence of 1–3%, with the prevalence of mild retardation being inversely related to family socioeconomic status.
- Sex: Twice as many males as females are affected.

RISK FACTORS

Pregnancy Considerations

As a significant percentage of conditions with delayed development are prenatal in origin, the pregnancy history is critical to obtain information related to toxin exposures (fetal alcohol syndrome and illicit drugs), teratogens (anticonvulsant and other medical treatment), infections (TORCH and others), and maternal conditions (diabetes, etc).

ETIOLOGY

- Some children have delayed milestones or exhibit variations from normal. The norms and standard deviations from normal are well documented but, particularly in language development, are variable and broad (e.g., lack of speech development in the hearing child may be acceptable to 2–3 years of age depending on a variety of factors if receptive language is age appropriate).
- More severely affected children are usually recognized in the first year of life, and are somewhat more likely to have an identifiable etiology.
- Disorders of cognition, language, and social development may have many different causes. Nonprogressive pathology affecting the CNS includes fetal insults (*in utero* infection or toxic exposure), disorders of chromosomal or molecular genetics, and major brain dysgenesis or malformation.
- Prenatal factors (including genetic conditions, neurometabolic disorders, neurocutaneous syndromes, and nonchromosomal dysmorphic syndromes) account for 60–70% of cases. Perinatal problems (prematurity, birth asphyxia, or injury) cause 10%, with postnatal brain injury (meningitis/encephalitis or trauma) being somewhat less than 10%.
- Fragile X syndrome is the most common inherited cause of global developmental delay.

COMMONLY ASSOCIATED CONDITIONS

- Children with developmental delay may present with other disorders affecting brain growth and development.
- Cerebral palsy (CP) is a nonprogressive abnormality of movement and posture. CP can be further characterized by a description of the pattern of abnormality and the affected limbs: Spastic, hypotonic; diplegic, hemiplegic, quadriplegic.
- Seizures can be severe (infantile spasms, Lennox–Gastaut) and may reflect underlying cortical malformations (schizencephaly, lissencephaly/pachygyria, polymicrogyria, heterotopias). Children with both developmental disabilities and epilepsy are less likely to outgrow their seizures, compared to developmentally normal children.
- Autistic spectrum disorders are characterized by impaired language development, abnormal behaviors, and impaired social interactions.
- Vision impairment may occur in up to 50%, while hearing impairment may affect 18% of these patients. Treatment of these conditions may significantly affect developmental outcomes.
- Other commonly associated conditions are attention deficit and hyperactivity disorders.

DIAGNOSIS

- Thorough history taking should be done to determine which developmental areas are affected and to estimate the child's actual developmental age and to compare it with the chronological age. The comprehensive evaluation of the child's current level of functioning should include physical motor, cognitive, communication (speech and language), and social and play development.
- The pregnancy history may reveal risk factors for poor fetal growth and development. Growth measurements, particularly head circumference, are invaluable in assessing a child who has failed to thrive or has micro- or macrocephaly.
- Additional medical history may help narrow the differential diagnosis into a specific syndrome.
- It may be useful to ask parents to bring photographs or videotapes that demonstrate previous developmental skills, especially if there is true developmental regression and loss of milestones.
- Family history must be reviewed in detail; it is essential to complete a three-generation pedigree.
- A good social history should be taken to identify any potential psycho-socio-economic contributors to the etiology.
- Physical examination is focused on detection of dysmorphic features, and other organ or system involvement. Head circumference measurements should be done; if abnormal in the index patient, parental head circumference measurements should also be included. Particular attention should be paid to the presence or absence of abnormal growth parameters, pigmentary retinopathy, organomegaly, neurocutaneous lesions, and any dysmorphic features. Findings on physical exam may help localize the abnormalities to the CNS, or to the periphery (such as peripheral nerve or muscle).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- There is no consensus on the choice of diagnostic investigations for developmental delay. The decision to perform diagnostic imaging and laboratory procedures is based on the comprehensive historical and physical examination described above. In addition to the diagnostic yield of any given test, other factors to consider include the ability of a test to identify a treatable disorder; invasiveness; and cost of testing. The potential diagnostic yield can be greatly improved by careful and thoughtful consideration of the medical history and physical exam. However, many etiologies cannot be definitively proven or disproven (such as unknown genetic disorders or toxin exposures).

- The following investigations may be considered in the initial evaluation:
  - Microarray studies are an evolving technology and have the highest diagnostic yield of currently available genetic tests. The diagnostic yield of a microarray ranges from 5% to 10%, but can be greatly increased in certain situations such as dysmorphisms, congenital anomalies, or more severe neurological impairments.
  - If a specific diagnosis is suspected based on examination findings, directed testing (such as Down's, Fragile X, Rett, or Prader–Willi) should be pursued.
  - Routine metabolic screening has a yield between 0.2% and 4.6%, depending upon associated clinical features and specific testing performed. Some tests (such as lactate and ammonia) are nonspecific and notoriously subject to technical factors. Therefore, metabolic testing should be carefully and selectively performed. Higher yield situations include consanguineous parents, siblings with similar symptoms, early childhood deaths, multiple organ system dysfunction, unusual odors, or dietary selectivity.
  - Some of these tests are:
    - Serum amino acids, lactate, ammonia, very-long-chain fatty acids, congenital disorders of glycosylation
    - Urine organic acids, oligosaccharides, and mucopolysaccharides
  - Other considerations:
    - TSH
    - Lead
    - CPK

Imaging

Brain MRI may identify abnormalities in 48–65% of patients.

Neurophysiology

Electroencephalogram is indicated if there is realistic concern for seizures. Otherwise, the diagnostic yield in patients with developmental delay is <1% in the absence of symptoms suggestive of seizures.

Diagnostic Procedures/Other

- Audiologic and ophthalmologic evaluation should be performed in all children with developmental delay, as treatment of these disorders will impact developmental outcome.
- Children with developmental delay also need neuropsychological evaluation. Program recommendations and current level functioning are provided by educational, speech, physical, and occupational therapy assessment.

DIFFERENTIAL DIAGNOSIS

- Developmental delay/mental retardation must be distinguished from primary speech and language disorders and autistic spectrum conditions. Children with isolated motor delays require evaluation for neuromuscular disorders (muscular dystrophy, congenital myopathies).
- Broad categories of etiologic diagnosis include malformations of brain development, prenatal infections, or exposure and neurogenetic disorders.
- A careful history is necessary to distinguish delayed development from disorders in which there is a loss of acquired skills and developmental regression (the neurodegenerative disorders of childhood).

TREATMENT

INTERVENTIONS

Early intervention with speech, occupational, and physical therapy is the cornerstone of treatment of children with developmental disabilities. The goal is to maximize their developmental potential. Any visual or hearing impairment should be addressed and optimized.

MEDICATION

- There are no specific pharmacologic treatments for children with developmental delay, although if situations arise when behavioral management methods fail, then psychotropic medication options can be cautiously considered.
- Alternative drugs: There are no evidence-based studies to support the use of alternative treatment methods.

ADDITIONAL TREATMENT

General Measures

As there are many diverse origins for developmental disorders, management is based on thorough assessment and program planning; for example, the child with an isolated speech delay requires audiologic evaluation, communication testing, and focused speech and language treatment programming.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - General treatment and rehabilitation measures are necessary following assessment recommendations, with educational programming provided in structured classroom environment for the older children.
  - The multidisciplinary team approach is considered the most comprehensive assessment and treatment model. Management is usually best arranged and supervised at a special children's treatment center.
  - Genetics
  - Ophthalmology
  - Audiology
- Adjunctive treatment
  - Parents who have children with developmental disorders may be assisted in caring for their child through the provision of a variety of nonmedical services, for example, behavioral counseling and respite care.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- After a comprehensive diagnostic evaluation and arrangements made for developmental and rehabilitation treatment carried out by appropriate members of the multidisciplinary team, medical follow-up can focus on general monitoring of expected progress in providing anticipatory counseling. Such issues as the need for formal genetic counseling (in defined disorders) and assessment for requirement for medication intervention with behavioral problems may need to be addressed.
- In cases in which no specific diagnosis is made, a thoughtful tailored reinvestigation should be conducted every 2–3 years.

PATIENT EDUCATION

Parents of children who have a defined developmental diagnosis should be referred to the appropriate family association and provided with a list of Internet resources.

ADDITIONAL READING

- Bear LM. Early identification of infants at risk for developmental disabilities. *Pediatr Clin N Am* 2004;51:685–701.
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- Shevell M. Global developmental delay and mental retardation or intellectual disability: conceptualization, evaluation and etiology. *Pediatr Clin N Am* 2008;55:1071–1084.
- Shevell M, Ashwal S, Donley D, et al. Practice parameter: evaluation of the child with global developmental delay. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2003;60: 367–380.
- Shevell MI, Majnemer A, Rosenbaum P, et al. Etiologic determination of childhood developmental delay. *Brain Dev* 2001;23(4):228–235.

See Also (Topic, Algorithm, Electronic Media Element)

- Developmental delay
- Mental retardation
- Developmental disability

CODES

ICD9

- 315.9 Unspecified delay in development
- 319 Unspecified intellectual disabilities
- 783.42 Delayed milestones

DYSMYELINATING DISORDERS

Alexander D. Rae-Grant, MD

BASICS

DESCRIPTION

Dysmyelination of the CNS refers to the production of an abnormal and unstable myelin sheath, often associated with hypomyelination. Usually of metabolic origin, many dysmyelinating disorders are represented in the sphingolipidoses (see chapter "Sphingolipidoses"). Four novel disorders are presented: Adrenoleukodystrophy (ALD), Pelizaeus–Merzbacher disease (PMD), Canavan disease, and Alexander disease.

EPIDEMIOLOGY

ALD: Incidence is not known. Estimates range from 1 in 20,000 to 1.1 in 100,000 births.

- Race
  - – ALD is panethnic; Canavan disease affects all ethnic groups but is especially prevalent among Ashkenazi Jews and Saudi Arabians.
- Age
  - – See Signs and Symptoms, below.
- Sex
  - – Because of X-linked inheritance, patients with ALD and PMD are male.

RISK FACTORS

Genetics

- ALD and PMD are X-linked; Canavan disease is autosomal recessive; Alexander disease is presumed to be autosomal recessive despite infrequency of involved siblings.
- Genes for ALD, PMD, and Canavan have been identified. Prenatal diagnosis is available for ALD, PMD, and Canavan disease.
- Alexander disease is caused by mutations in the gene for glial fibrillary acidic protein that maps to chromosome 17q21. This is caused by a de novo mutation in parental gametes and is not carried by the parents.

DIAGNOSIS

- ALD: Peroxisomal disorder that can cause damage to the CNS and adrenal cortex. Patients present with a history of normal early development with onset of neurological/behavioral symptoms, commonly hyperactivity, and school failure, between 4 and 8 years of age. Subsequent onset of adrenal insufficiency is seen in 90% of patients. The course is characterized by progressive dementia, visual loss with optic atrophy, pyramidal tract dysfunction, dysphagia, deafness, and seizures. A second phenotype, which is characterized by progressive paraparesis and sphincter disturbance due to spinal cord disease (adrenomyeloneuropathy), is seen in young men.
- PMD: Infantile onset variant is the classic form. A prominent, irregular nystagmus and head tremor or head rolling are noted at birth or during the first few months of life. Progressive dementia, ataxia, spasticity, and choreoathetotic movements ensue. The connatal variant is present at birth and is much more rapidly progressive.
- Canavan disease: Onset of symptoms by 3 months of age. Megalencephaly is common but not invariable (also seen in Tay–Sachs disease and Alexander disease). Lack of psychomotor development, progressive spasticity, optic atrophy, seizures, and dysphagia.
- Alexander disease: Patients with the infantile form present between 6 months and 2 years of age with megalencephaly and/or hydrocephalus (the large head is usually due to an enlarged brain, but some do develop hydrocephalus due to obstruction at the aqueduct of Sylvius), psychomotor retardation, spasticity, and seizures. A juvenile-onset form and an adult-onset form characterized by progressive bulbar weakness, spasticity, ataxia, and cognitive deterioration are described.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- MRI in patients with ALD shows characteristic symmetric periventricular white matter lesions in the posterior parietal and occipital lobes.
- MRI in PMD shows diffuse T2 hyperintensity in white matter.
- The MRI in patients with Alexander disease is significant for marked dysmyelination with frontal predominance.

Diagnostic Procedures/Other

- ALD: Abnormally high levels of very long chain fatty acids in plasma and fibroblasts. Mutation is found in the gene for ALD, which encodes for a transport protein in the peroxisomal membrane.
- PMD: Mutation in the gene encoding proteolipid protein on the long arm of the X-chromosome (Xq21-22).
- Canavan disease: Deficient aspartoacylase activity in skin fibroblasts. Detection of mutation in the gene encoding aspartoacylase. Elevated levels of *N*-acetylaspartate (aspartoacylase levels) in urine, blood, and cerebral spinal fluid.
- Alexander disease: Rosenthal fibers, protein inclusions formed in astro cytic footplates, are the characteristic histological finding. Molecular gene testing is now available.

Pathological Findings

- ALD—diffuse dysmyelination with sudanophilic granules in cerebral macrocytes, adrenocortical cells, testicular Leydig's cells, Schwann cells.
- PMD—tigroid appearance of the white matter on myelin stains because of islands of spared myelin against a nonmyelinated background.
- Canavan disease—microscopic examination of brain: Widespread vacuoles in deeper layers of cerebral cortex and subcortical white matter, loss of myelin, increase in number of protoplasmic astrocytes in cortex, basal ganglia and cerebellum.
- Alexander disease—abnormal white matter especially brainstem and cerebellum with deposition of Rosenthal fibers (fibrous, eosinophilic deposits).

DIFFERENTIAL DIAGNOSIS

The dysmyelinating diseases presented in this chapter must be differentiated from other inherited metabolic neurodegenerative disorders. Additionally, disorders of dysmyelination, which are characterized by the production of an abnormal and unstable myelin sheath, should be distinguished from disorders of demyelination, which are characterized by destruction of apparently normal myelin. Examples of demyelinating disorders in childhood are multiple sclerosis, Devic's disease (neuromyelitis optica), acute disseminated encephalomyelitis, acute necrotizing encephalomyelitis, and central pontine myelinosis. Other causes of progressive dementia to consider include encephalitis, chronic infections such as subacute sclerosing panencephalitis, exposure to neurotoxins and drugs of abuse, side effects of medications, collagen vascular diseases, and CNS complications of other diseases such as sickle cell anemia and end-stage renal disease.

TREATMENT

MEDICATION

No specific medication treatment is available to slow or stop the progression of these diseases.

ADDITIONAL TREATMENT

General Measures

Patients with ALD who demonstrate early cerebral involvement by MRI, neuropsychological testing, and/or neurological exam should be considered candidates for bone marrow transplant. Matched unrelated human umbilical cord blood transplantation may be an option when a suitable bone marrow donor is not available.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Patients with ALD usually do require treatment for adrenal insufficiency.
- Adjunctive treatment
  - Physical therapy may improve quality of life.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are usually admitted for evaluation and treatment of complications of their disease.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patient follow-up is guided by the predicted course and potential complications of the disease.

Screening

Screen should be offered to family members who are at risk for ALD.

PATIENT EDUCATION

- United Leukodystrophy Foundation, 2304 Highland Drive, Sycamore, IL 60178; phone: 800-728-5483; website: *www.ulf.org*
- Canavan Foundation, 600 West 111th Street #8A, New York, NY 10025; phone: 212-316-6488; website: *www.canavanfoundation.org*
- National Tay-Sachs and Allied Diseases Association, 2001 Beacon Street, Suite 204, Brighton, MA 02135; phone: 800-90-NTSAD; website: *www.ntsad.org*
- Adrenoleukodystrophy association; website: *http://www.aldfoundation.org/*

PROGNOSIS

- ALD: Rapid deterioration to a vegetative state once neurological symptoms become evident.
- PMD: By school age, boys are mute and confined to a wheelchair. Patients die of an intercurrent illness in late adolescence or early adulthood.
- Canavan disease: Death may occur within the first decade, although survival into the second and third decade is not uncommon.
- Alexander disease: Most die in a vegetative state in infancy or during the preschool years. A few children survive to the second decade.

ADDITIONAL READING

- Gordon N. Canavan disease: a review of recent developments. *Eur J Paediatr Neurol* 2001;5(2): 65–69.
- Kapelushnik J, Varadi G, Nagler A. Matched unrelated human umbilical cord blood transplantation for X-linked adrenoleukodystrophy. *J Pediatr Hematol Oncol* 1998;20(3):257.
- Kumar S, Mattan NS, de Vellis J. Canavan disease: a white matter disorder. *Ment Retard Dev Disabil Res Rev* 2006;12:157–165.
- Malm G, Ringden O, Anvret M, et al. Treatment of adrenoleukodystrophy with bone marrow transplantation. *Acta Paediatr* 1997;86:484.
- Namboodiri AM, Peethambaran A, Mathew R, et al. Canavan disease and the role of *N*-acetylaspartate in myelin synthesis. *Mol Cell Endocrinol* 2006;252: 216–223.
- Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. *Lancet* 2000;356:713–718.

CODES

ICD9

- 277.86 Peroxisomal disorders
- 330.0 Leukodystrophy
- 341.9 Demyelinating disease of central nervous system, unspecified

DYSTONIA

Punit Agrawal, DO

BASICS

DESCRIPTION

Involuntary sustained or repetitive posturing/twisting movements in the face, neck, trunk, or limbs caused by abnormal activity in both agonistic and antagonistic muscles.

EPIDEMIOLOGY

Incidence and prevalence has been estimated for primary dystonia.

Incidence

2 per million for generalized dystonia and 24 per million for focal dystonia (1).

Prevalence

3.4 per 100,000 for generalized dystonia and 30 per 100,000 for focal dystonia.

RISK FACTORS

- Family history
- Central or peripheral nervous system injury
- Dopamine-blocking agents
- Recreational drugs
- Neurodegenerative condition
- Disease of eye

Genetics

Several genes have been identified classified to primary dystonia, dystonia plus syndromes, and paroxysmal disorders. Some of the better recognized ones are discussed here.

- Primary dystonia
  - DYT1 is the most common primary genetic dystonia with onset in childhood or adolescence with autosomal dominant inheritance. Accounts for half of early onset primary dystonia. Causes focal, segmental, or generalized forms. Due to torsion A gene.
  - Others: DYT4, DYT6, DYT7, and DYT13 are autosomal dominant. DYT2 is autosomal recessive.
- Dystonia plus syndromes
  - Dopa-responsive dystonia or Segawa's disease (DYT5). Early childhood onset (1–12 years old) in the foot/leg with trouble walking plus hyperreflexia and slow generalization. Marked improvement and sustained response to levodopa. Two genetic deficits described:
    - Guanosine triphosphate cyclohydrolase 1: Autosomal dominant
    - Tyrosine hydroxylase: Autosomal recessive
  - Myoclonus dystonia (DYT11): Autosomal dominant. Defect in epsilon-sarcoglycan. Childhood or adolescence onset of dystonia and myoclonus in the limbs, trunk, or face.
  - Dystonia-parkinsonism syndromes
    - DYT12: Autosomal dominant. Rapid onset dystonia and parkinsonism during adolescence that tends to level off with time without progression. Little or no response to dopaminergic agents.
    - DYT3: X-linked dystonia-parkinsonism syndrome of Lubag of the Philippines.
- Paroxysmal dystonias are rare and include autosomal dominant DYT8–10. Characterized by brief episodes of abnormal movements with normal periods between attacks.
  - Paroxysmal kinesigenic dyskinesia (DYT10). Triggered by sudden movement. Childhood onset.
  - Paroxysmal non-kinesigenic dystonia (DYT8). Triggered by alcohol, caffeine, chocolate, or fatigue. Usual childhood onset, but possible adult onset. Also DYT9 familial variant with childhood onset associated spasticity and triggered by stress, exercise, caffeine, or chocolate (2).

PATHOPHYSIOLOGY

Exact pathophysiology is not known. Dysfunction in the sensory–motor portion of the basal ganglia or thalamus may lead to impaired inhibition of thalamic–cortical activity, which results in increased unwanted movements (2). This has been demonstrated with dystonia arising after structural lesions in these brain areas. Drugs and toxins that disrupt proper function of the basal ganglia can predispose to dystonia. Dopamine is implicated in some forms of dystonia supported by therapeutic effects in dopa-responsive dystonia, and also tardive dystonia seen with use of dopamine-blocking agents.

ETIOLOGY

Divided into 3 categories, but in many cases the cause may be difficult to determine.

- Primary dystonia includes both idiopathic and genetic causes and occurs in the absence of other abnormal neurological symptoms. It implies the absence of trauma, birth defect, nervous system lesion, or neurodegenerative condition.
- Dystonia plus syndromes are caused by specific genetic mutations with features of dystonia and other specific abnormalities (see "Genetics" section).
- Secondary dystonia is due to neurodegenerative disease, drugs, insult to the nervous system, or other exogenous cause.

COMMONLY ASSOCIATED CONDITIONS

- Primary and inherited
- Secondary dystonia
  - Drugs include dopamine-blocking agents (antipsychotics, anti-emetics, metoclopramide), anticonvulsants, dopaminergic agents, antidepressants, cocaine, amphetamines, and stimulants.
  - Toxins include manganese, thallium, methanol, carbon monoxide, carbon disulfide, and cyanide.
  - CNS lesions such as infection, trauma, cerebrovascular accident, tumor (brain or spine), hypoxia, cerebral palsy, perinatal insult, multiple sclerosis, or CNS inflammatory/autoimmune disorder.
  - Neurodegenerative conditions
    - Parkinson's disease
    - Huntington's disease
    - Cortical–basal ganglionic degeneration
    - Multiple systems atrophy
    - Progressive supranuclear palsy
    - Wilson's disease
    - Neuroacanthocytosis
    - Spinocerebellar ataxias
  - Inborn errors of metabolism (2)

DIAGNOSIS

HISTORY

- Age of onset with a wide range, but with bimodal peak at 9 and 45 years of age. Insidious onset usually with focal dystonia. May start as a slow repetitive uncontrolled movement associated with brief posturing. Generalized dystonia of early onset common to start in a limb and then spreads to contiguous areas (2,3)[C]. Dystonia with onset after age of 25 years tends to start in the cervical–cranial area (2,3)[C]. Features helpful in guiding assessment and treatment include age of onset, any preceding illness or injury, concomitant drugs/medications, aggravating or attenuating factors, and family history of dystonia (2,3)[C].
- Possible features:
  - Diurnal variation in some inherited forms
  - Sensory trick or geste antagoniste (i.e., simple placement of the hand on the involved part of the body reduces the dystonia)
  - Occurring with action or at rest
  - Present only with certain task performance (task-specific dystonia)

Classification

- Primary or secondary
- Age of onset: Before or after 25 years
- Distribution/extent of the involved areas
  - Focal – involves a single body area (neck, face, voice, arm, leg, or trunk)
  - Segmental – 2 contiguous areas
  - Multifocal – 2 or more noncontiguous areas
  - Hemidystonia – unilateral upper and lower limb (likely due to structural lesion)
  - Generalized – involving the whole body

PHYSICAL EXAM

- Neurological exam to evaluate for the presence of other abnormalities to suggest secondary dystonia (2,3)[C].
- Evaluate abnormal movements with regard to characteristic appearance of posturing. Identify involved agonistic and antagonistic muscles.
- May have associated dystonic tremor with repeated directional component, but irregular rhythm due to variable amplitude and frequency.
- Task-specific dystonia will require evaluation while performing the specific task such as writing.

- Forms of dystonia include:
  - Cervical dystonia
  - Hemifacial spasm
  - Blepharospasm
  - Craniocervical dystonia (Meige's syndrome)
  - Oromandibular dystonia
  - Focal limb dystonia
  - Task-specific dystonia (i.e., writer's cramp)
  - Segmental dystonia
  - Hemidystonia
  - Generalized dystonia
- Suggestible or distractibility may suggest psychogenic etiology.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- If secondary dystonia suspected (2,3)[C]:
  - CBC with smear for acanthocytes with a presence suggesting neuroacanthocytosis.
  - Serum ceruloplasmin and/or 24-hour urine copper collection with abnormality suggesting Wilson's disease.
  - Hepatic profile to evaluate for liver disease, and possible elevated bilirubin in kernicterus.
  - Inflammatory markers if concerns for autoimmune disease or paraneoplastic panel if suspected underlying malignancy.
  - Other testing may be warranted if other metabolic disorders, specific toxic, or other medical conditions are suspected.

Follow-up & special considerations

If dystonia occurs in absence of other abnormal symptoms with onset before the age of 26 years, then consider commercially available DYT1 genetic testing, especially if positive family history of dystonia (2)[C].

Imaging

MRI/CT if hemidystonia or secondary dystonia to assess for CNS structural lesions (3)[C].

Diagnostic Procedures/Other

- EEG if present focal twitching and if history suspicious for seizures.
- 3-week trial of levodopa if suspect dopamine-responsive dystonia, especially in children (2,3)[C].
- Slit light exam if suspect Wilson's disease.

DIFFERENTIAL DIAGNOSIS

- Chorea
- Tic disorder
- Myoclonus
- Partial epilepsy
- Psychogenic
- Spasticity
- Contracture or joint deformity

TREATMENT

MEDICATION

First Line

- Botulinum toxin therapy by an experienced practitioner (3,4)[A,B]. The dose varies on the type of botulinum toxin used, muscles involved, and severity of dystonia. Potential side effects include irritation/pain at the injection site and unexpected weakness of muscle of surrounding area if excessive spread. Rare formation of neutralizing antibodies.
- Trihexyphenidyl titrated to 2–15 mg divided (possible higher tolerability up to 80 mg in children) (2,3,5)[B]. Common side effects include confusion, psychosis, dry eyes, blurred vision, dry mouth, constipation, urinary retention, lightheadedness, and GI upset.
- Baclofen titrate to 15–80 mg divided (2,5)[C]. Common side effects include sedation, nausea, confusion, dizziness, and polyuria.
- Clonazepam titrated to 1–12 mg divided (2)[C]. More concerning side effects include potential for dependency. Other common side effects include sedation, cognitive trouble, and incoordination.
- Tardive dystonia and other drug-induced causes require weaning the offending agent.

Second Line

- Carbidopa/levodopa titrated to 25/100–50/200 mg 3 times a day for dopa-responsive dystonia (2,3,5)[C]. Common side effects include GI upset, flushing, lightheadedness, confusion, or psychosis.
- Tetrabenazine titrated to 37.5 mg divided (2,3,5)[C]. Common side effects include sedation, depression, fatigue, akathisia, anxiety, and nausea.

ADDITIONAL TREATMENT

Issues for Referral

- Expert evaluation may improve accuracy of diagnosis (3)[C]. This may include neurology, subspecialty movement disorder specialist, physical medicine, ophthalmology, or otolaryngology.
- Genetic counseling

Additional Therapies

Physical, occupational, or speech therapy

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Surgical considerations for medication and botulinum toxin therapy refractory dystonia:

- Intrathecal baclofen (2,3,5)
- Deep brain stimulation therapy (2,3,5)
- Stereotactic pallidotomy or thalamotomy
- Rhizotomy/myomectomy

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Botulinum toxin therapy requires repeat treatment, but no sooner than 3 months apart. Also may require more frequent visits to observe for effects.

PATIENT EDUCATION

- Treatment goal is to lessen disability caused by dystonia.
- Review potential side effects of treatment.
- Genetic testing is not typically indicated, and genetic counseling advised if done.
- Other patient resources
  - www.wemove.org
  - www.dystonia-foundation.org

PROGNOSIS

Chronic disorder that often requires ongoing symptomatic treatment. Focal dystonia may be self-limiting with plateau in progression. Generalized dystonia may spread and eventually cause severe disability.

COMPLICATIONS

Contractures may develop with sustained postures. Generalized dystonia may affect swallowing and breathing as well.

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See Also (Topic, Algorithm, Electronic Media Element)

- Torticollis
- Choreoathetosis
- Tics
- Tremor

CODES

ICD9

- 333.6 Genetic torsion dystonia
- 333.89 Other fragments of torsion dystonia
- 333.99 Other extrapyramidal diseases and abnormal movement disorders

CLINICAL PEARLS

- Classification of dystonia aids in treatment
- There are primary and secondary etiologies
- Treatment is tailored to each individual, and the current most effective treatment is botulinum toxin therapy

DYSTONIC REACTIONS

Peter J. Barbour, MD

BASICS

DESCRIPTION

- Dystonia: Involuntary muscular contraction:
  - Leading to sustained postures
  - With or without athetoid-like movements
- Dystonic reaction (DR): Acute dystonia due to an identifiable cause

EPIDEMIOLOGY

Incidence

- Not clearly defined
- 30–40% exposed to classical antipsychotics
- Related to potency, dose, rate of titration
- May also occur with other agents

RISK FACTORS

- Previous DR with exposure to agent
- Predictors: In-patients receiving neuroleptics:
  - Age:
    - Children and young adults highest risk
  - Sex: Males greater than females (2:1)

Genetics

- Higher incidence of DR among relatives of patients with idiopathic or torsion dystonia
- Cytochrome P450 2D6 polymorphism (1)[C]

GENERAL PREVENTION

- Avoidance/caution with agents that most commonly induce DR in those at risk
  - Young adult males with psychiatric illness
  - Neuroleptics given in setting of cocaine use

PATHOPHYSIOLOGY

- The pathophysiology of DR is not known.
- DR appears to be mediated by:
  - Acute dopamine blockade or relative hyperactivity of the cholinergic environment

ETIOLOGY

- Agents implicated (see "Additional Reading")
- Dopamine-blocking antipsychotic agents:
  - Butyrophenones, phenothiazines, benzamides
- Dopamine-blocking antinausea agents:
  - Metoclopramide, prochlorperazine, domperidone
- Serotonin agonist anxiolytic agents:
  - Buspirone
- Serotonin agonist antimigraine agents:
  - Sumatriptan
- Selective serotonin reuptake inhibitor
  - Antidepressants, e.g., fluoxetine, paroxetine
- Tricyclic antidepressants
- Monoamine oxidase inhibitor antidepressants
- Diphenhydramine
  - Note: Diphenhydramine is a treatment for DR
  - Antihistamine/decongestant cold prep
- Erythromycin (single case report)
- Illicit drugs:
  - Cocaine: Especially with neuroleptics
  - Ecstasy
- Anesthesia
  - Propofol
  - Ketamine

COMMONLY ASSOCIATED CONDITIONS

- Possible increased risk associated with neuroleptic use and the following:
  - Hyperthyroidism
  - Hypoparathyroidism
  - Hyperglycemia
- Parkinson's disease:
  - Dopamine excess and deficiency

DIAGNOSIS

- DR observed in the appropriate setting: Exposure to agent known to cause DR
- Movements associated with DR: (2)[C],(3)[C]
  - Forced eye deviation with rotation of head up and back [oculogyric crisis (OGC)]
  - Blepharospasm
  - Torticollis
  - Trismus
  - Dysarthria
  - Opisthotonus
  - Pisa syndrome: (4)[C]
    - Tonic lateral flexion of the trunk with backward rotation (neuroleptic induced)
  - Laryngeal/pharyngeal spasm (rarely)
    - May interfere with breathing
    - Implicated in sudden death with neuroleptics
- Symptom onset:
  - 2–24 hours after exposure, 100% by 9 days
  - Immediately with parenteral administration of an antiemetic such as prochlorperazine
- Duration of reaction:
  - Variable: May last days waxing and waning
- Distribution of signs:
  - More generalized in children
  - More circumscribed in adults
  - Region of the body involved may be constant or fluctuate during a DR
- Associated symptoms may be painful.

HISTORY

- History is directed towards the identification of the offending agent.
- Identify history of prior reactions
- Identify concomitant psychiatric history
- History of endocrinopathy
- Review exposure to:
  - Prescription and non-prescription drugs
  - Illicit drugs
- Family history of torsion dystonia

PHYSICAL EXAM

- Observe for movements associated with DR
- Look for signs of underlying disorders that may mimic DR
  - Parkinsonism: Rigidity, bradykinesia, rest tremor
  - Seizure: Tongue bite, confusion
  - Attempt to precipitate the dystonia if history suggests (task-specific behaviors) writing – writer's cramp, walking – foot dystonia; Parkinsonism

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Investigation is tailored to setting.
  - DR immediately after receiving a neuroleptic agent, no investigation may be indicated.
  - Where the offending agent is not known but strongly suspected, consider drug screen.
  - If the tonic posture (opisthotonus) or other findings suggest a non-drug related cause (as in the setting of renal dialysis), search for metabolic or infectious cause.
- Unexplained movement disorder, especially in a young patient, testing may include:
  - Ceruloplasmin, serum copper, slit-lamp examination (to rule out Wilson's disease)
  - Creatine kinase, myoglobin, glucose, lactate, pyruvate, uric acid, creatine, liver function studies, ESR, antinuclear antibody screen (see "Dystonia," "Torticollis").

Imaging

Initial approach

If history and physical examination suggest the possibility of a focal underlying process, such as stroke, MRI of the brain is indicated. However, for DR that is obviously drug-induced, imaging is not required.

Diagnostic Procedures/Other

If seizure remains a question on a clinical basis, electroencephalography is indicated.

Pathological Findings

DR is a pathophysiologic reaction to a substance. No anatomic pathological findings are defined.

DIFFERENTIAL DIAGNOSIS

- Secondary dystonias
  - Sudden onset:
    - Post-traumatic cervical dystonia
    - Parkinson's disease: Peak dose dystonia – too much dopamine. Early morning foot dystonia; too little dopamine
    - Post-encephalitic parkinsonism (early 20th century avian flu, Von Economo's encephalitis, associated with OCG)
- Insidious onset:
  - Primary dystonias: Task specific (writer's cramp)
- Seizure: The signs of DR are dramatic, frightening, may be mistaken for seizure.
  - DR is not associated with altered consciousness or postictal confusion.
  - Simple partial seizures that are not associated with loss of consciousness may still pose a problem for differentiation.
- Paroxysmal dyskinesia: Poorly understood disorders associated with sudden movements that may include dystonia.
  - Paroxysmal dystonic choreoathetosis
  - Paroxysmal exertion-induced dyskinesia
  - Transient paroxysmal dystonia
  - Torticollis of infancy

TREATMENT

MEDICATION

First Line

- May be self-limiting
- Moderate-to-severe reactions:
  - Adults: Benztropine 1–2 mg IV or IM, repeat in 20 minutes if no effect (3)[C]. Maximum cumulative dose: 6 mg (2)[C]. DR may return; therefore oral anticholinergic for 4–7 days in tapering dose
  - Adults: Diphenhydramine 1–2 mg/kg up to 100 mg slow IV or IM, followed by several days of oral treatment (5)[C]
  - Children: Benztropine 0.2 mg/kg to max 1 mg IV or IM, may repeat once (wait 30 minutes if IM). Continue same dose orally b.i.d., for up to 48 hours (5)[C]
- Contraindications:
  - Known hypersensitivity to these medications
  - Diphenhydramine should not be used in neonates or nursing mothers.
  - Benztropine is contraindicated in patients less than 3 years of age.
- Precautions:
  - Antihistamines (diphenhydramine) caution in patients with asthma, increased intraocular glaucoma, cardiovascular disease, hyperthyroidism, benign prostatic hypertrophy, and bladder neck obstruction.
- Acute dystonia related to Parkinson's disease: The acute dystonic cramp may respond to adjustment in medication.

Second Line

- Moderate-to-severe reaction
  - Promethazine 25–50 mg IV or IM (5)[C]
  - Diazepam 5–10 mg IV (reserved for patient who incompletely responds to above) (5)[C]

ADDITIONAL TREATMENT

General Measures

- Reassurance
- Observe for airway compromise

Issues for Referral

Laryngeal/pharyngeal involvement

SURGERY/OTHER PROCEDURES

- Not indicated for DR
- Late-occurring dystonia, tardive dystonia, in the setting of chronic neuroleptic drug exposure, consider chemodenervation with botulinum toxin (6)[C]

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Monitor airway and breathing

Admission Criteria

Consider hospitalization for observation as DR may recur and laryngeal/pharyngeal involvement is possible.

IV Fluids

DRs are frightening, dramatic, may be painful, requiring IV access.

Nursing (for DR Involving Head & Neck)

- Monitor heart rate, respiration, blood pressure and pulse oximetry until DR resolves
- Begin IV D5W at KVO
- For DR compromising swallow/breathing
  - NPO until DR resolves
  - Bed rest with head of bed elevated until DR resolves

Discharge Criteria

- Parenteral medications are usually effective within 20 minutes. The effect may wear off with recrudescence of DR, necessitating a second injection.
- Discharge after period of observation with no recurrence of DR.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Treatment of DR may include:
  - Dose adjustment of the offending agent
  - Discontinuation of the offending agent
  - Administration of medication to abort this reaction if it recurs
- Reassurance: DR frightening and painful
- Patients who have experienced acute DRs are at higher risk for future reactions.
- Prophylaxis: May be considered if long-term neuroleptic use is required.
  - Consider the following agents: Anticholinergics, Antihistamines, Amantadine

PATIENT EDUCATION

- Primarily regarding agents to avoid instructions in case of recurrence.
- Mild DR, consider oral treatment:
  - Diphenhydramine 50 mg PO t.i.d. for several days
- Severe DR
  - Return for further treatment (IV required)

PROGNOSIS

DR, due to neuroleptic agents, is self-limited and does not require ongoing treatment once the offending agent is removed and DR resolves.

COMPLICATIONS

Failure to respond to several doses of parenteral anticholinergic medication should prompt additional evaluation (see above).

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ADDITIONAL READING

- Google Scholar: Dystonic reaction "suspected agent," such as cocaine, propofol, ecstasy.

See Also (Topic, Algorithm, Electronic Media Element)

- Parkinson's disease
- Wilson's disease
- Dystonia
- Torticollis

CODES

ICD9

- 333.6 Genetic torsion dystonia
- 333.72 Acute dystonia due to drugs
- 781.0 Abnormal involuntary movements

CLINICAL PEARLS

- DR is acute dystonia due to an identifiable cause (usually medication).
- Most prone: Young adult males with psychiatric illness exposed to neuroleptics.
- Benztropine or diphenhydramine are the first-line medications to consider in a moderate-to-severe acute DR.

ENCEPHALITIS

John Davis, PhD, MD

BASICS

DESCRIPTION

Encephalitis is defined as an inflammatory process of the brain parenchyma, and is usually associated with clinical or laboratory evidence of neurologic dysfunction. It is important to distinguish acute (usually infectious) encephalitis from post-infectious processes [such as acute demyelinating encephalomyelitis (ADEM)] and two other entities—meningitis and encephalopathy—which are different pathogenic processes with separate etiologies and prognoses.

EPIDEMIOLOGY

Incidence/Prevalence

In the USA, the overall incidence of encephalitis (acute) has been estimated at 7.3/100,000. It accounts for 19,000 hospitalizations annually in the USA. Globally, most estimates of encephalitis incidence range from 6.24 to 7.4/100,000, though a recent study has found extremes of estimates from 0.07 to12.6/100,000.

RISK FACTORS

Risk factors for encephalitis depend on the etiology (see Etiology, below). For infectious etiologies, epidemiologic exposure and concurrent immunosuppressive conditions are the two greatest risk factors.

Genetics

Genetic predisposition to acquisition of infectious encephalitis is rare, though mutations that affect prognosis have been described, as have some genetic factors associated with non-infectious encephalitis (e.g., hereditary Creutzfeldt–Jacob disease).

GENERAL PREVENTION

Some infectious encephalitides may be preventable by minimizing epidemiologic exposures (e.g., mosquito or tick prevention/avoidance; avoiding areas of high endemicity, etc.). Some causes of encephalitis are vaccine preventable (e.g., Japanese encephalitis).

PATHOPHYSIOLOGY

Infectious agents may spread to the brain parenchyma by four main routes: Hematogenous seeding, direct inoculation (usually traumatic), direct extension (e.g., from sinus disease), or from peripheral nerves [e.g., rabies, herpes simplex virus (HSV)]. Infectious agents cause damage/destruction of brain tissue. Regardless of the etiology, the inflammatory response can also cause damage to surrounding brain parenchyma, which leads to examine the findings consistent with the damaged area(s).

ETIOLOGY

- Etiologies of encephalitis may be infectious or non-infectious. Non-infectious causes include autoimmune, paraneoplastic, and collagen vascular diseases. However, in most case series, the majority of encephalitides are of unknown etiology. Of those encephalitides with identified etiologies, the majority are infectious. Infectious etiologies may be classified by agent (e.g., prion, virus, bacterium, fungus, parasite), or by epidemiology (e.g., time of year, geographic location, vector).
- Viral: Of infectious etiologies, viral are most common, and include all herpesviruses [mostly HSV-1, HSV-2, and varicella-zoster virus (VZV)], enteroviruses (especially poliovirus), most arboviruses (WEE, EEE, WNV, St. Louis encephalitis virus, California encephalitis virus/La Crosse encephalitis virus, Powassan virus, Japanese encephalitis virus, yellow fever virus, tick-borne encephalitis virus), and a few notable others, including HIV, JC virus, EBV, measles, mumps, influenza, adenovirus, and rabies.
- Bacterial: Common bacterial etiologies of isolated encephalitis include *Borrelia burgdorferi* (agent of Lyme disease), *Treponema pallidum* (agent of syphilis), *Mycobacterium tuberculosis*, *Mycoplasma*, *Rickettsiae*, *Coxiella*, and *Anaplasma*.
- Fungal: Common fungal causes of isolated encephalitis include: *Coccidioides*, *Histoplasma*, *Cryptococcus* and *Aspergillus*.
- Parasitic: Common parasitic causes of encephalitis include: Several of the free-living amebae (*Naegleria*, *Balamuthia*, *Acanthameba* and *Sappinia*), *Toxoplasma gondii*, agents of microsporidiosis (e.g., *Encephalitozoon cuniculi*), *Plasmodium* spp. (agents of malaria), *Trypanosoma* spp. (agents of African trypanosomiasis in particular), and the common agents of eosinophilic meningitis and encephalitis (*Baylisascaris*, *Angiostrongylus*, and *Gnathostoma*).
- Other comments: Prions are also etiologic agents of encephalitis (vCJD, Kuru). New agents of encephalitis are continually being reported (e.g., lymphocytic choriomeningitis virus, *Sappinia diploidea*), as are newly appreciated encephalitic manifestations of well-known pathogens (e.g., hepatitis A, rotavirus).

COMMONLY ASSOCIATED CONDITIONS

Encephalitis can often be associated with meningitis, or can follow as a consequence of treated/resolved meningitis (ADEM). Encephalitis may be seen in conjunction with, or be confused for, focal suppurative infections (e.g., brain abscess, subdural/epidural empyema, etc.).

DIAGNOSIS

HISTORY

Patients with acute encephalitis usually present with fever, headache, and altered mental status. Fever and headache in particular help to differentiate between encephalitis and encephalopathy. Epidemiologic aspects of the history are essential in narrowing the broad differential of acute encephalitis.

PHYSICAL EXAM

As above, fever may be present, along with depressed or fluctuating mental status, or focal neurologic deficits. Seizures are not uncommon. Some infectious etiologies of encephalitis present with a rash, either concurrent with the encephalitis, or offset by a characteristic time.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Initial evaluation of encephalitis should include peripheral blood CBC with differential, complete blood chemistries with liver function tests.

Imaging

Initial approach

Magnetic resonance imaging (MRI) is the most helpful modality, as it can help distinguish between isolated white- or gray-matter processes, focal suppurative infection and other processes. If MRI is not possible, brain CT with contrast may be helpful.

Diagnostic Procedures/Other

Lumbar puncture is essential in classifying a process as meningitic, encephalitic, or post-infectious. In addition, CSF can be subjected to numerous tests that allow for confirmation of etiologies of encephalitis. The standard evaluation of CSF should include cell count with differential, total protein, and glucose concentration, Gram stain and general bacterial culture, and other stains and cultures as appropriate (e.g., fungal stain and culture, AFB smear and mycobacterial culture). In addition, CSF may be sent for specific confirmation of particular pathogens such as *T. pallidum* (VDRL); *Cryptococcus* and *Aspergillus* (antigen tests); and the human herpesviruses, JC virus, HIV, WNV, enterovirus, adenovirus, *B. burgdorferi*, *M. tuberculosis*, *T. gondii* and *Aspergillus* spp. (PCR testing available in many places). Where PCR testing is not available, paired (acute and convalescent) serologies or antibody titers in the CSF may be helpful in making the diagnosis. In cases where a diagnosis is required, brain biopsy is the gold standard diagnostic test, though this is done very rarely.

Pathological Findings
The most common specimen analyzed is the CSF. The characteristic finding of encephalitis is a pleocytosis in the CSF. For viral etiologies, this is usually lymphocytic in nature, though early in viral processes it may be neutrophil predominant. HSV has been reported to have a characteristic hemorrhagic component (RBCs seen in the CSF), though this may be present in any encephalitis with a necrotizing component. A marked neutrophilic pleocytosis, particularly in the setting of hypoglycorrhachia (low CSF glucose) is indicative of a bacterial process, as is the case with bacterial meningitis. Hypoglycorrhachia with a lymphocytic pleocytosis is often indicative of a fungal process.

DIFFERENTIAL DIAGNOSIS
Differential considerations along with encephalitis include meningitis (both infectious and non-infectious), encephalopathy (global dysfunction without associated inflammatory process), and focal suppurative infections (e.g., brain abscess, empyema, etc.).

TREATMENT

MEDICATION
First Line
- Empiric treatment of possible infectious encephalitis (in the setting of possible meningitis): vancomycin 1 g IV q12h, ceftriaxone 2 g IV q12h, ampicillin 2 g IV q6h, acyclovir 10 mg/kg IV q8h.
- HSV or VZV encephalitis: acyclovir 10 mg/kg IV q8h.
- Cytomegalovirus encephalitis: Ganciclovir 5 mg/kg IV q12h.
- *B. burgdorferi* (Lyme disease): ceftriaxone 2 g IV q24h (preferred) or penicillin 5 MU IV q6h (preferred) or doxycycline 100 mg PO TID (alternative).
- *M. tuberculosis* (empiric treatment in the absence of susceptibility data): isoniazid 300 mg PO q24h, rifampin 600 mg PO q24h, pyrazinamide 25 mg/kg PO q24h (max 2 g daily), ethambutol 15 mg/kg PO q24h (max 1.6 g daily).
- *Leptospira* spp.: Penicillin 1.5 MU IV q6h (severe disease) or ceftriaxone 1 g IV q24h (severe disease) or doxycycline 100 mg PO q12h (mild disease).
- *T. gondii*: Pyrimethamine (200 mg PO loading dose x1, then 75 mg PO daily) given with either sulfadiazine 1.5 g PO q6h (preferred) or clindamycin 600 mg PO q6h (alternative).
- *Rickettsia rickettsii* (agent of Rocky mountain spotted fever): Doxycycline 100 mg PO q12h.
- Allergies to first line agents should trigger consultation with an infectious diseases expert.

ADDITIONAL TREATMENT
General Measures
Hospitalization and close clinical monitoring are warranted, as patients with encephalitis can be clinically tenuous, and can become critically ill quickly.

Issues for Referral
Infectious diseases consultation is appropriate for assistance in evaluation of possible infectious etiologies and further optimization of evaluation and diagnostic tests.

Additional Therapies
- Anti-epileptics (for seizure management)
- Measures for management of elevated intracranial pressure (ICP) (e.g., controlled hyperventilation, osmotic diuresis, sedation/neuromuscular blockade).

COMPLEMENTARY AND ALTERNATIVE THERAPIES
None have been studied in randomized, controlled trials in the setting of acute encephalitis.

SURGERY/OTHER PROCEDURES
Neurosurgical intervention may be required if brain biopsy is desired. Occasionally, elevated ICP may complicate encephalitis, and neurosurgical placement of an external ventricular drain, or other decompressive strategy such as craniotomy, may be required. As most infectious encephalitides are diffuse processes, there is usually little role for surgical debridement.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Supportive care is dictated by the clinical status of the patient. Some may require only close clinical monitoring on a medical floor. Others may be obtunded and require intubation for airway protection. As mentioned above (see Surgery/Other Procedures), some may develop increased ICP and may require intensive care level monitoring and treatment. Some may require pressor support for dysautonomia that can accompany severe encephalitis. Still others may develop seizures and require intensive care monitoring and control of their seizure activity with anti-epileptic medication.

Admission Criteria
The inclusion of encephalitis on the differential diagnosis is sufficient to warrant admission to the hospital.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Some causes of encephalitis are reportable to authorities, depending upon local statutes (e.g., arboviruses, HIV, rabies, syphilis, etc.).

PROGNOSIS
The mortality rate associated with encephalitis in the USA has been reported at 5.1/100,000. The rate is higher in men, African-Americans, and those of extremes of age (<1 year or >65 years). The rate is much higher for the immunocompromised, and patients with HIV have over a thousand-fold increase in rate of death due to encephalitis compared to their non-HIV infected counterparts. By etiology, the highest cause of death was encephalitis of unknown etiology (approximately 86% of all encephalitis deaths), whereas the highest cause of known etiology was due to HSV (approximately 10%).

COMPLICATIONS
- Seizure
- Elevated ICP (and its sequelae)
- Permanent neurologic deficit
- Death

ADDITIONAL READING

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- Granerod J, Tam CC, Crowcroft NS, et al. Challenge of the unknown: A systematic review of acute Encephalitis in non-outbreak situations. *Neurol* 2010;75:924–932.
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See Also (Topic, Algorithm, Electronic Media Element)
Meningitis

CODES

ICD9
- 049.9 Unspecified non-arthropod-borne viral diseases of central nervous system
- 323.62 Other post-infectious encephalitis and encephalomyelitis
- 323.9 Unspecified causes of encephalitis, myelitis, and encephalomyelitis

CLINICAL PEARLS
- The distinction between an active infectious process (encephalitis, meningitis) versus a non-infectious process (post-infectious encephalitis, encephalopathy) must be made quickly.
- Empirical antimicrobial therapy should be started immediately.
- Diagnostic maneuvers (MRI, LP) should be undertaken as soon as is clinically feasible.

ENCEPHALOPATHY, HEPATIC

G. Bryan Young, MD

BASICS

DESCRIPTION

Hepatic encephalopathy is classified into acute and chronic varieties according to its associated liver abnormality. Acute hepatic failure is characterized by an encephalopathy and coagulopathy within 6 months of the onset of liver disease. A subcategory is fulminant hepatic failure that develops within 8 weeks of the onset of the hepatic dysfunction. Chronic liver disease evolves over a longer time and is associated with a fluctuating course of cerebral dysfunction, although some patients accumulate progressive motor and cognitive deficits.

EPIDEMIOLOGY

- Incidence
  - Acute hepatic failure affects >2,000 Americans per year. All are encephalopathic, and the mortality is about 80%.
  - Conservatively, 1 in 3,000 of the American population is susceptible to chronic hepatic encephalopathy, based on the prevalence of cirrhosis.
- Age
  - The age range is wide, but most cases with chronic hepatic encephalopathy are middle-aged adults.

RISK FACTORS

- The risk for chronic hepatic encephalopathy is increased after portal-systemic shunting procedures are used to treat portal hypertension, especially bleeding esophageal varices, including transjugular intrahepatic portal-systemic shunting.

Pregnancy Considerations

- Acute fatty liver of pregnancy occurs late in pregnancy. It is associated with jaundice and a small liver. Often, the fetus is male with a deficiency of long-chain 3-hydroxyacyl-COH dehydrogenase.

ETIOLOGY

- Many cases of acute liver failure are due to acute viral hepatitis or drug-induced liver injury (especially acetaminophen overdose). Less common causes include ischemia of the liver and toxins (e.g., mushroom poisoning or Wilson's disease).
- Chronic liver disease has a more varied association with encephalopathy, and the incidence is not well defined. Most cases are related to alcoholic cirrhosis. GI bleeding is a common precipitant of the encephalopathy in such patients, as this presents an increased load of nitrogen to the hepatic and then systemic circulation. Electrolyte disturbances, drugs (especially sedative drugs), infection, and surgery are other precipitants.
- The specific cause of the brain dysfunction is not known, but exposure of the brain, via the systemic circulation, to nitrogenous substances (including ammonia and increased aromatic amino acids, which can act as false neurotransmitters) is a probable cause. Increased γ-aminobutyric acid, manganese, and opioids in the brain are also proposed to cause brain dysfunction. The cerebral edema that often accompanies acute hepatic encephalopathy is related to osmotic-induced astrocytic swelling (probably related to ammonia), as well as brain hyperemia.

COMMONLY ASSOCIATED CONDITIONS

- Hypoglycemia, hyponatremia, pulmonary infections, and sepsis, coagulopathy (with bleeding complications, including subdural hematoma) are common accompaniments.
- *Hepatorenal syndrome* occurs in some patients with cirrhosis and patients with acute liver failure, and it consists of worsening azotemia with sodium retention, oliguria, and hypotension. It is probably related to altered renal hemodynamics.
  - *Hepatopulmonary syndrome* comprises hypoxemia-related right-to-left intrapulmonary shunts associated with increased endothelin-1 and pulmonary nitric oxide.
- *Acquired (non-Wilsonian) hepatocerebral degeneration* associated with cognitive changes, extrapyramidal findings, ataxia, and myelopathy with widespread CNS damage may complicate protracted or repeated bouts of portal-systemic encephalopathy.

DIAGNOSIS

- Patients usually have stigmata of liver disease. In acute hepatic failure, jaundice, hyperventilation with respiratory alkalosis, and bruising from the associated coagulopathy are common. Patients with chronic, portal-caval anastomotic liver disease may not be jaundiced when they have exacerbations of liver dysfunction and encephalopathy. However, they usually have other signs, e.g., evidence of portal hypertension (such as ascites and splenomegaly), spider nevi, gynecomastia in adult males, and parotid gland enlargement.
- Acute hepatic failure is characterized by an initial delirium, often with delusions and hyperkinesis. Chronic hepatic encephalopathy shows greater fluctuation, with relapses and remissions over a long time, although acute decompensation is also possible. Even at their best, patients with chronic portal-caval shunting show decreased psychomotor speed and deficits in visual perception, orientation, and constructive ability. Disorders of attention underlie these deficits. Some patients develop extrapyramidal movement disorders, including chorea or athetosis. Asterixis or flapping tremor is a transient loss of tone of muscles, causing the part of the body that is sustained against gravity to slump. This can include the outstretched arms and wrists, the head or the neck, or the whole body while standing upright.
- There are four stages of hepatic encephalopathy (Table 1).

Table 1 Stages of Hepatic Encephalopathy

Stage	Mental status	Asterixis
I	Euphoria or depression, mild confusion, slurred speech, disturbed sleep	+/–
II	Lethargy, confusion	+
III	Stupor: Sleeps but rousable, confused and incoherent	+
IV	Coma	–

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- EEG shows typical triphasic waves in adult patients who are moderately encephalopathic, succeeded by diffuse delta (frequencies ≤4 Hz) and suppression in coma.
- No diagnostic liver abnormalities found on commonly available biochemical testing, but elevated serum ammonia is highly suggestive.
- Respiratory alkalosis is characteristic; with advanced hepatic failure, lactic acidosis supervenes.
- Elevated glutamine in the CSF is characteristic, but lumbar puncture is often contraindicated.

Imaging

- CT scanning is helpful in gauging the degree of cerebral edema (cortical sulci less visible, increased visibility of white matter, and basal cisterns obliterated) in acute hepatic encephalopathy. With chronic hepatic encephalopathy, there is an increased T1 signal in the basal ganglia and substantia nigra, probably related to manganese deposition.

Diagnostic Procedures/Other

- In young patients, Wilson's disease is worth excluding. The diagnosis is made by finding any of the following combinations:
  - Serum ceruloplasmin <20 mg/dL and Kayser–Fleischer rings.
  - Serum ceruloplasmin <20 mg/dL and a copper concentration >250 μg/g dry weight on a liver biopsy sample.
  - Compatible clinical picture and urinary excretion <100 μg copper/day in the urine.

DIFFERENTIAL DIAGNOSIS

- Intoxications with alcohol and drugs
- Infections, e.g., sepsis, meningitis
- Subdural hematomas, especially if bilateral, may be associated with fluctuating level of consciousness without strong lateralized features.
- Alcohol withdrawal syndromes
- Other metabolic disorders, including hypoglycemia

TREATMENT

MEDICATION

- *Induction therapy:* Acutely, lactulose syrup 30–60 mL is given every hour until diarrhea occurs. (Although some question the usefulness of lactulose, decreasing the protein in the gut is advisable.) Neomycin 0.5–1.0 g every 6 hours is given orally.
- *Maintenance therapy:* Chronic encephalopathy, especially in patients with portal-systemic shunting, can be controlled by regular oral administration of lactulose and reducing dietary protein.
- Contraindications
  - Avoid sedating drugs, especially benzodiazepines and barbiturates, and any measure that produces a systemic alkalosis, which increases ammonia production from ammonium ion.
- Precautions
  - Avoid hypocalcemia, which increases ammonia production. Vigorous paracentesis may produce electrolyte imbalance and precipitate or aggravate encephalopathy. Prevention of constipation is important. Any patient who is to undergo surgery should be monitored closely and the anesthesiologist informed well in advance of the surgery.
- Alternative drugs
  - Alternative antibiotics such as metronidazole may be worthwhile.

ADDITIONAL TREATMENT

General Measures

- Decrease ammonia production in the gut. Evacuate the bowel with laxatives and lactulose (also helps to convert ammonia to ammonium, which is less well absorbed) and enemas. Use neomycin to kill colonic bacteria.
- Give 20% glucose IV to prevent and correct for hypoglycemia.
- Restrict dietary protein and give carbohydrate supplements to exceed 1,600 calories/day.
- Check for and correct coagulopathy.
- Survey for and treat infections.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Patients with impaired consciousness should be cared for in an intensive care setting with the usual supportive measures.
  - Mannitol or hypertonic saline has limited effectiveness in controlling cerebral edema in acute hepatic failure.
  - Consider mild hypothermia as a means of preventing brain hyperemia and increased intracranial pressure in acute or hyperacute liver failure. The combination of hyperosmolar therapy and hypothermia may be more effective than either separately.
  - Patients with bleeding complications may require transfusions of platelets or fresh frozen plasma.
- Adjunctive treatments
  - Branched-chain amino acid infusions, flumazenil (a benzodiazepine receptor blocker), hemoperfusion, and extracorporeal liver-assist techniques are unproven, but the latter two occasionally can "bridge" the patient who is to undergo liver transplantation.

SURGERY/OTHER PROCEDURES

- Liver transplantation is appropriate for certain patients with acute hepatic failure. The King's College criteria are still commonly used (Table 2). Surgery should be done promptly, before the patient develops severe cerebral edema.

Table 2 Criteria for Consideration of Liver Transplantation in Acute Liver Failure

Acetaminophen toxicity	pH <7.3 (regardless of coma grade) or prothrombin time >100 seconds and serum creatinine >3.4 mg/dL (300 μmol/L) in patients with grade III or IV encephalopathy
All other causes	Prothrombin time >100 seconds (regardless of coma grade) and any three of the following:
	Age <10 years or >40 years
	Liver failure caused by non-A, non-B hepatitis, halothane-induced hepatitis, or idiosyncratic drug reactions
	Duration of jaundice before the onset of encephalopathy >7 days
	Prothrombin time >50 seconds
	Serum bilirubin >17.5-mg/dL (300 μmol/L)

From O'Grady JG, Gimson AES, O'Brien CJ, et al. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology 1988;94:1186, with permission.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Patients with impaired consciousness require hospital admission, as do patients with acute hepatic failure or disease, in anticipation of encephalopathy. Patients with upper GI bleeding require emergency therapy for the bleeding and careful monitoring for encephalopathy.
- Discharging patients is an individual matter, with due consideration to medical status and support measures being in place.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Acutely, patients need to be checked at least daily for clinical level of consciousness. Serial or continuous EEG monitoring offers a sensitive and objective assessment. The Mini-Mental State Examination is commonly used to track attention and concentration, but the Confusion Assessment Method and the Delirium Symptom Interview are alternatives. After discharge, follow-up with a family physician helps to ensure compliance with the treatment regimen.

PATIENT EDUCATION

- Regular follow-ups, checks for compliance with diet, prompt recognition and treatment of GI bleeding and infections, and care with medications are important measures.

PROGNOSIS

- Mortality and morbidity are high in patients with all types of hepatic coma. Survivors may be left with neurologic impairment. Severity of encephalopathy, small liver size and epileptiform activity on EEG are unfavorable prognostic features.

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See Also (Topic, Algorithm, Electronic Media Element)

- Portal-systemic encephalopathy
- Hepatic coma

CODES

ICD9

- 570 Acute and subacute necrosis of liver
- 572.2 Hepatic encephalopathy
- 572.8 Other sequelae of chronic liver disease

CLINICAL PEARLS

- Hepatic encephalopathy may develop in acute and chronic liver failure caused by many different etiologies.
- Management involves protein restriction, medications to decrease ammonia production, correction of coagulopathies, avoidance of sedatives and detection, and treatment of infections.
- Acute liver failure and hyperacute liver failure are often associated with cerebral edema and increased intracranial pressure. Hypothermia and hyperosmolar therapy should be considered in these patients. Extreme suppression of EEG and clinical features can be reversible.

ENCEPHALOPATHY, HYPERTENSIVE

G. Bryan Young, MD

BASICS

DESCRIPTION

Hypertensive encephalopathy (HE) is a complication of malignant or accelerated hypertension and consists of focal and generalized central neurologic features. It is a medical emergency.

EPIDEMIOLOGY

- Incidence
  - HE is uncommon, but the exact incidence is unknown. Its incidence has lessened since effective antihypertensive therapy has been more available and more widely utilized.
- Age
  - HE can occur at any age, even young children. Manifestations are similar for different ages.
- Race
  - Given that hypertension is more prevalent in patients of African origin, HE is likely more common in this population. The racial difference is likely increased where there are discrepancies in medical care.

RISK FACTORS

Renal artery stenosis, renal failure, coarctation of the aorta, pregnancy (especially with a previous history of toxemia)

Pregnancy Considerations

Eclampsia is HE in the context of pregnancy-induced hypertension. Its manifestations are identical to those of HE. Hemolysis, elevated liver enzymes, and low platelets syndrome may occur as a complex associated with eclampsia. Intracerebral hemorrhages, often in the posterior cerebrum and commonly fatal, are frequent complications of hemolysis, elevated liver enzymes, and low platelets syndrome.

ETIOLOGY

- HE mainly occurs in the context of sudden elevations in BP. This is common in acute or chronic renal failure, especially with volume overload or with the use of erythropoietin. The sudden withdrawal of some antihypertensives, especially clonidine, a centrally acting α-agonist, may precipitate HE. Other causes include the ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors, sudden BP elevation in patients with pheochromocytoma, and lower GI or urinary tract stimulation in patients with paraplegia (autonomic hyperreflexia).
- In HE, the normal autoregulation of blood flow through capillaries is overwhelmed, allowing for engorgement of the capillary beds by high-pressure blood flow. This leads to vasogenic edema, fibrinoid necrosis of the walls of small vessels, and focal or multifocal ischemia, possibly due to vasospasm or occlusion of vascular beds by increased interstitial pressure.

COMMONLY ASSOCIATED CONDITIONS

HE occurs most commonly in patients with chronic renal failure, pregnancy (toxemia or eclampsia), and immunosuppression or interferon therapy.

DIAGNOSIS

- Clinical features include headache, visual disturbance (especially field defects, blurred vision, and cortical blindness), confusion, focal neurologic signs, and focal, multifocal, or generalized seizures.
- Hypertensive changes are found in the fundi, including papilledema. Papilledema is not always present and is commonly absent in the reversible posterior leukoencephalopathy syndrome.
- Many patients show end-organ damage, including renal dysfunction with proteinuria and cardiac left ventricular hypertrophy and strain if the hypertension has been present for a prolonged period of time.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- MRI studies commonly show occipital–parietal lobe edema bilaterally that classically involves the white matter. However, the adjacent cortex may also be involved in the reversible posterior leukoencephalopathy or occipitoparietal encephalopathy syndrome (PRES).
- Altered blood–brain barrier permeability can be demonstrated using gadolinium (or equivalent large molecule markers with other scanning modalities, such as CT) scans.
- Imaging is helpful in excluding some of the conditions mentioned in the Differential Diagnosis.

DIFFERENTIAL DIAGNOSIS

- Occipital blindness and seizures occur as complications of cancer chemotherapy, transplantation, transfusion, or HIV-1 infection.
- Focal deficits in patients with hypertension require the exclusion of intracerebral hemorrhage or infarction.
- Occipital blindness, in particular, requires the exclusion of infarction in the posterior cerebral artery distribution.
- HE may mimic amphetamine or cocaine overdose, encephalitis, or cortical venous thrombosis.
- Thrombotic thrombocytopenic purpura can occasionally present with hypertension, renal impairment, and neurological findings, including cortical blindness. The diagnosis is easily made with examination of the blood smear, the hematologic profile and elevated lactic acid dehydrogenase from hemolysis.

TREATMENT

MEDICATION

- Induction therapy
  - BP is lowered effectively by sodium nitroprusside 0.25–8.0 μg/kg/minute IV, although other rapidly acting, IV-administered antihypertensives, such as labetalol, may be helpful.
  - Eclampsia is best treated with magnesium sulfate 4–5 g IV, followed by an infusion of 1 g/hour for 24 hours. Alternatively, 10 g is given IM, followed by 5 g IM every 4 hours for 24 hours. Patients should be monitored for magnesium toxicity by checking for loss of deep tendon reflexes and with serum magnesium concentration determination.
- Maintenance therapy
  - There are six classes of maintenance antihypertensive therapy: Diuretics, antiadrenergic drugs, vasodilators, calcium channel blockers, ACE inhibitors, and angiotensin receptor antagonists. The appropriate class and the specific drug should be selected based on the underlying cause of the hypertension, severity of the hypertension, age of the patient, use of other medications, and goals of therapy. Guidelines were developed by the World Health Association in 1999.
- Contraindications
  - Labetalol should not be used in patients with heart failure, asthma, bradycardia, or heart block. Avoid diazoxide in patients with aortic dissection or myocardial infarction (cardiac stroke volume may increase with diazoxide).
- Precautions
  - Care should be taken that the DBP does not fall below 95 mm Hg during the acute treatment phase, because this may compromise cerebral or myocardial perfusion.
- Alternative drugs
  - Diazoxide 50–100 mg can be given as an IV bolus. The same dose can be repeated in 5–10 minutes, up to 600-mg total daily dose.

ADDITIONAL TREATMENT

General Measures

- With the clinical picture and exclusion of other processes (mainly by imaging), it should be possible to make a definitive diagnosis of HE. The main therapy is to lower the BP and to stop the ongoing process. Close observation in an intensive care environment, with monitoring of BP, neurologic status, renal output, and airway protection, is indicated.
- The cause of the hypertensive crisis should be sought and removed or treated directly, if possible.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Acute epileptic seizures should be treated. If coma is protracted, continuous EEG monitoring is helpful in detecting and treating nonconvulsive seizures. Antiepileptic drug therapy for ongoing seizures usually begins with lorazepam or diazepam, followed by IV phenytoin (PHT) or fosphenytoin (15–20 mg/kg IV of PHT or PHT equivalents). For refractory cases, endotracheal intubation, assisted ventilation, and anesthesia with midazolam, propofol, isoflurane, or pentobarbital may be necessary.
- Adjunctive treatments
  - ACE inhibitors are slow in action but appear to have a beneficial effect in blocking vascular permeability in the brain, related to angiotensin II. Furosemide helps to maintain sodium diuresis in the face of declining BP. In renal failure, extra fluid can be removed using hemodialysis or peritoneal dialysis.

SURGERY/OTHER PROCEDURES

In severe, recurrent, refractory hypertension, bilateral nephrectomy is sometimes performed. This is a last resort measure because all renal functions (including renal erythropoietin production and vitamin D metabolic activity) will be lost, unless a transplant is performed.

IN-PATIENT CONSIDERATIONS

Admission Criteria

All patients with malignant hypertension and HE should be admitted and preferably managed in an ICU setting. Discharge can be considered when BP is controlled and renal function is stable in the absence of significant permanent neurologic sequelae.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients require regular follow-up for BP checks and neurologic review.

PATIENT EDUCATION

The importance of regular medical checkups and compliance with medications should be stressed. Weekly BP monitoring in the home by the patient, cohabitant, or visiting nurse is ideal.

PROGNOSIS

Neurologic prognosis usually is excellent. Most patients recover without neurologic deficits, but small infarcts may produce some focal signs and symptoms (uncommon in younger individuals). Most with acute symptomatic seizures do not require long-term antiepileptic drug therapy. Rarely, patients with HE/PRES develop intracerebral hemorrhages, sometimes fatal, in the region of abnormalities in earlier CT or MRI scans.

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See Also (Topic, Algorithm, Electronic Media Element)

- Reversible posterior leukoencephalopathy
- Occipitoparietal encephalopathy syndrome

CODES

ICD9

- 401.0 Malignant essential hypertension
- 437.2 Hypertensive encephalopathy

CLINICAL PEARLS

- HE may occur as a complication of accelerated or malignant hypertension due to a number of causes.
- Aggressive management of hypertension and complications such as seizures in an ICU setting is required.
- Consistent patient education and compliance with treatment of BP is mandatory for the prevention of recurrence.

ENCEPHALOPATHY, HYPOXEMIC

Aarti Sarwal, MD

BASICS

DESCRIPTION

Hypoxic-ischemic encephalopathy (HIE) or post-resuscitation encephalopathy occurs in the setting of cardiopulmonary arrest.

EPIDEMIOLOGY

Incidence

- In the usa, 375,000 to 750,000 patients undergo attempted resuscitation each year.
- With 40% of these patients attaining return of spontaneous circulation, almost 100,000 to 200,000 cases present to icus annually with brain injury after cardiac arrest.

RISK FACTORS

- Cardiac arrhythmias account for around 50% of cases of cardiac arrest. The remainder is associated with acute respiratory failure or hypotension.
- In general, the outcome of HIE worsens with the duration of coma. If the duration of coma exceeds 6 hours, the proportion of patients who will regain independence during the first year after HIE drops is 10%.

PATHOPHYSIOLOGY

- With cessation of circulation and respiration, a surge of energy-depleting biochemical events occurs that culminates in neuronal cell death. These events are called the ischemic cascade and are mediated by glutamate excitotoxicity, calcium influx and adenosine triphosphate (ATP) depletion.
- Primary brain injury is caused by ischemia but secondary brain injury continues for hours to days due to reperfusion and the ischemic cascade.

DIAGNOSIS

HISTORY AND PHYSICAL EXAM

- The history of a cardiac or respiratory arrest is usually clear.
- Clinical examination is the key element.
- The neurologic examination is directed primarily toward assessment of:
  - level of responsiveness,
  - pupillary responses,
  - corneal responses,
  - oculocephalic responses (doll's eyes, cold calorics),
  - respiratory pattern,
  - patterns of motor response (hemiplegic, decorticate, or decerebrate posturing, flaccid).
- Altered mental status is ranging from amnesic confused state to comatose.
- Brainstem reflexes are often abnormal.
- Involuntary movements including myoclonus or generalized tonic-clonic seizures can occur.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- There are no specific laboratory findings in HIE.

Imaging

- CT scan is usually normal in first few days unless significant cerebral edema develops.
- MRI brain may show widespread diffusion or fluid-attenuated inversion recovery abnormalities in the cortex, thalamus, and cerebellum that portends poor outcome.

Diagnostic Procedures/Other

- Median N20 somatosensory evoked potentials. Bilateral loss of cortical peaks (N20 peaks) is consistent with poor outcomes.
- EEG may predict prognosis when done at 24 hours after arrest. Patterns on EEG, such as burst suppression, a very low-voltage pattern, alpha coma, or electrocerebral inactivity, all have a poor prognosis. EEG may be useful earlier if there is clinically evidence seizure activity.

Pathological Findings

- On autopsy, there are ischemic neurons, loss of neurons, and occasionally generalized edema. The most affected cell populations include cerebellar Purkinje cells, hippocampal cells, and certain cortical neuronal populations (layers 3 and 5).

DIFFERENTIAL DIAGNOSIS

- Diagnosis usually is obvious and is based on the clinical scenario. Differential includes other metabolic and structural encephalopathies such as sepsis, multifocal embolism, and medication effects.
- "Man-in-the-barrel" syndrome caused by bilateral anterior cerebral artery (ACA)–middle cerebral artery (MCA) watershed region

TREATMENT

MEDICATION

First Line

- There is good evidence (1)[A] to recommend the use of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest caused by ventricular fibrillation.
- Hypothermia should be initiated as soon as possible and should be maintained for 12–24 hours with gradual rewarming
- Despite multiple studies of various clinical agents, no specific medications have been shown to be useful in improving the outcome after HIE.
- Hemodynamic stability and maintenance of adequate oxygenation are the corner stone of therapy who are not the agents for hypothermia.

Second Line

- Seizures should be treated with benzodiazepines and antiepileptic drugs.
- Myoclonus may respond to sedation with benzodiazepines. Some antiepileptic drugs may be useful in control of intractable myoclonus.
- Cerebral edema
  - There is no good evidence to suggest the routine use of intracranial pressure (ICP) monitoring in the management of patients after cardiac arrest.
    - Avoid the use of dextrose-containing solutions to attenuate cerebral swelling.

General Measures

- Maintain normoglycemia.
- If the patient is not a candidate for hypothermic treatment, then normothermia should be aggressively maintained.
- Maintenance of normal range electrolytes
- Prevention of recurrent cardiac arrhythmia
- Early nutritional support and fluids
- Reduce the risk of nosocomial infections.
- Prevent venous thromboembolism.
- Avoiding stress peptic ulceration.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Neuroprotective agents and strategies have been explored to prevent secondary brain injury but have failed to improve clinical outcomes.

SURGERY/OTHER PROCEDURES
There is no role of invasive ICP monitoring.

IN-PATIENT CONSIDERATIONS
- Most patients with a cardiac arrest or other cause of acute hypoxemic encephalopathy will require admission to the hospital.
- Discharge depends on the extent of injury and speed of recovery. Patients with significant HIE may require inpatient rehabilitation to achieve an optimal functional status. Some may require long-term skilled nursing care.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Patients with significant HIE should be followed for signs of late deterioration. Usual follow-up is via the attending service or cardiology service.

PATIENT EDUCATION
- Close communication with the patient's family is key to caring for patients with HIE. Providing information about the patient's level of response, results of testing, and prognosis for recovery are key to allowing families to make important decisions regarding care.

PROGNOSIS
- Among those patients who achieve a return to spontaneous circulation, more than half die during the subsequent hospital course.
- Prognosis is influenced by factors such as age, co-morbidities, and circumstances of cardiac arrest.
- A few parameters have a strong predictive value in coma after cardiac arrest. The following predict a poor outcome in most cases.
  - absent pupillary light reflexes or corneal responses at 24 hours
  - absent motor responses at 3 days
  - absent somatosensory evoked potential N20 cortical peaks
    - presence of generalized myoclonus
    - burst suppression on EEG
    - diffuse MRI changes
- Note that with the advent of hypothermic treatment for HIE the prediction of prognosis has become less reliable as some patients may have delayed motor responses after this therapy. Caution is advised in predicting outcome after this therapy.

COMPLICATIONS
- Immediate
  - Post-resuscitation syndrome as a result of whole-body ischemia and reperfusion injury
  - It resembles the sepsis response.
  - Systemic inflammatory response (increase in cytokine levels), myocardial dysfunction, coagulopathy, and adrenal dysfunction
  - Status myoclonicus
  - Delayed
    - Amnestic syndrome
    - Cortical blindness
    - Action myoclonus or Lance–Adam Syndrome
    - "Man in a barrel" syndrome
    - Leukoencephalopathy
    - Parkinsonian syndrome
    - Persistent vegetative state
    - Cerebellar ataxia

REFERENCE

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Anoxia
- Anoxic brain damage
- Anoxic encephalopathy
- Anoxic ischemic encephalopathy
- Hypoxia

CODES

ICD9
348.1 Anoxic brain damage

CLINICAL PEARLS
- Hypothermic therapy should be induced in comatose survivors of out-of-hospital cardiac arrest caused by ventricular fibrillation.

ENCEPHALOPATHY, METABOLIC AND TOXIC

Deepti Anbarasan, MD
David S. Younger, MD

BASICS

DESCRIPTION

- Although metabolic encephalopathy generally connotes a syndrome of *global neurologic dysfunction,* such as confusion, lethargy, or coma, as a result of *disruption of a biochemical process or introduction of a toxin, some affected patients* exhibit focal neurologic deficits due to exacerbation of a previous underlying lesion (e.g. glucose dysregulation causes worsening hemiparesis in a patient with previous recovery from stroke). A variety of disorders can culminate in encephalopathy, and the key to effective therapy is *diagnosis of the underlying cause*. There may be single or multiple metabolic derangements. When multifactorial, the resulting encephalopathy is often greater than would be predicted from the sum of individual insults. Patients with preexisting neurologic disease may have a heightened susceptibility to toxic and metabolic derangements as for example those with renal dysfunction, hepatic dysfunction, and sepsis, reviewed elsewhere.
- The underlying medical problem may not be entirely obvious as for example, patients who are critically ill on mechanical ventilation in whom timely recognition and treatment may be essential to prevent irreversible secondary injury.

EPIDEMIOLOGY

The precise frequency of metabolic encephalopathy is not known, but neurologists are commonly consulted in such cases. It occurs frequently in elderly populations, particularly in patients with multiple medical problems or polypharmacy.

RISK FACTORS

Various medications, advanced age, prior neurologic disease, dementia, various medical diseases

Pregnancy Considerations

Not a specific risk factor

ETIOLOGY

See Differential Diagnosis

COMMONLY ASSOCIATED CONDITIONS

See specific conditions

DIAGNOSIS

- Patients with encephalopathy will usually demonstrate *gradual progression* from their usual baseline along the way with discernible confusion, inattention, lethargy, stupor and finally coma if left untreated. They frequently exhibit delirium, agitation, hallucinations, increased motor activity, and sympathetic overactivity. Early in the course of toxic and metabolic encephalopathy, the patient may experience minor changes in personality, including mood elevation/depression, mood swings, and inappropriate affect. Minor disorientation, inattention, hallucination, and memory dysfunction may be overlooked in retrospect. Nevertheless, the ultimate level of alertness reflects the severity of the underlying disorder and the degree of encephalopathy.
- Motor dysfunction is common, including psychomotor retardation, hyperactivity, asterixis, myoclonus, gegenhalten (paratonic rigidity), and tremor. Decorticate and decerebrate posturing may be observed in severe cases.
- Extraocular eye movements usually are normal in patients with encephalopathy, but they may exhibit roving conjugate eye movements.
- The presence of pupillary light reflexes despite vestibulo-ocular reflex loss, decerebrate rigidity, or motor flaccidity suggests metabolic coma. The loss of pupillary reflexes implies a non-metabolic etiology of altered mental status (e.g. structural disease). Loss of brainstem reflexes can occur in severe metabolic encephalopathies but should suggest other disorders such as brainstem infarction.
- *Hypersympathetic function*, often observed in metabolic and toxic encephalopathies, may manifest as tachycardia, hypertension, fever, diaphoresis, hyperreflexia, and clonus.
- Abnormalities in breathing patterns are encountered with metabolic and toxic dysfunctions. These include, but are not limited to, apnea, sustained hyperventilation, and Cheyne–Stokes respiration (crescendo-decrescendo breathing with intervening periods of apnea).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- A comprehensive metabolic profile including liver function tests, serum electrolytes, osmolality, glucose, calcium, magnesium and ammonia levels should be obtained.
- Hematologic evaluation including CBC, platelets, differential, and peripheral smear are similarly important in assessing the disease state.
- Room air arterial blood gas determinations reflect the potentially changing acid/base status, as well as level of oxygenation and gas exchange of the lungs whether due to spontaneous breathing or assisted ventilation
- Prompt assessment of urine and serum toxicology, depending appropriate to the history of ethanol, drug abuse, or exposure to other toxins can establish the diagnosis with certainty and direct therapy.
- Cultures of blood, urine, sputum, CSF, and open wounds should be obtained.
- Thyroid-stimulating hormone and/or cortisol: Depending on degree of suspicion for endocrinopathy
- ECG: The clinician should look for baseline rhythm, as well as any signs of focality implying an ischemic event.
- Additional specific tests if ingestion is suspected. Check with local poison control.

Imaging

- Head CT is usually normal. If clinical examination shows focal signs not explained by previous historical details, then contrast may be needed to assess for focal lesions. Caution must be used with contrast, because it may worsen the underlying condition and metabolic encephalopathy.
- MRI often provides valuable information when the neurological examination reveals focal deficits or if there is a readily correctible cause of altered mental status. In toxic-metabolic encephalopathy, there may be a widespread, symmetric pattern of injury that often involves the deep gray nuclei and cerebral cortex. Characteristic features of certain etiologies of encephalopathy may aid in the identification of the correct diagnosis. For instance, cocaine encephalopathy is associated with MRI findings of increased T2 signal intensity and restricted diffusion in the globus pallidus, splenium, and cerebral white matter. Consultation with subspecialty texts is recommended for further descriptions of imaging findings in various causes of toxic-metabolic encephalopathy.

Diagnostic Procedures/Other

- Lumbar puncture: Include evaluation of glucose, protein, cell counts, lactic acid, and culture. The opening pressure should be noted to evaluate for increased intracranial pressures. Other specific tests should be performed as guided by the patient's history and examination (e.g., Lyme disease, syphilis). Before the patient undergoes a lumbar puncture, a head CT should be obtained to rule out possible sources for herniation, such as large focal mass lesions.

- EEG: Triphasic waves may be the earliest sign of an underlying metabolic encephalopathy but they are often transient; and when unilateral suggests an underlying focal cerebral injury. Although not typically epileptiform, there may be coincidental seizures, clinical or electrographic, which may be a clue to severe electrolyte disturbances. Nonconvulsive status epilepticus may be overlooked. It is always helpful to look for signs of generalized dysfunction as well as for categorization and prognostication. The degree of diffuse background slowing on EEG may be helpful to ascertain the severity of the encephalopathy. A burst suppression pattern on EEG indicates severe encephalopathy and may be associated with increased morbidity and mortality.
- Brainstem auditory evoked responses: Can assist the neurologist in localization of brainstem abnormalities.

DIFFERENTIAL DIAGNOSIS

- The following list reviews a variety of causes of metabolic and toxic encephalopathy. For the specifics of each of these disorders, consultation of subspecialty texts is recommended.
  - Glucose misregulation, e.g., hypoglycemia, nonketotic hyperosmolar state, hyperglycemia, diabetic ketoacidosis
  - Electrolytes/fluid imbalance, e.g., osmolarity/sodium dysregulation, pontine myelinolysis, calcium disorders, magnesium disorders, phosphate disorders
  - Endocrine dysfunction, e.g., cortisol abnormalities, thyroid dysfunction, adrenal dysfunction
  - Toxic exposures, e.g., iatrogenic, accidental, intoxication, environmental exposure, drug withdrawal
  - Pulmonary disease, e.g., pneumonia, pulmonary embolism
  - Nutritional deficiency, e.g., vitamin B_{12}, folate, niacin, thiamine (Wernicke's syndrome)
  - Psychiatric abnormalities, e.g., bipolar disorder, schizophrenia
  - Renal dysfunction
  - Sepsis/septic states, bacterial endocarditis
  - Hepatic dysfunction
  - Primary neurologic disease, e.g., non-convulsive seizures, tumor, traumatic brain injury, stroke, posterior reversible encephalopathy syndrome

TREATMENT

MEDICATION

Drugs to be used are dependent on the underlying condition.

ADDITIONAL TREATMENT

General Measures

- Once the underlying cause of the metabolic or toxic encephalopathy has been determined, the treatment should be directed toward it. Thus, the treatment will be variable depending on etiology. In general, avoid, if at all possible, sedating agents so as not to confound the clinical examination.
- If agitation prevents adequate medical or surgical care of the patient, short-acting sedative/anxiolytic agents, such as midazolam, propofol, or fentanyl, are more desirable than agents with prolonged effects. Haloperidol may be used in small doses for severe agitation.
- If the patient's mental status threatens adequate protection of the airway, intubation and mechanical ventilation should be used.
- In patients with a history of alcoholism, malnutrition, or renal failure on hemodialysis, treatment with thiamine should be considered.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - Specific treatments for septic, renal, and hepatic encephalopathies are discussed elsewhere. In patients with exposure to toxins, antidotes may be available (contact the local poison control center), or the patient may benefit from hemodialysis.
- Adjunctive Treatment
  - Depends on the underlying cause of encephalopathy

SURGERY/OTHER PROCEDURES

No specific surgical measures are needed.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Close monitoring of the neurologic examination is essential in patients with encephalopathy. As the patient becomes more lethargic, obtundation and airway protection may become a crucial consideration. Thus, if a patient is having a progressive decline in mental status, admission to a neurology or medicine critical care unit is highly recommended.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients often exhibit a hypersympathetic state; thus, monitoring of heart rate and BP should be done frequently. The nursing staff should be trained to perform a thorough neurologic evaluation if they are not commonly asked to make this evaluation.

PROGNOSIS

- Although metabolic encephalopathy is one of the most frequently encountered entities in patients who are critically ill, it is most often *not fatal*. Delirium has been demonstrated to be an independent predictor of higher mortality and morbidity in patients who are critically ill.
- If the underlying metabolic or toxic insult can be identified promptly and treated, the patient has *potential for complete recovery*. Persistent neuropsychiatric disturbances in cognitive domains of verbal fluency, psychomotor speed, visual and working memory, and visuoconstruction abilities may be noted in severe cases.
- The cause of death in patients who are critically ill and suffer from encephalopathy is often neurologic.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Acute confusional state
- Delirium
- Acute organic brain syndrome
- Acute brain disorder
- Clouded sensorium
- Septic syndrome
- Encephalopathy, Renal
- Encephalopathy, Hepatic
- Encephalopathy, Septic

CODES

ICD9

- 348.3 Encephalopathy, unspecified
- 349.82 Encephalopathy, toxic
- 349.82 Toxic encephalopathy

ENCEPHALOPATHY, PROGRESSIVE PEDIATRIC

David S. Younger, MD
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BASICS

DESCRIPTION

Progressive pediatric encephalopathy due to childhood degenerative disorders arises during the neonatal period through adolescence. 3 categories can be recognized, each with a diverse admixture of autosomal recessive (AR) dominant (AD), X-linked (XL), mitochondrial DNA (mtDNA), and sporadic (SP) inheritance patterns:

- *Storage disorders* in which large molecules are stored leading to slowly progressive multiorgan involvement and CNS decline, as manifested by lysosomal, leukodystrophy, and peroxisomal disorders
- *Disorders of cellular intoxication*, involving small disease molecules with precipitous toxic encephalopathy like onset, as manifested by amino and organic aciduria, and urea cycle disorders
- *Disorders of energy deficiency*, involving CNS, skeletal, cardiac muscles and liver, with slowly progressive or static encephalopathy and intermittent metabolic crises, as manifested by glycogen storage, fatty acid oxidation, and mitochondrial disorders

EPIDEMIOLOGY

Although each of the pediatric neurodegenerative disorders is exceedingly rare, the combined prevalence is estimated as 1:5,000

RISK FACTORS

- Genetic predisposition
- Infectious exposures and vaccination

ETIOLOGY

Neurodegenerative hereditary disorders of the neonate: Age <1 month

- Peroxisomal disorders[AR]
  - Dihydroxyacetone deficiency
  - Neonatal adrenoleukodystrophy (ALD)[XL]
  - Zellweger syndrome (ZS)
- Amino acid and organic acid disorders[AR]
  - Isovaleric acidemia
  - Maple syrup urine disease (MSUD)
  - Methylmalonic and propionic acidemia
  - Sulfite oxidase and molybdenum cofactor deficiency
- Urea cycle disorders[AR]
  - Arginosuccinaciduria
  - Arginosuccinate lyase deficiency
  - Ornithine transcarbamoylase deficiency
- Mitochondrial deficiency diseases[AR]
  - Carnitine palmitoyltransferase (CPT) II
  - Complex 1, III, IV (Cox)
  - Glutaricacidurua II deficiency
  - Pyruvate carboxylase deficiency
  - Pyruvate dehydrogenase (PDH) deficiency[XL]
  - Short- and long-chain acyl and hydroxyacyl CoA dehydrogenase deficiency
- Miscellaneous others[AR]
  - Glycogenosis II
  - Holocarboxylase synthetase deficiency
  - Menkes kinky hair syndrome[XL]
  - Smith–Lemni–Opitz syndrome[SP (DHCR7 gene)]

Neurodegenerative hereditary disorders of early infancy: Age 1 month to 1 year

- Lysosomal storage diseases[AR]
  - Farber's disease
  - Neuropathic Gaucher's disease type II
  - Glycogenosis type II
  - GM_1 gangliosidosis
  - Krabbe disease (KD)
  - Infantile neuronal ceroid lipofuscinosis (CLN)
  - Niemann–Pick disease type A (NPA)
  - Sialic acid storage disease
  - Tay–Sachs disease
- Leukodystrophies[AR]
  - Alexander disease
  - Canavan disease (CD)
  - Pelizaeus–Merzbacher disease (PMD)[XL]
  - Aicardi–Goutieres syndrome
- Mitochondrial diseases[AR]
  - CPT type I and II
  - Leigh's disease
  - Medium chain acyl-CoA dehydrogenase deficiency
- Amino and organic acid diseases[AR]
  - Glutaric aciduria type I
  - 3-Hydroxyisobutyric acidemia
  - 3-Methylglutaconicacidemia
  - Phenylketonuria (PKU)
- Miscellaneous others[AR]
  - Alpers' disease
  - Biotinidase deficiency
  - DeVivo (GLUT1) disease[SP (GLUT1 gene)]
  - Galactosemia
  - Glycogen storage disease type I
  - Lowe syndrome[XL]

Neurodegenerative hereditary disorders of late infancy: Age 1 to 3 years

- Lysosomal storage diseases[AR]
  - Fucosidosis
  - Gaucher disease type 3
  - KD
  - GM_1/GM_2 gangliosidosis
  - Mannosidosis
  - Metachromatic leukodystrophy (MLD)
  - Mucolipidosis IV
  - Mucopolysaccharidoses-Hurler syndrome
  - MPS II-Hurler syndrome[XL]
  - Multiple sulfatase deficiency
  - Neimann Pick disease type C (NPC)
  - Sialidosis, type II
- Disorders of DNA repair[AR]
  - Ataxia telangiectasia
  - Cockayne syndrome
- Miscellaneous others
  - Angelman syndrome[SP (UBE3A gene)]
  - Fragile-X syndrome[XL]
  - Leigh's syndrome[AR]

Neurodegenerative hereditary disorders of adolescence: Age >3 years

- Lysosomal disorders[AR]
  - Fabry disease[XL]
  - Neuropathic Gaucher's disease type III
  - KD
  - Late-onset GM_2 gangliosidosis
  - MLD
  - Juvenile NCL
  - MPS IS-Scheie syndrome
  - Sialidosis type I
- Mitochondrial encephalomyopathies[mt DNA]
  - Kearns–Sayre syndrome (KSS)
  - Myoclonic epilepsy with ragged red fibers (MERRFs)
  - Mitochondrial encephalomyopathy with lactic acidosis-stroke like episodes (MELAS)
  - Neuropathy—ataxia–retinitis pigmentosa–ptosis syndrome
  - Myoneurogastrointestinal encephalopathy (MNGIE)
- Manifesting movement disorders[AR]
  - Dystonia musculorum deformans
  - Hallevorden–Spatz disease (pantothenate kinase-associated neurodegeneration (PKAN)
  - Juvenile Huntington's disease (HD)[AD]
  - Juvenile Wilson's disease
  - Lesch–Nyhan syndrome[XL]
- Manifesting dermatologic disorders[AR]
  - ALD[XL]
  - Hartnup disease
  - Homocystinuria
  - Sjögren–Larsen syndrome
  - Tuberous sclerosis (TS)[AD]
- Manifesting cerebellar ataxia
  - Cerebrotendinous xanthomatosis (CTX)[SP (CYP27 gene)]
- Miscellaneous others[AR]
  - Lafora disease
  - Unverricht–Lundborg progressive familial myoclonal epilepsy (EPM1)

Acquired disorders

- Infectious
  - HIV-1 encephalopathy
  - Viral encephalitis
    - Herpes: Simplex, varicella zoster
    - Orthomyxovirus: Influenza
    - Picornavirus: Enterovirus
    - Rhabdovirus: Rabies
    - Paramyxovirus: Mumps, measles [subacute sclerosing panencephalitis (SSPE)]
    - Alphavirus: Eastern and Western equine
    - Spirochete: Lyme neuroborreliosis
- Systemic disturbances
  - Hepatic disorders
  - Renal disorders
  - Thyroid: Hashimoto encephalopathy
  - Cryptogenic: West syndrome/Lennox–Gastaut

COMMONLY ASSOCIATED CONDITIONS

- Megalencephaly: Alexander, Tay–Sachs, Canavan and, Sandhoff diseases
- Manifesting seizures
  - Early infancy: Alpers' disease, amino-, organic acidopathy, biotinidase deficiency, DeVivo, Menkes syndrome, mitochondrial deficiency, peroxisomal, urea cycle disorders
  - Late infancy/early childhood: Cockayne syndrome, Leigh's disease, lysosomal storage diseases, NCL
  - Childhood/adolescence: Gaucher II/III, fucosidosis, GM_2 gangliosidosis, Lafora disease, MELAS, MERRF, multiple sulfatase deficiency, NCL, Sanfilippo syndrome, sialidosis I, EPM1
- Manifesting eye abnormalities
  - Corneal: Fucosidosis, MPS I, mannosidosis, Maroteaux–Lamy syndrome, Morquio's disease, Wilson's disease
  - Pigmentary retinopathy: Bassen-Kornzweig syndrome, Cockayne syndrome, PKAN, KSS, CLN, ZS
  - Cherry red macula: GM1 gangliosidosis, NPA/B, Tay–Sachs disease, sialidosis type 1
  - Optic atrophy: ALD, CD, KD, MLD, PMD
  - Lens abnormalities: CTX, Fabry disease, galactosemia, homocystinura, Lowe syndrome
- Manifesting progressive ataxia
  - Late infantile GM1/GM2 gangliosidosis, juvenile sulfatide lipidosis, KD, NPC, CLN, PMD
- Manifesting spasticity
  - ALD, AMN
  - Arginase deficiency
  - CD Gaucher disease type III
  - Glutaric aciduria type I
  - GM1/GM2 gangliosidosis
  - PKAN
  - Menkes syndrome
  - MLD
  - NPC
  - PMD type III

DIAGNOSIS

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Diagnostic testing for affected children of all ages should be carefully planned recognizing that the highest yield will utilize specific clues from the history and physical examination.

- Blood:
  - Chemistries, ammonia (arginase deficiency) lactate, pyruvate (mitochondrial disease), carnitine and acyl carnitine (CPT), saturated very long chain fatty acids [ALD/adrenomyeloneuropathy (AMN)] (VLDFA), copper and ceruloplasmin (Wilson), lysosomal enzymes, amino acids (amino- and organic acid disorders)
  - Skin, sweat gland, myenteric plexus biopsy for granular osmophilic lysosomal bodies (NCL) by EM
- Urine for organic acids (organic aciduria)
- CSF lactate, pyruvate (KSS), viral serology (viral encephalitis)

Imaging

- Brain CT:
  - Calcification (Cockayne, TX, Aicardi–Goutieres syndrome)
- Brain MRI:
  - Cerebral atrophy (NCL), pallidal high signal (PKAN), white matter changes (KD)
- MR SPECT:
  - NAA peak in aspartoacylase deficiency (CD)
  - Lactate peak (mitochondrial disease)
- Karyotype analysis:
  - High-resolution chromosome banding (fragile X)
  - Fluorescent *in situ* hybridization (microdeletion syndromes)

Diagnostic Procedures/Other

- Abnormal EEG patterns
  - Hypsarrhythmia (West's syndrome)
  - Slow spike and wave (Lennox–Gastaut)
  - Periodic spike and slow wave (SSPE)
  - Reduced background activity (NCL)
- EMG and NCS
  - Demyelinating neuropathy (KD)
- Evoked potentials: Leukodystrophy, flash ERG (retinal pigmentary degeneration)
- Muscle biopsy: Ragged red fibers (mitochondrial)
- Genetic mutational analysis
- Neuropsychological testing

DIFFERENTIAL DIAGNOSIS

- Static encephalopathy
- Mental retardation
- Autism

TREATMENT

MEDICATION

General Measures

- Vitamin supplementation
  - B6 (homocystinuria), thiamine (PDH, MSUD), biotin (biotinidase deficiency)
- Dietary modification
  - Restrict phenylalanine (PKU), galactose (galactosemia), branched chain amino acids (MSUD), methionine (homocystinuria)
- Symptomatic metabolic treatment
  - Bicarbonate for lactic acidosis (mitochondrial encephalomyopathies)
- Detoxification by binding of the toxin to a substance that is nontoxic and readily eliminated
  - Penicillamine chelation of copper (Wilson's disease); benzoate and phenylbutyrate (hyperammonemia)
- Exogenous enzyme replacement therapy by intravenous infusion of recombinant enzyme
  - Laronidase (MPS I)
  - Idursulface (MPS II)
  - Agalsidase α/β (Fabry)
  - Imiglucerase (Gaucher)
- Enzyme inhibition
  - Miglustat inhibition (Tay–Sachs, Gaucher)
- Bone marrow transplantation (MPS, MLD, KD)
  - Most successful in preclinical or early stage with HLA-identical sibling donor
- Organ transplantation
  - When metabolic defect is confined to a single organ such as the liver (Wilson, Gaucher)

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Anticonvulsant therapy for seizure disorders
- Muscle relaxant therapy for spasticity

SURGERY/OTHER PROCEDURES

As needed for diagnosis and tendon release

IN-PATIENT CONSIDERATIONS

Admission Criteria

Intractable seizures, deterioration of mental status, acute respiratory distress, infection

Discharge Criteria

Discharge to home or facility usually requires extensive nursing facilities.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Serial neuroimaging, cognitive testing, visual examinations, and blood levels can be used to monitor these patients.

PATIENT EDUCATION

www.ninds.nih.gov; www.ncbi.nlm.nih.gov/Omim

PROGNOSIS

Infantile forms of neurodegenerative disorders relentlessly worsen

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Neurodegenerative disorder
- Childhood dementia

CODES

ICD9

- 348.30 Encephalopathy, unspecified
- 348.39 Other encephalopathy

ENCEPHALOPATHY, RENAL

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BASICS

DESCRIPTION
- Renal encephalopathy is the occurrence of CNS dysfunction associated with *either renal failure itself or the dialysis process*. Renal patients may have other diseases causing encephalopathy.
- *Uremic encephalopathy syndrome* consists of fluctuating lethargy, confusion, irritability, sleep dysregulation, abnormal movements, and/or seizures *developing over hours to days*. The progression of symptoms appears to correlate with the *rapidity with which renal failure ensues*.
- *Dialysis disequilibrium syndrome* (DDS) may include headache, muscle cramps, confusion, nausea, somnolence, and seizures. This is usually a self-limiting phenomenon that occurs *during or after dialysis*.
- *Dialysis dementia* is a *subacute*, *progressive* syndrome involving cognitive impairment, behavioral changes, myoclonus, and seizure in patients on *chronic hemodialysis*.

EPIDEMIOLOGY
- The precise frequency of renal encephalopathy is difficult to estimate. Uremic encephalopathy may occur in any patient with renal failure.
- Dialysis dementia has become a rare complication of hemodialysis due to the decreased use of aluminum in the dialysis process.

RISK FACTORS
- Patients with a rapid decline in renal function or with a prolonged time to initiation of hemodialysis are at risk for acute uremic encephalopathy (1).
- Patients with long-standing severe uremia or severe hypertension are more likely to suffer disequilibrium syndrome after initiation of dialysis (1,2).
- Aluminum in the dialysate and use of aluminum-based phosphate binders are risk factors for dialysis dementia.

Genetics
No reports available.

GENERAL PREVENTION
DDS may be prevented by modifying the osmolarity of the dialysate, limiting initial dialysis sessions to 2–3 hours, and dialyzing daily (1).

PATHOPHYSIOLOGY
- The development of uremic encephalopathy appears to be related to several factors. Potentially neurotoxic solutes such as urea, guanidino compounds, myoinositol, and various organic acids accumulate in the uremic state. Disturbances in intermediary metabolism and neurotransmitter balance leads to an overall decrease in brain energy use and oxygen consumption. Hormonal dysregulation associated with uremia has also been proposed to play a role in development of encephalopathy (2).
- DDS results from transient cerebral edema due to changes in the brain–blood osmotic gradient during dialysis.
- The exact mechanism of dialysis dementia remains unclear. Intracytoplasmic aluminum deposits have been demonstrated in dialysis dementia giving support to the theory of aluminum-mediated neurotoxicity. Other proposed influences include elevated brain calcium due to secondary hyperparathyroidism, chronic anemia, and silent cerebrovascular disease (3).

ETIOLOGY
See Pathophysiology.

COMMONLY ASSOCIATED CONDITIONS
- Hypertensive encephalopathy
- Wernicke's encephalopathy
- Transplant-related confusional states
- Uremic neuropathy
- Autonomic neuropathy
- Restless legs syndrome

DIAGNOSIS

HISTORY
- Uremic encephalopathy: Fluctuating confusion and lethargy associated with worsening renal function
- DDS: Headache and/or acute confusional state developing during or after dialysis
- Dialysis dementia: Progressive change in behavior, cognition, and sleep pattern on chronic dialysis

PHYSICAL EXAM
- Mental status: Irritability, agitation, disorientation, psychosis, drowsiness
- Motor abnormalities: Myoclonus, tremor, asterixis
- Other: Generalized or focal seizures, coma

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
Initial lab tests
- Chemistry panel including basic metabolic profile, liver function testing, calcium, magnesium, and phosphate
- Arterial blood gas to establish acid/base status and rule out hypoxemia/hypercarbia
- Complete blood count with differential
- Toxicology screen including drugs of abuse and specific toxins if ingestion is suspected
- Medication levels (i.e., phenytoin, lithium), if indicated. Impaired renal function leads to decreased clearance of many drugs.
- Blood cultures

Follow-up & special considerations
No reports available.

Imaging
Initial approach
CT head without contrast to rule out structural abnormalities (subdural hematoma, intracranial hemorrhage, or subacute stroke).

Follow-up & special considerations
Brain imaging is often unrevealing in isolated renal encephalopathies. If symptoms persist with correction of metabolic disorders or if focal neurological signs are present, MRI brain without contrast may be helpful in excluding other causes of encephalopathy or dementia.

Diagnostic Procedures/Other
- EEG findings in uremic encephalopathy are usually nonspecific. Generalized slowing with an excess of delta and theta waves is most common. Triphasic waves may also be seen.
- Consider a lumbar puncture if meningitis is a concern. Because the patient with renal failure may have a bleeding diathesis, caution should be used. CSF is often abnormal in patients with uremic encephalopathy. However, >25 WBC/mm^3 and protein >100 mg/dL should raise concern for CNS infection.

Pathological Findings
See Pathophysiology.

DIFFERENTIAL DIAGNOSIS
- Uremic encephalopathy
  - Hypertensive encephalopathy
  - Systemic inflammatory response syndrome
  - CNS infection
  - Toxic ingestion or drug-induced neurotoxicity
  - Glucose dysregulation (hypoglycemia, diabetic ketoacidosis, etc.)
  - Cerebral vascular disease
  - Nonconvulsive status epilepticus
- Dialysis disequilibrium syndrome
  - Other metabolic abnormality (glucose dysregulation, hypernatremia or hyponatremia, acidosis)
  - Hypotension induced hypoxic–ischemic encephalopathy
  - CNS infection
  - Wernicke's encephalopathy
  - Air embolism
  - Subdural hematoma

- Dialysis dementia
  - Alzheimer's dementia
  - Multifocal ischemic disease
  - Vascular dementia
  - Creutzfeldt–Jakob disease
  - Subdural hematoma
  - Wernicke's encephalopathy
  - Depressive psychosis

TREATMENT

MEDICATION

First Line

- Thiamine 100 mg parenterally should be given to all patients with a confusional state of unknown etiology.
- Fosphenytoin, if needed for recurrent seizures, may be given as a 15–20 PE/kg loading dose for adults. Maintenance dosing should be adjusted for the patient's level of liver dysfunction. Monitor free drug levels rather than total levels due to the reduced plasma protein concentration in renal failure patients.

Second Line

Uremic myoclonus may respond to clonazepam. No loading dose is needed. Start 0.25–0.5 mg b.i.d. for adults. Valproic acid and levetiracetam may also be effective.

ADDITIONAL TREATMENT

General Measures

- Uremic encephalopathy
  - Identify and treat the underlying cause of renal failure.
  - Dialysis if the patient has been exposed to a nephrotoxin or has acidosis, electrolyte imbalance, or fluid overload.
  - Treat any comorbid infections.
  - Maintain adequate nutrition to prevent further protein catabolism.
  - Treat seizures if they occur.
- DDS
  - This condition is usually self-limiting.
  - Increase the osmolarity of the dialysate by adding urea, sodium, mannitol, or glycerol.
  - Consider more frequent, shorter dialysis sessions (2)[C].
- Dialysis dementia
  - Monitor aluminum concentrations in dialysates and avoid aluminum-based phosphate binders.
  - Consider treatment with deferoxamine to chelate aluminum (1,2)[C].
  - IV benzodiazepines may be helpful initially.
  - Consider renal transplantation.

Issues for Referral

Most patients will be co-managed with nephrologists.

Additional Therapies

- Consider vitamin supplementation for all patients with renal failure.
- Recombinant erythropoietin to correct anemia in chronic dialysis patients may be associated with improved cognition (1,3)[C].

COMPLEMENTARY AND ALTERNATIVE THERAPIES

No reports available.

SURGERY/OTHER PROCEDURES

Renal transplant may be considered in severe cases of encephalopathy not responding to hemodialysis (1,2)[C].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Ensure appropriate respiratory and circulatory support.

Admission Criteria

Hospital admission is warranted for workup of alternative causes of encephalopathy and to monitor potential progression if the patient has fever, hypotension, seizures, or signs of encephalopathy that are not reduced by the regular dialysis session.

IV Fluids

Select appropriate IV fluids to correct metabolic abnormalities with care to avoid fluid overload.

Nursing

Avoid physical restraints in these patients with an increased tendency for seizure.

Discharge Criteria

Readiness for discharge depends on the underlying cause of the renal failure.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patients should continue nephrology follow-up.
- Patients with end-stage renal disease will need regular hemodialysis.

DIET

Low salt, low protein (renal) diet is advised.

PATIENT EDUCATION

- Patients, their families, and their caregivers should be encouraged to seek medical evaluation when mental status changes develop.
- Patients should be made aware of that poor compliance with hemodialysis may precipitate a life-threatening encephalopathy.

PROGNOSIS

The outcome for patients with renal encephalopathies can be excellent, provided there are few other comorbid conditions. Most of the manifestations of uremic encephalopathy are reversible within days or weeks after dialysis. Renal transplantation has been reported to reverse dialysis dementia.

COMPLICATIONS

Uremic encephalopathy may progress to coma and death if untreated.

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4. Lacerda G, Krummel T, Hirsch E. Neurologic presentations of renal diseases. *Neurol Clin* 2010; 28(1):45–59.

See Also (Topic, Algorithm, Electronic Media Element)

- Encephalopathy, metabolic and toxic
- Encephalopathy, septic
- Encephalopathy, hypertensive

CODES

ICD9

- 348.9 Unspecified condition of brain
- 586 Renal failure, unspecified
- 588.89 Other specified disorders resulting from impaired renal function

CLINICAL PEARLS

- Uremic encephalopathy is more strongly associated with the rate at which nitrogen products accumulate than an absolute blood urea nitrogen level.
- Recovery from uremic encephalopathy is usually excellent after treatment of the underlying cause of renal failure and/or hemodialysis.
- Although it may mimic more serious conditions, dialysis disequilibrium syndrome is self-limited and may be prevented by modifying dialysis methods.
- Dialysis dementia is now a rare complication of chronic hemodialysis.

ENCEPHALOPATHY, SEPTIC

David S. Younger, MD

BASICS

DESCRIPTION

Sepsis is a disease process that unleashes a variety of host reactions to the infectious process including a systemic inflammatory response (SIR) characterized by the balance between proinflammatory and anti-inflammatory responses to the pathogen. The SIR is initiated by the release of bacterial lipopolysaccharides (LPS) and other microbial substances into the circulatory and lymphatic organs and triggers a systemic response which unchecked can progress to multiple organ failure with profound pulmonary, cardiovascular, renal, and GI sequelae with a mortality of up to 30%. Survivors of sepsis can have pervasive dyspnea, fatigue, depression, and alterations in Central nervous system (CNS) function ranging from inattention, concentration difficulties, memory loss, to global cognitive impairment. Septic encephalopathy (SE) refers to the cerebral dysfunction that results from sepsis and septic shock. Although the brain is sequestered from the rest of the body and the SIR by the blood brain barrier (BBB), the sequelae of SE have the potential to disturb CNS homeostatic mechanisms that control the host responses at various behavioral, neuroendocrine, and autonomic levels and adversely influence the course of sepsis and shock, and in turn the adaptive responses leading to perpetuation of the immune-inflammatory response and even homodynamic failure.

EPIDEMIOLOGY

SE has been reported to occur in 8–70% of septic patients and is the most common form of encephalopathy among patients in intensive care units (ICUs). The reported variation in incidence probably reflects differing definitions of sepsis and encephalopathy. SE has been shown to be an independent predictor of death and is associated with a high mortality of 16–63%. No large-scale multicenter cohort studies have investigated the clinical signs and laboratory tests of so-called sepsis-associated delirium to allow an accurate estimate of its prevalence.

RISK FACTORS

Immunocompromised states increase risk of infection and sepsis; structural brain abnormalities increase susceptibility to encephalopathy.

ETIOLOGY

- The etiopathogenesis is clearly multifactorial with disturbances in the BBB and CNS microenvironment responsible for development of early or acute SE, and secondary sequelae of sepsis as dominant factors in late or chronic SE often in association with enhanced neurotoxicity of medications and nutritional deficiency.
- Early or acute SE: The BBB regulates brain capillary flow and maintains the internal microenvironment. Early in acute SE, breakdown of the BBB leads to disturbances of ionic homeostasis with entry of toxic metabolites and inflammatory cells that can lead to neuronal damage. Proinflammatory molecules such as tumor necrosis factor (TNF): α, interferon-γ, and products of complement activation are increased in the systemic circulation, along with heightened expression of intercellular adhesion molecule on microvessels in sepsis, and this could contribute to SE by increasing permeability of the BBB leading to edema, disruption of astrocyte endfeet, leukocyte recruitment with their entry into the brain leading to neuronal dysfunction and ultimately cell death. An excess of circulating nitric oxide (NO) in SE alters autoregulated cerebral blood flow (CBF) and disturbs the coupling between metabolism and CBF. NO reacts with superoxide molecules that produce the highly reactive nitrogen intermediate peroxynitrite that is toxic to neurons leading to neuronal energy failure. The rapid release of brain glutamate from astrocytes and neurons produces secondary NMDA receptor mediated excitotoxic death as well as induction of elevated levels of calcium, which promote further cellular injury. While the effects of local alteration in neurotransmitter systems remain unclear, those of the sympathetic nervous system have a role in the modulation of the SIR to sepsis, by β-adrenergic receptor activation by release of epinephrine which reduces the TNF-α release response to LPS, and enhances release of IL-10, reducing anti-inflammatory effects.
- Late or chronic SE: With sustained sepsis and evolving septic shock, the secondary sequelae of metabolic disarray, homodynamic and respiratory embarrassment, and multiple organ failure become dominant manifestations of late SE. Hepatic encephalopathy (HE) may be due to acute liver failure (type A), portal-systemic shunting in the absence of intrinsic hepatic disease (type B), and with cirrhosis and portal hypertension or portosystemic shunting (type C). There are four clinical stages with increasingly severe encephalopathy and neurological deficits ranging from lethargy, disorientation, amnesia, and confusion (stage 1), to somnolence (stage 2), stupor (stage 3), and coma (stage 4) with nystagmus, focal or generalized weakness, hyperreflexia, Babinski signs, and clonus. Correction of HE depends upon the inciting cause including treatment of dehydration, GI bleeding, limiting dietary protein, transjugular intrahepatic portosystemic shunt catheter placement, and measures to inhibit the absorption or production of ammonia.
- Uremic encephalopathy occurs with renal failure and varies in severity and speed of progression, with apathy, fatigue, irritability, and impaired concentration at onset, and marked confusion, disorientation, delusion, hallucinations, stupor and eventual coma, often in association with asterixis, focal or generalized twitching, hypertonicity, weakness, hyperreflexia, Babinski signs, clonus, and rarely meningeal signs, focal and generalized seizures.
- Pancreatic encephalopathy is associated with acute pancreatitis and elevation of the amylase level; there is no clear relationship between the latter and degree of encephalopathy. Clinical clues include severe upper abdominal pain, accompanied by nausea, vomiting, and fever. The impact of pancreatic encephalopathy has in large part been ascribed to activation of phospholipase A by trypsin and bile acid, which in turn converts lecithin and cephalin into their hemolytic forms, the latter of which can penetrate the BBB with CNS demyelination, hemorrhage, encephalomalacia, mitochondrial injury, impaired acetylcholine release, and edema due to heightened cytokine activation and increased vascular permeability. Unlike the insidious nature of hepatic and renal failure, electrolyte disturbances evolve in a rapid manner indicative of the severity of hypo- or hypernatremia, calcemia, magnesemia, and phosphatemia, all with varying degrees of encephalopathy and associated focal and generalized neurological deficits. Correction leads to prompt clinical improvement.
- Postmortem studies: 17 patients with fatal SE had postmortem studies revealing sterile microabscesses with active inflammation with associated central pontine myelinolysis, cerebral infarction, and varying fibrinoid necrosis of neighboring microvessels in 8 patients. Other postmortem findings have demonstrated proliferation of astrocytes and microglia.
- Drugs can result in varying encephalopathy, including benzodiazepines, narcotics, anticholinergics, cefepime, directly or secondarily due to enhanced neurotoxicity associated with increased permeability across a damaged BBB or reduced clearance in association with multiple organ insufficiency or failure.
- Malnutrition: Wernicke's encephalopathy is due to thiamine deficiency, which untreated, leads to profound encephalopathy and ultimately death. Anorexia followed by nausea, vomiting, ocular symptoms of diplopia, photophobia, and nystagmus, followed by cognitive impairment, sixth nerve palsy and complete ophthalmoplegia, memory loss, confabulation, and ataxia occur in the majority of severely affected patients, and predict the neuropathological sequelae of symmetrical shrinkage and discoloration of the mammillary bodies, periaqueductal gray, medial thalamus, superior and inferior colliculi and floor of the third ventricle, with symmetrical microscopic changes in other areas of the brainstem, fornix, and cerebellum. Although chronic alcoholism is the likeliest cause of thiamine deficiency in 90% of affected patients, protracted illnesses associated with vomiting, diarrhea, acute pancreatitis, and inflammatory bowel disease and malnutrition are important proximate causes. Replacement of thiamine is curative. Pellagra due to niacin deficiency presents with the triad of dermatitis, diarrhea, and dementia present altogether in a quarter of affected patients, which can progress to acute psychosis, delusions, hallucinations, encephalopathy, cogwheel rigidity, release phenomena of grasping, and suck reflexes.

Although deficiency of niacin is the likeliest cause, several drugs can interfere with the metabolism/bioavailability of niacin, including isoniazid, azathioprine, 6-mercaptopurine, 5-fluorouracil, puromycin, chloramphenicol, and pyrazinamide; and patients with cancer, tuberculosis, and other systemic infections may have increased requirements for niacin leading to insidious deficiency, which when replaced or supplemented, can forestall later neurological sequelae.

DIAGNOSIS

The diagnosis of SE rests upon documentation of a systemic infectious process with diffuse or multifocal disturbances of cerebral function and the exclusion of other recognized causes of encephalopathy.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Sepsis is associated with multiorgan dysfunction that may manifest in a wide variety of laboratory chemical abnormalities, the severity of which correlates with the severity of clinical disturbances.
- Comprehensive chemistries, CBC, coagulation parameters, ESR, CRP, arterial blood gas, blood, urine, sputum, and CSF cultures and indices.

Imaging

While brain CT is generally normal, MRI may show bilateral basal ganglia, cerebellar, brainstem, and temporal lobe signal abnormalities on fluid attenuated inversion recovery (FLAIR) sequences without abnormal enhancement after gadolinium administration.

Diagnostic Procedures/Other

- Lumbar puncture for CSF analysis should be performed to elucidate a possible CNS infectious or inflammatory process. The most common abnormality is mild elevation of protein. Cell counts, glucose, stains, and cultures are typically normal or negative.
- EEG is always abnormal in SE, with background rhythm slowing reflective of the degree of encephalopathy. Triphasic waves are common. A burst suppression pattern can be found in advanced cases; however, none of these findings are specific. The EEG is also prognostic but is not an absolute predictor of poor outcome. Mortality rises with the degree of EEG abnormality. Patients with burst suppression have made full neurological recoveries.
- Somatosensory evoked potential response may show increased interpeak latencies along central pathways; however, there was no correlation between the subcortical sensory evoked potential and the severity of illness.

DIFFERENTIAL DIAGNOSIS

SE is a diagnosis of exclusion. The differential diagnosis includes:

- Systemic infection
- Cortical venous thrombosis
- Intracranial hemorrhage
- Heat stroke
- Nonconvulsive status epilepticus
- Postictal confusion
- Endocarditis
- Deep vein thrombosis
- Intoxication/withdrawal
- Fat embolism
- Drug fever
- Acetylsalicylic acid toxicity
- Malignant neuroleptic syndrome
- Pulmonary, renal, or hepatic failure
- Adrenal failure
- Thyroid storm

TREATMENT

MEDICATION

Conventional management focuses on treatment of sepsis and septic shock and resolving immediate life-threatening problems related to the underlying infection and SIR with antibiotics and cardiovascular, ventilatory, and other organ support. Effective management of SE is important to reduce long-term neurological complications and morbidity especially cognitive impairment in survivors. Novel approaches to aggressive management of SE include extracorporeal therapy utilizing coupled plasma filtration absorption, immune suppression, and plasma filtration to remove circulating cytokines and mediators of the SIR. Systemic corticosteroids which normalize macrophage migration inhibitory factor contribute to the acute management of septic shock and may reduce long-term neurological sequelae.

ADDITIONAL TREATMENT

General Measures

There is no specific treatment for SE. Once secondary causes have been ruled out, the focus of treatment should be directed at the underlying cause.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment: Patients may improve with flumazenil, a γ-aminobutyric acid-A antagonist; the risk of potentiating seizures may limit its use. Infusions of branched chain rich amino acid solutions have improved the mental status of patients with HE. Not yet accepted treatments, these may be areas of future exploration.
- Adjunctive treatment should be directed at the underlying cause and comorbidities. Appropriate antibiotic regimens and supportive care should be aggressively pursued (including respiratory care, mechanical ventilation if indicated, hemodialysis for renal impairment, fluid/electrolyte management, pressors for hemodynamic instability, and antiepileptic medications if seizures are suspected).

SURGERY/OTHER PROCEDURES

No specific surgical measures are indicated.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with sepsis typically are already admitted into the hospital. Encephalopathic patients are unstable and require close observation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

The patient's underlying condition will dictate the degree of follow-up. Intensive care may be indicated. Serial neurological examinations by staff trained in such evaluation should be performed.

PROGNOSIS

Encephalopathy is a common occurrence in sepsis. Whether it is an independent predictor of mortality is unclear, but mortality is higher with more severe degrees of encephalopathy.

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See Also (Topic, Algorithm, Electronic Media Element)

- Acute confusional state
- Delirium; clouded sensorium
- Acute organic brain syndrome
- Septic syndrome

CODES

ICD9

348.31 Metabolic encephalopathy

CLINICAL PEARLS

Treatment of septic encephalopathy requires aggressive supportive care as well as treatment of the underlying infection.

EPILEPSY, ABSENCE SEIZURES

Khaled M. Zamel, MD

BASICS

DESCRIPTION

- Absence seizures are generalized seizures characterized by paroxysmal loss of consciousness with brief discontinuation of activity followed by abrupt recovery with no recollection of the event. Typical absence seizures are mostly seen in idiopathic generalized epilepsies (IGEs) such as childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE) and Juvenile myoclonic epilepsy (JME). Atypical absence seizures are seen only with severe symptomatic or cryptogenic epilepsies such as in Lennox–Gastaut syndrome.

EPIDEMIOLOGY

Incidence

- The vast majority of absence seizures start between the age of 4 and 12.
- Annual incidence of CAE is about 6 to 8/100,000 per year.
  - – Incidence of absence seizures in adults is uncertain but in general onset of absence seizures is rare after age 20.

Prevalence

- Absence seizures account for 2–16% of seizures in all ages and are the seizure type most commonly undiagnosed.
- CAE is the most common form of pediatric epilepsy accounting for 10 to 17% of all cases of childhood onset epilepsy.
- JAE may account for about 2–3% of all adult epilepsies and up to 10% of IGEs.
  - – Race
- No known difference
  - – Age
- Absence seizures are seen more often in childhood, but they also occur in about 10–15% of adults with epilepsies, often combined with other generalized seizures.
  - – Sex
- Some studies showed twofold preponderance in girls.

RISK FACTORS

- Family history of absence epilepsy, febrile seizures or other IGEs. In general, a family history of epilepsy is found in 15–44% of patients with generalized absence seizures.

Genetics

- Recent genetic studies linked CAE to gene mutations in the GABA-A receptor gamma 2 subunit as well as calcium channel CACNA1H.

GENERAL PREVENTION

Non-compliance with antiepileptic medications is a frequent cause of breakthrough seizures. Alcohol as well as many drugs such as neuroleptics and isoniazid can lower seizure threshold.

PATHOPHYSIOLOGY

- Not fully understood
  - – The thalamocortical networks are believed to be involved with abnormal oscillatory rhythms that generate the generalized spike and wave discharges that accompany the absence seizure episodes. This involves activation of the T-type calcium channels as a result of GABA-B mediated inhibition alternating with glutamate-mediated excitation.

ETIOLOGY

- There is strong evidence that genetic factors are involved in the etiology of typical absence seizures. On the other hand, acquired disorders are more common in atypical absence seizures.

COMMONLY ASSOCIATED CONDITIONS

- Later age of onset of absence seizures is linked to higher risk for developing convulsive generalized tonic-clonic (GTC) seizures.
  - – Attention deficit hyperactivity disorder, subtle cognitive deficits, linguistic difficulties, and anxiety disorders are more common in patients with absence epilepsy.

DIAGNOSIS

HISTORY

- The characteristic features of typical absences are abrupt onset of brief staring, cognitive impairment and change in facial expression. Duration is typically <20 seconds without postictal changes. Many patients have associated minor motor movements, such as eye rolling, eyelid fluttering, head nodding, or subtle oral automatisms. Less frequently, mild myoclonic jerks of the head or extremities or change in muscle tone may occur. Occasionally, autonomic features such as change in skin color, urinary incontinence, or pupillary dilation are seen. Hyperventilation for 3 minutes will provoke an absence in nearly all untreated children with CAE.
  - – In CAE, absence seizures begin between 4 and 8 years and may occur many times per day. Sometimes, decline in school performance is the only indication that leads to the diagnosis. About 30% of children with CAE later develop GTC seizures.
    - ○ JAE begins between 10 and 15 years. JAE patients usually have less frequent absences than those with CAE but higher risk for developing GTC seizures.
    - ○ JME usually begins in adolescence with initial manifestations of myoclonic seizures, which predominantly occur on awakenings. GTC and absence seizures usually develop later.
    - ○ Atypical absence seizures are seen most frequently in symptomatic generalized epilepsies accompanied by developmental delay or mental retardation. They are usually associated with other types of seizures
    - ○ In contrast to the typical absence, atypical absence seizures are characterized by a less abrupt clear onset and offset, which is usually progressive. Atypical absence seizures last longer and have a higher incidence of changes in postural tone.

PHYSICAL EXAM

- The neurologic examination is usually normal in patients with typical absence seizures.
- Hyperventilation for 3–5 minutes can aid the diagnosis as it frequently provokes absence seizures.
- Atypical absence seizures usually occur in children with subnormal mental function

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Video-EEG is the single most important diagnostic procedure. In CAE, the EEG has a normal background with 4–20 seconds bursts of rhythmic, generalized, high-amplitude 3-Hz spike-and-wave discharges typically exacerbated by hyperventilation. In JAE, discharges are similar but with faster frequency, mostly 4–5 Hz with frequent polyspike. JME is characterized by the occurrence of generalized polyspike and slow-wave discharges of 3–6 Hz. Atypical absences usually occur in the context of abnormal background and an ictal EEG of slow <2.5-Hz spike-and-slow wave.

Follow-up & special considerations

- Questionable cases could be evaluated with long-term video-EEG monitoring to record and characterize their events.

Imaging

Initial approach

- Patients usually have normal neuroimaging. Brain MRI, is indicated if the patient has atypical features of the seizures, developmental delay, or abnormal neurologic examination.

Diagnostic Procedures/Other

Specific investigations such as metabolic or genetic testing might be indicated in patients with atypical absence seizures to look for possible underlying metabolic or infectious etiology.

Pathological Findings

- Using advanced MRI techniques, studies in CAE patients have showed evidence of reduction in thalami, temporal lobes, the basal forebrain white matter, and the subcallosal and left orbital frontal gyri.

DIFFERENTIAL DIAGNOSIS

- Accurate diagnosis starts with a careful history: Description of the seizures, including duration, frequency, presence or absence of an aura, and postictal events. Other primary diagnostic considerations for staring spells include complex partial seizures and daydreaming. In contrast to absence seizures, complex partial seizures are much less frequent, often preceded by an aura, followed by postictal confusion and are rarely activated by photic stimulation or hyperventilation. Daydreaming usually is caused by boredom, is of variable duration, can be interrupted by stimulation, and is never associated with clonic components. Absence seizures may frequently be misdiagnosed as non-epileptic disturbances of behavior. In addition, clouding of consciousness with ocular and oromotor automatisms may occur in partial and other generalized epilepsies.

- Absence seizures comprise the primary seizure type in several epilepsy syndromes. The syndromic diagnosis is important to determine optimal treatment and prognosis.
  – CAE
  – JAE
  – JME
  – Myoclonic absence epilepsy
  – Eyelid myoclonus with absences
  – Perioral myoclonus with absences
  – Stimulus-sensitive absence epilepsies
- Atypical absence seizures occur in children with severe symptomatic or cryptogenic epilepsies.

TREATMENT

MEDICATION

First Line

The main antiepileptic agents for AES are ethosuximide, valproic acid (VA) and lamotrigine (LMT). The age of onset, side effect profile and presence of other accompanying types of seizures determine medication selection. Ethosuximide and VA both control absences in up to 75% of patients. LMT is less efficacious controlling absences in 30–50% of patients. This was recently confirmed in a multicenter double-blind, randomized, controlled clinical trial (1) that compared the 3 medications in 453 children with newly diagnosed CAE. This study also concluded that VA caused more attentional dysfunction than ethosuximide. When other types of generalized seizures are associated, antiepileptics other than ethosuximide should be selected.

- Ethosuximide: First drug of choice for isolated typical absences in CAE.
  – For children 3 to 6 years, initial dosage is 15 mg/kg/day or 250 mg once daily, with titration to daily maintenance dose of 20 mg/kg. For older children/adults, the initial dose is 500 mg with gradual increase by 250 mg every 4–7 days until control is achieved. Serious but rare side effects include aplastic anemia, Stevens–Johnson syndrome, and hepatic impairment. Common side effects include GI disturbances, anorexia, weight loss, drowsiness, photophobia, and headache.
- VA: Effective for 75% of patients with absence seizures, as well as generalized convulsive and myoclonic seizures. In children, it is the second choice if ethosuximide fails to control absence attacks or the patient develops GTC seizures. It is the preferred drug of choice in JAE due to the high incidence of GTC seizures. It should be avoided in women of childbearing age due to risks of fetal malformations and neurodevelopmental delay.
  – Initial dosage is 10–15 mg/kg/day. Maintenance dose in children is 30–60 mg/kg/day in three divided doses. Serious side effects include acute hepatic failure and acute pancreatitis. Common side effects include nausea, vomiting, dyspepsia, weight gain, polycystic ovaries, tremor, transient hair loss, and thrombocytopenia.
- LMT: Controls absences and generalized seizures in 50–60% of patients, but may worsen myoclonic jerks. LMT has less cognitive side effects. It requires long titration to establish therapeutic efficacy.
  – For children ages 2–12 years taking VA, LMT could be added at 0.15 mg/kg/day and increased every 2 weeks by 0.15 mg/kg/day to a maximum of 5 mg/kg/day. In adults and children >12 years, LMT can be added to VA at a dose of 25 mg every other day and gradually increased to a maximum of 200 mg/day. LMT monotherapy can be given to patients >12 years at 25 mg daily, increased to a maximum of 100 mg/day. An allergic rash that could progress to Stevens–Johnson syndrome is the most common serious adverse effect. Other common side effects include headache, nausea, diplopia, dizziness, tremors, and ataxia. Side effects are more common with rapid titration or when combined with VA.
  – VA is contraindicated for children <2 years and for patients with hepatic disease.
  – Vigabatrin, tiagabine, and carbamazepine are contraindicated for treatment of absence seizures, as they tend to exacerbate the seizures and could produce absence status epilepticus. Gabapentin, phenobarbital and phenytoin are ineffective for absence.

Second Line

- Clonazepam, clobazam, and acetazolamide may be useful adjunctive drugs.
- Levetiracetam has only a modest effect against absence seizures (2) but could be a good alternative to VA in treating patients with JAE and JME due to favorable side effect profile and proven efficacy in treating GTC and myoclonic seizures.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Dietary therapies such as ketogenic or modified Atkins diet are established as an effective treatment in symptomatic epilepsies with reduction of absence seizure frequency by >50%.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Prolonged periods of stupor, impaired memory, or cognitive functions could represent absence status epilepticus. Inpatient EEG monitoring may be diagnostic by showing prolonged generalized bursts of spike-and-wave discharges. Intravenous or rectal benzodiazepines could be helpful for both treatment and diagnosis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patients taking ethosuximide should have blood counts to monitor for aplastic anemia. Those taking VA should be monitored for thrombocytopenia and hepatotoxicity. Therapeutic trough levels range from 40–100 mg/mL for ethosuximide and 50–100 mg/mL for VA.

PATIENT EDUCATION

- Medication compliance should be encouraged to avoid breakthrough seizures.
- Epilepsy Foundation of America.
  – Phone: 1-800-EFA-100
  – website: *www.epilepsyfoundation.org*

PROGNOSIS

- Typical absence seizures generally have a favorable prognosis. CAE carries the best prognosis; up to 95% of children with CAE will have complete remission. JAE has a less favorable prognosis than CAE. JME is usually a lifelong epilepsy.
- Poor prognostic factors include history of associated GTC or myoclonic seizures or absence status, positive family history of epilepsy, abnormal EEG background, or subnormal intelligence.

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CODES

ICD9

- 345.00 Generalized nonconvulsive epilepsy, without mention of intractable epilepsy
- 345.10 Generalized convulsive epilepsy, without mention of intractable epilepsy

CLINICAL PEARLS

The main antiepileptic agents for AES are ethosuximide, VA and LMT.

EPILEPSY, COMPLEX PARTIAL

J. Layne Moore, MD, MPH
Charles W. Hall Jr., MD, PhD

BASICS

DESCRIPTION
- Epileptic seizures represent episodes of uncontrolled electrophysiological activity in the brain. This may manifest as sensory or motor activity, behavioral arrest, confusion or as convulsive activity.
- Most seizures begin focally (partial) and then spread.
- If consciousness is not lost (only sensory or motor symptoms), the seizure is Simple Partial.
- If consciousness is impaired, it is referred to as Complex Partial.
- If a convulsion ensues, it is called Secondary Generalized.

EPIDEMIOLOGY
Incidence
- The incidence is bimodal being highest in the 1st year and 7th decade.
- Prevalence: Approximately, 1.5% of the USA has a diagnosis of epilepsy.

RISK FACTORS
- Nearly 70% of epilepsy is cryptogenic, meaning that a causative etiology is not identified.
- A history of stroke is found in 15% of patients.
- About 5% of patients are found to have a developmental anomaly such as focal cortical dysplasia or gray matter heterotopias.
- Serious head injury
- Brain tumor
- CNS infections
- Neurodegenerative syndromes (1)[B]

Genetics
For most forms of epilepsy, the inherited risk is polygenetic. The risk of an affected parent passing on the disease is 3–4%.

GENERAL PREVENTION
Reducing the risk of injury to the central nervous system by way of infections or trauma reduces the risk of developing acquired epilepsy. The risk of epilepsy increases with economic deprivation and substance abuse.

PATHOPHYSIOLOGY
An imbalance of excitatory and inhibitory control of the neocortex for various reasons.

ETIOLOGY
No single etiology is present but injuries to the neocortex via foreign tissue lesions, strokes, infections or trauma predispose individuals. Most patients have none of those risk factors.

COMMONLY ASSOCIATED CONDITIONS
Co-morbidities include headache, cognitive impairment, depression and anxiety.

DIAGNOSIS

HISTORY
- Does the patient have a history of head injury with loss of consciousness, stroke (ischemic or hemorrhagic), CNS infections (viral, fungal, and bacterial), cocaine or alcohol abuse, febrile seizures, tumors, cortical malformations or vascular malformations? Also a family history increases the risk of developing epilepsy.
- Most persons with complex partial seizures describe brief lapses in awareness that impair task performance with confusion thereafter.
- Seizures of temporal onset consist of behavioral arrest or staring off, lip smacking or chewing, and semi-purposeful movements of the hands and feet (automatisms).
- Frontal lobe seizures tend to be nocturnal and violent. Many persons with frontal lobe seizures exhibit seemingly purposeful aggression.
- Children with Rolandic epilepsy tend to have simple partial seizures involving twitching motions of the face during the daytime hours, and violent generalized tonic clonic convulsions at night.
- Of all seizures, 90% last less than 2 minutes and longer duration spells may not be seizures.
- Some patients may experience bladder incontinence or tongue biting.
- Up to 10% of cases of new onset epilepsy present with status epilepticus.

PHYSICAL EXAM
A careful neurological examination including motor and sensory components.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- MRI brain
- An awake and sleep EEG
- Antiepileptic drug (AED) levels
- UA, CBC and électrolyte panel with calcium, magnesium and phosphorous (Ca, Mg)
- Toxicology screen
- TSH
- Pregnancy test

Follow-up & special considerations
- Patients must be seizure-free to operate a motor vehicle or engage in dangerous activities. Various state laws dictate the duration that a patient must be seizure-free to drive. If your state does not dictate a certain length of time for seizure-freedom, a minimum of 3 months is advisable (3)[B].

Imaging
Initial approach
- CT scans of the brain are appropriate for emergent evaluation of acute new-onset seizures or for persons with contraindications for MRI imaging.
- MRI of the brain with thin cuts-oriented perpendicular to the long axis of the hippocampus are desirable.

Follow-up & special considerations
- Patients are re-evaluated based on how frequently they are having seizures.
- Complete control is necessary for patients to drive and engage in dangerous activities.

Diagnostic Procedures/Other
- Inpatient video-EEG monitoring for spell classification, medication adjustment, seizure quantification, or presurgical evaluation
- Chronic intracranial monitoring
- Ictal or interictal SPECT

Pathological Findings
- Mesial temporal sclerosis with neuronal loss and reactive gliosis of amygdalohippocampal complex
- Encephalomalacia with hemosiderosis and gliosis in frontal and temporal poles due to head trauma with contusion
- Gray matter heterotopia (nodular and band) with gray matter appearing in atypical locations
- Focal cortical dysplasia with balloon cells
- Polymicrogyri, pachygyri, schizencephaly
- Vascular malformations—arteriovenous malformations, dural arteriovenous fistulas, and cavernomas.

DIFFERENTIAL DIAGNOSIS
- syncope, or syncopal seizures
- nonepileptic psychogenic spells
- parasomnia/REM behavioral disorder
- narcolepsy/cataplexy
- confusional migraine

TREATMENT

MEDICATION

First Line

- Choice of AED is dictated mostly by side-effect profile. Several AEDs are appropriate.
- Lamotrigine
- Levetiracetam
- Carbamazepine/oxcarbamazepine
- Topiramate
- Phenytoin
- Valproic acid

Second Line

- Pregabalin
- Zonisamide
- Felbamate
- Locosamide
- Tiagabine

Pregnancy Considerations

- AEDs must not be stopped during pregnancy.
- The best approach is to anticipate pregnancy and have young women on AEDs that are safest for developing fetuses (lamotrigine, carbamazepine).
- Referral to high risk obstetrician for appropriate screening, possible antenatal Vitamin K (2)[B].
- All women of child-bearing potential should be on at least 1 mg of Folic acid daily before conception.

ADDITIONAL TREATMENT

General Measures

- Patients should have dosages changed for side effects and break-through seizures rather than using only "therapeutic level" monitoring.
- Periodic laboratory monitoring to screen for bone marrow suppression (agranulocytosis, aplastic anemia), liver inflammation (transaminitis), or electrolyte abnormalities (hyponatremia).

Issues for Referral

- Seizures that remain uncontrolled for more than a year.
- Failure of 2 or more anticonvulsant medications
- Episodes of status epilepticus
- Changes in seizure character

Additional Therapies

- Resective surgery
- Vagus nerve stimulator, reactive nervous stimulation, deep brain stimulation
- Ketogenic and modified adkins diets
- Corpus callosum section

SURGERY/OTHER PROCEDURES

- Vagus nerve stimulator
- Resective surgery of epileptic focus
- Corpus callosum section

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Lorazepam, diazepam, midazolam, acutely to cessation of seizures (4)[A]

Admission Criteria

- Seizures that last for more than 5 minutes are unusual and suggest the onset of an acute seizure condition or status epilepticus.
- Any change in the nature or duration of seizures
- Prolonged periods of confusion

IV Fluids

- Phenytoin may never be given with glucose in the IV fluids because it may crystallize.

Discharge Criteria

- Adequate control of seizures

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Interval of follow up is based on frequency of seizures

Patient Monitoring

- Seizure control and side effects are most important for management
- Patients should be encouraged to keep seizure calendars.
- AED levels may be used adjunctively but are never the sole reason for changing dosages.

DIET

- Regular

PATIENT EDUCATION

- Patients must be counseled about medication adherence.
- Driving restrictions
- Pregnancy
- Avoid activity in which abrupt loss of consciousness could cause injury to self/others.
- Shower rather than bath.

PROGNOSIS

- Of patients, 70% will obtain seizure-freedom for an extended period of time.

COMPLICATIONS

- Patients with epilepsy may injure themselves or die unexpectedly without apparent cause. This sudden unexpected death in epilepsy is uncommon but probably occurs more in uncontrolled patients.

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Epilepsy, generalized
- Epilepsy, status epilepticus
- Epilepsy, absence seizures

CODES

ICD9

- 345.40 Partial epilepsy, without mention of intractable epilepsy
- 345.41 Partial epilepsy, with imtractable epilepsy
- 345.90 Epilepsy, unspecified, without mention of intractable epilepsy

CLINICAL PEARLS

- Of seizures, 80% are partial in onset.
- Of partial onset seizures, 80% arise from the temporal lobes.
- A routine EEG recording is normal in upwards of 40% of persons with epilepsy.
- A sleep-deprived EEG recording may be normal in upwards of 20% of persons with epilepsy.
- A prolonged EEG recording (24–48 hours) may be normal in upwards of 10% of persons with epilepsy.

EPILEPSY, FEBRILE SEIZURES

Juliann M. Paolicchi, MA, MD

BASICS

DESCRIPTION

- Febrile seizures (FSs) are seizures that occur in infancy or childhood, typically between 3 months and 5 years, associated with fever, but without evidence of intracranial infection or defined cause. FSs are distinct from epilepsy, which is characterized by recurrent nonfebrile seizures.
- Simple FS: Single, brief (<15 minutes), generalized seizures during fever (rise or fall) in developmentally/neurologically normal children
- Complex FS: Duration >15 minutes, focal features or postictal focal weakness, or recur within 24 hours
- Febrile status epilepticus (FSE): Continuous or intermittent seizures without neurologic recovery for a period of 30 minutes or longer.
- Febrile seizure syndrome (FSS): Genetic epilepsy with FSs plus: FSs with generalized tonic–clonic seizures, complex partial seizures, and absence seizures. Strong family history of similar seizures.

EPIDEMIOLOGY

Incidence/Prevalence

- Most FSs are simple (65%). The most frequent complex feature is focality, followed by recurrence and prolonged duration. FSE accounts for only 5% of all FSs, but accounts for 25% of all childhood status epilepticus and more than two-thirds of status epilepticus in the second year of life.
- Age: FSs occur in 2–5% of all children <5 years of age. 90% occur between 6 months and 3 years, with the peak period between 12 and 18 months. 4% occur before 6 months, and 6% occur after age 3 years.
- Sex: Slightly more frequently in boys.

RISK FACTORS

- Family history of seizures, FS, FSS.
- Previous neurologic injury, stroke, hemorrhage, infection
- Recent immunizations: On the same day as diptheria/tetanus/pertiussis vaccination, and 8–14 days after measles/mumps/rubella vaccination

Genetics

- Inheritance: Multifactorial in most cases. Children with a positive family history of FS are more likely to experience FS and to have recurrences. At least, five different genetic loci have been identified.
- FSS: Multiple genes identified including SCN1A, SCN1B, and GABA(A) gamma 2 subunit genes.

GENERAL PREVENTION

- Since the seizure typically occurs early in the onset of the FS, and is often the first presenting sign, prevention is not effective. Children with a history of recurrent FS can be treated with diazepam (see below).
- Adherence to vaccination schedules in infancy and childhood can reduce the incidence and severity of febrile illnesses.

ETIOLOGY/PATHOPHYSIOLOGY

Pathogenesis is likely multifactorial based on genetic predisposition, maturity of brain development, proconvulsant fever-induced factors (i.e. interleukin-1-beta), temperature sensitive neuronal ion channels, and fever-induced hyperventilation and alkalosis.

COMMONLY ASSOCIATED CONDITIONS

Any fever-inducing childhood infection; most frequently, upper respiratory infections, otitis media, roseola infantum, tonsillitis, and gastroenteritis and Herpesvirus-6 (exanthema subitum or roseola) are associated with FS.

DIAGNOSIS

HISTORY

- FS often occur early in the course of a febrile illness. The majority of events are brief (<15 minutes).
  - Tonic-clonic seizures are most common seizure type, but partial features can be present. A typical seizure involves a cry, loss of consciousness, and tonic posture. Breath-holding or circumoral cyanosis may be observed, along with vomiting and incontinence. Focality may be observed during the clonic phase. Postictal lethargy or sleep is common.
- Previous history of seizures, febrile or afebrile, neurologic or developmental abnormality
- Presence of neurologic and developmental abnormality increases risk of subsequent epilepsy. Previous afebrile seizures suggest a seizure precipitated by fever rather than FS.
- Diagnosis of FS after 6 years should be one of the exclusions.
- Precipitating factors: Degree and duration of fever, length and symptoms of preceding illness, recent history of head trauma, possibility of ingestion of toxic substance: Low fever, ingestion, head trauma, or prolonged illness before seizure suggest cause other than fever alone.
- Past medical history: Gestation, birth, general health, growth and development, and current medications. Birth complications and developmental delay may increase risk of epilepsy, but not of FS.
- Family history: Both febrile and afebrile seizures can be hereditary. A family history of FS is typically present.
  - Neurologic findings: Recent onset of headaches, vomiting not in the setting of GI illness, lethargy, weakness, sensory deficits, or changes in vision, behavior, balance, or gait suggest underlying brain pathology or infection and the need for neuroimaging and/or lumbar puncture

PHYSICAL EXAM

- Vital signs:
  - Degree of fever
  - Tachycardia or hypotension (suggests sepsis)
  - Tachypnea (suggests respiratory infection)
  - Head circumference
  - Signs of head trauma or possible abuse: Retinal hemorrhages and evidence of intracranial hypertension such as bulging fontanelle should be noted on HEENT exam.
  - Meningitis: Nuchal rigidity. ALERT: Not a reliable sign in infants, esp. <6 months of age.
- Careful neurologic examination: Specific attention should be directed to mental status and presence of focal abnormalities of motor strength, tone, or sensation.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Routine laboratory testing not necessary after a simple FS if child appears well.
- Additional laboratory analysis dependent on history, presentation and examination of the child, and as needed for diagnosis of the fever. Can include CBC, electrolytes, calcium, glucose, and toxicology screen.

ALERT

Infants with FS may have serious bacterial infections (bacteremia, meningitis, or sepsis) underlying fever. If suspect, diagnosis and treatment for meningitis should be a primary focus after patient is stabilized.

Imaging

- Urgent CT: Reserved for infants and children presenting with fever and seizures in whom the diagnosis of acute neurologic event/infection is suspect.
- MRI: Reserved for children with:
  - Complex (focal or prolonged) FS
  - Focal neurologic deficits, even transitory, after seizure
  - Focal abnormality on EEG
- Should be done after febrile illness has resolved, except if indicated for workup of febrile illness.

Diagnostic Procedures/Other

- EEG: Not routinely indicated after simple FS. Should be performed on children who are neurologically abnormal, experience complex FS, or have prolonged postictal encephalopathy.
- Lumbar Puncture: Indicated when history or examination suggests CNS infection. Special considerations:
  - children under 6 months of age with any new-onset FS
  - older child who appear toxic, have clinical signs suggesting CNS infection, have a prolonged postictal encephalopathy
  - LP may be indicated for children with new onset FS who have been pretreated with antibiotics.

DIFFERENTIAL DIAGNOSIS

- Non-epileptic imitators of seizures: i.e., chills or rigor due to fever in a child with illness
- Underlying CNS injury/illness presenting with seizure and fever, i.e.
  - CNS infection
    - Anoxia/Stroke/Hemorrhage
    - Trauma
    - Intoxication
    - Metabolic encephalopathy
    - Neurodegenerative disorder
    - Brain lesion or tumor
    - Neurocutaneous syndromes
    - Epileptic conditions
    - Previous history of afebrile seizures
    - Certain neurogenetic conditions present with seizures in the setting of high fevers, i.e., Angelman's and Dravet's syndrome.
    - Previous brain injury (stroke, CNS infection, hemorrhage, birth asphyxia, cerebral palsy)

TREATMENT

MEDICATION

First Line

- Primary therapy is abortive. Rectal diazepam, 0.3–0.5 mg/kg, can be administered if seizure persists for >5 minutes.
- Focality and a prolonged FS, >10 minutes, are more likely to have recurrence. Therapy with abortive medication should be considered with the first incidence of FS.
  - Oral administration of diazepam, 0.3 mg/kg q8h, during febrile illnesses reduces risk of recurrent FS; however, causes sedation, and is typically useful only for children with a history of recurrent FS within an illness.

Second Line

Antiepileptic medications that have evidence of efficacy in recurrent FS include phenobarbital, valproate, and primidone limiting side effects occur in 40% of patients. Phenytoin and carbamazepine are ineffective as prophylaxis. There are limited data to support the use levetiracetam for FS.

ADDITIONAL TREATMENT

General Measures

- Treatment of a single FS is not indicated
  - Antiepileptic medication is typically reserved for diagnosis of established epilepsy. Anti-epileptic medication does not prevent the subsequent development of epilepsy. Abortive therapy is recommended in children with complex FS, and recurrent simple FS.
  - Treatment with antipyretics does not significantly affect the recurrence rate of FS.

Issues for Referral

Neurologic referral indicated for children in whom underlying CNS illness is suspected from history, presentation or examination, or if history reveals previous afebrile seizures.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Routine vaccination reduces the occurrence of childhood febrile illnesses.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

If abortive therapy is ineffective, initiate status epilepticus protocol for children.

Admission Criteria

Admission indicated for FSE, seizures induced by CNS infection or lesion, frequent recurrent FS, persistent postictal encephalopathy, and children whose underlying source of fever warrants admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

The majority of children with FS can have adequate follow-up with their primary care provider. Neurologic follow-up is indicated for the development of afebrile seizures.

PATIENT EDUCATION

- Web site: http://www.epilepsy.com
- Parents/caregivers of children with FS should be counseled regarding treatment of subsequent seizures including placement of the child supine with head turned to avoid aspiration with nothing in the mouth. Abortive therapy should be initiated at 5 minutes of seizure activity and EMT services should be activated. Instruct to administer rectal diazepam for prolonged or serial seizures.
- Children with recurrent seizures of any kind should receive the following precautions: Not to swim or bathe unattended, sleep in a top bunk bed, or climb to high places. They should wear a helmet when biking or using any wheeled toy.

PROGNOSIS

- Recurrent FS occur in 30% of children with FS, and 50% of children with recurrence have a third FS. Four predictors of occurrence are young age at onset, FS in a first degree relative, low precipitating fever, and short duration between fever onset and seizure. The risk factors are cumulative: 70% with 4 factors, 20% with none.
- Age of presentation is the strongest predictor of recurrence: 50–60% of infants <12 months have recurrence. Of recurrences, 90% occur within 2 years, 75% within 1 year, and 50% within 6 months.
- The risk of children with FS developing epilepsy is 2%, compared to 1% in the general population.
- Risk factors for the development of epilepsy include: Focal, prolonged, and recurrent seizures. The risk factors are cumulative: 25% higher risk in children with 3 factors compared to none.
- No evidence that occasional FS or even FSE causes subsequent neurologic/cognitive deficits.

COMPLICATIONS

FS can present or recur as FSE. If seizure activity persists after an initial abortive therapy is administered, the protocol for status epilepticus in children needs to be initiated.

ADDITIONAL READING

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- Strengell T, Uhari M, Tarkka R, et al. Antipyretic agents for preventing recurrences of febrile seizures: Randomized controlled trial. *Arch Pediatr Med* 2009;163:799.

See Also (Topic, Algorithm, Electronic Media Element)

NIH Febrile Seizures Fact Sheet: http://www.ninds.nih.gov/disorders/febrile_seizures/detail_febrile_seizures.htm

CODES

ICD9

- 780.31 Febrile convulsions (simple), unspecified
- 780.39 Other convulsions

CLINICAL PEARLS

- FS is common in children <5 years, and unlikely to result in subsequent neurologic injury or epilepsy.
- The diagnosis is focused on evaluation for other neurologic conditions, such as CNS infection/injury that may present as a seizure in the setting of fever.
- Rectal diazepam is an effective abortive agent for recurrent and prolonged FS. Anti-epileptic medication should be reserved for children with epilepsy.

EPILEPSY, GENERALIZED

Jay K. Varma, MD

BASICS

DESCRIPTION

- Seizures and epilepsy syndromes can be broadly categorized into 2 groups: Partial (focal onset) and generalized. Generalized epilepsy syndromes are characterized by recurrent seizures arising from multiple, bilateral regions of the brain simultaneously. Partial epilepsy syndromes have seizures arising from a single focus often with secondary generalization or spread. A careful history, careful review of the EEG, and evaluation of seizure semiology with video-EEG recording can help distinguish between generalized and focal-onset epilepsies.
- Specific epilepsy syndromes that may manifest with generalized seizures include:
  - Childhood absence epilepsy (CAE) – characterized by typical absence seizures along with generalized tonic–clonic seizures in 40% of patients. Onset is between 3 years of age and puberty. Seizures may occur many times per day and can be elicited by hyperventilation. EEG shows characteristic generalized 3 Hz spike-and-wave discharges, up to 80% will have complete remission of seizures, typically by late adolescence.
  - Juvenile myoclonic epilepsy (JME) – characterized by myoclonic and generalized tonic–clonic seizures as well as absence seizures in 10–25% of patients. Age of onset is between age 7 and 30, but most typically in adolescence and symptoms may be lifelong. Myoclonic seizures and generalized tonic-clonic seizures tend to occur upon awakening. The EEG will reveal generalized spike-and-wave discharges, typically with a frequency greater than 3 Hz.
  - Juvenile absence epilepsy (JAE) – similar to CAE but with later age of onset (after puberty). Generalized tonic–clonic seizures are common (occurring in approximately 80% of patients) and remission is uncommon. Myoclonic seizures may occur in approximately 15% of patients but are less frequent and less conspicuous than in JME.
  - Lennox-Gastaut Syndrome (LGS) – characterized by multiple seizure types including tonic, atonic, atypical absence, generalized tonic–clonic, and myoclonic seizures. Age of onset is usually in childhood, typically before age 5. Developmental delay and/or static encephalopathy are typical, often preceding or following the onset of seizures. The interictal EEG will show slow spike-and-wave discharges (<2.5 Hz).
  - Generalized *e*pilepsy with *f*ebrile *s*eizures *p*lus (GEFS+) – most patients present with febrile seizures in early childhood, approximately at the age of 1. They may present with generalized tonic–clonic seizures, absence seizures, myoclonic, atonic, or tonic seizures. Seizures persist beyond the age of 6 and into late adolescence but usually remit in the early teenage years. A positive family history of febrile seizures is key to the diagnosis. Genetic subtypes have been described; defined by mutations in the SCN1A, SCN1B, SCN2A, and GABRG2 genes.
  - Benign myoclonic epilepsy in infancy – a rare syndrome manifested as myoclonic jerks beginning at 5 months to 5 years. Myoclonic seizures may be triggered by tapping or auditory stimuli. EEG shows a normal background with generalized fast spike-and-wave or polyspike-and-wave discharges concomitant with myoclonic jerks.
  - Myoclonic-astatic epilepsy (MAE, Doose Syndrome) – seizures begin at ages of 7 months to 6 years and may be manifested by brief, symmetric jerks involving the neck, shoulders, arms, and legs resulting in head nodding, abduction of the arms, and flexion at the knees immediately followed by a loss of muscle tone causing falls. Patients may also have atonic seizures, tonic seizures, generalized tonic–clonic seizures, and atypical absence seizures.
  - Severe myoclonic epilepsy of infancy (SMEI, Dravet Syndrome) – typically presents with febrile and temperature-sensitive seizures. They may have many different seizure types including myoclonic seizures, generalized tonic–clonic seizures, atypical absence seizures, and focal seizures. The patients develop developmental delay (usually with normal development prior to onset of epilepsy), often with ataxia and upper motor neuron pattern weakness. Sodium-channel modulating drugs (carbamazepine, oxcarbazepine, lamotrigine, phenytoin) may exacerbate seizures and result in status epilepticus. Most commonly associated with SCN1A mutation.

EPIDEMIOLOGY

Incidence

The incidence of epilepsy is between 30 and 80 per 100,000 in developed nations and is significantly higher in developing nations.

Prevalence

The prevalence of epilepsy in developed nations, including generalized and focal epilepsies, is between 4 and 10 per 1,000. The prevalence is higher in developing nations.

RISK FACTORS

A family history of epilepsy is a strong risk factor for generalized epilepsy. Children of patients with epilepsy are 3 times more likely to have epilepsy than the general population.

Genetics

- The genetic contribution to epilepsy is an area of active research. Genes have been implicated as a cause of epilepsy or increased susceptibility to seizures and also to medication response and development of adverse reactions to medications.
- Genetic variants of GABA receptors and nicotinic acetylcholine receptors have been associated with epilepsy as well as gene mutations encoding calcium, sodium, potassium, and chloride-ion channels. Non-ion channel mutations have also been associated with susceptibility to developing epilepsy.
- Genetic testing may be indicated in certain circumstances.

ETIOLOGY

- Idiopathic epilepsies are commonly thought to be genetic in origin.
- Symptomatic epilepsy syndromes are often associated with a structural lesion or inborn error of metabolism.

DIAGNOSIS

HISTORY

- The patient should report a history of recurrent episodes concerning generalized seizure types, described in further detail below:
  - Generalized tonic–clonic seizures – characterized by 2 phases, the tonic phase and the clonic phase. The tonic phase begins with loss of consciousness and often a loud vocalization (ictal cry) generated by activation of the respiratory musculature. The tonic phase is characterized by tonic stiffening of the limbs and is followed by the clonic phase. The clonic phase typically starts with rapid clonic movements of the limbs that slow down and often become larger in amplitude before ceasing. The patient may bite his or her tongue or sustain other injuries and experience bowel or bladder incontinence. The post-ictal state is often marked by confusion and lethargy. The tonic and clonic phases may recur, and the seizures may be accompanied by marked fluctuation in heart rate, respiratory rate, and blood pressure. The presence of an aura preceding a seizure suggests a focal onset as opposed to generalized onset.
  - Typical absence seizures – sudden loss of awareness and behavioral arrest, accompanied by staring, repetitive blinking, or eye flutter typically lasting less than 15 seconds. They may also be accompanied by motor or oral automatisms (lip smacking, purposeless, or pseudo-purposeful movements). EEG will reveal 3 Hz generalized spike-and-wave activity during the seizures, which can often be provoked by hyperventilation.
  - Atypical absence seizures – similar to typical absence seizures but accompanied by unusual features including atypical EEG findings, tonic posturing, prolonged duration, or post-ictal confusion.
  - Tonic seizures – sudden onset loss of awareness with tonic stiffening, often resulting in falls and head injury.
  - Atonic seizures – sudden loss of awareness and loss of muscle tone, often resulting in a fall with injury.
  - Myoclonic seizures – characterized by a brief jerking movement of the arms and trunk, typically without alteration of consciousness. They often occur in clusters in the morning.

PHYSICAL EXAM

- A thorough neurologic examination should be performed. Idiopathic generalized epilepsy syndromes are associated with a normal neurologic examination. Generalized seizures are common in individuals with structural abnormalities of the brain.
- Hyperventilation is a simple bedside maneuver that may induce an absence seizure and can clinch the diagnosis of CAE in suspected patients.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Provoking factors should be ruled out in the evaluation of an initial seizure. Electrolytes including calcium, glucose, liver function tests, renal function tests, serum antiepileptic drug (AED) levels, serum and urine drug tests may help determine the cause of an initial seizure or breakthrough seizure.

Imaging

Initial approach

Brain MRI is the imaging study of choice. Brain imaging may not be necessary if the physical examination is normal and the history and EEG are consistent with CAE or JME.

Diagnostic Procedures/Other

- EEG is often diagnostic; careful scrutiny should be made to distinguish between focal and generalized interictal activity.
- Video-EEG monitoring is the gold-standard test to diagnose and classify seizures if the diagnosis is unclear and also if the seizures are refractory to initial treatment.

DIFFERENTIAL DIAGNOSIS

- Psychogenic nonepileptic seizures can be confused with epileptic seizures. Video-EEG monitoring can help distinguish psychogenic spells from epileptic seizures.
- Tic disorders and other movement disorders may be confused for myoclonic or other seizures.

TREATMENT

MEDICATION

- Phenytoin can be used to treat generalized tonic–clonic seizures, but may exacerbate myoclonic seizures. Signs of toxicity include midline ataxia and diplopia. Idiosyncratic effects include gingival hypertrophy, peripheral neuropathy, and hormonal disturbances.
- Carbamazepine is effective in treatment of generalized tonic–clonic seizures but may worsen absence seizures. It is prone to causing rash, particularly in East Asian patients.
- Ethosuximide is the drug of choice to treat typical absence seizures. It is ineffective in treatment of other seizure types.
- Valproic acid is the drug of choice for a wide array of generalized seizure types including absence and generalized tonic–clonic seizures. It carries a small risk of pancreatitis and hepatotoxicity. Idiosyncratic reactions include tremor, weight gain, hair loss, and hirsutism. Valproate has been associated with a higher rate of teratogenicity than other AEDs.
- Lamotrigine is often used as a second-line agent, or in women of childbearing age due to lower potential for teratogenicity than valproic acid. It may exacerbate myoclonic seizures. Rash is a serious side effect, especially when initiated as an adjunct to valproic acid.
- Phenobarbital is effective against most seizure types but can worsen absences. Mental slowing and drowsiness are common side effects.
- Levetiracetam is effective for a broad range of seizure types. It is often used as a first-line alternate therapy to valproic acid. Irritability and psychiatric side effects can occur. Levetiracetam has no drug–drug interactions and is renally metabolized.
- Topiramate is effective against a broad range of seizures and is considered a second-line therapy. Cognitive slowing, weight loss, hypohidrosis, nephrolithiasis, paresthesias, and GI upset are common adverse reactions.
- Zonisamide is similar in profile to topiramate and is effective against a broad range of seizures.
- Felbamate is effective in LGS and other refractory forms of epilepsy. Close monitoring for hepatic failure and aplastic anemia is necessary especially when initiating the medication.
- Vigabatrin is effective against a broad range of seizure types. Patients must be monitored for irreversible peripheral vision loss from retinal toxicity.
- Rufinamide is approved for treatment of LGS. Headache, dizziness, fatigue, and somnolence are the most common side effects.
- Clonazepam is effective in treating a wide range of seizures. Concurrent administration of clonazepam and valproic acid has been reported to induce absence status. Clonazepam may induce hypersalivation and should be used with caution in patients with respiratory weakness.
- Clobazam is a newly FDA-approved long-acting benzodiazepine for treatment of LGS. Somnolence and respiratory depression are potential adverse effects.

ADDITIONAL TREATMENT

General Measures

The goal of treatment is seizure-freedom without side effects. The patient and family must be educated about epilepsy and general safety measures and precautions for seizures.

Issues for Referral

All patients with epilepsy should be followed by a neurologist who can monitor and adjust AED therapy. Patients with refractory epilepsy may benefit from evaluation at a comprehensive epilepsy center.

Additional Therapies

A ketogenic diet may be an effective treatment in refractory epilepsy.

SURGERY/OTHER PROCEDURES

- Vagus nerve stimulation may reduce the frequency of seizures.
- Callosotomy may be considered as a palliative treatment in patients with severe refractory tonic, atonic, or generalized tonic–clonic seizures.

Pregnancy Considerations

Women of childbearing age should be counseled on the risk of teratogenic effects of AEDs, particularly valproic acid. The risk of major congenital malformations increases with increase in doses and increase in numbers of medications.

ONGOING CARE

PATIENT EDUCATION

Patients with uncontrolled seizures should be counseled against driving and operating heavy machinery. State and local laws vary regarding mandatory reporting of a diagnosis of epilepsy to the authorities. They should take caution when standing at heights or when swimming or bathing. Patients with generalized tonic–clonic, tonic, and atonic seizures are at significant risk of injury from falling.

PROGNOSIS

Prognosis is highly dependent upon the epilepsy syndrome.

ADDITIONAL READING

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CODES

ICD9

- 345.00 Generalized nonconvulsive epilepsy, without mention of intractable epilepsy
- 345.10 Generalized convulsive epilepsy, without mention of intractable epilepsy
- 345.90 Epilepsy, unspecified, without mention of intractable epilepsy

CLINICAL PEARLS

Careful determination of the type of generalized seizure syndrome assists in identification of efficacious therapy.

EPILEPSY, INFANTILE SPASMS

Juliann M. Paolicchi, MA, MD

BASICS

DESCRIPTION

- An epileptic encephalopathy of infancy or early childhood consisting of myoclonic seizures and an associated electroencephalographic pattern: High-voltage slowing, asynchrony, disorganization, and multifocal spikes (hypsarrhythmia).
- Seizures can be flexor, extensor, mixed flexor/extensor, or arrest/akinetic. They occur in clusters, typically upon awakening or drowsiness, and can have focal features. Associated phenomena include nystagmus, eye deviation, autonomic features (flushing, pallor, and pupillary dilation), or a cry at the conclusion of the spasm.
- The combination of infantile spasms (ISs), hypsarrhythmia, and developmental arrest is known as West syndrome.
- ISs are symptomatic if the child has a coexistent neurologic condition, developmental delay at presentation, or if a specific etiology can be identified. They are cryptogenic if no underlying cause is found.

EPIDEMIOLOGY

Incidence

- Incidence is 0.16–0.42 per 10,000 live births. In tuberous sclerosis (TS), the incidence is 68%.

Prevalence

- Prevalence is around 1:3,200 to 1:3,500 of live births with a nearly equal ratio of boys:girls.

RISK FACTORS

- Almost any cause of pre-, perinatal or early infantile brain injury may lead to ISs, including infection, hypoxic–ischemic injury, trauma, stroke, and cerebral dysgenesis.

Genetics

- Most cases are sporadic with a positive family history present in 3–6%.
- TScomplex (TSC) may be sporadic or autosomal dominant.
- X-linked ISs syndromes (ARX, CDKL-5, STXBP1) show variable penetrance.

ETIOLOGY

- Genetic syndromes:
  - Neurocutaneous disorders: TSC, Sturge-Weber syndrome, incontinentia pigmenti, and neurofibromatosis type I
- Down syndrome
  - X-linked ISs syndromes: ARX, CDKL5, Aicardi syndrome
- Autosomal ISs syndromes:
  - Miller-Dieker syndrome (17p13.3), 18q and 7q duplication, partial 2p trisomy, and STXBP1 and MAGI2 deletions
- Metabolic disorders:
  - Congenital lactic acidosis and mitochondrial
  - Disorders
  - Phenylketonuria
  - Non-ketotic hyperglycinemia
  - Pyridoxine and Folinic acid deficiency syndromes
- Malformations of cortical development, especially lissencephaly and hemi-megalencephaly
- Approximately, 40% of ISs are cryptogenic

COMMONLY ASSOCIATED CONDITIONS

- Intrauterine infection, CNS infections
- Cerebral malformations: Malformation of cortical development
- Hypoxic-ischemic encephalopathy, perinatal asphyxia, prenatal/perinatal stroke
- Abusive head trauma
- Intraventricular hemorrhage
- Genetic and neurocutaneous conditions

DIAGNOSIS

HISTORY

- Prenatal and perinatal history, including maternal age, pregnancy complications, perinatal difficulties
- Family history of TS, epilepsy, or previous children with IS or early infant demise
- Developmental history to establish any pre-existing developmental delay.
- Description of spells to differentiate spasms from nonepileptic seizures

PHYSICAL EXAM

- General growth parameters, especially head circumference. Microcephaly suggests pre-existing brain abnormality, poorer prognosis
- Dysmorphism (Down stigmata)
- Retinal defects as in Aicardi syndrome or metabolic diseases
- Hepatomegaly, suggesting inborn errors of metabolism or congenital infection
- Careful skin examination, including Wood lamp examination, should be performed for evidence of neurocutaneous disorders, especially the hypo-pigmented macules associated with TS.
- Neurologic examination: Particular attention should be paid to level of alertness (visual attentiveness often impaired at presentation), developmental milestones, and motor tone.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Routine blood studies:
  - Electrolytes, calcium
  - Glucose (although generally unrevealing)
- Chromosomal analysis:
  - Karotype for Down's phenotype
  - Screening for clinical or radiologic evidence of TS. Genetic testing available for otherneurocutaneous disorders, if suspected
  - Chromosome microarray for suspected genetic or cryptogenic cases
  - Specific genetic panels available for IS-associated syndromes
- Metabolic screening, including blood lactate, pyruvate, and ammonia. Serum amino acids, cholesterol panel (pyridoxine disorders), urine organic acids. Review neonatal metabolic screening for phenylketonuria and biotidinase.
- TORCH titers if suspicion for congenital infection or microcephaly

Imaging

Initial approach

- MRI is the single most useful laboratory test for etiologic diagnosis; intracranial calcifications associated with intrauterine infections and TS are more apparent on CT, but CT is rarely needed.

Follow-up & special considerations

- Positron emission tomography (PET) imaging for refractory ISs, and suspected cortical malformations

Diagnostic Procedures/Other

- EEG: A prolonged EEG that includes sleep is recommended. Ictal video-EEG recording is optimal. The characteristic finding is hypsarrhythmia, a background interictal pattern of disorganized, high-voltage activity with bursts of multifocal, and generalized epileptic activity. Hemispheric asymmetry and focal epileptiform abnormalities are not uncommon. Early in IS, hypsarrhythmia may not be present or present only in deep sleep, so serial EEGs or epilepsy monitoring may be necessary. The ictal EEG pattern typically consists of an initial slow wave followed by low-amplitude fast activity (14–16 Hz) or diffuse attenuation, referred to as an *electrodecremental response*.
- Infants with signs of TS should undergo cardiologic and ophthalmologic evaluation, renal ultrasound; evaluation, and genetic counseling for family members.
- Pyridoxine or folinic acid challenge during EEG
- If no etiology is indentified, consider lumbar puncture for lactic acid, amino acids, folate metabolites, glucose, glycine, and abnormalities of neurotransmitter levels.

DIFFERENTIAL DIAGNOSIS

- Nonepileptic disorders:
  - Benign myoclonus
  - Benign sleep myoclonus
  - Paroxysmal torticollis
  - Posturing related to gastroesophageal reflux (Sandifer syndrome)
  - Shuddering spells
  - Hyperexplexia, or exaggerated startle Myoclonic epilepsies of infancy and other epilepsy syndromes: Such as early myoclonic encephalopathy, Lennox–Gastaut syndrome

TREATMENT

MEDICATION

First Line

- Primary options for treatment are adrenocorticotropic hormone (ACTH) and vigabatrin. A clear consensus on treatment of choice has not been reached. ACTH is the historical treatment option, and high- and low-dose protocols are in use.Treatment is initiated at 150 U/m^2/d IM (high dose) or 20–30 U/d (low dose) for 1–2 weeks.
- If the low-dose protocol is not effective after 2 weeks, high dose at 40 U/d is given; the dose is gradually tapered over 1–3 months. A recent study showed no difference in efficacy between high- and low-dose protocols but the high-dose group had a greater side effects. A recent consensus report recommended high-dose ACTH for 2 weeks followed by a taper.

- Vigabatrin is considered the 1st-line agent for IS secondary to TSC. Dosing is initiated at 50 mg/kg/d and increased to 100–200 mg/kg/d for efficacy. The duration of therapy is not established due to potential complication visual-field constriction. Comparison trials with ACTH suggest better tolerance, similar long-term outcomes, but potentially less short-term efficacy.

Second Line

- A trial of pyridoxine (100 mg IV) and folinic acid (2.5 mg IV) should be considered to rule out pyridoxine and folinic acid deficiency/dependency.
- Topiramate (at dosages up to 20–60 mg/kg/d)
- Zonisamide (5–15 mg/kg/d)
- Clonazepam (0.1–0.15 mg/kg/d)
- Nitrazepam (0.5–3.5 mg/kg/d)
- Prednisone (2 mg/kg/d)
- Additional: Valproate, tiagabine

ADDITIONAL TREATMENT

General Measures

The goal of treatment is cessation of spasms and resolution of the EEG. Serial treatment trials are recommended if spasms persist, since failure of one treatment choice does not preclude success with another.

Issues for Referral

Management of IS should be referred to a pediatric neurologist. Additional consultative services may include ophthalmology and genetics.

Additional Therapies

Given association of IS and developmental delay, referral should be made for early intervention services.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Reports exist of successful treatment of IS with daily high-dose pyridoxine (200–300 mg/d).

SURGERY/OTHER PROCEDURES

Surgery may be indicated in malformations of cortical development and treatment refractory IS, especially due to TS and focal cortical dysgenesis. Surgical resection is focused on areas of hypometabolism identified on PET, identifiable cortical dysgenesis, or hypometabolic tubers in TS. Referral to a pediatric epilepsy center is recommended for presurgical evaluation.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

If patient appears ill, focus on ABCs before treatment of spasms. ISs themselves rarely threaten vital functions.

Admission Criteria

- At the onset, patients are often admitted to an epilepsy monitoring unit for diagnosis and to start etiologic investigation and treatment regimen.
- Patients are typically admitted for the initiation of and education about ACTH therapy.
- Vigabatrin therapy and other anti-epileptic therapies can be initiated without hospitalization.

IV Fluids

Nursing

While ACTH is initiated, patient is monitored for blood pressure, stool guiac and urine glucose.

Discharge Criteria

Discharge is determined by establishment of the diagnosis, initiation of the etiologic evaluation, patient education, and, in the case of ACTH, tolerance of initiated therapy.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Close follow-up of patients is recommended to follow efficacy and side effects of treatment.
- Follow-up EEGs are obtained at regular intervals to determine the efficacy of treatment on the resolution of the EEG findings.
- For ACTH therapy, weekly monitoring of BP, glucose, electrolytes, BUN/creatinine, stool guaiac, and signs of infection is recommended.

DIET

- The ketogenic diet has been shown in a prospective trial to be effective in refractory IS. The ketogenic diet should be administered and monitored by a trained nutritionist.

PATIENT EDUCATION

- Parents/caregivers require education in the diagnosis and outcome of IS, side effects of therapy, and need for close follow-up and communication during therapeutic course.
- Given the frequently associated developmental delays, parents/caregivers should be informed about resources for children with disabilities in their communities and may qualify for special medical insurance programs (SSI).
- Parents/caregivers require extensive training in ACTH administration, managing side effects and precautions regarding immunosuppression.

PROGNOSIS

- Developmental retardation occurs in 85% of patients, and long-term outcome is dependent on underlying etiology. Cryptogenic IS is associated with a better prognosis than symptomatic IS.
- Of cases, 10% achieve normal cognitive, physical, and educational development.
- Of children, 50–90% develop other seizure types, most commonly in the symptomatic group. 27–50% develop severe epileptic encephalopathy (Lennox–Gastaut syndrome).

COMPLICATIONS

- ACTH therapy: Weight gain, irritability, sleep disturbance, hyperglycemia, hypertension, electrolyte abnormalities, cardiomyopathy, immunosuppression, gastritis/GI bleeding
- Vigabatrin therapy: Visual field constriction/peripheral retinal injury, hypotonia, drowsiness, irritability, and reversible MRI abnormalities
- Refractory IS can be associated with development of chronic epileptic encephalopathy (Lennox–Gastaut Syndrome).

ADDITIONAL READING

- Darle K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: A multi-centre randomized trial. *Arch Dis Child* 2010;95:382.
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- Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: A US Consensus report. *Epilepsia* 2010;51:2175.

See Also (Topic, Algorithm, Electronic Media Element)

- Epilepsy Foundation. Patient information available at: http://www.epilepsyfoundation.org
- The NINDS web site: http://www.ninds.nih.gov/disorders/infantilespasms/infantilespasms.htm

CODES

ICD9

- 345.60 Infantile spasms, without mention of intractable epilepsy
- 345.61 Infantile spasms, with intractable epilepsy
- 759.6 Other congenital hamartoses, not elsewhere classified

CLINICAL PEARLS

- IS is a serious epileptic encephalopathy of infancy; it is imperative to recognize and treat aggressively due to associated cognitive and developmental delays.
- The goal of treatment is cessation of spasms and resolution of the hypsarrrhythmic EEG.

E

EPILEPSY, LENNOX–GASTAUT SYNDROME

Juliann M. Paolicchi, MA, MD

BASICS

DESCRIPTION

- Lennox–Gastaut syndrome (LGS) consists of multiple seizure types, cognitive impairment, and a characteristic pattern on the EEG of a generalized, slow spike-and-wave pattern. Considered an epileptic encephalopathy, LGS typically leads to further cognitive deterioration, and the seizures tend to be refractory to antiepileptic drugs (AEDs).

EPIDEMIOLOGY

Incidence

LGS accounts for 1–4% of all childhood epilepsies, but 10% of epilepsies present in the first 5 years. The annual incidence is estimated at 2 per 100,000 children.

Prevalence

- Prevalence rates are 0.1–0.28 per 1,000.
- No racial differences have been identified.
- Although LGS is defined as having onset in children 1–8 years, the mean age at onset is 26–28 months (range 1 day–14 years).
- Males are affected more than females.

RISK FACTORS

30–40% of patients with infantile spasms (IS) develop LGS.

Genetics

Any of the genetic syndromes associated with IS can subsequently lead to LGS – especially strong is the association with tuberous sclerosis.

GENERAL PREVENTION

Early pre- and postnatal care, vaccinations, and trauma prevention play a role in lessening of neonatal brain injury that can lead to LGS.

PATHOPHYSIOLOGY

Although there are limited studies, a recent study of simultaneous recordings of EEG and functional MRI in patients with LGS revealed significant activation of brainstem and thalamus associated with epileptiform discharges compared to control patients (1).

ETIOLOGY

The syndrome is divided into primary (idiopathic) or secondary (symptomatic). Secondary cases (65–75% of patients with LGS) are associated with a host of injuries to the developing brain: Genetic causes (tuberous sclerosis), cerebral dysgenesis, infectious, hypoxic-ischemic, or traumatic etiologies.

COMMONLY ASSOCIATED CONDITIONS

At onset, 20–60% of patients have cognitive impairment which worsens due to deterioration that occurs with LGS. Behavioral/psychological conditions, ranging from hyperactivity to autism spectrum disorders, are common comorbidities.

DIAGNOSIS

HISTORY

- The patient with LGS typically presents with a history of epilepsy, developmental delay, or cognitive impairment, and often a previous neurologic insult or condition. Development of LGS is suggested by a change in seizure type, lack of response to medications, and/or cognitive deterioration.
- The most frequent seizure types in LGS are tonic, tonic–clonic, myoclonic, atypical absence, and "head drop," which are a form of atonic, tonic, or myoclonic seizures.
- Tonic seizures are the most prevalent, occurring in 74–90% of patients. They occur in both awake and sleep states, and can involve the head and trunk, including the arms or the whole body. Apnea and facial flushing are commonly associated. Events tend to be brief, lasting only a few seconds to a minute. They can occur multiple times per day, sometimes up to hundreds per day.
- Atypical absences are often subtle with a gradual onset and offset and an incomplete loss of consciousness. They may be accompanied by myoclonic jerks or automatisms.
- Atonic, myoclonic, and myoclonic–atonic seizures can produce sudden injurious "drop attacks." Frequency ranges from 10% to 56%.
- Generalized tonic–clonic seizures occur in 15% of patients; complex partial seizures occur in 5%. Status epilepticus (SE) (54–75% of patients) can develop from multiple seizure types and tends to be prolonged, resistant to treatment, and recurrent. Nonconvulsive status epilepticus (NCSE) can be difficult to detect clinically.

PHYSICAL EXAM

The neurologic examination typically demonstrates evidence of the etiological neurologic condition (cognitive impairment, developmental delay, cerebral palsy, etc.).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

If there is no previous history of neurologic insult or disease, evaluation requires extensive metabolic evaluation to determine the etiology.

Imaging

Initial approach

Brain MRI is indicated to determine etiologies such as cerebral dysgenesis, stroke, and hypoxic-ischemic encephalopathy.

Diagnostic Procedures/Other

- The EEG provides the pathognomonic finding of generalized, slow spike-and-wave, interictal pattern in an otherwise slow background. The slow spike-and-wave or sharp-and-slow-wave complexes occur as generalized bursts with frequencies between 1.5 and 2.5 Hz. The interictal background slowing may be transient or continuous. Continuous slowing is associated with a poor cognitive outcome. The ictal (seizure) EEG patterns depend on the seizure type.
- Monitoring in a video-EEG unit plays an important role in differentiating the cause of periods of epilepsy and cognitive deterioration.

DIFFERENTIAL DIAGNOSIS

- LGS can be clinically difficult to distinguish from other childhood epilepsy syndromes of multiple seizure types and cognitive dysfunction. Admission to a pediatric epilepsy video monitoring unit can be beneficial to establish the diagnosis.
- Myoclonic-astatic epilepsy consists of myoclonic, atonic, and atypical absence seizures, is predominantly idiopathic, and has a better prognosis.
- Patients with childhood myoclonic epilepsies (benign myoclonic epilepsy of infancy, severe myoclonic epilepsy of infancy, and progressive myoclonic epilepsy) have myoclonic seizures as their predominant feature, less frequent tonic seizures than LGS, faster EEG (>2.5 Hz) patterns, and more variable cognitive decline.

TREATMENT

MEDICATION

First Line

- Broad-spectrum AEDs are the mainstay of treatment. Sedating side effects can exacerbate seizure frequency, and tolerance is common. The following AEDs have specific FDA approval for adjunctive treatment of LGS:
  - Topiramate: In double blind studies, drop seizures decreased 15% per month, and 33% of patients had 50% or greater decrease in seizures. Side effects include somnolence, anorexia, cognitive or behavioral problems, renal stones, and glaucoma.
  - Rufinamide has similar effectiveness in total seizures (2). In double blind studies, it reduced drop seizures by 42.5%. Side effects include dose-related QT shortening, somnolence, and nausea/vomiting.
  - Lamotrigine is well tolerated, and a broad-spectrum AED for LGS seizures. The most concerning side effects are idiosyncratic skin reactions: Rash in 10–12% of patients treated for LGS, Stevens–Johnson syndrome, and toxic epidermal necrolysis. Risk factors for development of lamotrigine-induced rash include younger age (children > adults), concomitant valproate treatment, a high starting dose, and rapid dose titration.

– Felbamate: Although effective in LGS for tonic and drop seizures, it is associated with significant idiosyncratic reactions: Aplastic anemia and hepatotoxicity. The incidence of both of these reactions is low (1 in 4,000–8,000 and 1 in 18,000–25,000 treated patients, respectively), but their severity has limited its use.
– Valproate does not have a specific FDA approval, but has broad-spectrum effectiveness for the seizure types of LGS. Sedative/cognitive side effects are minimal, except at higher concentrations. Dose-dependent side effects include ataxia, tremor, and platelet dysfunction. Idiosyncratic reactions include weight gain, alopecia, and in children <2 years of age on multiple AEDs, hepatotoxicity.

Second Line

Clobazam has been approved by the FDA as an add-on therapy for LGS. Additional broad-spectrum AEDs used for LGS include levetiracetam, which can exacerbate behavioral side effects, and zonisamide – sedation can be lessened by once nightly administration.

Additional Considerations

- Carbamazepine and long-term phenytoin are avoided; they can exacerbate the slow spike-and-wave pattern causing increased seizures or obtundation.
- Clonazepam and diazepam are effective to temporarily decrease seizures due to illness or exacerbations. Tolerance and sedation limit their long-term effectiveness.

ADDITIONAL TREATMENT

GENERAL MEASURES

- The primary goal of treatment is maximizing seizure control and quality of life. Monotherapy is rarely effective. Patients can have periods of relative seizure control, which usually correspond to marked improvements in cognition, alertness, and developmental progress. Unfortunately, cognitive deterioration resumes with the seizures.
- Since seizure exacerbations are expected, due to illness and the syndrome itself, caregivers should have a detailed seizure treatment plan developed with their physician such as use of long-acting benzodiazepines (clonazepam) or temporary increases in current AEDs.
- To avoid toxicity and unnecessary changes in AEDs, LGS patients should have changes to their AED regimens when exacerbations are persistent, do not respond to emergency medications, or new seizure types develop.

Issues for Referral

Patients with LGS often require neurologic care in specialized epilepsy centers to address their multiple neurologic and medical needs.

Additional Therapies

The ketogenic diet is a treatment alternative for medically refractory epilepsy. The diet consists of a high proportion of fats compared to small amounts of carbohydrates and proteins in a ratio of 3-4:1, which induces ketosis. Effectiveness in LGS is based predominantly on case reports especially in children. Side effects include an inability to tolerate the diet, sedation, GI disturbance, and social discomfort. Less restrictive dietary treatments are the modified Atkins diet and the low glycemic diet. Nutritional supervision by a dietician trained in dietary treatments for epilepsy is recommended.

SURGERY/OTHER PROCEDURES

- Two surgical procedures have been used in LGS. Anterior corpus callosotomy is performed with the goal of palliation: 8% of patients are seizure-free, 61% have improvement. Drop attacks, atonic seizures, and secondarily generalized seizures are most responsive to this procedure. Benefits are not permanent.
- The vagus nerve stimulator is approved for medically refractory partial seizures but is also used for refractory generalized seizures including LGS. Seizure freedom is rarely achieved. In small studies, 72% of LGS patients experienced a 50% reduction in seizure frequency with up to 5-year follow-up.
- Isolated cases in which resection of localized lesions improved seizures have been reported.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Treatment of seizure exacerbations and SE is individualized for each patient, based on current and past responses to AED therapy. IV benzodiazepines, fosphenytoin, valproic acid, and levetiracetam are often utilized. Continuous EEG monitoring recommended due to the propensity for NCSE, and to monitor treatment effectiveness.

Admission Criteria

Exacerbation of seizures, NCSE, SE, and encephalopathy

Discharge Criteria

Patients are discharged when the admitting issue, encephalopathy, status, or seizure exacerbation, show sustained responsiveness to treatment. Seizure freedom is not usually a goal for discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patients with LGS should be monitored at regular intervals by epileptologists or neurologists familiar with medically refractory epilepsy.
- Caregiver education includes specific instructions on what conditions warrant a call or visit to the neurologist.

PATIENT EDUCATION

- Patient/caregiver education should address the many social, educational, and medical needs. Caregivers should work with available social workers and community services to obtain disability status for patients, nursing support, respite care, and residential living programs.
- The National Epilepsy Foundation provides information and support. Website: www.efa.org

PROGNOSIS

- Despite many advances, the outcome of patients with LGS remains poor. By adolescence, the combination of continued seizures, cognitive deterioration, and behavioral difficulties leads to profound social consequences. In a 10-year follow-up study, significant cognitive impairment was found in 95–100% of patients.
- Psychiatric problems can progress from mood instability and personality disturbances to acute psychotic episodes. Characteristics of mental deterioration include apathy, memory disorders, perseverance, and impaired vision or speech. Poor prognostic factors include secondary LGS, particularly after West syndrome, early onset and higher frequency of seizures, and continuous slow spike-and-wave EEG background. Mortality rates are 3–7% due to intercurrent illness/accidents.

COMPLICATIONS

SE, NCSE, progressive encephalopathy, cognitive deterioration and impairment

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2. Glauser T, Kluger G, Sachdeo R, et al. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; 70(21):1950–1958.

ADDITIONAL READING

- Conry JA, Ng YT, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut Syndrome. *Epilepsia* 2009;50(5):1158–1166.
- Glauser T, Diego M. Encephalopathic epilepsy after infancy. In: Pellock JM, Dodson WE, eds. *Pediatric epilepsy: diagnosis and therapy*, 2nd ed. Demos Medical Publishing, 2001:201.

See Also (Topic, Algorithm, Electronic Media Element)

- Infantile spasms

CODES

ICD9

All below – with mention of intractable epilepsy

- 345.01 Generalized nonconvulsive epilepsy, with intractable epilepsy
- 345.11 Generalized convulsive epilepsy, with intractable epilepsy
- 345.91 Epilepsy, unspecified, with intractable epilepsy

CLINICAL PEARLS

- LGS is a chronic epilepsy syndrome in which the degree and frequency of seizures fluctuate. Maintaining the patient on an individualized AED regimen with efficacy and low toxicity often affords better quality of life.
- Puberty is often a challenging time for seizure and behavioral control. Psychiatric co-management is often necessary. Young adulthood typically leads to a smoother period for the epilepsy and behavior.

EPILEPSY, STATUS EPILEPTICUS

Jay K. Varma, MD

BASICS

DESCRIPTION

Status epilepticus (SE) is defined as an episode of continuous seizure activity for 30 minutes or multiple recurrent seizures without a full return of consciousness in between events in the same span. Clinically, most seizures resolve within 3–5 minutes and those that last longer are less likely to resolve spontaneously; thus treatment should be initiated after 5 minutes of continuous seizure activity.

SE can be divided into convulsive and nonconvulsive forms. Convulsive forms may be generalized or partial; nonconvulsive forms may be absence (electroencephalogram (EEG) shows generalized spike and wave activity) or complex partial (in which the EEG shows localized rhythmic discharges).

EPIDEMIOLOGY

Incidence

- 10–61 per 100,000 per year.
- As with seizures in general, there is a higher incidence among the young and the elderly.

RISK FACTORS

- 30–44% of patients with SE have a history of epilepsy
- Prior SE
- Low levels of anti-epileptic drugs (AEDs)
- Metabolic abnormalities (hypo- or hyper-natremia, hypercalcemia, hyperglycemia, hepatic or renal insufficiency)
- Drugs/toxins: Alcohol abuse, theophylline, penicillins, cocaine, sympathomimetics, isoniazid (INH), amphetamines, baclofen, flumazenil, lithium, carbon monoxide, general anesthetics, antipsychotic medications, antidepressants, anticholinergic medications
- Structural lesions
- Head trauma
- Hypoxic injury
- CNS infection – meningitis, encephalitis, brain abscess
- Autoimmune or paraneoplastic antibodies (e.g. anti-*N*-methyl D-aspartate receptor antibodies, anti-GABA-B receptor antibodies, anti-voltage-gated potassium channel antibodies)
- Neoplasm (primary CNS or metastatic)
- Vascular lesion (arterio-venous malformation, acute or remote infarct, hemorrhage)

Pregnancy Considerations

Eclampsia is the new onset of generalized seizures during pregnancy or the postpartum period in a woman with signs or symptoms of pre-eclampsia (hypertension and proteinuria). Most older AEDs are pregnancy class D (evidence of risk to the fetus in humans), but the risks of SE to both the mother and fetus usually far outweigh the risks of the medications. Most of the newer medications are Category C (unknown adverse risk to the fetus).

Genetics

Rare genetic diseases may lead to epilepsy and/or a predisposition to developing SE.

GENERAL PREVENTION

Patients with epilepsy should be advised to strictly adhere to their prescribed medication regimen and to avoid factors that may incite seizures (e.g. sleep deprivation or alcohol use).

PATHOPHYSIOLOGY

Seizures are thought to be sustained by a combination of increased neuronal excitation and reduced inhibition. Whereas most seizures resolve spontaneously, SE is thought to be a failure of neuronal inhibition mechanisms, though the exact mechanism is unknown.

COMMONLY ASSOCIATED CONDITIONS

Epilepsy. See "Risk factors".

DIAGNOSIS

HISTORY

- The diagnosis of generalized convulsive SE is often straightforward. Patients lose consciousness, develop tonic contraction of the limbs, often with eye deviation or head turning and typically followed by rhythmic clonic movements.
- Partial convulsive SE may present with repetitive clonic movements of a specific muscle group, such as a limb or hand, with or without alteration of mental status.
- Nonconvulsive SE (complex partial or absence) can present with a wide range of alteration of mental status from coma to mild inattention with word finding.

PHYSICAL EXAM

- Neurological examination may reveal altered mental status, repetitive clonic or myoclonic movements or focal deficits suggestive of a structural lesion.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Provoking factors should be ruled out, even in patients with known epilepsy.
- Electrolytes including calcium, glucose, liver function tests (LFTs), and renal function tests as well as serum AED levels, serum and urine drug screens may identify an etiology.
- Lumbar puncture is indicated if meningitis or encephalitis is suspected.
- SE can result in metabolic acidosis; prolonged convulsive SE can lead to rhabdomyolysis and subsequent renal failure.

Imaging

Initial approach

Noncontrast head CT can quickly diagnose intracranial hemorrhage or tumor if these are suspected. When the patient is stable, brain MRI with gadolinium can better identify structural lesions that may be causing seizures.

Diagnostic Procedures/Other

- EEG can help to establish the diagnosis; in refractory or nonconvulsive SE, continuous EEG recording can help to guide treatment and monitor its effectiveness.
- Lumbar puncture should be performed if subarachnoid hemorrhage, meningitis, or encephalitis is suspected.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of convulsive SE, particularly generalized convulsive SE, is limited to psychogenic spells or movement disorders.
- The differential diagnosis for nonconvulsive SE is vast and is essentially the same as for altered mental status, including infectious, metabolic, toxic, autoimmune/inflammatory, trauma, and psychiatric causes.
- Video-EEG monitoring is the gold-standard study to distinguish between psychogenic spells and epileptic seizures.

TREATMENT

MEDICATION

First Line

- Thamine 100 mg IV should be administered first followed by 50 g of glucose unless the glucose level is known and not low.
- Benzodiazepines are the first-line agents in treatment of SE. The most commonly used agents are lorazepam and diazepam.
  - Lorazepam at 0.1 mg/kg IV up to a maximum dose of 8 mg administered at 2 mg/minute.
  - Diazepam 5–10 mg IV q5 minutes to a maximum of 30 mg in 8 hours.
- If the seizure resolves, begin treatment with phenytoin at 300 mg daily.
- If seizures continue, administer fosphenytoin 20 mg/kg IV at a rate of 150 mg/min. (If fosphenytoin is not available, phenytoin 20 mg/kg IV may be infused at a maximum rate of 50 mg/min.) Valproate may be substituted at 20 mg/kg IV in patients allergic to phenytoin or with hypotension.
  - Fosphenytoin is measured in "phenytoin equivalents". Pharmacists automatically and universally convert all ordered doses of fosphenytoin to phenytoin equivalents.
- If seizures persist, proceed to 1 of these 4 options. At this point, intubation likely is necessary, especially if proceeding to midazolam or propofol. Continuous EEG recording can help guide treatment, particularly if the goal is suppression-burst.
  - IV valproic acid initiated with a 40 mg/kg loading dose over 10 minutes; continue treatment with 1,000 mg IV q6h.
  - IV phenobarbital initiated at 20 mg/kg infused up to 60 mg/min with maintenance dosing at 1–3 mg/kg/day in 2–3 divided doses.

  - A continuous infusion of midazolam initiated with boluses of 0.2 mg/kg over 2–5 minutes repeated every 5 minutes until the seizures stop up to a maximum dose of 2 mg/kg. The infusion can be started at 0.1 mg/kg/hour increased to a maximum of 2.9 mg/kg/hour until the seizure is controlled.
  - IV propofol beginning with boluses of 1–2 mg/kg IV over 3–5 minutes, repeated every 3–5 minutes until seizures stop up to a maximum of 10 mg/kg. Maintenance infusion can be initiated at 33 mcg/kg/min with the rate increased to a maximum of 250 mcg/kg/min until seizures are controlled.
- If seizures continue, begin continuous IV pentobarbital with a loading dose of 5 mg/kg IV up to 50 mg/min with repeat 5 mg/kg boluses until the seizures stop. Begin maintenance infusion at 0.5 to 10 mg/kg/hour titrating to seizure control or suppression-burst EEG pattern.
- Treatment of nonconvulsive SE is controversial.
- If IV access is not available, diazepam can be administered as a rectal gel or the IV solution (5 mg/mL) can be administered intramuscularly, intranasally, or buccally. Fosphenytoin can be administered IM. Phenytoin should not be administered intramuscularly due to inconsistent absorption.

Second Line

- Newer, nonsedating AEDs may be effective in the treatment of SE:
  - Levetiracetam IV administered with a loading dose of 2,500 mg IV over 5 minutes with maintenance dosing of 3,000–6,000 mg daily in 3–4 divided doses.
  - Lacosamide IV administered with a loading dose of 300 mg IV over 30 minutes with maintenance dosing of 200–300 mg IV or PO q12h.

ADDITIONAL TREATMENT

General Measures

- ABCs: Airway, breathing, and circulation.
- Continuous monitoring of oxygenation, heart rate, blood pressure, and EKG should be initiated early.
- Intubation and mechanical ventilation may be necessary and should occur if continuous benzodiazepine or barbiturate infusion is initiated.
- IV fluids or pressors may be necessary to treat hypotension.

Issues for Referral

Neurological consultation should be considered for all patients with SE.

Additional Therapies

- A ketogenic diet is an experimental treatment that may be a potentially effective treatment of highly refractory SE in combination with AEDs.
- Induced hypothermia is another experimental treatment that may be effective in treating refractory SE.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

A ketogenic diet has been reported to have successfully treated several cases of highly refractory SE in combination with AEDs.

SURGERY/OTHER PROCEDURES

Surgery may be considered in extreme cases of highly refractory SE in patients with a known lesion amenable to resection.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Nearly all patients with SE should be admitted for further observation. Patients should be admitted to the intensive care unit if respiratory or cardiovascular support is necessary.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- The patient should be observed closely for 24–48 hours to ensure the resolution of the seizure and the completion of the search for provoking factors. AEDs should be continued, particularly the medication that aborted the seizure. If only benzodiazepines were used to abort the seizure, the patient should be started on AEDs based on comorbidities and side-effect profile of the medications; neurological consultation is recommended.
- Continuous EEG recording can help diagnose nonconvulsive SE or recurrent subtle seizures, which should be suspected in patients with persistent altered mental status or prolonged focal weakness.

PATIENT EDUCATION

- Factors that provoke seizures can also provoke SE. Patients should be counseled regarding the need for medication adherence, avoidance of sleep deprivation, fatigue, and avoidance of physical or emotional stress.
- Patients with a history of SE may be prescribed abortive medications to be used in the pre-hospital setting, i.e. nasal, rectal, or buccal midazolam or oral lorazepam or clonazepam.

PROGNOSIS

- Morbidity from SE typically stems from the underlying cause (hemorrhage, stroke, tumor, etc.) and treatment (ventilator-associated pneumonia, hypotension, sepsis, etc.).
- Mortality from SE is between 10 and 40%, mostly dependent upon the etiology. SE as a result of alcohol withdrawal or intoxication or from low AED levels is associated with a lower mortality than SE due to an acute neurological insult.

COMPLICATIONS

- Many treatments for SE may induce hypotension, including fosphenytoin, phenytoin, midazolam, pentobarbital, phenobarbital, and propofol.
- Phenytoin and fosphenytoin can cause cardiac arrhythmias. Phenytoin is diluted in 40% propylene glycol, and administration can result in metabolic acidosis.
- Pentobarbital infusion can result in gastric stasis, myocardial suppression, thrombocytopenia, and metabolic acidosis (diluted in propylene glycol).
- Propofol infusion can cause hypertriglyceridemia, pancreatitis, and propofol infusion syndrome – a combination of metabolic acidosis, bradycardia, cardiac arrest and rhabdomyolysis.
- Lacosamide may prolong the PR interval.

ADDITIONAL READING

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- Trinka E. What is the evidence to use new intravenous AEDs in status epilepticus? *Epilepsia* 2011;52(Supp 8):35–38.

CODES

ICD9

- 345.00 Generalized nonconvulsive epilepsy, without mention of intractable epilepsy
- 345.01 Generalized nonconvulsive epilepsy, with intractable epilepsy
- 345.3 Grand mal status

CLINICAL PEARLS

- Seizures lasting more than 5 minutes require emergent and aggressive intervention since they are unlikely to resolve spontaneously.
- Underlying provocative causes for status should be sought even in patients with known epilepsy.

FIBROMYALGIA

Kevin V. Hackshaw, MD
Linda M. Burns, DO

BASICS

DESCRIPTION

- Fibromyalgia is a chronic musculoskeletal pain amplification syndrome.
  - Patients typically present with complaints of generalized pain, stiffness, and fatigue for several months to years.
  - Physical findings of specific areas of tenderness with no evidence for any specific etiology for cause of symptoms.
  - Many terms have been used for similar medical conditions over the years, including tender points with rheumatism, neuralgia, fibrositis, psychogenic rheumatism, myofascial pain syndrome, shell shock, chronic fatigue syndrome, and variant reflex dystrophy.

EPIDEMIOLOGY

Incidence

Clinically detectable fibromyalgia as defined by strict American College of Rheumatology criteria is present in approximately 3–7% of the US population.

Prevalence

- Race
  - All races are affected.
- Sex
  - There is a female predominance of approximately 5:1.
- Age
  - The typical onset is between ages 9 and 60 years; most commonly presenting between ages 40 and 60. In the pediatric population, early precursors of this condition may include "growing pains" or "early migraines."

RISK FACTORS

Risk factors include preceding trauma (whiplash injury), infection (hepatitis C, Epstein–Barr virus, etc.), and/or other inciting events all superimposed on a genetically predisposed individual.

Pregnancy Considerations

Fibromyalgia has no known untoward effects on the mother or the developing fetus during pregnancy.

Genetics

- It is estimated that first-degree relatives have approximately eightfold increase risk of development of this disease.
  - Genetic markers have not yet been identified.

GENERAL PREVENTION

There is no known method of prevention; however, maintaining an ideal body weight, healthy sleep hygiene, and stress management can help control the disease.

PATHOPHYSIOLOGY

- The exact pathophysiology is not well understood.
  - It is believed that affected individuals have dysfunctional pain processing with hypersensitivity for pain stimuli.

ETIOLOGY

- The specific cause of fibromyalgia is unknown; however, a number of inciting events are known to be associated with this condition.
  - Recently, a link has been found with a functional polymorphism in the serotonin transporter gene in affected individuals.
  - Sleep disturbances also play an important role in the pathology. Fibromyalgia patients lack stage 4, non-REM (or slow-wave) sleep relative to controls. Intrusion of α-waves on slow δ-waves is seen on EEG patterns. Normally during stage 4 sleep, we should see δ-waves only. α-Waves are an indication of a lighter (more easily arousable) sleep. This same EEG pattern can be experimentally induced by sleep depriving healthy subjects. Serotonin may be the neurotransmitter that mediates slow-wave sleep.

COMMONLY ASSOCIATED CONDITIONS

- Associated conditions may include anxiety disorder, depression, irritable bowel syndrome, restless legs syndrome, temporomandibular joint (TMJ) dysfunction syndrome, premenstrual syndrome, interstitial cystitis, and migraine disorders.
- Posttraumatic stress disorder, Gulf War syndrome, chemical sensitivity syndrome, chronic fatigue syndrome, and variant reflex dystrophy are all conditions with considerable overlap with patients with fibromyalgia.

DIAGNOSIS

HISTORY

- In childhood, a common presentation is "growing pains" or "migraines." In young adulthood, "chronic fatigue" eventually may evolve to global pain.
  - Patients will generally describe aches/pains and/or articular pains with possible joint tenderness, although no actual synovitis is detected.
  - Subjective feeling of swelling usually involves the hands, usually worse in the morning and better by midday. Stiffness lasts approximately 1 hour after awakening.
  - An associated sleep disorder characterized by a nonrestorative sleep is common.
  - Barometric weather changes may exacerbate symptoms. Activity may exacerbate some individuals' symptoms, causing them to seek a more sedentary state.

PHYSICAL EXAM

- Physical examination is characterized by the presence of diffuse tender points (>11 of 18) in all 4 quadrants of the body.
  - The amount of pressure applied is approximately 4 lb (8.8 kg) at each point.
  - Typically patients will be tender at other sites outside of the 18 tested points.
  - On occasion, testing a tender point might elicit a sudden withdrawal-like response from the subject (jump sign).
  - The term *trigger point* is sometimes used. Trigger points are soft-tissue regions that, either spontaneously or following direct pressure, cause radiating pain, paresthesias, and autonomic symptoms.

DIAGNOSTIC TESTS AND INTERPRETATION

The diagnosis of fibromyalgia is made once the above noted symptoms and examination findings have been persistent for >3 months. This condition is a clinical diagnosis and is confirmed by the presence of normal laboratory data helping to exclude other conditions.

Lab

Initial lab tests

- Laboratories helpful for excluding other conditions include the presence of normal ESR, CRP, TSH, muscle enzyme levels, complete blood count, renal and hepatic function, total 25-hydroxy vitamin D.
- Depending on history and physical exam findings, or if symptoms are <3 months in duration, rheumatoid factor (RF), and antinuclear antibody (ANA) may be helpful. ANA levels may be positive in 30% of affected individuals; however, these do not indicate an underlying autoimmune condition.

Imaging

There are no specific imaging abnormalities that are currently useful in clinical practice.

Diagnostic Procedures/Other

There are no other diagnostic procedures required for the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Early stage of inflammatory connective tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis, polymyalgia rheumatica, Ehlers–Danlos benign hypermobility joint syndrome, hypothyroidism, psychogenic rheumatism, dyskinetic phase of parkinsonism, diffuse idiopathic skeletal hyperostosis (DISH), Paget's disease, multiple myeloma, and cyclic edema are some of the disorders that can mimic fibromyalgia.
  - A number of disorders can cause secondary fibromyalgia, including cervical/lumbar syndromes, referred pain syndromes, chronic steroid use (tender shins, diffuse fibromyalgia), occult/overt neoplasm, connective tissue diseases, hypokalemia, vitamin D deficiency, depression, and diabetic neuropathy.

TREATMENT

MEDICATION

- The choice of medication is patient dependent and consideration should be made to coexisting conditions.
  - Medications used include nonsteroidal anti-inflammatory drugs, muscle relaxants, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and dual receptor inhibitors. On occasion, injection of trigger points with lidocaine and corticosteroid is indicated.
  - Tricyclic antidepressants at night time (e.g., doxepin or nortriptyline 10 mg; increase by 10 mg every 3–4 weeks until the patient is able to sleep through the night).
  - Use of SSRIs (e.g., fluoxetine), usually in the morning, may often provide patients with an energy boost.
  - The serotonin-norepinephrine and the norepinephrine-serotonin reuptake inhibitors have been shown to be efficacious in fibromyalgia. Duloxetine 60 mg once or twice daily. Venlafaxine 37.5 mg/day titrated up slowly to 75 mg b.i.d. Milnacipran (FDA approved for fibromyalgia) is slowly titrated up to 50–100 mg twice daily.
- Contraindications
  - Hypersensitivity to a particular drug. SSRIs should not be used in conjunction with monoamine oxidase inhibitor drugs.

ADDITIONAL TREATMENT

General Measures

- An explanation of the condition is the initial approach. Reassurance; job modification with avoidance of repetitive activities; physical therapy consisting of weight loss, abdominal support exercises, and posture training; and heat therapy consisting of ultrasound and hot packs may all play a role.
- Slow initiation of aerobic exercise is essential, with eventual target heart rate >150 beats/min. This is usually more effective than flexibility maneuvers.
  - Healthy sleep hygiene is an important component of treatment of fibromyalgia, including treatment for any underlying obstructive sleep apnea.
  - Other adjuncts used to modulate pain include sleep aids such as antihistamines or benzodiazepines, and anticonvulsants (γ-aminobutyric acid inhibitors, e.g., gabapentin).
- The γ-aminobutyric acid inhibitor pregabalin is effective in fibromyalgia. Pregabalin can be prescribed either as monotherapy or in addition to the aforementioned medications. The typical dose is 300 mg/day in divided doses but up to 450 mg/day has been used in some patients.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Use of analgesics, acupuncture, biofeedback, and other stress management and relaxation techniques in conjunction with the medications listed below often is beneficial.
- Adjunctive treatment
  - *Autonomic dysfunction therapy:* TMJ syndrome is treated with orthodontic bracing/night brace. Irritable bowel syndrome uses agents that decrease GI motility or might benefit from the use of peppermint oil extract. Zinc, magnesium, or manganese supplements might help modulate some symptoms.
  - *Tai Chi*: In a recent study, the use of tai chi had been shown to decrease pain and improve patient outcomes in fibromyalgia.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission is not required for this condition.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

For many patients, fibromyalgia is a chronic disease. Encouragement and regular follow-up are helpful to ensure compliance with a graded exercise program, identification of contributing stress and depression, and adjustment of symptomatic medications.

DIET

There is no definite diet plan for patients with fibromyalgia. A number of diets supported by anecdotal evidence only have been proposed. A normal healthy balanced diet is the best approach.

PATIENT EDUCATION

- Numerous fibromyalgia support chapters are presently active throughout the US.
- General information relayed to the patient on the condition has been shown to have a therapeutic effect.

PROGNOSIS

Generally, fibromyalgia has a fluctuating course. Treatment is aimed at empowering the patient to understand the illness and be an active participant in its treatment. Promotion of a positive outlook helps to minimize depression as a result of the chronic pain and helps to reduce disability seeking. On average, 20% of patients obtain complete relief, 60% obtain a 50% decrease in symptoms, and 20% obtain little relief of symptoms.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Fibrositis

CODES

ICD9

729.1 Myalgia and myositis, unspecified

CLINICAL PEARLS

- Fibromyalgia is clinical diagnosis, pay attention to symptoms that can be "red flags" and elevated inflammatory markers which may be suggestive of an alternative diagnosis.
- One should suspect fibromyalgia in patients with established autoimmune or connective tissue disease if a patient continues to have generalized pain despite adequate therapy for the underlying condition.

FRIEDREICH'S ATAXIA

J. Chad Hoyle, MD

BASICS

DESCRIPTION

Friedreich's ataxia (FRDA) is an autosomal recessive disorder that classically presents with progressive ataxia, lower extremity areflexia, pyramidal signs, proprioceptive/vibratory sensory loss, and dysarthria before the age of 25.

EPIDEMIOLOGY

Incidence

No data available. See prevalence.

Prevalence

- Although rare, FRDA is the most common inherited ataxia in Europe, the Middle East, South Asia, and North Africa. Cases are not encountered in Southeast Asia, sub-Saharan Africa, or among Native Americans. Mexico also has a lower than average prevalence.
- The statistical prevalence is about 1 in every 30,000–50,000 people with no gender predilection.
- The average age of onset of symptomatology is 10–15 years old, classically with an age of onset less than 25 years old, though late onset disease occurs in 15% of patients. "Late onset FRDA" is defined as age of onset between 26 and 39 years old and "Very late onset FRDA" is defined as age of onset at age 40 and older.
- Acadians may have a milder phenotype.

RISK FACTORS

Genetics

- Autosomal recessive linked to chromosome 9q13 affecting the frataxin gene.
- Homozygous GAA trinucleotide repeat expansion (95–98% of cases) with remainder having GAA repeat expansion on one allele and a point mutation or other intragenic mutation on the other allele (no homozygous point mutations have been observed).
- Above mutations silence the frataxin gene.
- Though the length of the repeat does correlate to a degree with disease severity, there are exceptions and prognosis cannot be made solely on the basis of repeat size.

Pregnancy Considerations

- Genetic counseling and carrier testing should be made available for FRDA patients for family planning discussions.
- In a milder disease cohort of FRDA patients with an average age of onset of 24.4, pregnancy complications did not appear to be increased and despite the mothers' neurological deficits, nearly 4/5 births were still vaginal.
- Counseling for psychosocial aspects of childrearing for FRDA patients should be offered.

GENERAL PREVENTION

No reports available. See treatment.

PATHOPHYSIOLOGY

Frataxin protein deficiency causes pathological changes with a predilection for certain tissues, including the dorsal root ganglia dorsal column, spinocerebellar tracts, and corticospinal tracts. The cerebellum is affected to a milder degree (i.e., dentate nuclei). Systemic involvement of the heart and pancreas relate to the hypertrophic cardiomyopathy and diabetes.

ETIOLOGY

- The excessive GAA triplet repeats in FRDA impede transcription structurally and through heterochromatin formation. This reduces the level of frataxin protein.
- Deficiency of frataxin protein appears to be associated with mitochondrial dysfunction, iron dysregulation, and oxidate stress.
- Homozygous symptomatic patients have frataxin protein levels of 5–30% of normal.
- As carriers are asymptomatic, theoretically frataxin protein levels only need to be >50% of normal to avert disease, and thus investigative approaches to increase frataxin levels are an active area of research.

COMMONLY ASSOCIATED CONDITIONS

- Hypertrophic cardiomyopathy (67%)
- Scoliosis (67% clinically; 100% radiographically)
- Pes cavus (55%)
- 10–30% have optic atrophy, sensorineural hearing loss, glucose intolerance, or diabetes mellitus

DIAGNOSIS

HISTORY

- The first symptom typically is gait unsteadiness followed by limb incoordination, difficulty with fine motor movements, and dysarthria. Gait unsteadiness is worse in the dark.
- Rarely scoliosis or cardiomyopathy may precede gait incoordination on presentation.
- Loss of ambulation typically occurs 10–15 years after diagnosis of classic FRDA, though late onset cases have a slower progression and less secondary skeletal abnormalities.

PHYSICAL EXAM

- Classic findings are gait ataxia, limb dysmetria, absent lower extremity reflexes, upgoing plantar responses, decreased vibratory/proprioceptive loss, and dysarthria.
- Lower extremity weakness develops as the disease progresses.
- Muscle atrophy of the hand intrinsics and legs becomes apparent with disease progression.
- Nystagmus is not typical, though square wave jerks can be a common eye movement finding.
- Common systemic musculoskeletal exam findings include scoliosis and pes cavus. Optic atrophy on fundoscopic exam or decreased hearing would be less common exam findings.
- An uncommon finding would include retained or exaggerated deep tendon reflexes (known as FRDA with retained reflexes, which tends to be later onset with a lower incidence of secondary skeletal involvement and cardiomyopathy).
- Very rare finding of isolated spastic paraparesis with ataxia developing later.
- Chorea also would be a very rare variant exam correlate.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- GAA repeat testing to confirm homozygous trinucleotide repeat expansion. If only one allele with GAA repeat expansion, then perform sequence testing to evaluate other allele for possible point mutation or other intragenic frataxin mutation.
- A vitamin E level as deficiency can mimic the FRDA clinical phenotype closely.

Follow-up & special considerations

In unclear cases of ataxia, one could perform a very wide range of labs depending on age and time course of symptom onset, including routine labs, b12, thyroid studies, ammonia, celiac antibodies, GAD antibodies, paraneoplastic panel, metabolic labs for inborn errors of metabolism, mitochondrial studies, further genetic testing, among other possibilities given clinical clues.

Imaging

Initial approach

MRI of the brain/cervical spine recommended to rule out other pertinent pathology.

Follow-up & special considerations

In FRDA, imaging is negative other than spinal cord atrophy and much less commonly mild cerebellar atrophy (not of the hemispheres).

Diagnostic Procedures/Other

- EKG commonly demonstrates T-wave inversions, axis deviation, and other changes.
- An echocardiogram commonly demonstrates hypertrophic changes. Cardiac MRI might offer higher quality surveillance for early and pertinent changes.
- EMG may have absent sensory responses related to polyneuropathy (dorsal root ganglia pathology) with motor amplitudes less affected.

Pathological Findings

No reports available.

DIFFERENTIAL DIAGNOSIS

- Vitamin E deficiency most closely mimics FRDA. (Autosomal recessive [AR] disorders, such as ataxia with isolated vitamin E deficiency and abetalipoproteinemia should be considered with significant vitamin E deficiency)
- Other AR ataxias could present similarly, as well, though would typically be associated with more significant cerebellar atrophy and other clues per individual disorder (ataxia with oculomotor apraxia, ataxia telangiectasia, spastic ataxia of Charlevoix Saguenay, and spinocerebellar ataxia with axonal neuropathy)

- Spinocerebellar ataxia
- Vitamin B12 deficiency
- Mitochondrial disorders and POLG mutations
- Ataxic presentation of primary coenzyme Q10 deficiency (associated with cerebellar atrophy)
- Other structural, metabolic, toxic, or acquired disorders in general presenting with ataxia
- Of note, isolated "sporadic ataxia" presentations (defined by progressive ataxia with onset after age 20, no family history, no other clinical symptoms, and no established cause), may test positive for FRDA in about 4% of cases

TREATMENT

MEDICATION

First Line

- There are no proven or FDA-approved disease modifying therapies for FRDA.
- Symptomatic medication therapy can be utilized. Baclofen is utilized for spasticity if needed. Start at roughly 5 mg PO t.i.d. and titrate slowly to a maximum of 60–80 mg PO total daily dosing as needed and depending on age.

Second Line

- Idebenone supplementation (coenzyme Q10 analog with antioxidant properties) without definitive benefit but some trends of decreasing cardiac hypertrophy of uncertain clinical significance. Also, possible dose-dependent trend toward improvement in neurological symptoms at high dose. As no significant side effects, some still consider treatment (low dose 5–10 mg/kg/day versus high dose 35–45 mg/kg/day).
- Further therapies listed below are in an investigational stage and are NOT recommended outside of a clinical trial at this point.
- Agents that increase the level of frataxin have been identified. Erythropoietin (EPO) raises frataxin levels through a posttranscriptional mechanism and histone deacetylase inhibitors (HDAC inhibitors) raise frataxin levels through decreasing heterochromatin silencing of the frataxin gene. EPO has shown mild initial clinical encouragement in an open label study but has concerns of increasing hematocrit requiring phlebotomy and HDAC inhibitors have yet to be tested clinically.
- Iron chelation therapy with deferiprone also demonstrated possible mild initial encouragement in an open label study, though there were side effect concerns of possible agranulocytosis.
- Pioglitazone is a peroxisome proliferator-activated receptor (PPAR) γ-agonist that involves another pathway being studied in FRDA.

ADDITIONAL TREATMENT

General Measures

No reports available.

Issues for Referral

- Cardiology to monitor cardiomyopathy and treat as appropriate.
- Orthopedics for surgical consideration of significant scoliosis cases (typically >40 degrees/significant progression of curve). Less commonly orthopedic surgery consultation for significant foot deformity.
- Endocrinology for diabetes.

Additional Therapies

- At discretion of cardiologist, stationary cycling for 20–25 minutes at 70–85% of maximum heart rate, as measured with a graded exercise test, is recommended.
- Physical/occupational therapy evaluation for assistive or adaptive devices.
- Orthoses for scoliosis or foot deformities as needed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Some recommend supplementation with idebenone as antioxidant therapy. See treatment section.

SURGERY/OTHER PROCEDURES

Orthopedic surgery considerations in select cases of significant scoliosis or severe foot deformities (see issues for referral).

IN-PATIENT CONSIDERATIONS

No reports available.

Nursing

No reports available.

Discharge Criteria

No reports available.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Yearly EKG and ECHO surveillance in patient initially without cardiac disease. Cardiac MRI might be a promising alternative to ECHO.
- Plain films to assess scoliosis roughly yearly with emphasis during periods of growth and during transition to wheelchair.
- Glucose monitoring yearly.
- Hearing assessment every 2–3 years.

DIET

Diet is at the discretion of cardiologist.

PATIENT EDUCATION

Friedreich's Ataxia Research Alliance: www.curefa.org or contact office at 484-879-6160 or 484-875-3105.

PROGNOSIS

Average mortality is roughly 36 years past the initial onset of symptoms (older than previous estimate of 37 years old).

COMPLICATIONS

Mortality is most often related to heart failure, arrhythmia, or aspiration and pneumonia.

ADDITIONAL READING

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CODES

ICD9

334.0 Friedreich's ataxia

CLINICAL PEARLS

- FRDA is an autosomal recessive neurodegenerative disorder that classically presents in childhood and is associated with progressive ataxia, sensory loss, lower extremity areflexia, and dysarthria.
- Cardiomyopathy, scoliosis, and diabetes are the most common systemic manifestations.
- Late onset and other clinical variants are more recognized now in an age of genotype–phenotype correlation.
- FRDA is associated with frataxin deficiency and resultant mitochondrial dysfunction, iron dysregulation, and oxidative damage.
- Treatment is mainly supportive, but clinical research is on the horizon related to agents that increase frataxin expression, which may be a future disease modifying strategy.

GANGLIOSIDOSES

Chang-Yong Tsao, MD, FAAN, FAAP

BASICS

DESCRIPTION

Gangliosidoses are a group of diseases that result from enzymatic block and subsequent neuronal ganglioside deposition. Gangliosides are present predominantly in the gray matter. The gangliosidoses include (a) G_{M2} gangliosidoses (deficiency of hexosaminidase A), consisting of infantile G_{M2} gangliosidosis or Tay–Sachs disease, juvenile G_{M2} gangliosidosis, adult G_{M2} gangliosidosis, and normal phenotype with hexosaminidase A deficiency; (b) Sandhoff's disease (deficiency of HEX A and HEX B); and (c) G_{M1} gangliosidoses, which has infantile, juvenile, and adult variants. All of the gangliosidoses are autosomal recessive disorders.

EPIDEMIOLOGY

Incidence

The carrier rate of Tay–Sachs disease is between 1 in 30 and 1 in 50, with a disease incidence of 1 in 4,000 in Ashkenazi Jews; whereas in the non-Jewish population, the carrier rate is 1 in 300, with an incidence of 1 in 112,000. The carrier rate of Sandhoff's disease is 1 in 500, with an incidence of 1 in 1,000,000 in the Jewish population. In non-Jewish populations, the carrier rate is 1 in 278, with a disease incidence of 309,000. The incidence of G_{M1} gangliosidoses is 1 in 100,000–200,000.

Prevalence

Prevalence varies from 1:17,000 to 1:3700 in G_{M1} gangliosidoses.

RISK FACTORS

Tay–Sachs disease and Sandhoff's disease are seen more frequently in the Jewish populations.

Pregnancy Considerations

The prenatal diagnosis of Tay–Sachs disease, Sandhoff's disease, and other G_{M2} gangliosidoses can be made by quantifying HEX A and HEX B in the amniotic fluid (at 16–18 weeks) or the chorionic villi (9–12 weeks) during pregnancy. Prenatal diagnosis of G_{M1} gangliosidoses can be made by measuring acid β-galactosidase activity in amniocytes or chorionic villi.

Genetics

All forms of G_{M1} gangliosidoses and G_{M2} gangliosidoses are autosomal recessive disorders.

GENERAL PREVENTION

Vaccinations may prevent infections and rapid clinical deterioration.

PATHOPHYSIOLOGY

G_{M1} gangliosidoses and G_{M2} gangliosidoses are caused by gene mutations resulting in gangliosides deposition in brain and other organs, neurodegeneration and other dysfunctions.

ETIOLOGY

- There are two isoenzymes of β-hexosaminidase, HEX A, and HEX B. Tay–Sachs disease is caused by gene mutations and complete deficiency of HEX A, with normal HEX B. Patients with juvenile and adult G_{M2} gangliosidoses have partial deficiency of HEX A. Sandhoff's disease is induced by mutations of the HEX B gene (encodes β-subunit of HEX A and HEX B), with deficiency of HEX A and HEX B. G_{M2} activator deficiency is due to mutations of the G_{M2} A gene and deficiency of the G_{M2} activator protein, with normal HEX A and HEX B.
- G_{M1} gangliosidosis is due to mutations of β-galactosidase gene.

COMMONLY ASSOCIATED CONDITIONS

- Myoclonic epilepsy, infantile spasms, and a variety of partial or generalized epilepsies are seen in Tay–Sachs disease and other G_{M2} gangliosidoses. Epilepsy is also present in infantile and juvenile G_{M1} gangliosidoses.
- Progressive ataxia and dementia occur often in G_{M2} gangliosidoses. Ataxia is also present in juvenile and adult G_{M1} gangliosidoses.

DIAGNOSIS

HISTORY

- In Tay–Sachs disease, hyperacusis, startle response, severe irritability occur in the first few months; myoclonic seizures, infantile spasms, partial and generalized motor seizures are frequently seen in the first year. Further deterioration in the second year of life results in decerebrate posturing, incoordinate swallowing, and a vegetative state.
- In juvenile G_{M2} gangliosidosis, incoordination and ataxia become apparent between 2 and 6 years. Dementia, loss of speech, spasticity, seizures, and dysfunction of the basal ganglia, cerebellum, corticospinal tracts, and anterior horn cells then are noted over several years.
- In chronic or adult onset G_{M2} gangliosidosis, the onset is at puberty or early adulthood, symptoms of spinocerebellar degeneration and lower motor neuron disease are often seen. Psychosis, depression, personality changes, dystonia, and extrapyramidal signs can occur.
  - The presentation of infantile Sandhoff's disease is similar to Tay–Sachs disease, including the onset and progressive deterioration of neurologic function.
  - G_{M2} activator deficiency has a clinical phenotype similar to Tay–Sachs disease and infantile Sandhoff's disease.
  - In infantile G_{M1} gangliosidosis symptoms are noted early, with severe motor and mental retardation evident in the first year. Intractable seizures often occur. Feeding difficulty and poor appetite lead to weight loss.
  - In juvenile G_{M1} gangliosidosis, the onset is between 6 and 20 months. Psychomotor development is normal in the first year. Ataxia begins at age 1 year. Seizures and blindness often occur after age 2 years.
  - In adult G_{M1} gangliosidosis, initial symptoms are abnormalities of gait and dysarthria. Mental impairment usually is mild and seizures are rare.

PHYSICAL EXAM

- In Tay–Sachs disease, developmental retardation, dementia, hypotonia, progressive weakness, poor head control, decrease in attention, visual decline and blindness, and cherry-red spot are seen.
  - In juvenile G_{M2} gangliosidosis, optic atrophy and retinitis pigmentosa can occur in the later stages.
  - In chronic or adult onset G_{M2} gangliosidosis, dystonia, and extrapyramidal signs can occur.
  - In infantile Sandhoff's disease, these patients have organomegaly and occasional bony deformities.
  - In infantile G_{M1} gangliosidosis, cherry-red spots are seen in 50% of patients.
  - In juvenile G_{M1} gangliosidosis, strabismus, choreoathetosis, loss of speech, and generalized muscle weakness are seen.
  - In adult G_{M1} gangliosidosis, progressive dystonia of the face and extremities is seen.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

EEG may reveal a variety of epileptiform abnormalities (e.g., hypsarrhythmia). In adult G_{M2} gangliosidosis, electromyograms frequently reveal chronic active denervation and reinnervation, and other changes consistent with anterior horn cell disease.

Follow-up & special considerations

Vacuolated lymphocytes and foam cells in the bone marrow can be detected in infantile and juvenile G_{M1} gangliosidosis.

Imaging

Initial approach

- MRI of Tay–Sachs disease reveals low-signal lesions in areas of abnormal cerebral white matter and the basal ganglia.
- In all G_{M1} gangliosidoses, diffuse brain atrophy is present on neuroimaging. Low-signal abnormalities of the basal ganglia and high-signal lesions of the white matter may be present in infantile and late-onset G_{M1} gangliosidoses.
- In infantile G_{M1} gangliosidosis, bone x-ray films may detect vertebral deformities, hypoplasia, anterior beaking at the thoracolumbar region, retarded bone age, short long bones, and bilateral dislocation of the hip joints.

Follow-up & special considerations

During later stages, diffuse brain atrophy and compensatory ventriculomegaly may be noted in Tay–Sachs disease. Severe cerebellar atrophy and mild cerebral atrophy may be noted in juvenile and adult G_{M2} gangliosidoses.

Diagnostic Procedures/Other

- Genetic testing of the gangliosidoses requires analysis of either blood or fibroblast samples. The HEX A gene is mapped to chromosome 15q23-24, HEX B gene to chromosome 5q13, and G_{M2A} gene to chromosome 5q32-33. At least 100 mutations in the HEX A gene have been reported in Tay–Sachs disease, and the most frequently seen mutation in Ashkenazi Jews is a four base-pair insertion in exon 11 (1)[A].
- The human β-galactosidase gene is mapped to chromosome 3p21.33. Mutations include missense, nonsense, and insertion varieties. More than 102 mutations of β-galactosidase gene are noted (2)[A].

Pathological Findings

G_{M1} gangliosides, G_{M2} gangliosides deposition in the brain and brain atrophy are seen.

DIFFERENTIAL DIAGNOSIS

- Because myoclonic epilepsy, ataxia, loss of milestones, and dementia are all present in the gangliosidoses, the differential diagnosis includes neurodegenerative diseases such as neuronal ceroid lipofuscinosis, progressive myoclonic epilepsy syndrome, aminoacidopathies, organic acidopathies, fatty acid β-oxidation disorders, inborn errors of creatine metabolism and mitochondrial cytopathies.
- Because adult and juvenile patients with gangliosidosis can have dystonia, psychosis, spinocerebellar degeneration, corticospinal tract degeneration, or spinal cord anterior horn cell dysfunction, the differential diagnosis includes Kugelberg–Welander disease, spinocerebellar ataxia, Friedreich's ataxia, amyotrophic lateral sclerosis, and other late-onset variants of lysosomal sphingolipidoses.

TREATMENT

MEDICATION

First Line

Anticonvulsants as required for seizure control. Spasticity of the extremities may benefit from antispasticity drugs such as oral diazepam, dantrolene, baclofen (1,2)[A].

Second Line

Intrathecal baclofen infusions and IM botulinum toxin injections may be effective (1,2)[A].

ADDITIONAL TREATMENT

General Measures

There are no definitive treatments for the G_{M1} and G_{M2} gangliosidoses. Only symptomatic and supportive therapies are available.

Issues for Referral

Patients may need referral for treatment for infections, epilepsy, respiratory care, nutrition, and psychosis.

Additional Therapies

- Physical, occupational, and speech and language therapies are helpful for patients with muscle weakness, coordination difficulty, and language/speech problems.
- Treatment of epilepsy with a variety of new and old antiepileptic drugs is available. Nutritional support, fluid and electrolyte maintenance, and infectious control with appropriate antibiotics are important. Constipation may be a significant problem and require stool softeners or laxatives.

SURGERY/OTHER PROCEDURES

Gastrostomy tube placement and Nissen fundoplication may be needed for patients with feeding and swallowing difficulties, and gastroesophageal reflux.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Status epilepticus may need stabilization with IV anticonvulsant such as diazepam or phenytoin therapy at emergency department.

Admission Criteria

Patients with exacerbation of epilepsy or severe pneumonia often need to be hospitalized.

IV Fluids

If severe infections occur (e.g., aspiration pneumonia), patients should be admitted for IV fluids, antibiotics and chest physical therapy.

Nursing

Severe pneumonia or status epilepticus may need ICU nursing care and treatment.

Discharge Criteria

When vital signs are stable, seizures are under good control, and no need for IV fluid or IV medications, patients may be discharged.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Monitor for seizure control, neurologic function, psychosis or mental decline, and nutritional status.

DIET

No restriction for diet.

PATIENT EDUCATION

National Tay–Sachs and Allied Diseases Association, 2001 Beacon Street, Suite 204, Brookline, MA 02135. Phone: 617-277-4463; fax: 617-277-0134, website: http://www.ntsad.org

PROGNOSIS

The majority of patients with Tay–Sachs disease survive to age 2–4 years. Aspiration pneumonia is often the cause of death. Patients with juvenile G_{M2} gangliosidosis also frequently die of intercurrent infection between 10 and 20 years of age. Adult patients with G_{M2} gangliosidosis may live into the 6th or 7th decade of life. Patients with infantile G_{M1} gangliosidosis typically die of infection and cardiopulmonary failure by age 2 years. The average lifespan for juvenile G_{M1} gangliosidosis varies between 3 and 10 years. Patients with adult G_{M1} gangliosidosis may survive up to age 60.

COMPLICATIONS

Infections, malnutrition, status epilepticus, and constipation may occur.

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See Also (Topic, Algorithm, Electronic Media Element)

- Tay–Sachs disease
- Sandhoff's disease
- G_{M2} gangliosidosis
- G_{M1} gangliosidosis

CODES

ICD9

330.1 Cerebral lipidoses

CLINICAL PEARLS

- G_{M1} gangliosidosis is due to β-galactosidase deficiency.
- Tay–Sachs disease is due to deficiency of HEX A.
- Sandhoff's disease is due to deficiencies of HEX A and HEX B.

GIANT CELL ARTERITIS

Steven E. Katz, MD
James A. McHale, MD

BASICS

DESCRIPTION

Giant cell arteritis (GCA) is a systemic vasculitis characterized by focal granulomatous inflammation of medium and small arteries. Involvement of elastic-containing cranial vessels predominates, including the superficial temporal, ophthalmic, posterior ciliary, occipital, and vertebral arteries. The aorta, carotid, and coronary arteries are less commonly involved. A high degree of suspicion should be maintained for GCA in patients age >60 years because of the risk of acute and severe visual loss. Ocular symptoms complicate approximately 50% of cases.

EPIDEMIOLOGY

Incidence

Average annual incidence was 17.8/100,000 population older than 50 years of age in Olmstead County, Minnesota (1)[A].

RISK FACTORS

- Age: Generally individuals >60 years; incidence increases with age; majority will be in their eighth decade
- Sex: Female to male ratio of 2:1
- Race: Rare in African Americans and Asians

Genetics

A genetic predisposition may exist, as evidenced by an increased prevalence of HLA-DR1, 3, 4, and 5 antigens, along with familial and geographic clustering of cases.

GENERAL PREVENTION

No reports available.

PATHOPHYSIOLOGY

- The inflammatory response is initiated by activated T-lymphocytes that enter the vessel wall via the vaso vasorum.
- Macrophages in the adventitia produce matrix metalloproteinases which cause fragmentation of the internal elastic lamina and tissue destruction.
- The presence of multinucleated giant cells correlates with intimal hyperplasia and occlusion of the vessel lumen by smooth muscle cells (2)[A].

ETIOLOGY

The etiology of GCA is unknown, but an immune-mediated process (cellular more so than humoral) is most widely suspected.

COMMONLY ASSOCIATED CONDITIONS

- Polymyalgia rheumatica
- Rheumatoid arthritis

DIAGNOSIS

HISTORY

GCA is a syndrome that may present with any combination of the following:

- Headache (initial manifestation in 50–90% of cases)
- Pain often gradual onset, diffuse, and severe, may be unilateral, usually prominent if not intractable, may be perceived as superficial and may be unresponsive to analgesics
- Temporal scalp tenderness
- Abrupt, progressive monocular visual loss with involvement of the fellow eye in 25–50% of cases, usually within 10 days
- Visual loss may be insidious or preceded by episodes of transient monocular loss of vision
- Partial to complete blindness, largely irreversible
- Less common ophthalmic complaints may include amaurosis fugax, diplopia, periorbital swelling and eye pain
- Polymyalgia rheumatica (>50 years of age, proximal arthralgias and myalgias, morning stiffness, increased erythrocyte sedimentation rate >40)
- Jaw claudication
- Facial pain
- Fatigue, general malaise, night sweats
- Anorexia
- Extremity claudication
- Transient ischemic attack or stroke

PHYSICAL EXAM

- The superficial temporal artery may exhibit point tenderness, diminished pulse, induration, hemorrhagic bullae, or overlying skin necrosis
- Anterior ischemic optic neuropathy (AION) is the most common cause of visual loss; less frequent causes include central and branch retinal artery occlusion, choroidal infarction, and posterior ischemic optic neuropathy
- Signs of optic neuropathy may include decreased visual acuity, decreased color vision, afferent pupillary defect, and visual field loss
- Often altitudinal visual field defect (i.e., respecting the horizontal midline)
- In cases of AION, the optic disc may show pallid swelling, although hyperemic disc swelling is occasionally seen; peripapillary hemorrhages and cotton wool spots may be noted; as optic disc swelling resolves, optic atrophy occurs
- Fever of unknown origin (generally low grade)
- Weight loss
- III, IV, or VI cranial neuropathies
- Orbital inflammatory syndrome
- Ocular ischemic syndrome, hypotony
- Horner's syndrome (i.e., ptosis, miosis +/– anhydrosis)
- Neurologic sequelae (ataxia, confusion, hearing loss, ischemic peripheral neuropathy)
- Myocardial, renal, visceral, or cerebral infarction
- Large-vessel involvement (aortic aneurysm or rupture, most commonly thoracic)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- There is no specific laboratory test for the diagnosis of GCA.
- Westergren erythrocyte sedimentation rate (WESR) often exceeds 70 mm/hour.
- A normal WESR does not rule out the diagnosis of GCA; however, as approximately 15% of biopsy positive GCA cases will have a WESR within normal limits.
- WESR is a general measure of systemic inflammation, as are C-reactive protein (CRP), platelets, fibrinogen, and complement levels, which may also be elevated.
- Additionally, anemia (hypochromic, microcytic or normochromic, normocytic), polyclonal hypergammaglobulinemia, and a mild leukocytosis may be observed. Liver alkaline phosphatase levels may be elevated in GCA.

Follow-up & special considerations

- Drawing the WESR and CRP together is more sensitive than the WESR alone for the diagnosis of GCA (3)[A].
- WESR, CRP, and other acute phase reactants may be used to monitor response to therapy and disease control.

Imaging

Initial approach

- Fluorescein angiography (FA) of the fundus may demonstrate a delayed or absent choroidal filling pattern suggesting arteritic ischemic optic neuropathy.
- FA in cases of nonarteritic ischemic optic neuropathy may show delayed optic disc filling, yet the choroidal circulation is generally not affected.
- CT or MRI scans are generally not indicated but may be necessary to rule out compressive or infiltrative lesions in atypical cases (e.g., multiple cranial neuropathies, proptosis or seizure).

Follow-up & special considerations

If large-vessel involvement is suspected, ultrasound and/or angiography should be pursued.

Diagnostic Procedures/Other

- Temporal artery biopsy should be taken from the affected side.
- Some authors recommend bilateral temporal artery biopsies; however, biopsy of the symptomatic side usually is adequate.
- A large biopsy (>2 cm) is needed because of the commonly observed "skip" lesions in GCA.

Pathological Findings

- A positive biopsy is diagnostic and demonstrates segmental cellular infiltrates of the vessel wall which are predominantly consisted of T-lymphocytes, plasma cells, and macrophages (4)[A].
- Fragmentation of the internal elastic lamina and the presence of multinucleated giant cells are common, but not necessary to make the diagnosis of GCA.

DIFFERENTIAL DIAGNOSIS

- Nonarteritic AION
- Angle-closure glaucoma
- Migraine
- Temporomandibular joint syndrome
- Trigeminal neuralgia
- Malignancy
- Infection
- Systemic vasculitis, i.e., polyarteritis nodosa, Wegener's granulomatosis
- Systemic lupus erythematosus
- Rheumatoid arthritis

TREATMENT

MEDICATION

First Line

- Oral prednisone is given with the initial dose ranging from 40 to 120 mg/day. The overall degree of suspicion and presence of visual involvement influence the dose and route. Some authors recommend IV methylprednisolone 1 g/day for 3 days in cases presenting with visual deficit; however, the benefit is unproven. The goal of therapy is to maintain the lowest dose of corticosteroid that resolves clinical symptoms and maintains WESR <30–40 mm/hour.
- Absolute contraindications to corticosteroid use include hypersensitivity to the drug and systemic fungal infection. Relative contraindications include diabetes, hypertension, tuberculosis, osteoporosis, and congestive heart failure.

Second Line

In cases where active inflammation is not controlled or intolerable side effects occur, a second immunosuppressive agent (e.g., azathioprine or methotrexate) may be added to spare the steroid dose.

ADDITIONAL TREATMENT

General Measures

Treatment of GCA focuses on the prevention of serious vascular complications, particularly blindness. Corticosteroids are the mainstay of therapy for GCA and should be instituted when the diagnosis is suspected, even in the face of normal WESR and prior to obtaining temporal artery biopsy. Unfortunately, visual loss is often irreversible and may be progressive even when high-dose IV methylprednisolone is given (5)[B]. Headache typically responds to corticosteroid treatment within 1–2 days. Duration of steroid therapy for treatment of GCA may range from 1–3 years.

Issues for Referral

Visual symptoms/loss associated with GCA require that the patient see an ophthalmologist on an emergency basis and may involve hospital admission.

SURGERY/OTHER PROCEDURES

Temporal artery biopsy should be performed to confirm the diagnosis of GCA. It is performed under local anesthetic and on an outpatient basis. A negative biopsy does not rule out the diagnosis of GCA.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Admission for GCA is indicated for IV steroid therapy, unstable vitals, large vessel involvement, ischemic limb, and renal, gastrointestinal, cardiac, or cerebral complications.
- Alternatively, IV therapy may be given on an outpatient basis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be seen every 4–6 weeks to assess the response to therapy. Clinical symptoms and signs, ESR, and other acute phase reactants should be followed as corticosteroids are tapered.

DIET

No reports available.

PATIENT EDUCATION

It is necessary to educate each patient regarding the chronic nature of GCA, the spectrum of symptoms, the possibility of relapse, and possible sequelae of long-term steroid therapy.

PROGNOSIS

Relapse most commonly occurs during the initial year of therapy, especially following reduction of steroid dose. Up to 50% of GCA patients may require corticosteroids for >2 years. In general, patients have been reported to have the same life expectancy as age-matched controls; however, profound visual loss in GCA has been found to correlate with decreased quality and duration of life.

COMPLICATIONS

- GCA patients may experience steroid-related complications such as progressive obesity, osteoporosis, hip and spinal compression fractures, immunosuppression, cushingoid appearance, diabetes, hypertension, peptic ulcer disease, gastrointestinal bleed, cataracts, or glaucoma.
- Gastric prophylaxis may include taking steroids with meals or in divided doses. Additionally, ranitidine (Zantac), sucralfate (Carafate), or omeprazole (Prilosec) may be indicated.
- Bisphosphonates have been shown to decrease bone loss and may be indicated for some patients.

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See Also (Topic, Algorithm, Electronic Media Element)

- Temporal arteritis
- Ischemic optic neuropathy

CODES

ICD9

- 446.5 Giant cell arteritis
- 725 Polymyalgia rheumatica

CLINICAL PEARLS

- Medicare + symptoms = WESR, CRP
- Maintain a high degree of suspicion for GCA in patients >55 years of age
- Treat on suspicion
- Lay hands on your patient's head
- Prednisone is a loaded gun
- Lose not thy patient to follow-up

GUILLAIN–BARRÉ SYNDROME

Victoria Lawson, MD
John Kissel, MD

BASICS

DESCRIPTION
An acute, immune-mediated polyradiculoneuropathy of varying clinical presentations. Presents classically as a demyelinating neuropathy but axonal (AMSAN, AMAN) and cranial nerve (Miller Fisher syndrome) variants have been described.

EPIDEMIOLOGY
Incidence/Prevalence
- 1–4/100,000 annually
- Affects men and women equally in the USA (NIH, The National Women's Health Centre, 2004)
- Increased incidence in elderly (4/100,000 in ages >75 years) and during pregnancy

RISK FACTORS
- Race: All
- Age: All; peak 38–40 years
- Infection precedes disease onset by a few weeks in 60–70% of patients. *C. jejuni* most common precipitating infection occurring in 30–40%, with gastroenteritis that precedes weakness by 7–14 days. Other infections are noted below under *Etiology*.

PATHOPHYSIOLOGY
- Trivial infection (diarrhea, URTI)
- Molecular mimicry with humoral response
- Complement activation
  - Damage to Schwann cell myelin
  - Damage to terminal axons
- Macrophage-mediated myelin stripping

ETIOLOGY
- Antecedent infection in 2/3 patients:
- Respiratory infection >>diarrhea
  - *Campylobacter jejuni* >> CMV, EBV > *M. pneumoniae* >> *H. influenzae*, Parainfluenza, Influenza A/B > Adenovirus, HSV, VZV

COMMONLY ASSOCIATED CONDITIONS
- Hepatitis A, B, C; HIV
- Hematologic malignancies: Lymphoma
- Autoimmune disorders
  - Collagen vascular disorders: SLE, sarcoidosis
  - Transplants: Organ rejection/GVHD following solid organ or BMT
- Recent surgery
- Immunomodulatory agents (TNFα-blockers), recreational drugs (heroin)
- Immunizations (e.g., swine flu)

ALERT
- Consensus-based recommendations for immunization (Arch Neurol, 2005):
  - Not recommended during acute phase of GBS or for up to 1 year after onset
  - Should not be withheld after that (but need for immunization should be reviewed)
  - If GBS occurs within 6 weeks after a particular immunization, consideration should be given to avoiding that immunization in the future
- Surveillance by for increased incidence of GBS following 2009 H1N1 virus vaccination is being conducted by CDC and AAN. Reports collected through VAERS, CDC's Vaccine Adverse Events Reporting System.
- GBS following H1N1 vaccine deemed unlikely, but recent data are pending.

DIAGNOSIS

HISTORY
- Most common initial symptoms:
  - paresthesias, LE weakness
  - >50% have burning, aching pain in back and thighs
  - Ascending numbness (from feet to legs, then fingers to arms) (1)

PHYSICAL EXAM
- LE weakness, followed by sensation changes.
- Diaphragmatic/cranial nerve weakness (50%).
- Autonomic involvement in >50% (blood pressure lability, bowel and bladder involvement, pupillary changes, cardiac arrhythmias).
- At nadir, upper extremity weakness (90%), facial weakness (60%), and sensation loss (75%); approximately 50% have a weak swallow and 30% require ventilatory assistance; ophthalmoparesis, ptosis and even sphincter involvement can develop in 5–15% of patients (1).

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- CSF analysis: elevated protein (>55) without leukocytosis (usually <10 cells/mm^3) in ~90% at time of maximal weakness. Cell count >50 cells/mm^3 indicates alternate diagnosis unless in setting of HIV.
- Anti-GM1 testing and serologic testing for *C. jejuni* usually not helpful in diagnosis and does not change therapy, but may indicate poor prognosis if positive.
- Anti-GQ1b antibodies helpful in confirming diagnosis of Fisher's syndrome

Imaging
MRI: Nerve root or cranial nerve enhancement.

Diagnostic Procedures/Other
- Nerve conduction studies:
  - Early: Abnormalities in H-, F-waves; then low CMAP amplitudes with prolonged distal latencies (changes in motor precede changes in sensory nerves); "sural sparing"
  - 2–3 weeks: Conduction block, abnormal temporal dispersion
- Electromyography:
  - Fibrillations and positive sharp waves if axonal disruption has occurred, usually after the 2nd week
- Autonomic instability:
  - HR variability with deep breathing or Valsalva.

Pathological Findings
- Nerve biopsies:
  - Early infiltration of nerve roots, motor nerve terminals, and sites of potential entrapment with inflammatory cells
  - Later evidence for segmental demyelination, axonal degeneration, and re-myelination

DIFFERENTIAL DIAGNOSIS
- *Other neuropathies*: Vasculitis, thiamine deficiency, acute intermittent porphyria, diptheria, tick paralysis, chronic inflammatory demyelinating polyradiculoneuropathy, toxic (*n*-Hexane, Buckthorn toxin, marine toxins, heavy metals)
- *Polyradiculopathies*: CMV, WNV, Lyme, malignant infiltration of nerve roots
- *Muscle disorders*: Periodic paralysis, fulminant polymyositis
- *Neuromuscular junction diseases*: *Botulism*, organophosphate poisoning, prolonged neuromuscular blockade with anesthesia
- *Spinal cord disorders*
- *Brainstem disorders*
- *Metabolic disorders*: Severe hypokalemia, hypophosphatemia
- *Psychiatric disorders*: Conversion disorders, malingering

TREATMENT

MEDICATION
- Plasma exchange (PLEX) and IV immunoglobulin (IVIG) are equally effective and one of these treatments should be considered for all patients.
- IVIG for GBS associated with antibodies against GM1, GM1b, GalNAc-GD1a gangliosides.
- PLEX (200–250 mL/kg divided into 4–6 exchanges over 10–14 days) reduces time to initial improvement, time to ambulation and time on the ventilator; increases percentage of patients improving at 1 and 6 months; and increases percentage of patients showing full recovery at 1 year (2)[A].
  - Albumin may be superior to fresh frozen plasma as the exchange fluid.
  - Start PLEX <7 days after disease onset
  - Still beneficial in patients treated up to 30 days after disease onset

- IVIG 0.4 g/kg/day for 5 days increases proportion patients improved at 1 month, reduces median time to improvement and to reach independent ambulation (3)[B].
  - – Start within 2 weeks from onset
  - – Adverse events were not significantly more frequent with either treatment
  - – More research is needed in mild disease and in patients whose treatment starts more than 2 weeks after onset. Dose-ranging studies are also needed (3).

Pediatric Considerations

- Lower incidence in children; be especially aware of tick paralysis in differential.
- The value of plasma exchange in children <12 years old is not known.
- Low quality evidence supports the use of IVIG in children (3)[C].

ALERT

- Corticosteroids alone do not significantly hasten recovery from GBS or affect the long-term outcome (4)[B].
- No evidence for combination therapy (IVIG and PLEX) (3)[A].
- *Relative contraindications to PLEX*:
  - – Cardiovascular instability, congestive heart failure, hypotension, renal failure, or severe anemia, sepsis due to chronic indwelling central catheter.
- *Relative risks to PLEX*:
  - – Theoretical risk of bleeding complications due to depletion of clotting factors, especially fibrinogen.
- *Relative contraindications toIVIG*:
  - – Congenital IgA deficiency (anaphylactic-like reaction).
- *Precautions*:
  - – IV fluids for hypotension during plasma exchange.
  - – Hypocalcemia secondary to anticoagulants.
  - – Mild allergic reactions, including chills, aching, fevers, flushing, and tachycardia; usually respond to slowing of infusion rate, but antihistamines, steroids, or both may be needed.

ADDITIONAL TREATMENT

General Measures

- Mechanical ventilation: Intubation for ventilatory failure or airway protection in patients with severe bulbar weakness
- Dysautonomia: Cardiac/BP telemetry
- DVT prophylaxis
- Aggressive neuropathic pain management
- Rehabilitation: PT/OT
- Evidence for improved disability in short term with a multidisciplinary approach is supported by observational studies (no RCT/CT) (5)[C].

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Chinese herbal medicine tripterygium polyglycoside hastened recovery more than corticosteroids (small, unconfirmed CT) (6)[C].
- Psychological support
  - – Letter boards or electronic devices for patients who cannot speak
  - – Pharmacologic treatment for depression

SURGERY/OTHER PROCEDURES

Tracheostomy for patients requiring prolonged intubation.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- ICU hospitalization in setting of respiratory compromise, autonomic instability, or complicating medical conditions
  - – Monitor ventilatory status with frequent forced vital capacity (FVC) and negative inspiratory force (NIF) metrics. Consider ventilatory assistance if FVC falls below ~15–20 mL/kg or NIF < –20 to –25 cm H_2O. Neck flexor strength that is not at least antigravity often heralds ventilatory failure
  - – Cardiac monitoring for and treatment of arrhythmias or blood pressure instability

Admission Criteria

Hospitalization for all but the mildest cases.

IV Fluids

Hydration in patients with bulbar weakness; BP management in dysautonomia.

Nursing

Decubitus ulcers; range of motion; and pain.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Reassess periodically for relapse
- Issues following acute care hospitalization
  - – Rehabilitation (respiratory complications, dysautonomia, immobilization, pain, fatigue)
  - – Persistent disability and fatigue (energy conservation, adaptive devices, neuropathic pain agents)

DIET

- Swallowing study for suspected bulbar paresis; NPO for paralysis
- Tube feedings if severe bulbar weakness or requirement for ventilatory support

PATIENT EDUCATION

- Careful explanation of natural history of disease; realistic goals for recovery; awareness of potential for long-term residual symptoms, including fatigue
- Guillain–Barré Syndrome Foundation International, P.O. Box 262, Wynnewood, PA 19096. Website: *www.guillain-barre.com*

PROGNOSIS

- Degree and extent of progression variable; ~75% patients reach nadir within 7 days of onset; essentially all by 4 weeks. Some patients progress rapidly to ventilator dependence within days, whereas others have very mild progression for weeks and never lose ambulation.
- ~30% patients require ventilatory assistance. Recovery over weeks to months is usual (~70% of patients).
- Poor prognostic factors include advanced age, need for ventilatory support, rapidly progressive weakness, prolonged course of active disease, and axonal involvement, especially reduction of the mean distal compound motor action potential amplitude.
- ~10% of patients have a malignant course with prolonged ventilator dependence and recovery phase extending beyond 2 years.

COMPLICATIONS

- 3–5% of patients die, usually from respiratory distress syndrome, sepsis, or both.
- 10–25% of patients will have permanent weakness or other impairments that interfere with activities of daily living.
- 5% of patients may relapse after initial improvement. Relapse best treated like initial episode.
- Disability/recovery may persist for years.

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CODES

ICD9

- 356.8 Other specified idiopathic peripheral neuropathy
- 357.0 Acute infective polyneuritis

CLINICAL PEARLS

- GBS manifests as acute onset paresthesias in setting of progressive lower extremity weakness.
- Be aware of associated conditions.
- Patients should be treated with IVIG or PLEX.
- Management considerations include autonomic instability, ventilatory compromise, and bulbar weakness.
- Even patients who show an excellent recovery can still have significant persistent disability and fatigue.

HEADACHE, ACUTE

Jennifer S. Kriegler, MD
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BASICS

DESCRIPTION
An acute headache is a discrete episode of moderate-to-severe head pain with or without accompanying symptoms that can last hours to days.

EPIDEMIOLOGY
Incidence
The incidence of migraine peaks during the second decade. Less than 10% of primary headaches begin after age 50 years. Subarachnoid hemorrhage (SAH) occurs in 30,000 patients per year (incidence about 10 per 100,000), with 55 being the mean age of onset.

Prevalence
More than 80% of the US population has had at least one headache over their lifetime. Headache disorders are more common than diabetes and asthma combined. One in four US households has at least one migraineur. Headache accounts for 2.2% of all US ED visits yearly.

RISK FACTORS
Infection, diabetes, hypothyroidism, depression, anxiety, autoimmune disease, fibromyalgia, sleep disorders, hypertension, hyperlipidemia, obesity, atrial fibrillation, long-term steroid use, drug/alcohol use, congestive heart failure, head/neck trauma, back and neck pain travel.

Genetics
The genetic contribution to headache varies greatly with the underlying disorder for both primary and secondary headaches. Familial hemiplegic migraine is associated with mutations in three genes (CACNA1A, ATP1A2, and SCN1A).

GENERAL PREVENTION
For primary headaches, avoidance of triggers and use of preventive medications can decrease headache frequency. For secondary headaches, general prevention involves the management of risk factors for the underlying disorders.

PATHOPHYSIOLOGY
The brain itself lacks pain receptors, but irritation of blood vessels, meninges, and trigeminal and cervical nerves can produce head pain. Pain is related to neuro-inflammatory processes involving calcitonin gene-related peptide, neurokinins, prostaglandins, and substance P.

ETIOLOGY
Headache disorders can be primary or secondary. Primary headaches, such as migraine, tension-type headache, and cluster headache, are the most common headaches. They are not linked to systemic or structural abnormalities. Secondary headaches do have identifiable underlying causes, some of which are potentially life-threatening, such as intracranial hemorrhages, tumors, and stroke. A mnemonic for remembering the red flags associated with secondary headache is "SNOOP."

- **S** – systemic signs or symptoms (fever, meningismus, persistent vomiting, unintentional weight loss, malignancy, immunocompromised, pregnancy, anticoagulation, etc.)
- **N** – neurological symptoms/signs (mental status change, cognitive dysfunction, seizures, syncope, papilledema, weakness, numbness, diplopia, paresthesias, incoordination, gait disturbance, etc.)
- **O** – onset abrupt and severe ("thunderclap" headache, "worst headache of life"); onset temporally associated with straining, sneezing, exertion, trauma, or toxin exposure
- **O** – older age at onset (>40 years of age)
- **P** – progression of headache (worsening of severity/frequency, change in location)

Pregnancy Considerations
Migraine headaches may initially present during pregnancy. Headaches are commonly associated with eclampsia. Cortical vein thrombosis in the peripartum period may present as headache. Pregnant women with berry aneurysms or intracranial malformations have increased risk for intracerebral or subarachnoid hemorrhages.

COMMONLY ASSOCIATED CONDITIONS
Depression/anxiety, fibromyalgia, obesity, abuse (physical and emotional), neck/back pain, and sleep disorders are commonly associated with primary headaches.

DIAGNOSIS

HISTORY
- Description of current headache: Location of pain, type of pain (throbbing, aching, dull, sharp, stabbing, pressure, etc.), magnitude of pain on 11-point scale (0 – none; 10 – worst imaginable), onset (abrupt or gradual), frequency, duration, factors that make headache better or worse (sneezing, coughing, positional increase or decrease, etc.), most likely time of day for headache to begin, triggers.
- Associated symptoms: Photophobia, phonophobia, nausea, vomiting, blurred vision, lacrimation, congestion, conjunctival injection, agitation, confusion, dizziness or vertigo, focal neurological symptoms (weakness, sensory symptoms, diplopia, dysarthria, cognitive changes, visual change, gait disorder, etc.).
- Prior headache history: Description of headaches over lifetime; previous work-up and therapies; change in headache pattern, if any.
- Current medications for all conditions, both prescribed and over-the-counter (OTC) (how much, how often).
- Past medical and surgical history, including history of any trauma (physical or psychological) or alcohol/drug abuse, caffeine intake.

PHYSICAL EXAM
Vitals (blood pressure, pulse, respirations, height, weight), general exam (head, ears, jaw, neck, bruits, heart, lungs, skin), neurological exam (mental status, cranial nerves, retina/fundus, muscle tone and strength, deep tendon reflexes, sensation, coordination and gait, plantar response).

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
Depending on the history and physical exam, the following labs may be useful (underlying causes in parentheses): CMP (hyper- or hypoglycemia, hypercapnia, dehydration), CBC with differential (infection, inflammation, anemia), TSH, T4 (hypothyroidism), ESR and CRP (giant cell arteritis), carboxyhemoglobin (carbon monoxide poisoning), PT/PTT (coagulopathy), and drug screen (opiates, cocaine, benzodiazepines).

Imaging
Initial approach
- Any patient with new onset of headache or a change in their headache pattern needs brain imaging. If there is suspicion of an intracranial hemorrhage or SAH, CT is the study of choice in the first 48 hours after onset of symptoms and should be done immediately. The CT will be positive in only 90% of those with SAH; so if the CT is negative, a lumbar puncture (LP) should be done to look for frank blood or xanthochromia in the CSF.
- If there is need to evaluate the posterior fossa, such as with suspicion of a space-occupying posterior fossa lesion in a patient with headache worsened by cough or exertion, MRI imaging is preferred. MRI is also the preferred imaging for intracerebral infection, inflammatory disorders, or encephalitis (gadolinium contrast may be necessary to look for meningeal or intraparenchymal enhancement). MRA (angiography) is indicated when there is suspicion of aneurysm, other vascular anomalies, vasculitis, dissection, or reversible cerebral vasoconstriction syndrome (RCVS). MRV (venography) can provide confirmation of venous sinus thrombosis.

Diagnostic Procedures/Other
An LP should be done when there is suspicion of meningitis, encephalitis, abnormal intracranial pressure, or, in cases of suspected SAH, if an initial CT has been negative for blood. The opening pressure should be measured with the patient in the lateral recumbent position. To avoid the possibility of herniation, LP should be done only after imaging has eliminated concern of mass effect or lateralized lesions. Four-vessel angiogram remains the standard for assessing cerebral aneurysms.

Pathological Findings
Pathological findings for secondary headaches will depend upon underlying etiology.

DIFFERENTIAL DIAGNOSIS
- Infection: Meningitis, encephalitis, brain abscess, otitis media, complicated sinusitis
- Trauma: Epidural/subdural hemorrhage, head/neck trauma
- Toxic: Carbon monoxide poisoning, drug dependency/withdrawal
- Immune: Temporal (giant cell) arteritis, Tolosa-Hunt syndrome

- Neoplasm: Brain tumors, pheochromocytoma
- Degenerative: Dental caries, wisdom tooth impaction, temporal–mandibular joint dysfunction, acute angle-closure glaucoma
- Vascular: Stroke, transient ischemic attack, dissection, unruptured aneurysms, SAH, venous thrombosis, pituitary apoplexy, arteriovenous malformation, RCVS
- Metabolic: Eclampsia, pre-eclampsia, intracranial hypertension or hypotension
- Others, head/neck: Cluster headache, tension-type headache, migraine, exertional or coital headache, neuralgias

TREATMENT

MEDICATION

First Line

- The choice of medication depends on headache type and severity. For infrequent, mild-to-moderate primary headaches without migrainous features, nonspecific treatments, such as OTC ibuprofen, acetaminophen, and naproxen sodium, work well. For mild-to-moderate acute migraine or moderate-to-severe tension-type headache, prescription naproxen sodium or diclofenac potassium can be effective. For moderate-to-severe migraine, dihydroergotamine (DHE) or triptans are indicated. Oral antiemetics can be particularly effective in patients with nausea/vomiting. In the ED setting, sumatriptan SQ and DHE IV can be effective for migraine (1)[A]. Intravenous ketorolac and antiemetics, such as chlorpromazine, can effectively treat nausea and headache pain (2)[A], (3).
- NSAIDs are contraindicated in patients who have renal failure, peptic ulcer disease, or other risks for GI bleeding. Triptans and DHE are contraindicated in pregnant patients and those with cardiovascular disease, uncontrolled hypertension, diabetes, or at least two other risk factors for cardiovascular disease. Triptans are also contraindicated in patients with severe liver disease or taking monoamine oxidase inhibitors.
- In patients with primary headaches, even limited use of opioids or barbiturates can put patients at risk for medication overuse or "rebound" headache and render other abortive and preventive medications ineffective (2)[A]. High-dose caffeine use should be limited to 2 days a week to avoid rebound headaches.

Second Line

For patients with severe secondary headaches, uncomplicated by medication overuse, which do not respond to first-line medications, IV opioids may be effective.

ADDITIONAL TREATMENT

General Measures

Patients with photophobia and phonophobia should be placed in a dark, quiet environment. Those with vomiting should be rehydrated, if necessary.

Issues for Referral

Depends on underlying etiology.

Additional Therapies

Patients with primary headaches that result in an unacceptable level of functional disability should be treated with preventive medications.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Some headache patients respond well to physical therapy, massage, nutraceuticals, acupuncture, mindfulness training, and biofeedback. Vitamins and herbs that show benefit include magnesium, riboflavin, Co-enzyme Q10, and butterbur.

SURGERY/OTHER PROCEDURES

For secondary headaches, the need for surgery is dependent upon the underlying cause.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Hydration and placement in a dark, quiet room is beneficial.

Admission Criteria

Patients with suspected secondary etiologies requiring further work-up and those with identified underlying disorders requiring in-patient treatment should be admitted for diagnosis and/or treatment. Primary headache patients may need in-patient management of vomiting and related issues. Those with refractory headache may require admission for IV medications.

IV Fluids

Normal saline should be used for dehydration secondary to vomiting.

Nursing

There are no specific nursing requirements that apply to headache management.

Discharge Criteria

Patients can be discharged when a diagnosis is determined and any required in-patient treatment is accomplished.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients with primary headaches should follow up with a neurologist or headache specialist. Patients with secondary headaches should follow up with a physician specialized in the underlying disorder.

Patient Monitoring

Patients should be monitored for medication adverse events and for recurrence of headache. Secondary headaches may require additional monitoring specific to the underlying disorder.

DIET

Primary headache patients should eat at least three small meals and two balanced snacks a day and avoid high-sugar foods. They should avoid all foods known to trigger their headaches.

PATIENT EDUCATION

The pathophysiology of headaches, the risk of medication overuse headache, the need to limit the use of triptans/OTC medications to 2 days a week, the actions/side effects of all medications, and the impact of lifestyle on headaches should be explained.

PROGNOSIS

Primary headaches can be life-long, but they do tend to remit or lessen in severity with age. For secondary headaches, the expected course and prognosis depends upon the underlying disorder.

COMPLICATIONS

Depends on underlying etiology.

REFERENCES

1. Gawal MJ, Worthington I, Maggisano A. A systematic review of the use of triptans in acute migraine. *Can J Neurol Sci* 2001;28:30–41.
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3. Jakubowski M, Levy D, Goor-Aryeh I, et al. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. *Headache* 2005;45:850–861.

ADDITIONAL READING

- Goadsby PJ, Lipton RB, Ferrari MD. Drug Therapy: migraine – current understanding and treatment. *N Engl J Med* 2002;346:257–270.

CODES

ICD9

- 339.10 Tension type headache, unspecified
- 346.90 Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus
- 784.0 Headache

CLINICAL PEARLS

- The "worst headache" of a patient's life is a secondary headache until proven otherwise.
- Most primary headache patients will benefit from daily exercise.
- SNOOP4 secondary headaches.
- Ice pick pains occur in approximately 40% of migraineurs.

HEADACHE, CHRONIC

Monique A. Anawis, MD, JD

BASICS

DESCRIPTION

Headache occurring more than 15 days/month, for at least 3 months (exception: Trigeminal autonomic cephalalgias, with disorder unremitting >1 year)

- Primary chronic headache
  - No identifiable cause
  - No temporal correlation between the onset of an underlying disorder that causes secondary chronic headache and the headache onset
- Secondary chronic headache: Caused by an underlying disorder

EPIDEMIOLOGY

- Incidence unknown
- Prevalence: 3.2–4.7%, versus 12–38% for episodic headaches

RISK FACTORS

- Medication overuse
- History of episodic migraine
- Family history of chronic headache
- Coincident major depressive disorder
- Sex
  - Female predominance: Chronic migraine, chronic tension-type (CTT) headache, hemicrania continua, chronic paroxysmal hemicrania, and idiopathic stabbing headache
  - Male predominance: Cluster headache

Genetics

- CTT headache: Multifactorial inheritance
- Chronic cluster headache: Autosomal dominant inheritance

ETIOLOGY

- Development of chronic headache
  - 75% develop from episodic migraine
  - 8% develop from episodic tension-type headache
  - 16% develop without previous headache history ("new onset daily headache"): should be classified as chronic migraine or tension-type headache
- Medication overuse: Frequently causes evolution of episodic into chronic headache

COMMONLY ASSOCIATED CONDITIONS

- Psychiatric disorders: Often remit following successful treatment of chronic headache
  - Anxiety disorders (23–70%)
  - Mood disorders (25–59%)
  - Somatoform disorders (6%)
- Medication overuse headache (30–40%)
  - Defined as:
    - Regular overuse of ≥1 drug for acute or symptomatic headache treatment for ≥3 months
    - Headache ≥15 days/month
    - Headache developing or worsening during period of overuse of medication
    - Headache resolves or returns to previous pattern within 2 months of discontinuation of overused medication
  - Concerns
    - Short-acting medications cause rebound headaches that are confused with underlying headache.
    - Medication overuse may make chronic headaches refractory to prophylactic medications.
    - Medication overuse may mask undiagnosed psychiatric disorder.
    - Systemic toxicities of analgesics

DIAGNOSIS

CHRONIC MIGRAINE

51–78% of chronic headache patients

- Headache ≥15 days/month for >3 months
- ≥5 attacks fulfilling migraine without aura criteria plus
- Two of the following pain characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
  - Aggravated by or causing avoidance of routine physical activity
- And at least one of the following:
  - Nausea and/or vomiting or
  - Photophobia and phonophobia
- Period of increasing headache frequency with decreasing severity of migrainous symptoms (nausea, vomiting, photophobia, phonophobia)
- Triggers generally persist and can induce acute migraine attacks
- Pain is severe but patients attempt to sleep

CHRONIC TENSION-TYPE (CTT) HEADACHES

15–46% of chronic headache patients

- Headache ≥15 days/month for >3 months
- Pain lasting hours or continuing
- Two of the following pain characteristics:
  - Bilateral location
  - Pressing, non-pulsating quality
  - Mild-to-moderate intensity
  - Not aggravated by routine physical activity
- Also requires:
  - Not more than one: Photophobia, phonophobia, or mild nausea
  - Neither moderate/severe nausea nor vomiting
- CTT headache with disorder of pericranial muscles: Tenderness of pericranial muscles

CHRONIC HEMICRANIA CONTINUA (CHC)

- Present >3 months
- Unilateral, continuous pain fluctuating from moderate-to-severe intensity, without pain remission, but with exacerbation
- Absence of triggers
- At least one autonomic symptom (conjunctival injection, ptosis, lacrimation, nasal congestion, rhinorrhea, eyelid edema) during periods of severe headache
- Complete symptomatic relief following indomethacin treatment

CHRONIC CLUSTER HEADACHE (CCH)

- ≥5 attacks, recurring over >1 year with or without remission periods lasting <1 month:
  - Severe pain, strictly unilateral, always on the same side, orbital, supraorbital, and/or temporal region, lasting 15–180 minutes without treatment
  - Attacks associated with ≥1 autonomic symptom: Miosis, facial sweating, plus those autonomic symptoms listed for hemicrania continua
  - Attacks frequency 1/2 to 8/day occurring at the same time of the day
- Pain is severe, boring, throbbing, or compressive, causing agitation
- Migrainous symptoms in <50%; rarely associated with aura
- Chronic cluster may switch to episodic cluster headache, and vice versa
- Triggers: REM sleep (sleep deprivation shortens REM period: Avoid excessive sleep, alcohol, nitrates)

CHRONIC PAROXYSMAL HEMICRANIA (CPH) SJAASTAD SYNDROME

>5 attacks per day during at least half of the headache period or ≥20 attacks

- Attacks lasting 2–30 minutes and recurring over >1 year without remission or having periods of remission lasting <1 month
- Strictly unilateral pain, always on the same side, in the orbital, supraorbital, or temporal region; attacks associated with autonomic symptoms ipsilateral to pain
- Indomethacin completely alleviates symptoms
- Pain is boring, throbbing, and severe, causing agitation and restlessness
- Occurs at irregular intervals during day and night
- Absence of migrainous symptoms
- Differs from CCH in male patients by temporal pattern of attacks and response to indomethacin
- Episodic subtype analogous to cluster headache
- 10% triggered by head movements or pressure applied to cervical spine

CHRONIC HYPNIC HEADACHE (CHH)

- Dull headache developing in elderly patients only during REM sleep, rarely during napping, and awakening patient
- Absence of autonomic symptoms
- At least 2 of the following characteristics:
  - >15 times per month
  - Lasting ≥15 minutes after waking
  - Onset in patients after age of 50 years

IDIOPATHIC STABBING HEADACHE/ ICE-PICK HEADACHE/JABS-AND-JOLTS SYNDROME/OPHTHALMODYNIA

- Attacks 24 days/month at irregular intervals; absence of autonomic symptoms or triggers
- Pain lasting <1 second, sharp, causing shock-like response ("jolt"); typically unilateral, located in the orbit, forehead and/or temple
- Additional subtype of headache in 58%
- High coincidence of ocular pathology
- Partial or complete relief with indomethacin

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- Brain MRI or CT
  - Chronic migraine: Imaging not indicated if symptomatically stable unless abnormal neurologic examination
  - CTT headache: Treatable abnormality identified in 0.5–2.4% of patients
  - Brain MR venogram: Venous sinus thrombosis in 10% of chronic migraine and CTT

Diagnostic Procedures/Other

- Lumbar puncture: Opening pressure may be >20 cm H_2O in 21% of chronic headache patients.
- Only half of chronic headache patients with elevated intracranial pressure have papilledema.

DIFFERENTIAL DIAGNOSIS

- Primary chronic headache
  - Chronic migraine
  - CTT headaches
  - Hemicrania continua
  - Chronic cluster headache
  - Chronic paroxysmal hemicrania
  - Chronic hypnic headache
  - Idiopathic stabbing headache
- Secondary chronic headache
  - Post-traumatic headache
  - Cervical spine disorders
  - Cranial neuropathies
  - Ophthalmic disorders
  - Vascular disorders: Arteriovenous malformation, arteritis, arterial dissection, subdural hematoma
  - Nonvascular disorders: Increased or decreased CSF pressure, infection, neoplasm, Chiari malformation
  - Oromandibular, sinus, ear disorders

TREATMENT

MEDICATION

- Chronic migraine
  - Acute treatment: Triptans
  - Prophylaxis: Amitriptyline (AMT)
- CTT headache
  - Acute treatment: Long-acting NSAIDs
  - Prophylaxis: AMT
- Hemicrania continua:
  - Indomethacin PRN for acute treatment, scheduled for prophylaxis
  - Reconsider diagnosis if no relief following indomethacin
- CCH:
  - Acute treatment: Oxygen supplementation, triptans
  - Prophylaxis: Lithium
- CPH: Indomethacin
- CHH: Lithium carbonate
- Idiopathic stabbing headache: Indomethacin
- Contraindications:
  - Avoid ergots [dihydroergotamine (DHE)] in patients with vascular disease, pregnancy, or using oral contraceptives
  - Avoid triptans in patients with vascular disease or hypertension
- Precautions:
  - Topiramate: Dose-dependent cognitive impairment, osteopenia, metabolic acidosis, angle-closure glaucoma, anterior uveitis
  - Toxicity with overdosage of lithium and anticonvulsant medications
  - Limit methysergide use to less than 5 months due to retroperitoneal fibrosis

ALERT: TOPIRAMATE USE IN PREGNANCY INCREASES RISK OF CLEFT PALATE OR LIP IN NEWBORNS

Alternative Drugs

- Chronic migraine
  - Acute treatment:
    - Outpatient: Long-acting NSAIDs, botulinum toxin injection
    - Inpatient: DHE, antiemetics
  - Prophylaxis: Fluoxetine, doxepin, tizanidine, β-blockers, anticonvulsants (divalproex, topiramate), gabapentin
- CTT: Tizanidine, botulinum toxin injection into tender points
- CHC: Aspirin, long-acting NSAIDs
- CCH:
  - Acute treatment: DHE, intranasal lidocaine
  - Prophylaxis: Anticonvulsants (valproate, topiramate), lithium, gabapentin
    - May supplement with steroids
- CPH: Aspirin, verapamil
- CHH: Verapamil, indomethacin
- Idiopathic stabbing headache: Verapamil

ADDITIONAL TREATMENT

General Measures

- Exclude secondary causes
- Identify comorbid psychiatric factors
- Insomnia: Sleep studies for apnea particularly in obese patients; AMT decreases REM sleep
- Medication detoxification:
  - Gradually taper barbiturates, benzodiazepines, and opioids
  - Gradually switch from short-acting NSAIDs (regular indomethacin, aspirin) to long-acting NSAIDs (sustained-release indomethacin, naproxen, ketoprofen, tolfenamate, mefenamate, ibuprofen)

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Adjunctive treatment
  - Psychotherapy: Stress management, relaxation therapy, and biofeedback proven efficacious
  - Physiotherapy: Cervical spine manipulation, massage, transcutaneous electrical nerve stimulation, and ergonometric review have limited evidence for CTT headaches
  - Acupuncture (traditional or ear) may be effective for prophylaxis and pain relief
  - Vitamins/supplements for prophylaxis: Riboflavin, magnesium, coenzyme Q10, feverfew, and butterbur
  - Neuromodulation for refractory migraine: Transcranial magnetic stimulation

SURGERY/OTHER PROCEDURES

CCH: Gamma-knife radiosurgery, trigeminal rhizotomy, or root transection if medically refractive; nerve stimulation replacing surgery

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Emergency admission may be required for:
  - Complicated migraine
  - Suspicion of secondary chronic headache
  - Dehydration from persistent vomiting
  - Severe comorbid psychiatric disorders
- Nonemergent admission may be required for:
  - Detoxification from opioids, barbiturates, benzodiazepines, or ergots
  - Failed outpatient detoxification

ONGOING CARE

DIET

Encourage regular, balanced meals

PATIENT EDUCATION

- Encourage regular sleep habits, nutrition, moderate exercise, and relaxation
- Avoid triggers (i.e., fluorescent lights) and medication overuse
- Organizations: International Headache Society. Website: www.i-h-s.org

PROGNOSIS

Response to prophylactic medications takes up to 10 weeks following detoxification; 40–80% of medication overuse headaches revert to episodic headaches following detoxification

ADDITIONAL READING

- International Headache Society. Diagnostic criteria and classification. www.i-h-s.org

See Also (Topic, Algorithm, Electronic Media Element)

- Chronic daily headache
- Headache, migraine

CODES

ICD9

- 339.41 Hemicrania continua
- 346.90 Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus
- 784.0 Headache

CLINICAL PEARLS

Failure to improve following aggressive management is highly suggestive of psychiatric comorbidity.

HEADACHE, CLUSTER

Ann Pakalnis, MD

BASICS

DESCRIPTION

- Cluster headache is an uncommon primary headache disorder that has often been thought of as the most painful of the headache syndromes. Unique features of cluster headache are the extreme intensity but short duration of attacks usually lasting for 15–180 minutes. They often present in a circadian fashion and are unilateral, often maximal periorbitally, and associated with stabbing or piercing pain. These can awaken a patient from a sound sleep. Ipsilateral autonomic symptoms usually occur, such as ptosis, miosis, lacrimation, or rhinorrhea.
- The international classification of headache disorders (ICHD-2) is shown in Table 1.

Table 1 International Headache Society Criteria for Cluster Headache

Cluster headache

1. At least five attacks fulfilling Criteria 2 and 4
2. Severe, unilateral, orbital, supraorbital, and/or temporal pain lasting 15–180 minutes untreated
3. Headache is associated with at least one of the following signs that have to be present on the pain side:
   - Conjunctival injection
   - Miosis
   - Ptosis
   - Eyelid edema
   - Forehead and facial sweating
   - Lacrimation
   - Nasal congestion
   - Rhinorrhea
4. Frequency of attacks: One every other day to 8/day

Episodic cluster headache

1. Occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting 14 days or more; cluster periods usually last between 2–3 weeks and 3 months
2. At least 2 cluster periods lasting from 7 days to 1 year (untreated), separated by remissions of at least 14 days.

Chronic cluster headache

1. Attacks occur for more than 1 year without remission, or remissions last less than 14 days

- Clusters are usually episodic following a somewhat circadian rhythm with attacks generally (clustering) seasonally at least once every 24 hours, with attacks most common in spring or fall. Unfortunately, in some individuals the episodes may be chronic over time with little (14 days or less) or no remission.

EPIDEMIOLOGY

Incidence

- Cluster headache, unlike migraines, is predominantly a disorder of men.
- Mean age of onset is 28–30 years.
- Mayo clinic study from 1989 to 1990 showed incidence of 4.25/100,000 for men and 0 for women. There appears to be overall a significant decline in incidence of cluster from earlier epidemiologic studies.

Prevalence

- Family history in 7% of patients.
- Prototype of primary headache disorders known as trigeminal autonomic cephalalgias (TACs) – pain is present in first division of trigeminal nerve.

RISK FACTORS

Features associated with cluster:

- Type A personality
- Hazel-colored eyes
- Heavy use of tobacco and alcohol (alcohol can precipitate acute attacks)

Genetics

- About 7% of cluster sufferers have a positive family history.
- Inheritance may be autosomal dominant or recessive with variable penetrance.

Pregnancy Considerations

Clusters are very uncommon in adult women (data is not available during pregnancy).

GENERAL PREVENTION

- Avoidance of alcohol during cluster cycle.
- Sleep apnea and decrease in blood oxygen concentration with sleep-disordered breathing may trigger nocturnal headaches.
- Other factors, such as stress, depression, and hormonal changes, may play little, if any, role in genesis of cluster headaches.
- Cessation of cigarette smoking may be of benefit with increasing blood oxygen concentration.

ETIOLOGY

Related to genetics and innate probable hypothalamic dysfunction

COMMONLY ASSOCIATED CONDITIONS

Concomitant cigarette smoking and heavy alcohol use

DIAGNOSIS

HISTORY

- Cluster is one of the TACs. There is some similarity to episodic paroxysmal hemicrania (EPH); however, this disorder is more commonly seen in women and attacks are shorter in duration and usually occur multiply during the day, with pain generally unilateral but more diffuse. Alcohol is not a distinct trigger with EPH, and these headache attacks are uniquely susceptible to relief with indomethacin.
- Migraine headaches are longer in duration (4–72 hours) and with a strong female preponderance, which differ from cluster and do not have as notable associated autonomic features.

PHYSICAL EXAM

Thorough physical and neurological examination should be normal.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- No specific laboratories are indicated.
- Temporal arteritis may appear in older adults in similar location.
- ESR would be helpful to differentiate from temporal arteritis.

Imaging

Initial approach

Brain MRI to rule out structural lesions in cavernous sinus, pituitary adenoma in new onset cluster. These can help reassure patients and family.

Diagnostic Procedures/Other

In atypical cases, ophthalmological examination may be helpful to exclude glaucoma.

DIFFERENTIAL DIAGNOSIS

- Migraine
- Temporal arteritis
- EPH
- Trigeminal neuralgia
- Focal lesions in area of cavernous sinus, pituitary or carotid artery

TREATMENT

MEDICATION

First Line

Abortive

- Oxygen inhalation – most effective, but least convenient (7–10 L/min) via non-rebreathable mask for 15–20 minutes
- Triptans – use with care in individuals with risk factors for cardiovascular disease
- Subcutaneous sumatriptan
- Sumatriptan nasal spray, zolmitriptan nasal spray
- Intranasal lidocaine
- Subcutaneous octreotide
- Subcutaneous dihydroergotamine

Prophylaxis

Most patients require preventive therapy due to cluster attack semiology (rapid onset, extremely) brief headaches

- Corticosteroids (prednisone and dexamethasone) response begins within several days. Prednisone 60 mg/day for 3 days followed by 10 mg decrements every 3 days over 18 days.
- Dexamethasone 4 mg b.i.d. for 2 weeks, then 4 mg/day for 1 week then discontinue. Steroids can cause hyperglycemia, weight gain, insomnia, gastritis, and other significant side effects, especially if used frequently (should be limited to 2–3 cycles per year).

Calcium channel blocker

- Verapamil is generally the drug of choice: 120–600 mg/day in divided doses may cause hypotension, constipation, and edema.

Anti-epileptic drugs

- Topiramate 50–200 mg/day in divided does may cause paresthesia, weight loss, kidney stones, and some cognitive issues.
- Valproic acid 500–2,000 mg/day in divided doses. May cause weight gain, hepatic dysfunction, and teratogenic side effects.
- Lithium carbonate 600–900 mg/day in divided doses – side effects include polydipsia, nausea, and weakness.

ADDITIONAL TREATMENT

General Measures

- Avoid potential triggers such as alcohol
- Avoid day-time naps, change in sleep–wake cycle
- Air travel/altitude
- Excessive physical activity

Issues for Referral

- Neurosurgery – peripheral nerve and sphenopalatine nerve blocks
- Deep brain (hypothalamic) stimulation

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Little information available

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Stress-free environment

Admission Criteria

- Attacks are very short-lived but exceedingly severe.
- May be considered if concomitant psychosocial stressors such as significant depression to institute prophylactic therapy/psychological evaluation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Follow-up care
- Keeping diary of events
- Avoidance of trigger factors

Patient Monitoring

- Avoid alcohol during cluster
- Appropriate sleep hygiene

PROGNOSIS

- Episodic, recurrent attacks with prolonged symptom-free periods
- A minority of patients evolve to chronic cluster (<5% with recurrent attacks without periods of remission)

ADDITIONAL READING

- Ashkenazi A, Schwedt T. Cluster headache–acute and prophylactic therapy. *Headache* 2011;51: 272–286.
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- Rozen TD, Fishman RS. Inhaled oxygen and cluster headache sufferers in the United States: use, efficacy and economics–results from the United States Cluster Headache Survey. *Headache* 2001;51: 191–200.

CODES

ICD9

- 339.00 Cluster headache syndrome, unspecified
- 339.01 Episodic cluster headache
- 339.02 Chronic cluster headache

CLINICAL PEARLS

- Differentiate cluster from other types of primary headaches disorders.
- To gain knowledge concerning both abortive and preventive treatment strategies for cluster headaches.

HEADACHE, MIGRAINE

Jaclyn Laine, DO
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BASICS

DESCRIPTION

Migraine is an episodic primary headache disorder characterized by at least 5 episodes lasting 4–72 hours. Patients experience throbbing, moderate-to-severe pain which may be unilateral in location. Complaints of nausea, vomiting, photophobia, and phonophobia are common. Migraine aura manifests as characteristic reversible, focal neurologic symptoms. This will gradually develop from 5 to 20 minutes, but should last less than 1 hour.

- Migraine classification according to the International Headache Society IHS ICHD-II includes these migraine variants:
  - Migraine without aura
  - Migraine with aura
    - Typical aura with migraine
    - Typical aura with non-migraine headache
    - Typical aura without headache
    - Familial/sporadic hemiplegic migraine
    - Basilar migraine
  - Retinal migraine
  - Chronic migraine headache ≥15 days/month, no medication overuse
  - Medication overuse occurring in migraine:
    - Headache present ≥15 days/month
    - Regular overuse for >3 months

EPIDEMIOLOGY

Incidence

- 20–29-year-old population most at risk to develop migraine.
- Occurs more often in males prior to puberty, more common in females after menarche.

Prevalence

- Occurs in 12% of the US population affecting 17% women and 6% of men.
- The World Health Organization (WHO) estimates a worldwide prevalence of current migraine of 10% and a lifetime prevalence of 14%.
- Female-to-male ratio 2.8:1 at puberty and 3.5:1 at 40 years old.
- Lower among African Americans and Asian Americans than whites.

RISK FACTORS

Migraine family history, highest risk if first-degree relative with migraine with aura.

Pregnancy Considerations

- Migraine improves for half of women during pregnancy.
- Low estradiol levels trigger migraine during menstruation and high levels may be protective during pregnancy.
- Migraine during pregnancy increases the risk of stroke, thrombosis, and other vascular diseases.

Genetics

- Migraine develops from a combination of polygenic and environmental factors.
- Hemiplegic migraine—50% sporadic.
- Familial hemiplegic migraine (FHM1) – autosomal dominant mapped to the *CACNA1* gene coding for voltage-gated P/Q calcium channel on chromosome 19.
- FHM2 is associated with the gene *ATP1A2* on chromosome 1 encoding for the alpha 2 subunit of the Na^+/K^+ pump.

GENERAL PREVENTION

Maintain a regular sleep schedule, avoid triggers, do not skip meals, maintain adequate hydration, regular exercise.

PATHOPHYSIOLOGY

- Migraine is a neurovascular headache, involving a cortical spreading depression of activity in migraine with aura. There is an abnormal afferent activation of the trigeminocervical complex on dural blood vessels, associated with vasodilation and pain signal.
- Serotonin receptors (5HT) in the trigeminal sensory neurons aid regulating neuropeptide release, producing neurogenic inflammation and secondary vessel dilation.

ETIOLOGY

Combination of genetic predisposition and environmental factors contributes to development.

COMMONLY ASSOCIATED CONDITIONS

Depression, anxiety, ischemic stroke, irritable bowel syndrome, epilepsy, hypertension.

DIAGNOSIS

HISTORY

To distinguish migraine from other headache disorders consider:

- Gradual onset throbbing pain, more often unilateral although bilateral location is common
- Associated nausea, vomiting, lightheadedness, and blurred vision
- Photophobia, phonophobia and pain aggravated by activity
- Spreading sensory/motor symptoms between locations on body over minutes

PHYSICAL EXAM

Normal neurologic and fundus exam.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

No specific tests are indicated routinely.

Follow-up & special considerations

Additional testing may be needed to exclude secondary headache disorders.

Imaging

Initial approach

Imaging is not needed in patients with non-focal exam, with characteristic symptoms and normal exam (4)[B].

Follow-up & special considerations

- Brain imaging is recommended:
  - Change in headache pattern (4)[C]
  - Abnormal or changed neurologic exam (4)[B]
  - Atypical aura or duration longer than 60 minutes (4)[C]
- White-matter abnormalities are more common in migraineurs. Subclinical posterior circulation infarcts are more common in migraine with aura.

Diagnostic Procedures/Other

Lumbar puncture to measure opening pressure and exclude vascular, inflammatory, and infectious etiologies.

Pathological Findings

No abnormal findings.

DIFFERENTIAL DIAGNOSIS

Tension-type headache, cluster headache, temporomandibular joint dysfunction, trigeminal neuralgia, vasculitis, tumor, infection, idiopathic intracranial hypertension, arteriovenous malformation, arterial dissection, venous sinus thrombosis.

TREATMENT

MEDICATION

First Line

Abortive

NSAIDs

- Naproxen sodium 1,100 mg/day, *effective in menstrual migraine* (4)[A]
- Ibuprofen (4)[A]

Combination analgesics

- ASA, caffeine, acetaminophen (4)[A]

Triptans

- Sumatriptan 50 mg, 100 mg oral, nasal spray, subcutaneous injection (4)[A]
- Rizatriptan, zolmitriptan, *faster acting*
- Naratriptan, frovatriptan, *longer half life*
- Treximet® (sumatriptan 85 mg/naproxen 500 mg) (4)[A], *triptans contraindicated in vascular disease, basilar and hemiplegic migraine*

Prophylaxis
Antiepileptics

- Divalproex 500–1,500 mg/day, *weight gain, hair loss, tremor, liver dysfunction* (4)[A]
- Topiramate 50–200 mg/day, *mental slowness, paresthesias, kidney stones* (4)[C]

Antihypertensives

- Propranolol 80–240 mg/day, *use caution with depression and asthma* (3)[A]
- Timolol 20–30 mg/day (3)[A]

Tricyclic antidepressants

- Amitriptyline 30–150 mg/day, *can cause arrhythmia, drowsiness, anticholinergic effects* (3)[A]
- Nortriptyline, *better tolerated thanamitriptyline* (3)[C]

Second Line

Abortive
Combination treatment

- Butalbital/ASA/caffeine/codeine, *caution with overuse and rebound* (4)[B]

Ergot derivatives

- Ergotamine/caffeine (3)[B]
- Dihydroergotamine, nasal spray, *contraindicated in peripheral or coronary artery disease and uncontrolled hypertension* (3)[A]

Prophylaxis
Calcium channel blockers

- Verapamil 240 mg/day, *constipation* (3)[B]

Selective serotonin reuptake inhibitor

- Fluoxetine 20–40 mg/day, *insomnia, fatigue, tremor* (3)[B]

Other

- Cyproheptadine, *used more in pediatric migraine, can cause weight gain* (3)[C]
- Butterbur 100–150 mg/day, *reflux and burping*

Nausea associated with migraine

- Prochlorperazine (2)[B]
- Chlorpromazine (2)[B]

Treatment in pregnancy
Acute attack:

- Acetaminophen (preg B) (4)[B]
- Prochlorperazine (preg C) (4)[B]
- Prednisone (preg B) refractory cases (4)[B]

Prophylaxis: Reserved for refractory cases

- Magnesium (preg B) 400–600 mg/day (3)[B]
- Riboflavin (vitamin B2) (preg B) up to 400 mg/day (3)[B]
- Propranolol (preg C) <160 mg/day

ADDITIONAL TREATMENT

General Measures

Indications for prophylaxis: 4 or more headaches per month, abortive therapy fails or used more than twice per week, headache lasting more than 24 hours, symptoms causing significant disability.

Issues for Referral

Neurosurgery for possible surgical intervention and neuro-ophthalmology for concerning visual field testing or fundus exam.

Additional Therapies

Cognitive behavioral therapy, physical therapy, relaxation therapy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Biofeedback, massage, acupuncture.

SURGERY/OTHER PROCEDURES

Onabotulinum toxin (Botox type A) – FDA-approved treatment for chronic migraine.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Ensure patient environment is quiet, dark, with little disruption.

Admission Criteria

Intractable headache that fails to respond to appropriate outpatient or emergency department measures, failed outpatient detoxification, effective treatment of dehydration due to intractable vomiting (1)[C].

Nursing

Education for: Dietary management, stress management, exercise programs.

Discharge Criteria

Significant improvement of pain level and associated nausea and vomiting, detoxification, and transition to alternative prophylaxis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients should keep a headache journal for accurate account of headaches.

DIET

- Adequate hydration, avoid triggers: Chocolate, alcohol, aspartame, monosodium glutamate, and tyramine-containing foods.
- Caffeine: Wean off one cup per week for chronic migraineurs.

PATIENT EDUCATION

Appropriate timing in self-administered abortive treatment, reinforcing lifestyle changes.

PROGNOSIS

Migraine is a chronic condition, but frequency and severity decreases with age.

COMPLICATIONS

- Migrainous infarction may occur as a serious complication of migraine. This risk is highest in patients with migraine with aura, are female, smokers, and with estrogen use.
- Status migrainous, persistent aura without infarction, migraine-triggered seizure.

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CODES

ICD9

- 346.00 Migraine with aura, without mention of intractable migraine without mention of status migrainosus
- 346.10 Migraine without aura, without mention of intractable migraine without mention of status migrainosus
- 346.90 Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus

CLINICAL PEARLS

- Migraine is a neurovascular headache and development depends on both environmental and genetic factors.
- Ensure that secondary headache causes are ruled out.
- Treatment relies on changes in lifestyle, diet, and individualized abortive and prophylactic drug choices.

H

HEADACHE, POST LUMBAR PUNCTURE

John Castaldo, MD

BASICS

DESCRIPTION

- Positional, often disabling, headache is a common complication of diagnostic lumbar puncture (LP). The International Headache Society has defined post lumbar puncture headache (PLPHA) by the following essential characteristics:
  - The headache is bilateral and develops within 7 days after LP procedure.
  - The headache occurs or worsens within15 minutes of taking the upright position and disappears or improves within 30 minutes of recumbency.
  - The headache generally disappears within 14 days of the LP procedure.
- The pathophysiology of PLPHA is still uncertain. The prevailing theory postulates that leakage of CSF through the dural LP needle puncture site leads to intracranial CSF hypotension and hypovolemia. This in turn is compensated by dilation of intracranial veins and traction on pain-sensitive meningeal structures with erect posture that can only be relieved with recumbency.

EPIDEMIOLOGY

PLPHA occurs in 40% of cases with use of conventional cutting-point LP (Quincke) needles, and in 4–12% of cases with use of atraumatic, pencil-point (Whitacre or Sprotte) LP needles. No specific clinical characteristics reliably predict whether PLPHA will occur.

RISK FACTORS

- Risk factors include young age (ages 18–40 highest risk), female gender, lower body mass index, needle size and shape, history of prior PLPHA, and patients who suffer chronic or recurrent headache disorders. Diagnostic LP has a higher but variable risk for the disorder than does LP for spinal anesthesia.
- Recently, the Technology and Therapeutics Subcommittee of the American Academy of Neurology produced a consensus statement on this issue. These authors and others concluded that factors that do not affect the occurrence of PLPHA are race, quantity of CSF removed, duration of recumbency, sitting or lying position during the procedure, and experience of the proceduralist or multiple attempts at LP. Needle size and design (cutting vs. atraumatic), failure to replace stylet prior to removal from the subarachnoid space, and inattention to maintaining the cutting edge parallel to the dural fibers, however, do play a role in the evolution of the disorder (Class A).

Pregnancy Considerations

Not a specific risk factor

DIAGNOSIS

- The most characteristic symptom of PLPHA is a headache that occurs after LP and worsens with upright posture. Patients who develop this syndrome may have done well for a few days after the LP and may slowly and progressively worsen over ensuing days. Others will develop the symptoms immediately after the tap and complain of positional headache from the moment they leave the procedure room.
- PLPHA may be severe and associated with nausea, vomiting, vertigo, dizziness, tinnitus, photophobia, teichopsia, diplopia, or neck or scapular pain, and require that patients remain in bed all day.
- Most often the headache resembles migraine in its disabling severity and throbbing character and associated autonomic symptoms of nausea, vomiting, visual disturbances, and light and sound sensitivity. The presence of positional diplopia or tinnitus is unique for this disorder. Unlike migraine, however, PLPHA is rarely unilateral in location and often is completely, or nearly completely, ameliorated with taking the recumbent position.
- When the syndrome is prolonged and does not respond to conservative measures, diplopia due to cranial nerve VI palsy may develop along with persistent headache that may not fully resolve with taking the recumbent position.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- No laboratory tests are required to make the diagnosis of PLPHA. When the diagnosis is in doubt, especially when meningitis or a spontaneous dural CSF leak is suspected, an LP should be performed to assess opening CSF pressure and cell count.
- CSF pressure in PLPHA is usually less than 60 mm H_2O and can be unmeasurable. In prolonged cases of the syndrome, the CSF may be abnormal showing a primary lymphocytic pleocytosis (up to 200 cells/mm^3) and elevated protein content up to 1,000 mg/dL.

Imaging

No diagnostic testing is needed to make a diagnosis of PLPHA. In severe or prolonged cases that fail to resolve with the usual measures in 14 days, a gadolinium-enhanced MRI may be helpful. The typical finding is meningeal enhancement in a diffuse pattern over the convexity. A less common observation is "sagging" of the brain toward the skull base.

Diagnostic Procedures/Other

- When the diagnosis is in doubt, patients should be brought to the outpatient office for physical examination. Funduscopic and neurologic examination findings are normal. The patient is examined in both recumbent and sitting positions, and the time and pattern of headache onset and resolution are noted. Early in the course of the syndrome, abdominal hand pressure applied in the sitting position sometimes ameliorates the head pain.
- A pragmatic trial of oral or IV triptans may alleviate some of the post-LP vascular headache and should not be used to support a suspected diagnosis of migraine.

DIFFERENTIAL DIAGNOSIS

- The diagnosis usually is evident from the clinical circumstances. Consider post-LP meningitis if the patient develops progressively increasing recumbent headache, nausea, vomiting, fever, or severe neck stiffness. The diagnosis of PLPHA is made when a patient within 1 week of LP complains of positional headache that resolves with recumbency. Most commonly, the LP is a diagnostic tap, but the syndrome is also seen post LP for radiologic myelographic procedures and occasionally after spinal or epidural anesthesia.
- The differential is more complex in patients with previously established headache disorders such as migraine, pseudotumor cerebri, meningitis, and toxic metabolic states where vascular headache may worsen after LP. In these cases, recumbency may ameliorate the headache, but not completely.

TREATMENT

MEDICATION
There is no specific drug therapy for PLPHA. Fluid resuscitation and caffeinated beverages may be helpful in prevention. Either nonspecific pain medications (acetaminophen, aspirin, ibuprofen) or migraine medications (caffeinated medications, triptans) may be tried, but in themselves rarely abort the syndrome.

ADDITIONAL TREATMENT
General Measures
Needle design is a provocative culprit in the occurrence of the disorder. The "pencil-point" atraumatic needles, such as Whitacre or Sprotte, have a duller tip and an oval opening just proximal to the tip, in contrast to the Quincke needle with sharp edges and an opening at the tip. There is convincing Class I evidence for less PLPHA with atraumatic needles compared to sharp cutting needles with bevels parallel to dural fibers. In the last decade, a number of prospective randomized, controlled trials of Sprotte versus Quincke 22-gauge needles for neurologic diagnostic taps showed considerably less headache in the patients assigned to receive the atraumatic Sprotte needle for the procedure (Type A recommendation). The recommendation for use of the atraumatic LP needle, however, needs to be considered in light of the greater technical expertise needed to use them.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Symptomatic treatment
  - The treatment of PLPHA is bed rest, fluid and salt replacement, and time. Most often the syndrome resolves in 24–48 hours of bed rest, with bathroom privileges only.
- Adjunctive treatment
  - When the PLPHA does not respond within a few days of conservative methods, an epidural blood patch is warranted (Level B recommendation). This is usually performed by anesthesiologists/pain management physicians who take a small amount of blood from the patient's antecubital vein and infuse it in the lumbar epidural space in the region of the tap. Theoretically this provides a "blood patch" to the needle hole in the dural sac, allowing time for it to seal off, scar, and heal. Paradoxically, however, lumbar epidural blood patch may be effective in even spontaneous cervical dural tears. The technique of epidural blood patch is safe and generally painless, and produces rapid "on the table" response in most patients.

SURGERY/OTHER PROCEDURES
Not usually applicable. Rare case reports of PLPHA refractory to epidural blood patch have required open surgical closure.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Most patients with PLPHA do not require admission. Patients with refractory headache not responding to outpatient blood patch, with uncontrolled vomiting, or patients who are suspected of having meningitis or other illness should be hospitalized.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Patients should be monitored for resolution of headache.

PATIENT EDUCATION
Patients should be informed of the cause of the PLPHA. They should be educated about consumption of additional fluids, use of the recumbent position, and need to call the office for symptoms of progressive headache, fever, or chills.

PROGNOSIS
Most patients can expect a full recovery in 1–2 weeks.

ADDITIONAL READING

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CODES

ICD9
349.0 Reaction to spinal or lumbar puncture

CLINICAL PEARLS

When PLPHA does not respond to conservative measures, an epidural blood patch is frequently a highly effective treatment.

H

HEAVY METAL POISONING, NEUROLOGICAL COMPLICATIONS

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BASICS

DESCRIPTION

Heavy metals have been known since antiquity to be both useful and potentially harmful. In general, exposures at an early age and continuously over a lifetime are both of the greatest medical concern. Diagnosis of metal poisoning is essential to minimize neuronal damage, the removal of the probability of at-risk persons to further exposure, and to reduce levels of metal in body tissues by therapeutic chelation. This chapter considers the neurological sequelae of lead, mercury, manganese, arsenic, thallium, trimethyltin, triethyltin, and aluminum exposure.

EPIDEMIOLOGY

- Race
  - – All races and ethnic groups can be affected.
- Age
  - – 2 peaks are present, 1 in pediatric patients and the other in adults exposed to occupational hazards.
- Sex
  - – Both sexes can be affected; most often diagnosed in males.

RISK FACTORS

- Occupation: Welders, iron workers, smelters, miners
- Hobbies: Lead-stained glass crafting, painting
- Water supply: Lead pipes, manganese
- Fish and seafood consumption: Mercury
- Age: Children at greater risk for lead and mercury encephalopathy
- Psychosocial factors: Pica and object mouthing
- Nutrition: Iron deficiency anemia susceptibility to lead poisoning, over consumption of foods dense in manganese
- Air contamination
- Concurrent medical problems: Diabetes, liver failure, anemia

Pregnancy Considerations

- Pregnancy has not been shown to affect the course of neurological complications of heavy metal intoxication. Heavy metal intoxication during pregnancy may adversely affect the fetus.
- Fetal exposure to excessive amounts of mercury is linked with developmental delays, bilateral motor disturbances, and spongiosis of the cerebral cortex.

ETIOLOGY

- The etiopathogenesis of heavy metal neurological dysfunction depends upon the exposure of the central and peripheral nervous system (CNS and PNS).
- The toxic effects of heavy metal poisoning can present insidiously or abruptly, depending on whether the exposure is acute or chronic and high or low in levels.
- Heavy metal neurotoxicity may be multifactorial:
  - – Generation of free radicals that initiate lipid peroxidation
  - – Alteration of neuronal cell membranes
  - – Disruption of cellular respiration, oxidative phosphorylation, and ATP-dependent processes

DIAGNOSIS

- Signs and symptoms are generally diffuse and nonspecific in the CNS and PNS
- All of the heavy metals can be associated with encephalopathy
- Headache and cerebral edema occur with lead, organotins, and manganese
- Nausea and emesis occur with thallium, arsenic, and organotins
- Psychosis occurs with manganese, mercury, thallium, and arsenic
- Memory loss is seen with lead, aluminum, thallium, arsenic, and magnesium
- Seizures are associated with lead, organotins, thallium, arsenic, aluminum, and mercury
- The development of Alzheimer's and Parkinson's disease are seen in conjunction with mercury exposure
- Peripheral and cranial neuropathies are associated with toxic thallium and lead exposure; arsenic, lead, mercury, organotoxins
- Tremor and movement disorders occur with aluminum, lead, manganese, mercury, and thallium intoxication
- Lead neuropathy is characterized initially by disturbance of wrist and finger extensors and then weakness, muscle atrophy, and sensory loss
- Heptic encephalopathy occurs with manganese

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Screening for heavy metal exposure is performed on blood and urine specimens.
  - – Ranges of toxicity vary depending on the metal in question
  - – Lead neuropathy occurs when whole blood levels exceed 80 μg/dL; however, long-term poisoning may occur at lower levels
  - – Mercury intoxication occurs with urine levels of >50 μg Hg/liter
- Hair or nail samples can be used to determine remote exposure and may even reveal abnormally elevated levels when blood and urine are normal
  - – These samples are particularly useful in diagnosing arsenic poisoning because arsenic serum levels decrease quickly
- Sural nerve biopsy demonstrates a spectrum of histopathological changes in heavy metal exposure
  - – Wallerian degeneration with secondary demyelination in arsenic and thallium intoxication
  - – Segmental demyelination in lead exposure

Imaging

- Conventional radiographs of the long bones in children shows increased density of epiphyseal bands termed lead lines
- Neuroimaging with MRI and CT should be performed in all patients with changes in baseline mental status, cognitive impairment, seizures, and focal neurological findings
  - – There may be coexistent intracranial disturbance including subdural hematoma, abscess, tumor, or stroke
  - – Neuroimaging in mercury intoxication shows cerebellar atrophy, hyperintense lesions in paracentral area, frontal white matter, and basal ganglia
  - – Organotin is associated with hippocampal atrophy
  - – Generalized cerebral cortical atrophy occurs with lead poisoning
  - – High-intensity signal abnormalities are seen in the globus pallidus, striatum, and substantia nigra in those with manganese poisoning
  - – Fluorodeoxyglucose-brain positron emission tomography (PET) reveals reduced uptake in asymptomatic patients exposed to manganese
  - – Nuclear medicine cerebral perfusion with single photon emission computerized tomography shows abnormal region hyperperfusion

Diagnostic Procedures/Other

- Electrodiagnostic studies including electromyography (EMG) and nerve conduction studies (NCS) may reveal neuropathic lesions along peripheral nerves
- Awake and drowsy 20-channel EEG with photic stimulation and hyperventilation is useful in screening for cerebral dysfunction and interictal seizure activity
- Computer-assisted quantitative sensory tests is useful in establishing normal and abnormal vibratory, cold temperature, and pain thresholds derived from epidermal nerve fiber territories in the limbs
- Neuropsychological testing is useful at any age to assess cognition and impaired memory

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of heavy metal intoxication is extensive because it can resemble other PNS and CNS disorders.

TREATMENT

MEDICATION

- Chelation therapy is the mainstay of treatment for lead, thallium, arsenic, manganese, and mercury poisoning
- The chelating agents include:
  - – $CaNa_2EDTA$
  - – 2,3-Dimercaptopropanol (BAL)
  - – Dimercaptosuccinic acid (DMSA)
  - – Penicillamine.
- Contraindications: None
- Precautions
  - – BAL causes hypertension and tachycardia
  - – Penicillamine induces renal impairment
  - – Ethylenediaminetetraacetic acid (EDTA) can induce hypocalcemia and should be administered with a calcium supplement

Specific Heavy Metal Exposures

- Lead poisoning:
  - – Mannitol is administered to control cerebral edema associated with lead encephalopathy.
  - – Immediate chelation therapy is given for encephalopathic patients with serum levels >70 μg/100 mL.
  - – Intravenous diazepam is administered to control seizure activity associated with encephalopathy.
  - – Hemodialysis is necessary in patients with renal failure.
  - – Chelation therapy with a single dose of 1,000 mg/m^2 of EDTA is recommended when blood levels range between 70 and 200 μg/dL.
  - – Meso-2-3dimercaptosuccinic acid is a recently FDA-approved chelating agent which is administered orally 10 mg/kg every 8 hours for 5 days.
  - – Penicillamine increases lead excretion as well.
- Thallium poisoning:
  - – Gastric lavage with activated charcoal and whole bowel irrigation is given to remove thallium from the GI tract following acute ingestion
  - – Traditional chelating agents are not effective in thallium poisoning
  - – Prussian blue or activated charcoal should be administered to enhance fecal elimination
  - – Diuretics can be used to enhance urinary excretion
  - – Hemodialysis and hemoperfusion may be necessary in patients with thallium-induced acute renal failure
- Arsenic poisoning
  - – Gastric lavage and whole bowel irrigation removes arsenic from the GI tract following acute ingestion
  - – Chelation therapy is started immediately after acute ingestion with either BAL, DMSA, or penicillamine
- Manganese poisoning:
  - – Chelation improves clinical symptoms and reduces the body burden in patients with encephalopathy
  - – $CaNa_2EDTA$ is the chelating agent of choice when there are high-signal abnormalities in the corpus striatum but may not improve parkinsonism
  - – Diethyl-2-phenyl-2-tellurophenyl vinylphosphonate is effective in reducing motor disturbances in laboratory animals
  - – Those with liver failure benefit from low-manganese diets
- Mercury poisoning
  - – Symptomatic patients with serum mercury levels of >15 μg/L should undergo chelation therapy with derivative BAL, DMSA, 2,3-dimercapto-1-propanesulfonic acid (DMPS) or penicillamine
  - – Traditional BAL relocates mercury to the CNS and exacerbates neurotoxic effects
  - – $CaNa_2EDTA$, DMPS, and DMSA attenuate the toxicity of $HgCl_2$, the most toxic form of mercury
  - – Chelators can potentially increase the toxicity of inorganic mercury in a patient
  - – EDTA is the most common chelator in chronic mercury poisoning
  - – Gastric lavage should be performed in those who have ingested elemental or inorganic mercury
  - – Hemodialysis with L-cysteine or DMSA infused into the dialyzer may be necessary

ADDITIONAL TREATMENT

General Measures

- Workers at risk of metal poisoning should undergo routine evaluations of blood, renal, nervous and reproductive systems.
- A comprehensive personal, occupational, and medical history is required to document potential past or current chemical exposures.
- The chemicals that the patient may have come in contact should be catalogued with dates of exposure.
- Home water supply and regional environment should be investigated.
- Symptomatic patients should be considered for chelation therapy to reduce the body burden of accumulated metals.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission is generally necessary for those with acute neurological events such as seizure activity, encephalopathy, severe weakness, persistent headache, and psychosis. Heavy metal tissue levels and history of exposure should be determined by an analysis of urine excretion following chelation therapy.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Neurological recovery from heavy metal intoxication and serum and/or tissue metal levels should be monitored.
  - – Serial neuropsychological testing
  - – EMG and NCS
  - – EEG
  - – Neuroimaging
  - – Serum levels
  - – Urinary excretion

PATIENT EDUCATION

- Patients must be educated on strategies to avoid future exposures to heavy metals
- Refer website: www.medhelp.org/healthtopics/Heavy_Metal_Poisoning.html
- Heavy metal poisoning information; website: www.rxaddict.com/g/conditionpage/Poisoning_Heavy_Metals

PROGNOSIS

- Most patients improve with chelation therapy and supportive care
- Prognosis and potential for permanent neurological sequelae are variable and depend on the chronicity and severity of exposure
- The most common residual deficits are memory loss and impaired cognition following encephalopathy
- Persistent motor dysfunction in patients with severe peripheral neuropathy

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Encephalopathy
- Neuropathy
- Parkinson's disease

CODES

ICD9

- 985.0 Toxic effect of mercury and its compounds
- 985.1 Toxic effect of arsenic and its compounds
- 985.8 Toxic effect of other specified metals

HEMIBALLISMUS

Ruth Ann Baird, MD
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BASICS

DESCRIPTION
Hemiballismus is a hyperkinetic movement disorder characterized by violent flailing movements involving proximal limbs on one side of the body. Hemiballismus is considered an extreme form of chorea because as ballistic movements subside with time, they have the appearance of classic chorea.

EPIDEMIOLOGY
Incidence
- Uncommon, with an annual incidence of around 1 per 500,000 in the general population.
- Age
  – Mean age at presentation >60 years.
- Sex
  – Hemiballismus occurs equally in men and women.

Prevalence
- Of 3,084 patients seen at a tertiary care movement disorders clinic, only 21 had hemiballismus (1)[C].

RISK FACTORS
Vascular risk factors, especially hypertension, are most important because stroke is the main cause of hemiballismus.

Genetics
Patients of East Asian origin may be at increased risk for hemiballism due to hyperglycemia.

GENERAL PREVENTION
Because stroke is the most common cause of hemiballismus, prevention would involve treatment of vascular risk factors (i.e. hypertension, diabetes, tobacco use).

PATHOPHYSIOLOGY
Damage to the subthalamic nucleus or surrounding pathways leads to loss of normal subthalamic inhibition, which results in abnormal involuntary movements on the contralateral body. Hemiballismus may also result from pathology within the globus pallidus, thalamus, substantia nigra, putamen, or caudate.

ETIOLOGY
- Hemorrhagic and ischemic strokes account for about two-thirds of all cases of ballismus.
- The second most common cause is hyperglycemia associated with diabetes mellitus.
- Other potential etiologies include head trauma, space-occupying lesions, CNS infections, demyelinating disease, autoimmune diseases (especially systemic lupus erythematosus), medications (levodopa, oral contraceptives, phenytoin, tardive syndromes from neuroleptics), and basal ganglia calcification.

Pregnancy Considerations
There is no specific relationship with pregnancy except that chorea gravidarum occasionally can be severe and unilateral.

Pediatric Considerations
Hemiballismus is rare in children; however, Sydenham's chorea can be unilateral and of such large amplitude to resemble hemiballismus.Hemiballistic limb movements have been reported in pediatric patients with ifosfamide-induced encephalopathy (2)[C].

COMMONLY ASSOCIATED CONDITIONS
- *Cerebrovascular disease:* Ischemic and hemorrhagic stroke, vascular malformations
- *Autoimmune disorders:* Systemic lupus erythematosus, antiphospholipid antibody syndrome, Sydenham's chorea, scleroderma
- *Metabolic disorders:* Diabetes, nonketotic hyperglycemic coma, hypoglycemia
- *Infectious diseases:* HIV/AIDS, syphilis, tuberculosis, toxoplasmosis, cryptococcosis, influenza A
- *Tumors:* primary CNS malignancies, metastatic tumors, cystic lesions, abscesses
- *Drugs:* Levodopa, dopamine agonists, neuroleptics, anticonvulsants (e.g., phenytoin), oral contraceptives, gabapentin, cocaine, amphetamines, CNS stimulants
- *Iatrogenic:* Subthalamotomy for Parkinson disease, ventriculoperitoneal shunt placement
- Head trauma

DIAGNOSIS

HISTORY
- Acute or subacute onset, depending on mechanism of injury
  – Movements may be suppressed for brief periods of time
  – Interference with normal motor activity and stress makes them worse
- Previously unrecognized diabetes may present with hemiballism

PHYSICAL EXAM
- Large amplitude, proximal usually rotatory throwing or kicking movements
- In half of patients, the leg and arm of the same side are equally affected.
- In two-thirds of patients the face is also involved.
- For unknown reasons, the left hemibody is more commonly affected.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Directed at determining underlying cause
  – CBC, blood glucose, serum osmolality, routine blood chemistries, sedimentation rate, Venereal Disease Research Laboratory antinuclear antibodies, antiphospholipid antibodies, PT, aPTT, pregnancy test, urinalysis

Follow-up & special considerations
- In selected patients: HIV test, anticonvulsant blood levels, throat culture, antistreptolysin antibody titers, anti-dsDNA, Sjögren's syndrome A (SSA) and Sjögren's syndrome B (SSB) antibodies
- HgbA1c may be useful in patients who do not have a prior history of diabetes

Imaging
Initial approach
Brain MRI or CT +/– contrast should be performed to search for a structural cause of hemiballismus.

Follow-up & special considerations
Brain MRI in acute stages of hemiballism due to nonketotic hyperglycemia may show T1 hyperintensity in the contralateral striatum (3)[C].

Diagnostic Procedures/Other
No special procedures are required for diagnosis.

DIFFERENTIAL DIAGNOSIS
- Tic disorder
- Psychogenic movement disorder

TREATMENT

MEDICATION
First Line
Neuroleptics
These drugs are the first-line treatment for ballistic movements because of their proven efficacy. Antagonism of the postsynaptic D_2 dopamine receptor seems to be the common feature among agents effective in the treatment of hemiballismus. Chlorpromazine, promethazine, perphenazine, prochlorperazine, haloperidol, pimozide, and tiapride, among other neuroleptics, have been shown to be effective in the treatment of hemiballismus. Clozapine in low doses (50 mg/day) also is useful. Response usually is dramatic and starts within 2 days and almost always within 7 days. If treatment is prolonged or there are side effects, consider using a benzodiazepine, a dopamine-depleting agent (e.g., reserpine, tetrabenazine), or a GABA-ergic agent such as valproate.

- Contraindications
  - Neuroleptics should not be used in patients with prior history of hypersensitivity, neuroleptic malignant syndrome, prolonged QT syndrome, or neuroleptic-induced movements.
  - Tetrabenazine is indicated for neuroleptic-induced ballistic movements.
- Precautions: The main problem with the use of neuroleptics is the development of extrapyramidal side effects, such as akathisia, drug-induced parkinsonism, neuroleptic malignant syndrome, and tardive dyskinesia. Other side effects include sedation, cardiac conduction abnormalities, weight gain, maculopapular rash, cholestatic jaundice, transient leukopenia, and photosensitivity.

Second Line

- *Sedative/hypnotics:* A variety of sedative drugs (e.g., barbiturates, chloral hydrate, benzodiazepines) have been used for treatment of hemiballismus. Their efficacy is modest and related to their tendency to induce sleep.
- *Catecholamine-depleting agents:* Tetrabenazine, reserpine
- *GABA-ergic agents*: Valproic acid

ADDITIONAL TREATMENT

General Measures

Management requires identification of the cause of hemiballismus, mainly focusing on neuroimaging and identifying and treating risk factors, with special emphasis on vascular risk factors.

Issues for Referral

Patients should follow-up with a neurologist.

Additional Therapies

Botulinum toxin injections may be effective in decreasing amplitude of movements (4)[C].

SURGERY/OTHER PROCEDURES

- Surgery is reserved for patients with refractory hemiballismus. The tendency for movements to improve spontaneously over time should be taken into account before planning an invasive procedure.
- Thalamotomy and pallidotomy have been shown to improve hemiballismus secondary to STN lesions. Deep brain stimulation of the globus pallidus and thalamus has been effective in reducing movements in small numbers of patients (5,6)[C].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Ensure stable cardiorespiratory status

Admission Criteria

All patients should be admitted for diagnostic evaluation and started on treatment for the ballismus.

IV Fluids

Normal saline should be administered to prevent dehydration.

Nursing

Padding of the limb and bedrails may be necessary to prevent injury.

Discharge Criteria

Discharge criteria and workup depend on the underlying diagnosis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients should be monitored for medication-induced adverse effects, i.e. drug-induced parkinsonism with neuroleptics, depression with tetrabenazine.
- Patients with stroke as a cause for hemiballismus may require rehabilitation with physical and occupational therapy.

Patient Monitoring

- Patients with stroke should be monitored periodically on an outpatient basis to assess recovery and ongoing treatment of vascular risk factors
- Diabetic patients will need appropriate outpatient blood glucose monitoring

DIET

Varies according to underlying diagnosis

PATIENT EDUCATION

There are no support groups or organizations providing information for patients with hemiballismus. The condition is mentioned briefly at www.wemove.org.

PROGNOSIS

- Spontaneous resolution occurs in majority of cases, usually within 3 months.
- Hemiballismus may evolve into a hemichorea or hemidystonia.

COMPLICATIONS

Severely affected patients may experience medical complications of excessive movement such as dehydration or rhabdomyolysis. Supportive care directed at preventing complications of hospitalization, such as aspiration pneumonia, pulmonary embolism, and urinary tract infection, should be provided.

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See Also (Topic, Algorithm, Electronic Media Element)

- Ballism
- Hemichorea

CODES

ICD9

333.5 Other choreas

CLINICAL PEARLS

Stroke is the cause of hemiballismus in a majority of cases.

HEREDITARY SPASTIC PARAPARESIS

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BASICS

DESCRIPTION
Hereditary spastic paraparesis/paraplegia (HSP) is a group of genetically diverse neurodegenerative diseases, characterized by insidiously progressive spasticity and muscle weakness of lower extremities (1). HSP patients frequently suffer from bladder disturbances. Uncomplicated (pure) HSP is characterized by neurological impairment limited to progressive weakness/spasticity in lower extremities, bladder disturbances and mild dorsal column impairment in lower extremities. Complicated HSP is characterized by common neurological deficits seen in uncomplicated HSP with additional neurological findings and/or other non-neurological system involvement.

EPIDEMIOLOGY
Incidence
Unknown

Prevalence
Estimated prevalence for uncomplicated HSP is 3–10 in 100,000 population (2,3).

RISK FACTORS
Other than consanguinity, no other known risk factors.

Genetics
- At least 41 loci [SPastic parapleGia (SPG)] are mapped and 17 genes are identified.
- Autosomal dominant, autosomal recessive, and X-linked recessive inheritance are reported (4).

GENERAL PREVENTION
Not applicable

PATHOPHYSIOLOGY
Key neuropathology in HSP involves degeneration of axons that is maximal at the distal ends of the longest axons (corticospinal tracts—motor, and dorsal column pathway—sensory).

ETIOLOGY
Reported genes responsible for HSP suggest that mutation of HSP genes can result in disturbance in membrane trafficking of organelles, axonal transport, and/or mitochondrial function. Dysfunction of these genes would ultimately lead to length-dependent axonal degeneration.

COMMONLY ASSOCIATED CONDITIONS
In complicated HSP patients, intellectual disability, dementia, seizure/epilepsy, and/or amyotrophy can be associated.

DIAGNOSIS

HISTORY
- Insidiously progressive course.
- Bilateral lower extremity spasticity and weakness.
- Urinary urgency [frequently seen (5)].
- Family history consistent with autosomal dominant, autosomal recessive, or X-linked recessive inheritance.

PHYSICAL EXAM
- Corticospinal tract deficits subserving bilateral lower extremities (spasticity, muscle weakness, hyperreflexia, bilateral extensor plantar responses).
- Mildly impaired vibratory sensation in the distal lower extremities (dorsal column involvement).
- Hyperreflexia in upper extremities can occur.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Exclusion of other diagnoses such as
  - Vitamin B12
  - Vitamin E
  - Human T-cell leukemia virus (HTLV) antibodies
  - HIV antibodies
  - Venereal disease research laboratory (VDRL)
  - Plasma very long chain fatty acids
  - Serum copper and zinc

Follow-up & special considerations
- Evaluation of Krabbe disease (galactocerebrosidase enzyme activity) or metachromatic leukodystrophy (arylsulfatase A enzyme activity) may be necessary for suspected leukoencephalopathy.
- For childhood onset, levodopa-responsive dystonia (aka Segawa's disease) should be considered, since it is treatable with levodopa–carbidopa therapy.
- Evaluation for arginase deficiency may be necessary (elevated plasma arginine concentration) in childhood onset cases.
- Rule out multiple sclerosis (along with imaging studies, consider lumbar puncture).

Imaging
Initial approach
- Rule out structural abnormalities of the brain and/or spinal cord (by MRI studies)
- Examples: Chiari malformation, arteriovenous malformation, cervical spine degenerative disease, neoplasms
- Rule out multiple sclerosis

Follow-up & special considerations
Rapidly progressive course or new focal neurological deficit(s) should be evaluated by physical exam and follow-up imaging studies to consider other disorders.

Diagnostic Procedures/Other
Electrodiagnostic studies (EMG/nerve conduction studies) can be helpful to distinguish HSP from amyotrophic lateral sclerosis (ALS).

Pathological Findings
Neuropathology is typically limited to central nervous system (axonal degeneration that is maximal at the distal ends of corticospinal tracts and dorsal column fibers), and therefore peripheral nerve biopsy is not helpful for diagnosis of living HSP patients.

DIFFERENTIAL DIAGNOSIS
- B12 deficiency
- Vitamin E deficiency
- Copper deficiency/zinc toxicity
- HTLV-associated myelopathy/tropical spastic paraparesis
- HIV
- Syphilis
- Adrenomyeloneuropathy
- Krabbe's disease
- Metachromatic leukodystrophy
- Levodopa-responsive dystonia*
- Arginase deficiency*
- Multiple sclerosis
- Transverse myelitis
- Chiari malformation
- Arteriovenous malformation
- Neoplasm
- Motor neuron diseases (ALS, primary lateral sclerosis)
- Spinocerebellar ataxia
- Friedreich's ataxia
- Cervical spine degenerative disease

Pregnancy Considerations
Prenatal diagnosis for some HSP genes can be performed by DNA analysis extracted from fetal cells via amniocentesis or chorionic villus sampling. Preimplantation genetic diagnosis may be available. The disease-causing allele(s) have to be identified prior to either prenatal or preimplantation genetic diagnostic procedures.

(*should be included with childhood-onset patients)

TREATMENT

MEDICATION
- No cures or specific drug treatments exist. Currently available treatment is symptomatic alleviation
- Baclofen (oral or intrathecal administration (6)[C])
- Tizanidine (7)[C]
- Dantrolene
- Benzodiazepines
- Botulinum toxin injection (8)[C]
- Oxybutynin (bladder hypertonicity)
- Tolterodine (bladder hypertonicity)

ADDITIONAL TREATMENT
General Measures
- Intermittent self-catheterization to prevent urinary retention (if post-void residuals exceed 100 ml), recurrent urinary tract infections, or vesicorenal reflux. Indwelling catheter should be avoided as much as possible due to the risk of infection.
- Skin care (prevention of decubitus ulcer).

Issues for Referral
- Genetic clinics (genetic counseling)
- Neurology clinics
- Urology clinics (urodynamic evaluation)
- Neurosurgery clinics (evaluation of intrathecal baclofen pump implantation)

Additional Therapies
- Physical therapy
- Occupational therapy
- Ankle–foot orthotics
- Assisting devices (e.g., walker)

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Not applicable

SURGERY/OTHER PROCEDURES
- Intrathecal baclofen pump implantation can be applied for some patients to alleviate muscle spasticity.
- Suprapubic catheter placement can be considered for some patients.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Follow-up with neurologist
- Physical therapy to establish home exercise regimen
- Evaluation of necessity to provide assistive device (walker, wheel chair) and/or ankle–foot orthotics
- Urodynamic evaluation to determine choice of medication and necessity for intermittent self-catheterization (if urinary retention is present)
- Counseling for additional family members

Patient Monitoring
- Adjustment of medications for symptomatic alleviation.
- Safety evaluation (to prevent falls and injuries).
- Prevention and early intervention of complications such as urinary tract infection or pressure sores.
- HSP tends to be a slowly progressive condition. If patient shows rapid progression or new neurological symptoms, complete history and neurological examination is necessary to evaluate other etiologies or even consider misdiagnosis (such as ALS, cervical myelopathy, etc.).

DIET
No restriction

PATIENT EDUCATION
- NIH (National Institute of Neurological Disorders and Stroke). http://www.ninds.nih.gov/disorders/hereditary_spastic_paraplegia/hereditary_spastic_paraplegia.htm
- Spastic Paraplegia Foundation, PO Box 1208, Forston, GA 31308

Email: information@sp-foundation.org; website: http://www.sp-foundation.org
Tel: 1-877-SPF-GIVE (1-877-773-4483)
Fax: 877-SPF-GIVE

PROGNOSIS
Prognosis of HSP patients is highly variable from severe disability to mild disability. Even within the same family, onset and prognosis of affected individual family members can be varied. Most of individuals with uncomplicated HSP have normal life expectancy.

COMPLICATIONS
- Injuries due to falls (fractures, head trauma)
- Recurrent or chronic urinary tract infections
- Muscle contractures

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See Also (Topic, Algorithm, Electronic Media Element)
- Familial spastic paraparesis/paraplegia
- Stümpell–Lorrain disease/syndrome
- Hereditary spastic paraplegia

CODES

ICD9
334.1 Hereditary spastic paraplegia

CLINICAL PEARLS
- HSP is a genetically diverse neurodegenerative disorder.
- Diagnosis of HSP may be made by interview of history, physical exam and exclusion of other disorders. Some cases of HSP can be also confirmed by genetic tests.
- Currently, there is no treatment to cure or delay the progression of HSP. Symptomatic alleviation (muscle relaxant, management of hypertonic bladder) can be done by medications.

H

HERPES ZOSTER

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BASICS

DESCRIPTION
- Herpes zoster is a painful vesicular skin rash, commonly known as shingles.
- Rash occurs in a dermatomal distribution.
- Rash includes skin inflammation and blisters, which last about 2–4 weeks.
- Pain which can be intense usually occurs in the distribution of rash.

EPIDEMIOLOGY
Incidence
- Approximately 1 million people in the USA are affected by Herpes annually.
- Approximately 15% of the U.S. population develop herpes zoster.

RISK FACTORS
- Herpes zoster can occur at any age.
- Primary risk factor being previous chickenpox infection as a child.
- Risk also increases with age; most common in people above 60 years of age.
- Risk increases in people who are immunocompromised such as patients with HIV/AIDS, diabetes mellitus, cancer, patients receiving chemotherapy, radiotherapy, or steroids.
- Having varicella before the age of 1 also increases risk.

Pregnancy Considerations
Pregnancy does not increase the risk of herpes zoster.

GENERAL PREVENTION
- Zostavax is a concentrated formulation of varivax approved by FDA to prevent herpes zoster and its complications in immunocompetent adults.
- It was initially approved for people aged ≥60 years. More recently, as of March 2011, it has also been approved by FDA for patients aged 50–59 years.
- The approval was based on a multicenter study conducted in the United States and 4 other countries among approximately 22,000 people who were 50–59 years of age. Half received Zostavax and half received a placebo. Study participants were then monitored for at least 1 year to see if they developed shingles. Compared with placebo, Zostavax reduced the risk of developing shingles by approximately 70%.
- It is a live vaccine.
- Single dose, given in deltoid region of arm. No booster dose required.
- People need not be asked or tested for previous varicella.
- Vaccine is indicated regardless of whether the person has had prior episode of herpes zoster.
- Antiviral medications should not be used within 24 hours before or 14 days after vaccination.
- Side effects include itching, headache, redness, and pain at injection site.
- Pregnant women should not be given the vaccine.

PATHOPHYSIOLOGY
Herpes zoster occurs when the varicella zoster virus, which causes both chickenpox and herpes zoster, is reactivated from its latent state in the dorsal or cranial nerve ganglia and spreads through the afferent nerve to the skin.

ETIOLOGY
Caused by reactivation of varicella zoster virus, same virus that causes chickenpox.

COMMONLY ASSOCIATED CONDITIONS
The incidence of herpes zoster increases in patients with human immunodeficiency syndrome.

DIAGNOSIS

HISTORY
Herpes zoster is usually preceded by approximately 2–4 days of pain, tingling, or burning in a dermatomal distribution.

PHYSICAL EXAM
- Usually characterized by a band-like rash in the dermatome that corresponds to the affected nerve.
- The lesions progress from vesicles to pustules to crusting lesions until the rash resolves.
- Rash is unilateral and does not cross the midline.
- Most commonly involved dermatomes are thoracic, followed by cranial, lumbar, and cervical. Sacral dermatomes are least frequently involved.
- Rarely, there may be pain and paresthesia in a dermatomal distribution without any rash; this is known as *zoster sine herpete*.
- Pain lasting >1 month is known as postherpetic neuralgia (PHN)
- Herpes zoster ophthalmicus, defined as zoster involving the distribution of the ophthalmic division of the fifth cranial nerve, is found in 10–25% cases of herpes and can sometimes involve the cornea. Common indication of the same is appearance of blisters on tip of nose which is known as Hutchinson's sign.
- Herpes zoster involving the distribution of facial nerve causing severe ear pain and paralysis of facial muscles is known as Ramsay Hunt syndrome.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Herpes zoster is usually a clinical diagnosis based on the observation of the characteristic rash.
- Further laboratory testing may be required in cases with atypical rash and possible disseminated disease.
- PCR is rapid and is the most sensitive and specific test available. Direct flourescent antibody is another alternative if PCR is not available, as it is more sensitive than a culture. Both the tests can be performed on specimens obtained from skin lesions.
- Viral cultures can also be obtained, although this is done infrequently in practice. The sensitivity of viral culture is 30–70% and the specificity is 100%.

Diagnostic Procedures/Other
Occasionally, skin biopsy may be required for diagnosis.

Pathological Findings
Pathologic findings include ballooning degeneration of keratinocytes, intraepidermal vesicle formation, and associated leukocytoclastic vasculitis.

DIFFERENTIAL DIAGNOSIS
Usually herpes zoster is very typical in presentation. Other entities to consider include:
- Zosteriform herpes simplex virus.
- Contact dermatitis
- Chemical dermatitis

TREATMENT

MEDICATION

First Line

Medications:

- Antiviral agents given during first 72 hours reduce the duration and severity of PHN.

Medication	Dose	Frequency	Duration	Route
Famciclovir	500 mg	3 times a day	7 days	Oral
Valacyclovir	1000 mg	3 times a day	7 days	Oral
Acyclovir	800 mg	5 times a day	7 days	Oral

- Famciclovir and valacyclovir are preferred because of simplified dosing schedule and improved pharmacokinetics.
- Various randomized controlled trials have shown all 3 antiviral agents to reduce duration of pain, shorten the duration of new lesion formation, accelerate cutaneous healing, and reduce viral shedding.
- Some experts recommend using IV acyclovir in patients who are immunocompromised with multidermatomal involvement. It is also recommended if CNS or multivisceral involvement is suspected. The dose is 10–15 mg/kg every 8 hours for patients with normal renal function.
- Aggressive pain management is required in herpes zoster, as reducing pain early on may reduce the risk of PHN.

Second Line

Role of corticosteroids is unclear. Some authors recommend adding a 10–14 day tapering course of oral corticosteroid to antiviral therapy in patients with herpes zoster older than 50 years of age who have moderate-to-severe pain at presentation.

ADDITIONAL TREATMENT

General Measures

- Keep cutaneous lesions clean and dry.
- Wash rash with soap and water and then pat dry.
- Topical capsaicin should not be used for acute herpes zoster because it can exacerbate the pain, but it can be used to treat PHN.

Issues for Referral

- Patients with disseminated herpes zoster infection or ocular involvement may need hospitalization.
- Consider consulting specialist in cases of dissemination, CNS, ophthalmologic, auditory, dental, or visceral involvement.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with dissemination or neurological complications such as meningitis or myelitis require hospitalization for treatment including intravenous antiviral therapy.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Monitor for secondary infection, ophthalmologic, or meningeal involvement and for complications such as PHN.

PATIENT EDUCATION

- Patient should be psychologically prepared to deal with both acute and chronic pain.
- Patient with herpes zoster should learn about the risk of varicella zoster virus transmission. Transmission of the virus can cause varicella in a person who is seronegative for varicella zoster virus.
- Patient with active herpes zoster should avoid contact with susceptible infants or small children, pregnant women, and immunocompromised patients.

PROGNOSIS

Herpes zoster typically resolves within 2 weeks, but approximately 20% of patients may develop PHN which can be quite debilitating.

COMPLICATIONS

- PHN
- Vision impairment
- Hearing difficulties
- Neurological complications including vasculopathy, myelitis, cranial and peripheral neuropathies, polyradiculitis
- Bacterial superinfection of cutaneous lesions
- Immunocompromised hosts usually have an increased risk of acquiring varicella infection of lungs, CNS, and life-threatening bacterial infections

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Varicella zoster virus
- Shingles
- PHN

CODES

ICD9

- 053.9 Herpes zoster without mention of complication
- 053.29 Herpes zoster with other ophthalmic complications

CLINICAL PEARLS

- Herpes zoster is a clinical diagnosis.
- Early initiation of antiviral therapy and adequate analgesia with pain medications is cornerstone of its management.
- It can be prevented by administration of Zostavax, which now has been approved for patients ≥50 years of age.

HORNER'S SYNDROME

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With the Assistance of Laura Kolbe

BASICS

DESCRIPTION

- Silas Weir Mitchell first recognized the combination of a droopy eyelid, enlarged pupil, and lack of sweating on the side of a neck injury of a wounded Civil War soldier (Mitchell et al., 1864).
- Johann Frederick Horner later described the same disorder named in his honor that comprises ptosis, meiosis, and anhydrosis (Horner, 1869).
- Horner's Syndrome (HS) results from interruption of the sympathetic outflow between the hypothalamus and orbit through an extensive anatomical course along central, pre-, and post-stellate ganglionic connections.

EPIDEMIOLOGY

- Nearly 20% of the population has at least 0.4 mm of unequal pupil diameter between the 2 eyes, termed "anisocoria."
- HS occurs equally in either gender, across all ages, and without racial preference.

RISK FACTORS

Occupational exposure: Physical work as laborer that entailed 90 degree neck turning predisposed to internal carotid artery (ICA) thrombotic dissection (Morgan et al., 2011).

PATHOPHYSIOLOGY

- First-order neurons located in the ventral posterior hypothalamus give rise to a longitudinal descending fiber tract that occupies a lateral position in the brainstem and spinal cord.
- Central first-order neuron fibers synapse with sympathetic preganglionic neurons located in the lateral gray column of the cervical spinal cord from C8 to T2.
  - Lesions of these fibers occur in the petrosal apex (Gradenigo) syndrome, herpes zoster ophthalmicus, Raeder paratrigeminal neuralgia, cluster headache syndrome, multiple sclerosis, stereotactic thalamotomy, superior cerebellar artery, and anterior inferior cerebellar basilar branch occlusions; posterior inferior cerebellar artery branch or vertebral artery occlusion leading to pontine and medullary (Wallenberg) brainstem syndromes of infarction, poliomyelitis, syringobulbia, syringomyelia, unilateral cordotomy or injury above T1, and epidural blocks.
- Preganglionic second-order neuron rami exit the spinal cord at T1 and synapse in the superior cervical ganglion embedded in the connective tissue between the carotid sheath and the prevertebral fascia passing over the lung apex at the level of the thyroid cartilage.
  - Lesions of these fibers occur in pediatric mediastinal neurogenic tumors including neuroblastoma, ganglioneuroblastoma, and ganglioneuroma; C8 to T1 root avulsion, penetrating neck injury, apical bronchogenic tumor (Pancoast tumor); perinatal brachial plexus palsy, high thoracic paravertebral blocks, thoracoscopic sympathectomy, and aortic stenting.
- Postganglionic third-order neuron fibers leave the cephalic pole of the ganglion and via internal carotid nerve branches as a direct continuation of the sympathetic trunk into the head accompanying the ICA through the petrous, lacerum, cavernous, clinoid, and ophthalmic portions.
  - In the cavernous sinus the ICA occupies a medial position relative to the oculomotor, trochlear, ophthalmic, abducens and maxillary nerves which lie in vertically descending order embedded in connective tissue.
  - The majority of communicating sympathetic fibers from the cavernous plexus join the ophthalmic and oculomotor nerves, just before they pass through the superior orbital fissure.
  - Long ciliary nerves carrying sympathetic fibers, 2 or 3 in number, given off from the nasociliary branch of the ophthalmic nerve as it crosses the optic nerve accompanying the short ciliary nerves from the ciliary ganglion, pierce the posterior part of the sclera and run anteriorly carrying terminal third-order neuron fibers to the dilator pupillae muscle.
  - Sympathetic fibers accompanying the frontal nerve course with the supraorbital nerve to terminate in sweat glands of the forehead.
  - Sympathetic fibers coursing with the oculomotor nerve supply the ciliary muscle, superior and inferior palpebral muscles.
  - According to Raeder (1924), some sympathetic fibers pass by way of the deep petrosal nerve through the sphenopalatine ganglion to innervate the orbital muscle.
  - Causes of third-order lesions include basilar skull fractures, nasopharyngeal carcinoma, cavernous sinus tumors, carotid cavernous fistula, carotid siphon aneurysm, cavernous sinus and petrous apex surgery, carotid angiography, cervicocephalic and ICA dissections, neck surgery; percutaneous injections of thyroid nodules, orbital tumor, and internal jugular vein cannulation.
- Congenital childhood onset:
  - ICA agenesis
  - Autosomal dominant HS associated with heterochromia iridis
- Acquired childhood onset:
  - Commonly, mediastinal neuroblastoma

DIAGNOSIS

- The clinical diagnosis of HS in suspected patients is suggested by unilateral:
  - Meiosis
  - Anisocoria
  - Impaired pupillary dilation in dim light
  - Impaired pupillary dilation to near response and accommodation
  - Ptosis
  - Endophthalmos
  - Facial anhydrosis
  - Impaired facial blushing
- The diagnosis of HS is confirmed with certainty by pharmacological testing.

DIAGNOSTIC TESTS AND INTERPRETATION

- Pharmacologic pupillary testing aids in confirming the diagnosis of HS and in localization of the order of neuron affected.
- Testing should be performed in advance of any other eye drops placed, such that corneal penetration is not altered.
- 4–10% topical cocaine eyedrops are instilled into the eye to judge oculosympathetic function, and the pupils are checked 45 minutes afterward for the relative dilation of the affected pupil.
  - Cocaine is an indirect sympathomimetic that blocks the reuptake of the neurotransmitter norepinephrine (NE) from the synaptic space.
  - The normal pupil will dilate to cocaine due to release of NE in the synaptic cleft.
  - In HS the affected pupil fails to dilate since NE is not released into the third-order synaptic cleft.
  - Testing with topical cocaine has limitations as the normal pupil may not dilate due to the weak effect of cocaine; there may be false positive results if the affected pupil is unable to dilate for another reason; and cocaine is a controlled substance which is often difficult to obtain.

- 1% topical hydroxyamphetamine eyedrops are instilled into the eyes to judge oculosympathetic function, and the pupils are checked afterward for the relative dilation of the affected pupil.
  – Hydroxyamphetamine causes release of presynaptic NE.
  – Third-order neuron lesions with presynaptic terminal degeneration and a lack of NE vesicles fail to demonstrate a pupillary response to hydroxyamphetamine.
- 1% Apraclonidine eyedrops are instilled into the eyes and the relative dilation of the affected eye is observed.
  – Apraclonidine is a weak α-2 adrenergic agonist and an alternative agent to topical cocaine testing.
  – In HS there is upregulation of α-1 receptors in response to lost sympathetic innervation which results in supersensitivity of the affected pupil such that it dilates in response to topical apraclonidine.
  – A study of the true sensitivity and specificity of apraclonidine is needed.
- There is no pharmacologic test to distinguish first- and second-order HS.

DIAGNOSTIC PROCEDURES

Imaging

- Radiological evaluation is not necessary when the etiology of HS syndrome is readily appreciated at initial evaluation.
  – Attributed to prior surgery (thyroid, heart, mediastinal, coronary artery bypass graft, mediastinal, cervical lymph node, sympathectomy, skull base)
- Imaging is especially useful when the etiology of HS cannot be immediately determined at initial evaluation but the examination provides enough information to permit targeted imaging.
- Evaluative options
  – MRI and MRA brain and neck
  – Cervical CT angiography
  – MRI cervical spine

DIFFERENTIAL DIAGNOSIS

- Physiological anisocoria and involutional ptosis in the elderly
- Medication:
  – Opioid
  – Benzodiazepine
  – Clonidine
  – Pilocarpine
- Iritis and ocular trauma
- Neurosyphilis
- Cholinergic poisoning
- Adie pupil
- Levator aponeurosis dehiscence
- Cluster headache
- Herpes zoster ophthalmicus

TREATMENT

MEDICATION

- Symptomatic
- Surgical repair
- Treatment of coexisting disorder

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission for investigation of CNS disease

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See Also (Topic, Algorithm, Electronic Media Element)

- Claude Bernard-Horner syndrome

CODES

ICD9

- 337.9 Unspecified disorder of autonomic nervous system
- 379.41 Anisocoria

HUNTINGTON'S DISEASE

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BASICS

DESCRIPTION
Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder characterized by involuntary movements, psychiatric and behavioral disturbance, and dementia.

EPIDEMIOLOGY
Incidence
- Few reports addressing incidence (1).
  - Available data consistent with incidence between 0.2 and 0.4 per 100,000.

Prevalence
- Prevalence is between 5 and 10 per 100,000.
  - Approximately 25,000 North Americans have manifest HD.
  - An additional 125,000 at risk (first-degree relative with HD).

RISK FACTORS
- Race
  - The disease is endemic near Lake Maracaibo, Venezuela.
  - Reduced prevalence reported in Japan, Norway, and Sub-Saharan Africa.
- Age
  - Onset typically in 30s to 40s, though can emerge from infancy to the eighth decade.
- Sex
  - No sex predisposition.

Pregnancy Considerations
The impact of pregnancy on HD has not been well characterized although pregnancy and oral contraceptives can precipitate involuntary movements

Genetics
- HD is a fully penetrant, autosomal dominant disorder.
- An expanded trinucleotide repeat (cytosine adenine-guanine) in the short arm of chromosome 4 (4p16.3) encodes a lengthened polyglutamine tract in the huntingtin peptide (2).
- When the CAG number exceeds 37 HD will manifest. Expansions between 40 and 50 are typical of adult-onset HD while large expansions characterize juvenile disease.
- The CAG tract can enlarge during meiosis, especially spermatogenesis.
- Meiotic instability provides a mechanism for anticipation (earlier onset in offspring) and the association of juvenile-onset HD with an affected father.
- Whether the polyglutamine expansion results in loss of a normal function or a toxic gain of function is unclear.

ETIOLOGY
Select neurons are impacted by the polyglutamine expansion in the huntingtin peptide. Degeneration of striatal GABAergic medium spiny projection neurons is suggested to account for much of the HD phenotype. Neuronal loss also impacts the cerebral cortex and hippocampus while sparing the cerebellum.

DIAGNOSIS
- Movement disorder
  - Choreiform movements are typical but can observe dystonia, athetosis, tics, or myoclonus
  - Impaired extra-ocular motility (pursuits and saccades)
  - Motor impersistence (inability to sustain eye closure or tongue protrusion)
  - Hyperactive tendon reflexes
  - Incoordination
- Mood/behavior disorder (3)
  - Depression (may precede motor phenotype)
  - Increased risk of suicide
  - Psychosis
  - Obsessive/compulsive behaviors
- Cognitive dysfunction
  - Motor and psychiatric manifestations often impede recognition of cognitive decline
- Manifestations vary depending upon the age of onset
  - Onset prior to age 20 is associated with prominent rigidity and seizures (~20%)
  - Emergence after 50 years associated with pronounced chorea while progression is often slowed

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
- Genetic testing: A CAG-repeat expansion establishes the diagnosis of HD. At-risk or presymptomatic testing must involve a multidisciplinary team (genetic counselor, psychologist, and neurologist). Rarely is testing performed prior to attaining the age of majority.
- Laboratory evaluation to exclude alternative diagnoses
  - CBC with manual differential (acanthocytes)
  - Electrolytes
  - Liver function tests (Wilson's disease)
  - Thyroid function studies
  - Sedimentation rate, antinuclear antibody
  - Antistreptolysin O titers (Sydenham's chorea)
  - Ceruloplasmin, serum copper, 24-hour urine copper (Wilson's disease)
  - Pregnancy test (chorea gravidarum)

Imaging
- Anatomic imaging of the brain demonstrates progressive atrophy of the striatum (caudate nucleus and putamen). Functional MRI and spectroscopy are research tools.
- Radionuclide imaging (positron emission tomography and single-photon emission computed tomography) may improve diagnostic accuracy, but current use is restricted to research.

Diagnostic Procedures/Other
- EEG can facilitate the management of seizures in juvenile HD.
- Neuropsychometric evaluation can determine the extent of cognitive dysfunction.

DIFFERENTIAL DIAGNOSIS
- Hereditary
  - Benign familial chorea
  - Neuroacanthocytosis
  - Wilson's disease
  - Paroxysmal choreoathetosis
- Metabolic
  - Hyperthyroidism
  - Hypoparathyroidism
  - Chorea gravidarum
  - Electrolyte disturbance
- Infectious/immunologic
  - Sydenham's chorea (St. Vitus dance)
  - Viral encephalitis
  - Multiple sclerosis
  - Systemic lupus erythematosus
  - Paraneoplastic
- Cerebrovascular
  - Hemorrhage/infarct (subthalamic nucleus)
  - Polycythemia rubra vera

TREATMENT

MEDICATION
Movement disorder: Treatment of chorea is typically deferred until functional impairment or injury risk. The minimum dose yielding reasonable control is administered. Fractionating therapy may enhance efficacy and tolerability (4).

- Glutamatergic
  - Amantadine (Symmetrel) 100 mg b.i.d.
- Typical/classical neuroleptic
  - Haloperidol (Haldol) 0.5–5 mg per day
- Atypical neuroleptic
  - Risperidone (Risperdal) 0.5–3 mg per day
  - Olanzapine (Zyprexa) 2.5–15 mg per day

- Dopamine-depleting compounds
  - Tetrabenazine (Xenazine) is the first FDA-approved medication for the treatment of HD. Usual dose is 12.5–100 mg per day
  - Reserpine (Serpasil) 0.5 mg–2 mg per day
- Dopaminergic agents address akinesia and rigidity of advanced disease
  - Carbidopa/levodopa (Sinemet) 25/100 mg b.i.d.–q.i.d.
  - Pramipexole (Mirapex) 0.25–1.0 mg per day

Mood disorder: Antidepressants can moderate mood and behavior. Anticonvulsants can also be useful and may dampen movements. Neuroleptics can diminish psychotic features (see above)

- Selective serotonin reuptake inhibitor
  - Sertraline (Zoloft) 25–200 mg per day
  - Paroxetine (Paxil) 10–40 mg per day
- Tricyclic antidepressant
  - Amitriptyline (Elavil) 10–75 mg per day
  - Clomipramine (Anafranil) 25–250 mg per day
- Anticonvulsant
  - Divalproex (Depakote) 250–750 mg per day
- Memory disorder: The efficacy of cognition-enhancing medications in HD awaits further examination
- Contraindications: Prior sensitivity or adverse experience
- Precautions:
  - Dopamine-depleting compounds must be used with caution as they can worsen mood state
  - Tetrabenazine can worsen swallowing function and increase the risk of aspiration
  - Atypical neuroleptics and select anticonvulsants can mitigate weight loss
- Alternative drugs
  - Memantine (Namenda) 10 mg b.i.d. can diminish chorea
  - Tetrahydrocannabinol (dronabinol) 2.5–5 mg per day can mitigate weight loss and has been suggested to diminish chorea
  - Megestrol acetate (Megace) 400–800 mg per day can enhance appetite and stimulate weight gain

ADDITIONAL TREATMENT

General Measures

- Treatment is primarily to control movements, mood, and behavior.
- Disease-modifying therapy remains elusive.
- Involvement of social services is frequently needed because wage-earning years are curtailed.
- A stable environment with well-defined activities and schedules is highly beneficial.
- Ensuring a safe environment reduces the risk of falls and other injuries.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Nutritional therapies have yet to yield symptomatic or disease-modifying interventions.
  - Compounds of interest include coenzyme Q_{10} and creatine.

SURGERY/OTHER PROCEDURES

- Involuntary movements demand high caloric intake for which gastrostomy may be needed.
- The role for deep brain stimulation and fetal tissue transplantation remains to be defined (5).

IN-PATIENT CONSIDERATIONS

Admission Criteria

- Hospitalization is usually precipitated by:
  - Psychiatric/behavioral exacerbation
  - Need for gastrostomy
  - Long-term placement

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- The frequency of follow-up is dictated by patient need.
  - Semiannual visits provide an opportunity to address questions, assess symptom progression and management needs.

DIET

- High daily calorie consumption (>5,000) is often required for body weight maintenance.
  - May require >3 meals/day.

PATIENT EDUCATION

- Education for the individual and family is critical through the many stages of HD. Issues surrounding nutrition and long-term management need to be regularly addressed.
- Extensive information available through the Huntington's Disease Society of America (158 West 29th Street, 7th Floor, New York, NY 10001-5300. Phone: 1-800-345-HDSA; website: www.hdsa.org

PROGNOSIS

- The interval separating symptom emergence and death ranges between 15 and 20 years.
  - Hyperkinetic phenotype is eventually supplanted by rigidity and akinesia.
  - Aspiration pneumonia and other infectious complications are the ultimate causes of death.

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See Also (Topic, Algorithm, Electronic Media Element)

- Huntington's chorea
- Degenerative chorea
- Woody Guthrie's disease
- Chorea

CODES

ICD9

333.4 Huntington's chorea

CLINICAL PEARLS

- Autosomal dominant inheritance.
- Clinical triad of involuntary movement, mood disturbance, and cognitive decline.
- Onset typically between 30 and 50 years of age.
- Aspiration, or other infectious complication, is usual source of demise.

H

HYDROCEPHALUS

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BASICS

DESCRIPTION
Hydrocephalus is an active distension of the ventricular system of the brain related to the inadequate passage of CSF from its point of production within the ventricular system to its point of absorption into the systemic circulation (1).

EPIDEMIOLOGY
Incidence
Congenital hydrocephalus affects approximately 3–4 per 1,000 live births and is commonly associated with any congenital brain malformation. The overall combined incidence of congenital and acquired hydrocephalus in both children and adults is not known.

Prevalence
Difficult to determine due to most studies only quoting pediatric cases. Mathematical models predict the prevalence of adult and children shunt dependent in the US to be 290,000 patients in 2010 (2) though the real number is unknown.

RISK FACTORS
- Risk factors for hydrocephalus include prematurity (from intraventricular hemorrhage), several first-degree male relatives with congenital hydrocephalus, meningitis, intracranial hemorrhage (especially subarachnoid and intraventricular hemorrhage), congenital brain malformations (spinal dysraphism, Chiari malformations), posterior fossa, and third ventricle tumors.
- Pregnancy is not contraindicated in women with treated hydrocephalus. Development of hydrocephalus during pregnancy is rare.

Genetics
Although most cases are acquired, up to 40% of cases of hydrocephalus have a possible genetic cause, with up to 43 mutants/loci being identified (3). A number of genetic disorders are associated with hydrocephalus, such as X-linked hydrocephalus, cytogenetic abnormalities including trisomies 9, 3, and 18, and Mendelian conditions such as Hurler's syndrome, Walker–Warburg syndrome, and the craniosynostosis syndromes (Crouzon's and Apert's).

GENERAL PREVENTION
No real general preventative measures.

PATHOPHYSIOLOGY
Results from an excess of CSF in the brain due to an increase in production of CSF or, more commonly, an obstruction of normal CSF flow or decreased absorption of CSF. The result of this overabundance of CSF is an increase in intracranial pressure (ICP) with corresponding enlargement of the ventricular system of the brain.

ETIOLOGY
Hydrocephalus can be congenital or acquired and communicating or obstructive (noncommunicating). Acquired hydrocephalus can occur after intracranial hemorrhage, especially intraventricular hemorrhage associated with prematurity, infection, or severe head trauma, or in association with brain tumors. In addition, normal pressure hydrocephalus (NPH) can occur in adults.

COMMONLY ASSOCIATED CONDITIONS
Myelomeningocele (80–90% require shunts), Chiari malformations, certain genetic disorders (see "Genetics"), brain tumors, intracranial hemorrhage, severe head trauma, CNS infections.

DIAGNOSIS

HISTORY
Headache, nausea, and vomiting, diplopia, vision changes, decreased level of consciousness, confusion or difficulty concentrating in older patients. In children, irritability is commonly seen in hydrocephalus. In NPH, there is a classic triad of dementia, gait abnormalities, and urinary incontinence.

PHYSICAL EXAM
Papilledema, abducens and upward gaze palsies, and gait changes. In young children, enlarging head circumference, a bulging and tense fontanelle, splayed sutures, bradycardia, and sunsetting eyes.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
No laboratory tests diagnose hydrocephalus.

Follow-up & special considerations
With suspected CSF infection, CSF should be sampled prior to placement of a CSF shunt.

Imaging
Initial approach
CT, MRI, or ultrasound (in infants) scans shows enlargement of the ventricular system and may show the underlying cause of the hydrocephalus.

Follow-up & special considerations
- MRI scan is indicated in cases of suspected aqueductal stenosis and to rule out associated Chiari malformations.
- In cases of suspected NPH, a number of ancillary tests to predict responsiveness of NPH to shunting are available. These include a nuclear medicine CSF flow study (using ^{99m}Tc-DPTA) and lumbar puncture (LP). A patient whose symptoms improve after withdrawal of CSF by LP may be more likely to respond to permanent CSF shunting.

Diagnostic Procedures/Other
- Diffusion weighted and diffusion tensor MRI sequences can offer understanding of CSF flow through subarachnoid spaces and the degree of changes in white matter tracts, respectively (3).
- Antenatal U/S and MRI may be utilized (4).

Pathological Findings
Destruction of the ependymal lining of the ventricle, compression of peri-ventricular blood vessels, stretching of axons, and eventual loss of neuronal connections (5).

DIFFERENTIAL DIAGNOSIS
Brain atrophy (resulting in *ex vacuo* hydrocephalus) secondary to brain ischemia and neurodegenerative disorders, benign intracranial hypertension, hydranencephaly, developmental anomalies (agenesis of the corpus callosum, septo-optic dysplasia).

TREATMENT

MEDICATION
First Line
Medication is not the first-line treatment in hydrocephalus. Mannitol can be considered in the acute management of elevated ICP. Acetazolamide may temporarily decrease CSF production but is not a long-term therapy

Second Line
None indicated.

ADDITIONAL TREATMENT
General Measures
Once the diagnosis is established and the need for treatment confirmed, one should proceed to the specifically indicated surgical option. In cases of acute hydrocephalus where ICP is elevated to a life-threatening level, the usual emergency measures used to lower ICP can be done (elevate the head of the bed, administer 1 g/kg mannitol IV). These measures cannot be a substitute for prompt neurosurgical management of the underlying problem. In cases of neonatal intraventricular hemorrhage, serial LP or ventricular taps can be done until the child has grown large enough that a permanent shunt can be placed.

Issues for Referral
Patients typically follow-up post operatively in 4–6 weeks, after which annual follow-up with a neurosurgeon is typical.

Additional Therapies
None

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - The mainstay of symptomatic treatment is surgical therapy.
- Adjunctive treatment
  - Supportive care, especially in children, involves monitoring of heart and respiratory rates. Bradycardia and periods of apnea can be ominous signs of increased ICP.

SURGERY/OTHER PROCEDURES

Surgical treatment is the mainstay of therapy for hydrocephalus. Several surgical options are available, the goal of which is to bypass the regular CSF pathways (6)[A],(7)[A],(8)[A].

- CSF shunt
  - As a permanent solution to hydrocephalus, closed ventricular draining systems have been in use for >50 years. All CSF shunting systems consist of a proximal ventricular catheter; a 1-way valve and reservoir; and a distal catheter terminating in another body compartment. The most common sites for termination of the distal catheter are (in order) the peritoneum, the pleural space, and the venous system (usually the right atrium or superior vena cava).
- Endoscopic third ventriculostomy (6)[A]
  - In selected cases of hydrocephalus, specifically aqueductal stenosis, where the fourth ventricle is normal in size and the lateral and third ventricles enlarged, endoscopic third ventriculostomy (ETV) is a treatment option. In this procedure, a fiberoptic endoscope is passed into the lateral ventricle and then into the third ventricle through the foramen of Munro. A hole is made in the floor of the third ventricle, bypassing the obstruction at the aqueduct. A successful ETV will obviate the need for a permanent CSF shunt. ETV is less successful in cases of hydrocephalus without aqueductal stenosis.
- External ventricular drainage
  - In cases where placement of a permanent shunt is not feasible (e.g., infection or acute hemorrhage) or where drainage of CSF is required temporarily until CSF flow pathways are reestablished (e.g., posterior fossa tumor), placement of an external ventricular drain (EVD) can be a temporizing measure until a permanent shunt can be placed or the indication for CSF diversion is no longer present. The drain is passed into the lateral ventricle and tunneled out through the scalp, draining into an external system. Prolonged use of an EVD is associated with a high CSF infection rate.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Revolves around acute ICP management and prompt CSF diversion.

Admission Criteria

All patients with symptomatic hydrocephalus should be admitted for management of the condition.

IV Fluids

No specific recommendations in the literature; wavoiding hypotonic solutions recommended as these could aggravate ICP issues.

Nursing

Close monitoring of neuro-vital signs is recommended in the acute phase.

Discharge Criteria

Patients can be discharged within 1–3 days of surgery provided their symptoms of increased ICP have resolved and the surgeon is satisfied that the shunt is functioning properly. Many neurosurgeons obtain a CT or MRI scan of the brain before discharge to ensure that the ventricular catheter is in proper position and the ventricles reduced in size.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Many neurosurgeons monitor on an annual basis with intermittent CT or MRI imaging. Imaging is indicated urgently if a shunt malfunction is suspected.

Patient Monitoring

CSF shunt devices are associated with a high failure rate (40% at 1 year) and infection rate (5–10%). As such, patients with shunt devices *in situ* require immediate attention should they develop symptoms of shunt failure. Symptoms of shunt failure or obstruction are similar to those of untreated hydrocephalus and include headache, nausea and vomiting, and a decreased level of consciousness. Evaluation of the patient with a suspected shunt malfunction includes a CT or MRI scan of the brain and a "shunt series" (a series of plain radiographs tracing the path of the shunt from the skull to the abdomen). In cases where shunt function is equivocal, a radionuclide shunt study can be undertaken to determine if the shunt is patent. Shunt infection can manifest as a shunt obstruction or as fever with no other identifiable source. Shunt infection can be diagnosed by sampling CSF from the shunt reservoir. When shunt malfunction or infection is suspected, immediate referral to a neurosurgeon is indicated. It is not uncommon for a shunted patient to develop subdural fluid collections, which can indicate CSF overdrainage.

DIET

No specific recommendations.

PATIENT EDUCATION

- Patients and families of those with treated hydrocephalus, either by a CSF-shunting device or ETV, should be educated as to the signs and symptoms of shunt failure and to seek prompt medical attention should they develop. Patients with CSF shunts can pursue all regular activities.
- Hydrocephalus Association of America
- Spina Bifida and Hydrocephalus Association of Canada

PROGNOSIS

CSF-shunting devices are associated with a high failure rate. Prior to the development of an adequate surgical treatment of hydrocephalus, the outcome was universally poor. With the use of shunts, mortality for infants with non-tumor–related hydrocephalus has dropped from 64% (9) to 3–10%. Seventy percent are socially independent and <10% are unemployable.

COMPLICATIONS

Shunt failure, shunt infections, slit ventricle syndrome, and intracranial hypotension from excessive CSF drainage and acute neurological impairment from ETV can occur.

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CODES

ICD9

- 331.3 Communicating hydrocephalus
- 331.4 Obstructive hydrocephalus
- 742.3 Congenital hydrocephalus

CLINICAL PEARLS

- Acute hydrocephalus is an emergency and can be fatal if not diagnosed and treated promptly.
- Proper patient education is necessary to identify signs and symptoms of worsening hydrocephalus.
- CT or MRI is the first-line imaging study.
- Close long-term neurosurgical follow-up is needed in all patients.

HYPERAMMONEMIA

Alexander D. Rae-Grant, MD

BASICS

ALERT
A high index of suspicion is important in neonates with poor feeding, lethargy, and failure to thrive as these may indicate hyperammonemia.

DESCRIPTION
Ammonia is present in all body fluids as ammonium ion. Excess ammonia is excreted as urea. Impaired metabolism, from various causes, leads to hyperammonemia, which can cause serious CNS toxicity. This chapter focuses on hyperammonemia due to defects in urea cycle enzymes *N*-acetylglutamate synthetase, carbamyl phosphate synthetase I (CPS I), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS, citrullinemia), argininosuccinate lyase (AL, argininosuccinic aciduria), and arginase (argininemia).

EPIDEMIOLOGY
- Prevalence
  - Estimated to be 1 per 30,000 live births.
  - Urea cycle disorders incidence 1.9 per 100,000 births based on longitudinal data from British Columbia.
- Age
  - Usually seen in neonates; however, can be present in childhood.
- Sex
  - Seen in both sexes.
- Race
  - Cases have occurred in all races.
  - Genetics: Depends on specific causation.

ETIOLOGY
Excess ammonia causes activation of *N*-methyl-D-aspartate (NMDA) receptors, which then activates Na-ATPase leading to adenosine triphosphate (ATP) depletion and ammonia toxicity. Several other metabolic changes also are involved, such as increased lactate and pyruvate and decreased glycogen and glutamate.

COMMONLY ASSOCIATED CONDITIONS
- Urea cycle defects: Include deficiencies of *N*-acetylglutamate synthetase, CPS I, OTC, argininosuccinic acid synthetase, AL, and arginase
- Other metabolic defects: Organic acidemias, congenital lactic acidoses, fatty acid oxidation defects, dibasic amino acid transport defects
- Transient hyperammonemia of the newborn
- Reye syndrome
- Hepatic dysfunction (various causes not covered in this chapter)
- Drug-related disorders: Salicylates, carbamazepine, valproic acid, topiramate, chemotherapies, rituximab
- Other causes: Pregnancy, distal renal tubular acidosis, carnitine transport defects, urinary tract dilatation

DIAGNOSIS

- In neonates, the presentation is nonspecific. Symptoms include poor feeding, lethargy, and vomiting and can lead to coma.
- Patients with partial enzyme deficiencies have a delayed onset and may present with recurrent episodes of vomiting, lethargy, ataxia, and behavioral changes.
- Patients with argininemia present with spastic diplegia.
- Fragile hair (trichorrhexis nodosa) is seen in argininosuccinic aciduria.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests
Plasma ammonia level (usually >300 μmol/L), arterial blood gas (shows respiratory alkalosis), plasma and urinary amino acid analysis, organic acid, and orotic acid determination.

Follow-up & special considerations
Depends on specific etiology.

Imaging

Initial approach
CT or MRI of brain may show cerebral edema.

Diagnostic Procedures/Other
Assay for specific enzymes on liver biopsy specimen. DNA analysis is available for OTC deficiency.

Pathological Findings
Patients who die of hyperammonemia show brain edema, brainstem herniation, and microscopic changes of astrocytic swelling and white-matter change. Children with hyperammonemic disorders may show ventriculomegaly, basal ganglia lesions, neuronal loss, intracranial bleeds, and areas of focal cortical necrosis.

DIFFERENTIAL DIAGNOSIS
- Because the clinical presentation is nonspecific, differential diagnosis of hyperammonemia depends on laboratory studies.
- Hyperammonemia with respiratory alkalosis is caused by a urea cycle defect or transient hyperammonemia of the newborn. The presence of acidosis, ketosis, and low bicarbonate, along with hyperammonemia, suggests an organic acidemia. Hyperammonemia, in addition to acidosis, ketosis, and increased lactate, indicates congenital lactic acidoses.
- Differential diagnosis for late-onset cases of hyperammonemia also includes liver disease and Reye syndrome. Hepatic transaminases would be elevated in both conditions, but in Reye syndrome bilirubin level would be within normal range.
- Determination of orotic acid and plasma citrulline can help identify the enzyme deficiency. OTC deficiency is associated with elevated urinary orotic acid and trace citrulline level. Plasma citrulline level is very high in AS deficiency (>1,000 μmol/L) and moderately high (100–300 μmol/L) in AL deficiency.

TREATMENT

Toxin removal, enzyme induction, and improving anabolic metabolism are key components of treatment of hyperammonemic disorders. Early treatment of hyperammonemia before brain injury is critical. The overall treatment approach is similar no matter which diagnosis.

MEDICATION

Sodium benzoate, sodium phenylacetate, sodium phenylbutyrate; these drugs lower ammonia levels by conjugating with amino acids; available in IV and oral formulation.

For OCT deficiency, IV sodium phenylacetate plus sodium benzoate therapy (Ammonul) is associated with high survival rates.

- Contraindications: Hypersensitivity
- Precautions
  - High sodium content avoids congestive heart failure or renal insufficiency; benzoate may worsen neonatal hyperbilirubinemia by competing with bilirubin for the binding sites on albumin.
  - If a specific urea cycle defect is confirmed, treatment is customized to replacing the deficient product of metabolism.

ADDITIONAL TREATMENT

General Measures

- Neonates should be admitted to a neonatal intensive care unit with hemodialysis facilities; no protein intake; caloric intake in the form of hypertonic glucose and lipids; monitor ammonia level; treat any underlying infection; reduce protein intake initially to reduce ammonia production. Often patients are dehydrated due to poor oral intake.
- Dialysis may increase clearance of ammonia from the system in the acute setting. Ammonia is cleared rapidly by diffusion.
- Treatment of hepatic encephalopathy in general may be useful, see specific chapter.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Intravenous sodium benzoate and phenylacetate. Hemodialysis if patient is at comatose at presentation or if the ammonia level remains high after several hours of IV treatment.
- Adjunctive treatments
  - Arginine supplementation because it is an essential amino acid for patients with urea cycle defects.

SURGERY/OTHER PROCEDURES

Liver transplantation for patients with severe urea cycle defects or refractory and recurrent symptomatic hyperammonemia despite conservative therapy.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission needed when patients present in hyperammonemic state with an altered mental status, dehydration, or are not controlled by oral medications.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Growth and development of children; periodic levels of ammonia, arginine, and glutamine.

PATIENT EDUCATION

Depends on the specific disease entity.

PROGNOSIS

Strict adherence to the dietary recommendations and compliance with medications should result in adequate growth and a decrease in episodes of acute hyperammonemia. Overall, there is considerable risk of mortality during acute episodes, and the majority of survivors have significant cognitive delays.

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See Also (Topic, Algorithm, Electronic Media Element)

- Encephalopathy, hepatic
- Encephalopathy, progressive pediatric

CODES

ICD9

270.6 Hyperammonemia (congenital)

H

HYPOTONIC INFANT SYNDROME

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BASICS

DESCRIPTION

The term *hypotonic infant* refers to an infant with hypotonia or decreased muscle tone. Muscle tone is controlled by afferent muscle spindles and α- and γ-motor neurons in the spinal cord and also is affected by upper motor neurons and corticospinal tract. Hypotonia is characterized by diminished resistance to passive movements and an excessive range of joint mobility. Hypotonic infant syndrome may be seen not only with severe muscle weakness, but also with only mild weakness or even without obvious weakness.

EPIDEMIOLOGY

Incidence

Hypotonic infant syndrome is commonly seen in the clinical practice; however, its incidence or prevalence is not known because it is seen with a large variety of diseases.

Prevalence

Same as above.

RISK FACTORS

Occurs more often in the newborn period and the first year of life.

Genetics

Varies depending on the underlying conditions.

GENERAL PREVENTION

Vaccinations can prevent illness and worsening of hypotonia.

PATHOPHYSIOLOGY

Varies depending on the underlying conditions.

ETIOLOGY

Lesions at any level of the nervous system, including upper and lower motor units, can cause hypotonia. Hypotonia combined with severe muscle weakness usually is associated with lower motor neuron disorders, including diseases affecting anterior horn cells of the spinal cord, peripheral nerves, neuromuscular junctions, and muscles. Hypotonia without obvious weakness often points to diseases of the CNS, connective tissue disorders, and chromosomal diseases or those involving metabolic, endocrine, or nutritional problems.

COMMONLY ASSOCIATED CONDITIONS

Medically treatable hypotonia refers to a condition that can be cured with specific medical treatment. Hypothyroidism due to thyroid hormone deficiency may present with hypotonia, constipation, failure to thrive, developmental delay, jaundice, and retardation of bone growth. Biotinidase deficiency may present with hypotonia, seizures, ataxia, alopecia, skin rash, developmental delay, sensorineural deafness, and lactic acidosis. Neonatal myasthenia gravis may present with hypotonia, severe generalized weakness, and respiratory failure. Infantile botulism due to *Clostridium botulinum* toxins occurs in previously healthy infants in the first few months of life, with sudden generalized weakness, hypotonia, poor sucking and swallowing, constipation, ptosis, dilated pupils with sluggish light reflex, lethargy, and respiratory distress. Infantile Guillain–Barré syndrome is characterized by progressive generalized weakness and areflexia, hypotonia, and respiratory failure. Tick paralysis is caused by the persistent tick bite with secretion of its toxin, leading to sudden generalized weakness and areflexia and hypotonia in a formerly normal child.

DIAGNOSIS

HISTORY

Hypotonic infants may present with severe weakness, mild weakness, or no weakness; may have dysmorphic features, seizures, speech or language delay, or other organ abnormalities.

PHYSICAL EXAM

- Hypotonia is characterized by diminished resistance to passive movements and an excessive range of joint mobility.
- Hypotonia with significantly severe muscle weakness and atrophy, decreased or absent deep tendon reflexes, and fasciculation, but without Babinski's sign or clonus, frequently suggests lower motor unit diseases involving anterior horn cells, peripheral nerves, neuromuscular junction, or muscles.
- Hypotonia with little or no weakness, normal or increased deep tendon reflexes, craniofacial dysmorphic features, Babinski's sign, ankle or knee clonus, or other brain dysfunctions such as language delay, mental retardation, progressive intellectual decline, seizures, aggressive behavior problems, or attention deficit hyperactivity often indicates upper motor unit diseases that affect the cerebrum, cerebellum, brainstem, or spinal cord above anterior horn cells.
- However, there are diseases with both upper and lower motor unit involvements, such as mitochondrial encephalomyopathy, congenital myotonic dystrophy, and metachromatic leukodystrophy.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- For lower motor unit diseases
  - Serum creatine kinase may be increased in a variety of muscle disorders and some spinal muscular atrophy and should be done before electromyography and nerve conduction studies.
- For upper motor unit diseases
  - Serum studies: Very long chain fatty acids for neonatal adrenoleukodystrophy; amino and organic acids, lactate, pyruvate, ammonia, carnitine for disorders of amino acids, organic acids, lactic acids, and urea cycle; lysosomal enzymes for lysosomal disorders; thyroid hormones for hypothyroidism; antibody titers for intrauterine infections (toxoplasmosis, rubella, cytomegalovirus, herpes), blood and urine guanidinoacetate, creatine, and creatinine for inborn errors of creatine metabolism.

Follow-up & special considerations

- Blood DNA tests may detect survival motor neuron gene 1 homozygous deletions for spinal muscular atrophy, abnormal CTG trinucleotide repeat expansion for congenital myotonic dystrophy, and mitochondrial DNA mutations of some mitochondrial encephalomyopathies such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (1)[A].
- Other: Stool for culture and exotoxin detection of *C. botulinum* in infantile botulism; CSF for albuminocytologic dissociation in Guillain–Barré syndrome; serum acetylcholine receptor or muscle-specific tyrosine kinase antibodies for myasthenia gravis (1,2)[A].
- Blood microarray and chromosomal studies for Down's syndrome, Prader–Willi syndrome, and other chromosomal disorders (1,2)[A].

Imaging

Initial approach

Cranial ultrasound study may be necessary at the bedside for neonatal birth asphyxia when MRI is impossible because of the intubation and respiratory support of critically sick and unstable neonates.

Follow-up & special considerations

Cranial MRI may detect intracranial ischemia or hemorrhage, increased T2 density of the white matter in the adrenoleukodystrophy or metachromatic leukodystrophy, periventricular calcification for congenital cytomegalovirus infection, diffuse intracranial calcification in congenital toxoplasmosis, and a variety of other brain anomalies. In mitochondrial encephalomyopathy, it may reveal basal ganglia calcification or cerebral or cerebellar atrophy.

Diagnostic Procedures/Other

For lower motor neuron diseases:

- Electromyography is abnormal in the muscle diseases. Motor and sensory nerve conduction velocity study is useful in the evaluation of peripheral neuropathy (1)[A].

- Muscle or nerve biopsy may be indicated if there is evidence of myopathy or neuropathy and for more specific diagnosis of the muscle disorders and neuropathy. Muscles may be examined for the specific histochemical staining and special enzymes' studies for Pompe's disease, mitochondrial myopathy, specific congenital myopathies, muscular dystrophies, molecular genetic studies, and other studies (1)[A].
- Repetitive nerve stimulation with low frequency (2–3 Hz) often induces decremental response in myasthenia gravis, whereas stimulation with higher frequency (20–50 Hz) often induces incremental response in infantile botulism or Lambert–Eaton myasthenic syndrome (1)[A].
- Edrophonium (tensilon) IV infusion rapidly and dramatically improves the clinical features of myasthenia gravis, such as ptosis, extraocular ophthalmoplegia, and generalized weakness (1)[A].

Pathological Findings
Varies depending on the underlying conditions.

DIFFERENTIAL DIAGNOSIS
- Hypotonia with prominent weakness (lower motor unit disorders): Spinal muscular atrophy, congenital myotonic dystrophy, congenital muscular dystrophy, neonatal myasthenia gravis, congenital myasthenic syndrome, congenital myopathies, metabolic myopathies (Pompe's disease, mitochondrial myopathy), hereditary motor and sensory neuropathies, Guillain–Barré syndrome, tick paralysis, and infantile botulism
- Hypotonia without prominent weakness
  - Cerebral hypotonia: Perinatal hypoxia, birth trauma, Down's syndrome, Prader–Willi syndrome, Zellweger syndrome, Riley–Day syndrome, neonatal adrenoleukodystrophy, infantile G_{M1} gangliosidosis
  - Intrauterine infections (toxoplasmosis, rubella, cytomegalovirus, herpes)
  - Metabolic, endocrine, nutritional problems: Biotinidase deficiency, amino acidosis, organic acidosis, renal tubular acidosis, calcium abnormalities, hypothyroidism, celiac disease, malnutrition
  - Connective tissue disorders: Ehlers–Danlos syndrome, Marfan's syndrome
  - Acute illness
  - Benign congenital hypotonia

TREATMENT

MEDICATION
First Line
Intravenous immunoglobulin is easier to give to infants with Guillain–Barré syndrome. Intramuscular neostigmine given 30 minutes before feeding is useful for neonatal myasthenia gravis. Biotin is indicated for biotinidase deficiency. Thyroid hormone replacement is necessary for hypothyroidism (1,2)[A].

Second Line
Plasma exchange may be useful if intravenous immunoglobulin fails to improve Guillain–Barré syndrome. Pyridostigmine or prednisone may be alternative drugs for myasthenia gravis (1,2)[A].

ADDITIONAL TREATMENT
General Measures
Specific treatment depends on the underlying cause of hypotonia. For example, myasthenia gravis patients require anticholinesterase such as pyridostigmine or neostigmine. Guillain–Barré syndrome may need plasmapheresis or intravenous immunoglobulin or even respiratory support. Hypothyroidism requires treatment with thyroid hormone. Biotin replacement is needed for biotinidase deficiency. Tick paralysis requires removal of the tick from the skin of the patient.

Issues for Referral
When dysmorphic features are noted, genetic referral is needed. For neuromuscular disorders, referral to neuromuscular specialists is needed. For epilepsy, referral to neurologist or epileptologist is needed.

Additional Therapies
Physical, occupational, speech, and language therapy may be helpful when poor fine motor coordination, muscle weakness, and language delay are present.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Feeding problems may need special nipples, small and frequent feedings, gavage feedings, or even gastrostomy tube. Postural drainage, suctioning, or vigorous respiratory therapy would be necessary if hypotonia and muscle weakness impair cough reflex or pulmonary functions. Stool softener, laxatives, or dietary control may help constipation. Early infant intervention provides useful stimulation.

SURGERY/OTHER PROCEDURES
Gastrostomy tube placement and Nissen fundoplication may be required if the patients have severe feeding problems and gastroesophageal reflux. Tenotomy and tendon transfer or lengthening may be useful for the routine daily care of the patients.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Respiratory distress from muscle weakness or prolonged seizures may require stabilization at emergency department before admission.

Admission Criteria
Patients may need admission for treatment of prolonged seizures or acute evaluation and treatment of severe weakness associated with hypotonia such as spinal muscular atrophy, congenital muscular dystrophy, neonatal myasthenia gravis, mitochondrial encephalomyopathy, and infantile botulism.

IV Fluids
Infants with feeding difficulty may need IV fluid and nutritional support.

Nursing
Infants with respiratory problems or unstable vital signs may require intensive nursing care.

Discharge Criteria
Once acute weakness improves, vital signs are stable, and there is no need for respiratory support, IV fluid, and nursing care; patients can be discharged.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patients should be followed regularly after the underlying cause of hypotonia is identified.

Patient Monitoring
Patients with hypotonia may have progressive joint contractures or scoliosis and need proper treatment, such as physical therapy or braces. Other problems, such as seizures, may develop and require antiepileptic drug treatment.

DIET
Ketogenic diet may be needed for intractable epilepsy; gluten-free diet for celiac disease.

PATIENT EDUCATION
Many organizations associated with individual diseases exist to help support patients and their families and research to bring best treatments to the patients.

PROGNOSIS
The clinical course and prognosis depend on the underlying diseases of hypotonia.

COMPLICATIONS
Persistent muscle weakness may occur in severe Guillain–Barré syndrome or other severe neuromuscular disorders; cerebral palsy, mental retardation, and epilepsy may occur in severe perinatal hypoxic infants or other genetic syndromes.

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CODES

ICD9
781.99 Other symptoms involving nervous and musculoskeletal systems

CLINICAL PEARLS
- Hypotonia with severe muscle weakness indicates lower motor unit disorders.
- Hypotonia without prominent weakness is seen with upper motor unit disorders, connective tissue disorders, chromosomal disorders, acute or chronic systemic illnesses.
  - Mixed hypotonia may be present.

IMMUNIZATIONS, NEUROLOGICAL COMPLICATIONS

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BASICS

DESCRIPTION

CNS and peripheral nervous system (PNS) injuries occur in temporal relationship to immunization in a small number of patients. Vaccine-related nervous system injuries include acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), cerebellar ataxia, encephalopathy/encephalitis, seizure disorder, deafness, mononeuropathy, mononeuritis multiplex, brachial plexus neuritis, polyneuropathy, and Guillain–Barré syndrome (GBS), also known as acute inflammatory demyelinating polyradiculopathy. Virtually every vaccine has been reported to be associated with some form of nervous system injury. Although a causal role for vaccination is implied, such an association is rarely established.

EPIDEMIOLOGY

The exact incidence of neurologic complications following immunizations is unknown, but overall, the risk seems to be low. The incidence also varies with each type of vaccine and each type of injury. The encephalopathy associated with diphtheria, tetanus toxoid, and pertussis (DTP) immunization is reported to be 5 per 100,000 vaccinations in children <2-years-old and death related to vaccination in the same age group is reported to be 0 in >29 million immunizations. Epidemiologic studies with prospective case-control designs have been most helpful in establishing or rejecting causality of vaccination to adverse events. In most of these studies, the overwhelming safety of vaccination has become apparent.

- Age
  - Although, generally, a disorder of childhood, serious adverse events after vaccination have been reported in adults.
- Sex
  - Preponderance in either gender has not been reported.

RISK FACTORS

Congenital or acquired immunodeficiency states (various congenital immunodeficiency syndromes, cancer chemotherapy using cytotoxic drugs, pregnancy, chronic steroid therapy, HIV infection) can be associated with an increased risk of injury to the nervous system. Most of these states are relative rather than absolute contraindications. In general, however, vaccines with live viruses are best avoided in congenital or acquired immunodeficiency states.

Pregnancy Considerations

- Vaccinations are generally avoided during pregnancy because adverse reactions may occur.
- Pregnancy is a state of relative immune suppression during which otherwise benign viral infections can become fulminant.
- Live vaccines, such as rubella, can be associated with teratogenic effects in the fetus.
- One exception is the influenza vaccine, which is recommended by the American College of College of Obstetricians and Gynecologists and the Advisory Committee on Immunization Practices due to increased risk of severe complications from influenza.

ETIOLOGY

Neurologic injury from vaccines may be attributed to the active components of the vaccine or due to adjuvants, preservatives, or contaminants present in the vaccines. Generally, the basis of injury is considered to be due to autoimmune "antigenic mimicry" in which the viral/bacterial protein immunogen shares homology with nervous system proteins, usually myelin. This leads to cross-activation of autoreactive B or T cells. In rare instances an inactivated, nonvirulent bacterial or viral live vaccine can reactivate and cause direct injury to the nervous system such as what has been reported with oral polio and varicella zoster virus (VZV) vaccines.

DIAGNOSIS

HISTORY

- Symptoms from vaccine-related neurologic injury can present within minutes (anaphylaxis) to 2–3 weeks.
- Disorders that manifest >6 weeks after immunizations are unlikely to be due to the vaccine, unless the early events after vaccination were clinically silent as is sometimes the case in demyelinating disorders.
- Symptoms will vary depending on the type of injury (central vs. peripheral).

PHYSICAL EXAM

A thorough general physical exam and detailed neurologic exam should be performed. The general exam may reveal signs of virus vaccine reactivation such as vesicles in a dermatomal pattern seen with VZV.

Findings on the neurologic exam will help to localize the lesion and determine what type of injury is present.

- For example, in ADEM, one of the more common vaccine-related neurologic complications, some level of alteration of consciousness is almost always present.
  - Multifocal neurologic deficits are the rule.
  - Patients can develop clinical manifestations of meningoencephalitis, optic neuritis, focal solitary lesions that mimic neoplasm, and single or multilevel myelopathy.
  - In its most fulminant form, brain hemorrhages and coma can occur, with a mortality rate of up to 15%.
- GBS is an acute, inflammatory, demyelinating polyradiculopathy that presents with ascending weakness and paresthesias that may be accompanied by cranial nerve involvement and respiratory weakness. Areflexia is a common neurologic finding.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- CSF studies: Spinal fluid studies are extremely helpful in the diagnosis of ADEM.
  - During the acute phase, CSF most often is normal for protein, cell count, and cultures.
  - In fulminant cases, intracranial hypertension can be reflected in abnormally elevated opening pressures.
  - A modest pleocytosis (up to 50 cells) and mild elevation of proteins (always <100 mg/dL) may also be present.
  - In children, a predominantly lymphocytic pleocytosis is common, but a polymorphonuclear response can occur in the acute phase as well.
  - In acute fulminant cases with hemorrhagic inflammation, RBCs can be present in the CSF, with xanthochromia as well.
  - Although inflammation is the hallmark of ADEM, evidence of intrathecal IgG synthesis usually is not observed, and oligoclonal IgG bands are distinctly absent. This feature often is helpful in distinguishing ADEM from MS.
  - CSF studies are also helpful in the diagnosis of GBS. The typical albuminocytologic dissociation (elevated protein without elevation of the cell count) can be useful for diagnosis, but may not be evident in the early phase. It is, however, often seen in subsequent later samples of CSF.
- Immunologic studies: Although generally not the standard of care, patients who experience an adverse event following vaccination should undergo testing for congenital or acquired immune deficiency, including immunoglobulin and complement levels, and T- and B-cell quantification (including CD4 and CD8 subsets).
  - Delayed-type hypersensitivity should be examined, with skin tests for common antigens.
  - Preferably, all of these studies should be performed prior to the use of corticosteroids or immunosuppressive agents.
  - There is good evidence that patients who develop ADEM have circulating lymphocytes sensitized to myelin basic protein and other myelin proteins. However, these studies are not generally available for routine use.

Imaging

- For CNS vaccine-related injury, MRI of the brain and spinal cord is the imaging modality of choice.
- Lesions are a hallmark of ADEM and may be seen in some cases of cerebellar ataxia.
- If there are no lesions noted on MRI at the onset of suspected ADEM, imaging should be repeated in 3 weeks. If the MRI is consistently normal at 3 weeks or later, the diagnosis of ADEM is, for all practical purposes, ruled out.
- Administration of gadolinium is useful in defining acute lesions. Although the lesions of ADEM can mimic lesions of MS with a periventricular distribution, including corpus callosum lesions, the lesions in ADEM are often large, less defined, enhancing, and prone for edema and herniation.

- Although complete resolution can occur clinically, demyelinated lesions can persist for life and result in subsequent confusion regarding the diagnosis of MS.
- CT scan is helpful only if edema or herniation is present.
- In GBS, MRI with gadolinium of the lumbosacral spine may show nerve root enhancement.

Diagnostic Procedures/Other

- Nerve conduction studies (NCS) and electromyography (EMG) can be particularly helpful in diagnosing peripheral nerve injury.
- It is important to note that early on, especially in GBS, these studies can be normal and may need to be repeated in 1–2 weeks.

DIFFERENTIAL DIAGNOSIS

- For CNS presentations, the differential may include acute infectious encephalitis, spongiform encephalopathies, metabolic encephalopathies, neoplastic and paraneoplastic disorders, and MS.
- For PNS presentations, the differential may include acute infectious processes, intoxications, and paraneoplastic disorders.

TREATMENT

MEDICATION

- Corticosteroids are the mainstay of treatment for ADEM once acute infectious processes have been ruled out.
  - Pulse methylprednisolone, 1 gm IV every day or every other day for 5-g total dose is the standard treatment.
  - Considerable improvement can occur in the following 2–4 weeks.
  - Alternative therapies are best considered after a minimum of 3 weeks. In severe cases, when the response is suboptimal at the end of 2 weeks, consideration should be given for plasma exchange because there is good evidence that antibodies mediate the fulminant injury through activation of complement.
  - Plasma exchange is carried out at exchange volumes of 5% of body weight every other day for a total of 7 treatments.
  - For GBS, plasma exchange, 5 exchanges every other day, or a course of intravenous immunoglobulin (IVIG), 400 mg/kg IV qD × 5 days is usually given.
  - Often, an oral taper for 4–8 weeks is necessary to avoid recurrences.
- A short course of high-dose oral steroids is recommended for brachial plexus neuritis.

Precautions

- Steroids should be administered with caution in patients with hypertension, diabetes, and peptic ulcer disease. Although rare, use of high-dose steroids can be associated with aseptic necrosis of the femur. Psychosis may occur in some patients during administration. In the few patients requiring long-term oral steroids, prophylaxis with trimethoprim/sulfa is indicated for prevention of pneumonia secondary to *Pneumocystis carinii* infection.
- Observation without treatment is an acceptable alternative in any patient, especially patients with intolerance to steroids and patients with a mild disease course.

ADDITIONAL TREATMENT

General Measures

- Constitutional symptoms of headache, fever, malaise, and irritability are common in both children and adults with ADEM and should be managed using simple analgesics and antipyretics.
- Sleep disturbances may occur, particularly in children. Extreme irritability ("inconsolable crying of children"), well known to occur in encephalopathy following DPT, may require the use of sedatives. In general, however, use of narcotics and sedatives should be minimized because they can cloud assessment of mental status.

ADJUNCTIVE THERAPIES

Symptomatic Treatment

- As above. In addition, patients who develop GBS may require ventilator support during the acute phase of their illness.

Adjunctive Treatment

- Extensive rehabilitation with physical, occupational, and speech therapy may be necessary in patients with severe ADEM, GBS, brachial plexus neuritis, or severe mononeuritis multiplex.

SURGERY/OTHER PROCEDURES

- In cases where solitary lesions are present and the diagnosis of a neoplastic process is a primary consideration, biopsy of the lesion may be necessary. In severe cases where increased intracranial pressure due to cerebral edema occurs, intracranial pressure monitoring may be necessary.

IN-PATIENT CONSIDERATIONS

Admission Criteria

There are no established criteria for admission or discharge; judgment should be used on an individual basis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Following recovery, long-term recurrences are rare. During steroid therapy, especially long-term oral steroid therapy, patients should be monitored regularly for steroid-related complications, including hypertension, glucose intolerance, infections, bone demineralization, GI discomfort, and weight gain.

Patient Education

The Vaccine Adverse Event Reporting System (VAERS) is a cooperative program for vaccine safety of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS collects information on adverse events (possible side effects) occurring after the administration of US-licensed vaccines. The VAERS Website also provides a vehicle for disseminating vaccine safety-related information and for patient reporting of adverse events.

- Website: http://vaers.hhs.gov
- VAERS Table of Reportable Events from the US Department of Health and Human Services includes the following neurologic disorders, possibly related to immunization:
- Tetanus in any combination: Brachial neuritis
- Pertussis in any combination: Encephalopathy or encephalitis
- Measles, mumps, and rubella: Encephalopathy or encephalitis
- Oral polio—Paralytic polio in a non-immunodeficient recipient (30 days) and in an immunodeficient recipient (6 months)

The above-described list is not meant to be comprehensive. The reader is referred to the website for current listings of vaccine-related injuries.

PROGNOSIS

The majority of patients make an uneventful recovery; most show complete recovery by 3 months. Mortality or severe morbidity can rarely occur. The incidence of such events is unknown.

ADDITIONAL READING

- DeStefano F, Verstraeten T, Jackson LA, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol* 2003;60:504.
- Miravalle A, Biller J, Schnitzler E, et al. Neurological complications following vaccinations. *Neurol Res* 2010;32(3):285–292.
- Stratton KR, Howe CJ, Johnson RB. Adverse events associated with childhood vaccines. *Evidence bearing on causality*. Washington, DC: Institute Medicine, National Academy Press, 1994.

See Also (Topic, Algorithm, Electronic Media Element)

- Postinfectious encephalomyelitis
- Postimmunization encephalomyelitis
- Multiple sclerosis
- Transverse myelitis
- Guillain–Barré syndrome
- Brachial plexus neuritis

CODES

ICD9

- 323.51 Encephalitis and encephalomyelitis following immunization procedures
- 357.7 Polyneuropathy due to other toxic agents
- 999.9 Other and unspecified complications of medical care, not elsewhere classified

CLINICAL PEARLS

- Vaccination in the healthy, immunocompetent host is still preferred to the natural infection and its associated morbidities.
- In an immunocompromised host, live virus vaccines are probably best avoided. For specific circumstances, an infectious disease specialist should be consulted.
- The temporal association of neurologic sequelae to vaccination does not always imply causality to vaccination. Nonetheless, vaccine-related sequelae should always be considered in the etiology of such disorders.

INCLUSION BODY MYOSITIS

Boyd Koffman, MD, PhD

BASICS

DESCRIPTION

- Sporadic inclusion body myositis (s-IBM) is an acquired idiopathic inflammatory myositis of insidious onset. It is characterized by a specific pattern of proximal and distal weakness demonstrating early involvement of forearm flexors and quadriceps muscles. Clinical history, laboratory studies, electromyography (EMG), and muscle biopsy are used for diagnosis and to distinguish s-IBM from polymyositis or dermatomyositis.
- Hereditary inclusion body myopathies (h-IBM) are rare and include a spectrum of hereditary myopathies, often within various ethnic groups, characterized by vacuolated myofibers containing filamentous inclusion, without inflammation. h-IBM may be autosomal dominant (limb-girdle distribution) or autosomal recessive (quadriceps sparing) and have many of the histochemical and ultrastructural changes seen in s-IBM (rimmed vacuoles and intracytoplasmic and intranuclear tubulofilamentous inclusions).

EPIDEMIOLOGY

- Incidence
  - s-IBM
    - Less than 1 per 100,000 population
    - s-IBM may account for 15–28% of all idiopathic inflammatory myopathies
    - It is considered the most common myopathy in persons >50 years of age.
    - Olmstead County, MN: 0.79 per 100,000
  - h-IBM is much rarer than s-IBM in general, although among Iranian Jews the prevalence is estimated at approximately 1 per 1,500.
- Age
  - s-IBM typically affects persons >50 years of age, although some patients may be as young as 30 years.
  - h-IBM symptoms begin in the second or third decade.
- Race
  - *s-IBM:* No data are available; most case reports have been of Caucasians.
  - *h-IBM:* Most reports include isolated pedigrees within ethnic groups (Italy, the US, Germany, Ireland, Bahamas, Tunisia, and India).
- Sex
  - *s-IBM:* Male-to-female ratio is 3:1.
  - *h-IBM:* Males and females are equally affected.
- Prevalence
  - per million (Turkey) – 14.9 per million (Western Australia)
  - USA: 10.7 per million
  - Olmstead County, MN: 7.06 per 100,000

RISK FACTORS

- The risk of developing s-IBM is influenced by epistatic interactions between alleles at the HLA-DRB1 locus
- The HLA-DRB1 genotype may influence the s-IBM phenotype

Genetics

- s-IBM
  - Associated with HLA-DR3 and MHC 8.1 ancestral haplotype (HLA-A*01, -B*0801, -DRB1*0301, -DQB1*0201, -DQA1*05) in ~75% of cases in Australia, Europe, and the USA
  - Associated with HLA-B*5201 and HLA-DRB1*1502 in Japan
  - Rarely associated with Paget's disease and frontotemporal dementia (IBMPFD)
    - Maps to chromosome 9p21.1-p12
    - Autosomal dominant
    - Associated with missense mutations in the ubiquitin-binding domain of the valosin-containing protein gene
- h-IBM
  - Both autosomal dominant and autosomal recessive syndromes have been seen among h-IBM.
  - The autosomal recessive forms seen among Iranian Jews and in Japanese distal myopathy have both been linked to the same locus on chromosome 9p1-q1.

GENERAL PREVENTION

- None known

PATHOPHYSIOLOGY

- Evidence suggests that s-IBM is a muscle-specific autoimmune disease in which lymphocytes (T and B cells) and inflammatory mediators induce necrosis and degenerative changes in muscle fibers
- The event triggering inflammation is unknown; complex interactions between environmental factors, genetic susceptibility, and aging are suspected
- Chicken vs. egg: it is unclear whether the inflammation seen in s-IBM directly causes muscle degeneration or is a response to the degeneration and abnormal protein accumulation observed in the disease.

ETIOLOGY

Unknown for both s-IBM and h-IBM. The presence of amyloid deposits within the myofibers of muscle biopsy specimens suggests a degenerative process. Endomysial inflammation in s-IBM, primarily $CD8^+$ T cells, invades non-necrotic myofibers, but it is unclear whether cellular inflammation is primary or secondary. Additional biopsy findings of ragged red fibers and cytochrome *c* oxidase (COX)-negative fibers have indicated abnormal mitochondria. Mitochondrial DNA deletions have been detected in ~50% of 30 s-IBM patients studied. It is unclear whether these abnormalities are of pathogenic significance or are a secondary phenomenon.

COMMONLY ASSOCIATED CONDITIONS

Other immune-mediated conditions (e.g., Sjögren's syndrome and rheumatoid arthritis) occur in ~10% of s-IBM cases. Nonspecific antibodies, such as positive ANA, rheumatoid factor, and SS-A, may be present in 40% of s-IBM cases and do not preclude the diagnosis of s-IBM.

DIAGNOSIS

HISTORY

- *s-IBM*
  - Weakness >6 months
  - Age of onset >30 years
- h-IBM
  - Rarely observed in families

PHYSICAL EXAM

- s-IBM
  - Proximal and distal involvement of muscles of arms and legs
  - Patients should demonstrate one of the following:
    - Finger flexor weakness
    - Wrist flexor > wrist extensor weakness
    - Quadriceps weakness/atrophy
- h-IBM, has variable clinical phenotypes:
  - Limb-girdle distribution
  - Quadriceps-sparing weakness

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- CPK: normal or elevated (10–12 times normal)

Imaging

Initial approach

- MRI or CT demonstrate selective amyotrophy of particular muscle groups but is not necessary for diagnosis.

Diagnostic Procedures/Other

- EMG
  - Sensory nerve and compound muscle action potentials are usually normal, although nerve conduction studies may demonstrate findings consistent with a superimposed peripheral neuropathy
  - Needle EMG examination may reveal increased insertional activity, frequent fibrillation potentials and positive sharp waves, and low-amplitude, short-duration motor unit action potentials (MUAP) or a mixed pattern of both low-amplitude, short-duration and high-amplitude, long-duration MUAPs with early recruitment (chronic myopathic changes)

Pathological Findings

- Muscle biopsy
  - s-IBM features:
    - Vacuolated myofibers (red-rimmed vacuoles on trichrome stain), central or subsarcolemmal, 2- to 25-μm in diameter, prominent in type I fibers, or evenly distributed between type I and II fibers
    - Sparse-to-prominent endomysial inflammation and invasion of non-necrotic myofibers by cytotoxic ($CD8^+$) T cells
    - Nuclear or cytoplasmic 15- to 18-nm tubulofilaments (electron microscopy) *or* amyloid deposition in myofibers
    - Eosinophilic cytoplasmic inclusions
    - Ragged red fibers (often cytochrome *c* oxidase negative)
  - h-IBM features:
    - Muscle biopsy shows many of the same features as in s-IBM, but no mononuclear cell inflammation.
    - Ragged red fibers, cytochrome *c* oxidase-negative muscle fibers, and mitochondrial abnormalities are seen less often in h-IBM.

DIFFERENTIAL DIAGNOSIS

- Disorders with rimmed vacuoles: Desmin storage myopathy; acid maltase deficiency; lysosomal storage disease with normal acid maltase; McArdle syndrome; facioscapulohumeral dystrophy; oculopharyngeal muscular dystrophy
- Idiopathic inflammatory myopathies: Polymyositis; dermatomyositis; amyotrophic lateral sclerosis (ALS)

TREATMENT

MEDICATION

- ***First Line***
  - No medications are consistently effective for treatment of s-IBM, and none are FDA-approved for treatment. Several can be tried.
  - Corticosteroids 1–2 mg/kg may stabilize weakness or temporarily prevent progression (in ~10% of patients). Consider a 3- to 6-month prednisone trial and taper or discontinue if there is no benefit.
  - Contraindications
    - Corticosteroid hypersensitivity
    - Peptic ulcer, except in life-threatening situations
    - Use corticosteroids with extreme caution in patients with recent myocardial infarction (MI), because of potential association of corticosteroids and left ventricular free-wall rupture.
- Precautions
  - Corticosteroids may reduce resistance to and mask signs of infection, or reactivate tuberculosis. Use chemoprophylaxis in patients with active tuberculosis undergoing prolonged steroid treatment. Instruct patients to notify surgeons, anesthesiologists, or dentists if surgical procedure is required and they have been taking (within 12 months) glucocorticoids.
  - Use corticosteroids with caution in persons with diverticulitis, nonspecific ulcerative colitis, cirrhosis, hypothyroidism, hypertension, psychosis, and congestive heart failure.
  - Prolonged use of corticosteroids may cause adrenocortical insufficiency, and muscle wasting, pain, or weakness ("steroid myopathy").
- ***Second Line***
  - Several double-blind, crossover trials of intravenous immunoglobulin (IVIg) alone or with prednisone failed to demonstrate statistically significant objective improvement in muscle strength, although regional improvements (e.g., dysphagia) may have been seen. IVIg doses used include 0.4 g/kg/day for 5 days or 1 g/kg/day for 2 days to achieve a total dose of 2 g/kg.
- Contraindications
  - Avoid IVIg in hypoglobulinemia A (risk of anaphylaxis).
- Precautions
  - Headache, aseptic meningitis, nausea, emesis, or irritation at site of infusion
- Other/investigational treatments:
  - Etanercept trial in progress (2011) (clinicaltrials.gov; accessed 6/3/2011)
  - Alemtuzumab has been evaluated in a preliminary study

ADDITIONAL TREATMENT

General Measures

- Assistive devices to prevent falls

Issues for Referral

- Occupational and physical therapy (prevention of finger flexor contractures; strengthening)

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- 2 small studies suggest a limited response to exercise that may attenuate disease progress

SURGERY/OTHER PROCEDURES

Cricopharyngeal myotomy has been reported to relieve dysphagia in s-IBM if pharmacologic interventions fail.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- IBM is assessed on an outpatient basis; at end stage, morbidity associated with aspiration pneumonia or falls may necessitate inpatient admission.
  - Respiratory support if necessary

Admission Criteria

- Immobility, pneumonia, aspiration

Nursing

- Fall prevention

Discharge Criteria

- Stable strength
- Resolution of pneumonia
- Treatment/prevention of aspiration

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patient strength may be monitored at intervals of 6–12 months, with symptomatic treatment for dysphagia or falls as needed.

DIET

- Diet adjustments based on aspiration risk

PATIENT EDUCATION

- Advise patients to expect slow and relentless progression of weakness. There is no evidence that a particular diet or dietary supplement is of benefit. Activity is encouraged as tolerated.
- The Myositis Association (TMA), 1737 King Street, Suite 600, Alexandria, VA 22314. Telephone: 703-299-4850 (DC Area); 800-821-7356 (Toll-free); Fax: 703-535-6752; email: TMA@myositis.org. Website: http://www.myositis.org/template/page.cfm?id=24
- Muscular Dystrophy Association. 3300 E. Sunrise Drive, Tucson, AZ 85718. Telephone: 1-800-572-1717. email: mda@mdausa.org. Website: http://www.mda.org/

PROGNOSIS

- In the absence of definitive treatment, weakness progresses slowly and insidiously. With progression, there is an increased risk for aspiration pneumonia with dysphagia.

ADDITIONAL READING

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- Wilson FC, Ytterberg SR, St Sauver JL, Reed AM. Epidemiology of sporadic inclusion body myositis and polymyositis in Olmsted County, Minnesota. *J Rheumatol* 2008;35:445–447. [C]

See Also (Topic, Algorithm, Electronic Media Element)

- Polymyositis
- Dermatomyositis

CODES

ICD9

359.71 Inclusion body myositis

CLINICAL PEARLS

- s-IBM is the most common acquired myopathy in the elderly population, with a male predominance.
- A previous diagnosis of "polymyositis refractory to corticosteroids" should lead one to consider reevaluation for possible s-IBM.

INCONTINENCE, NEUROGENIC

Marie A. Namey, RN, MSN, MSCN

BASICS

DESCRIPTION

- Neurogenic urinary incontinence is a symptom resulting from damage to the nerves involved in bladder relaxation or bladder contraction and the coordination of the bladder neck mechanism.
- Common bladder problems associated with neurologic disorders include inability to store (detrusor hyperreflexia), inability to empty (hypotonic bladder/detrusor areflexia) with or without overflow incontinence, or a combination of the 2 [detrusor sphincter dyssynergia (DSD)].

EPIDEMIOLOGY

- Incidence
  - Common occurrence as a result of damage to the integrity of the control mechanisms of the bladder in the central nervous system or to the peripheral nervous system
  - Affects people of all ages, both genders, and people of all social and economic levels
  - The incidence of neurogenic bladder varies based on primary cause. In the US, the incidence in individuals with multiple sclerosis is 40–90%, Parkinson's disease 37–72%, and stroke 15%.
- Prevalence
  - At least 1.5 million individuals have neurogenic bladder

RISK FACTORS

- Risk factors are associated with specific neurologic conditions known to cause neurogenic bladder.
- Surgery
- Diabetes

GENERAL PREVENTION

- Avoidance of UTIs

PATHOPHYSIOLOGY

- Normal bladder function requires the coordinated action of the bladder muscle (detrusor, smooth muscle), internal sphincter (bladder neck, smooth muscle), and external (striated muscle) sphincter. Normal function includes the ability to store urine with limited increase in intraluminal pressure, to initiate voiding voluntarily, and to empty the bladder completely. Neural bladder function control occurs primarily in the sacral spinal cord, as well as the pons, diencephalon, and cerebral cortex. Parasympathetic innervation promotes detrusor contraction and sphincter relaxation, whereas sympathetic stimulation results in detrusor relaxation and sphincter contraction.

ETIOLOGY

- Neurologic diseases result in damage to the innervation of the lower urinary tract. If innervation of the lower urinary tract is damaged, it can affect the detrusor, urethra, and sphincter. Often the lesion is combined. Neurologic deficit can occur abruptly or more slowly over time.
- Lesions above the sacral micturition center typically result in loss of inhibition from higher centers, causing detrusor hyperexcitability, with or without sphincter hypertonia and DSD. Lesions at or below the sacral center will result in detrusor areflexia.

COMMONLY ASSOCIATED CONDITIONS

- Neurotrauma, brain tumor, meningitis-encephalitis, multiple sclerosis, Parkinson's disease, spinal cord injury (SCI), neuropathy, spinocerebellar degeneration, diabetes, and stroke

DIAGNOSIS

HISTORY

- Thorough patient history is essential to determine 24-hour urination patterns, including the actual volume of urine voided, how urgent the feeling is to urinate, and any factors that aggravate incontinence.
- A Bladder Diary can be a helpful tool to evaluate fluid intake and urinary output.

PHYSICAL EXAM

- Rectal, genital, and abdominal exam to check for enlargement of the bladder or other abnormalities
- A complete neurological examination is also essential.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Urinalysis/culture and sensitivity test to rule out bladder infection
- Measurement of postvoid residual (bladder ultrasound/intermittent catheterization)
- Urodynamic testing
- Cystoscopy

Follow-up & special considerations

- Education about bladder function and bladder health, signs and symptoms of UTIs, avoidance of UTIs

Imaging

Initial approach

- Ultrasound to identify the integrity of the organs (kidney, bladder, prostate)
- MR scan
- Intravenous pyelogram

Follow-up & special considerations

- Refer to Urology for abnormalities on scans

DIFFERENTIAL DIAGNOSIS

- Urinary tract infection
- Stress incontinence
- Bladder prolapse
- Constipation
- Enlarged prostate
- Surgical complications
- Nerve or muscle damage after pelvic radiation

TREATMENT

MEDICATION

- ***First Line***
  - Anticholinergic and antimuscarinic agents
    - Imipramine 25–50 mg at h.s.
    - Oxybutynin (Ditropan): 5–10 mg PO 2–4× daily (if cost is an issue)
    - Ditropan XL: begin at 5 mg PO daily and increase as needed to 30 mg/day
    - Tolterodine (Detrol): 2 mg/day and increase as needed to 4 mg twice a day
    - Darifenacin (Enablex) 7.5–15 mg/day
    - Solifenacin (Vesicare) 5 mg/day
    - Tropsium chloride (Sanctura) 20 mg twice a day
    - Fesoterodine (Toviaz) 4–8 mg once daily
- ***Second Line***
  - DDAVP (desmopressin)
    - This synthetic antidiuretic hormone is useful in treating enuresis
    - Nasal spray (1 puff per nostril qhs) or tablets 0.1–0.2 mg qhs
  - α-Blockers to relax sphincter
  - Terazosin (Hytrin): 1 mg qhs and increase as needed to 10 mg/day (reevaluate if no response after 6 weeks)
  - Quinazoline (Cardura): 1 mg q.i.d, may double dose every 1–2 weeks to maximum 8 mg/day
  - Tamsulosin HCl (Flomax): initially 0.4 mg/day, then increase to 0.8 mg after 2–4 weeks
- Contraindications:
  - Inability to empty bladder, uncontrolled narrow angle glaucoma
- Precautions
  - Risk of hypotension with anticholinergics and α-blockers

Geriatric Considerations
Caution required when prescribing DDAVP for patients >65. Additional concern about lower extremity edema

Pregnancy Considerations
Most anticholinergics are category B or C

ADDITIONAL TREATMENT
General Measures
- Adequate daily fluid intake (48–64 oz/day) is encouraged.
- Avoid caffeinated beverages, aspartame, alcohol, and smoking, which are bladder irritants.
- Treat constipation

Issues for Referral
- Reassess at each follow-up visit
- Hematuria
- Pain arising from upper or lower urinary tract

Additional Therapies
- Quick access to bathroom
- Absorbent products and devices
- Timed voidings
- External catheters
- Intermittent catheterization
- Indwelling urethral catheter
- Physical therapy for mobility aids and equipment
- Occupational therapy for assistance with upper extremity function and manageable clothing and equipment (commode chair)

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Behavioral therapy/biofeedback to teach special exercises to strengthen the pelvic floor muscle (Kegel's exercise)
- Acupuncture

SURGERY/OTHER PROCEDURES
- Suprapubic catheter
- Urinary diversion
- Bladder augmentation
- Botulinum toxin injections (detrusor or sphincter)

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Assess for infection; treat if needed
- Monitor electrolytes
- Monitor skin

Nursing
- Patient education
- Maintain dry skin; check/treat skin breakdown

Discharge Criteria
- Void with little or no incontinence

ONGOING CARE
FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
- Follow to monitor efficacy of intervention and overall symptom management

DIET
- Avoid bladder irritants: caffeine, nutrasweet, EtOH, spicy foods, carbonated beverages, and citrus fruits and juices

PATIENT EDUCATION
- Urinary incontinence is not normal
- Change in bladder habits may be attributable to bladder infection or other underlying concerns
- Seek advice from healthcare provider

PROGNOSIS
- Incontinence is relatively common and the clinical course may vary
- Worsening of neurologic symptoms with urinary tract infection usually is reversible after infection is treated.

COMPLICATIONS
- Skin breakdown
- There is risk of damage to the upper urinary tract, particularly in SCI.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Involuntary bladder
- Voiding dysfunction

CODES
ICD9
- 596.4 Atony of bladder
- 596.59 Other functional disorder of bladder
- 788.39 Other urinary incontinence

CLINICAL PEARLS
- Reporting incontinence may be embarrassing for patients. Routinely ask patients if they are experiencing bladder symptoms.
- Assume that a great percentage of patients can be significantly helped by treatment.
- Adequate assessment is crucial to determine appropriate intervention. Interventions to treat bladder incontinence include medications, bladder training, behavior modification, and surgery.

INCREASED INTRACRANIAL PRESSURE

Christopher R. Newey, DO

BASICS

DESCRIPTION

The Monroe–Kelli doctrine states that the cranium is a fixed volume composed of CSF, blood, and brain tissue and that an increase in any of these must be offset by an appropriate decrease in another content. If there is not an appropriate offset, the intracranial pressure (ICP) will increase. Intracranial compliance (i.e., change in volume divided by change in ICP) decreases with increased ICP. This can affect cerebral blood flow by affecting cerebral perfusion pressure (CPP) [i.e., mean arterial pressure (MAP) minus ICP], which ultimately can cause neurological deficits. Normal ICP ranges from 5 to 15 mm Hg. Normal CPP is >50 mm Hg.

EPIDEMIOLOGY

Incidence

The epidemiology varies depending on the underlying etiology.

RISK FACTORS

The risk factors comprise stroke, head injury, intracranial tumor (primary or secondary), CNS infection, and eclampsia.

GENERAL PREVENTION

Avoiding precipitating event, serially monitoring known intracranial lesions.

PATHOPHYSIOLOGY

As mentioned, the Monroe–Kelli doctrine describes the maintenance of normal ICP where if one intracranial constituent increases, another must decrease. Cerebral autoregulation is the natural attempt to maintain cerebral blood flow adequate for metabolic demands of the brain. As ICP increases, the autoregulation curve is disrupted causing a linear increase in cerebral blood pressure with increasing MAP. Once compliance limit has been reached (i.e., an ICP of approximately 20 mm Hg), parenchyma becomes displaced resulting in various herniation syndromes.

ETIOLOGY

- CSF flow obstruction (e.g., tectal mass)
- Mass lesions, e.g., hematoma and neoplasm
- Hemorrhage, e.g., epidural, subdural, intraparenchymal, and subarachnoid
- Venous obstruction, e.g., cerebral venous thrombosis
- Ischemic strokes, especially cerebellar infarcts, NIHSS >20, CT head with >50% MCA involvement, or DWI volume >145 cm^3 within 14 hours of event
- Traumatic brain injury
- Infections, e.g., meningitis and encephalitis
- Seizures, e.g., generalized and status epilepticus
- Hepatic encephalopathy
- Malignant hypertension
- Idiopathic, e.g., pseudotumor cerebri
- Eclampsia
- Hydrocephalus
- Pneumoencephalus

COMMONLY ASSOCIATED CONDITIONS

Commonly associated conditions depend on the underlying etiology: Pregnancy, liver/kidney failure, malignancy, cardiovascular disease, and hypercoagulable state.

DIAGNOSIS

HISTORY

Patients may give a history of headache (especially positional with recumbency), nausea/vomiting (especially projectile), blurry vision, difficulty walking, diplopia, weakness, altered mental status, prior cancer, and hematological disorder.

PHYSICAL EXAM

- Assess ABCs
- Determine level of consciousness
- Evaluate for Cushing's triad: Hypertension, bradycardia, and respiratory irregularity. Classic triad is seen infrequently (~33%), but if two signs present examine for increased ICP
- Respiratory patterns can help localize (e.g., Cheyne–Stokes: Bilateral cortex, hyperventilation: Midbrain, apneustic: Pons, cluster: Pons, ataxic: Medulla)
- Fundoscopy examination to evaluate for papilledema and/or engorged retinal veins
- Pupillary response to light: Small reactive (diencephalic), fixed/dilated (3rd nerve), midposition and fixed (midbrain), pinpoint and reactive (pons), and large and fixed with hippus (tectal plate)
- Evaluate cranial nerves for palsy. Cranial nerve VI susceptible to injury with increased ICP but can be false-localizing sign
- Motor examination for posturing (i.e., decorticate and decerebrate) and false-localizing sign (e.g., Kernohan's notch: Weakness ipsilateral to lesion due to herniation and compression of contralateral cerebral peduncle)
- Determine the Glasgow coma examination (GCS) score by determining eye opening (patients 1–4), verbal response (patients 1–5), and motor response (patients 1–6). Maximum score is 15, minimum score is 3

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Complete blood counts, coagulation profile including PT/INR and PTT, and type and screen should be ordered in preparation for possible surgical or medical (e.g., FFP) intervention. Metabolic profile. Check serum osmolarity.

Follow-up & special considerations

Daily labs, including blood counts, metabolic profiles, and coagulation panels.

Imaging

Initial approach

- CT head should be obtained to evaluate for intracranial blood, hydrocephalus, cerebral edema, midline shift, cistern compression, and mass.
- It is estimated that ~10% of patients with increased ICP will have normal head CT.

Follow-up & special considerations

Serial CT heads are indicated to monitor for increasing or decreasing mass effect.

Diagnostic Procedures/Other

- MRI of the brain has little role in the emergent setting of increased ICP. However, it can better define intraparenchymal lesions, such as a tumor.
- Angiography is useful to evaluate for sources of mass effect, such as aneurysm in cases of subarachnoid hemorrhage, large vessel occlusion in cases of ischemic strokes, AV malformations.
- Lumbar punctures are contraindicated in increased ICP. If performed, can lead to brain herniation and eventual death. Once increased ICP has been ruled out, lumbar puncture can safely be performed.
- Indications for ICP monitor include GCS <8 and either an abnormal head CT or ≥2 of the following risk factors (age >40 years, systolic blood pressure <90 mm Hg, and/or decerebrate/decorticate posturing). If hydrocephalus is present in subarachnoid hemorrhage patients, an intraventricular device is needed for external drainage.
- Measurement of intracranial pressure can be accomplished via several anatomic spaces:
  - Intraventricular (gold standard) disadvantages: Highest risk of hemorrhage and/or infection, must maintain transducer at the level of the ear. Benefits: Monitoring ICP and also allow for CSF drainage.
  - Intraparenchymal: Lower rates of hemorrhage and infection, but cannot recalibrate after placement and readings may vary by 3 mm Hg. No CSF drainage.
  - Subdural
  - Subarachnoid
  - Epidural (typically used in patients with liver failure)
- Other than infection and hemorrhage, other complications of ICP monitoring include malfunction/obstruction and/or malposition.
- Normal ICP is typically defined as <15 mm Hg. ICP waveforms have 3 components. P1 is the arterial wave (or percussion), P2 is the rebound wave (or tidal wave), and P3 is the venous outflow (or dicortic wave). An elevated P2 waveform indicates poor compliance.

Pathological Findings

- Varies depending on the underlying etiology.
- Pathological specimens may show evidence of gliosis, infection/inflammation, hemorrhage, and/or neoplasm.
- On ICP monitoring, the emergence of elevated ICP (20–100 mm Hg) for several minutes to hours is called a plateau wave (Lundberg A wave). Lundberg B waves are an elevation of ICP (10–20 mm Hg) that lasts a few seconds to minutes and are thought to be related to respiratory fluctuations in $PaCO_2$. Lundberg C waves are rapid sinusoidal fluctuations corresponding to arterial pressure.

DIFFERENTIAL DIAGNOSIS
- The differential diagnosis for increased ICP is broad.
  - DDx: Seizures, metabolic coma, encephalopathy, dilated pupil from medication or physiological anisocoria, meningeal irritation, migraine

TREATMENT

MEDICATION
First Line
- Osmotic agents:
  - Mannitol 20%: Typically loaded at 1–1.5 g/kg followed by maintenance of 0.5 g/kg every 4–6 hours if needed. The goal is titrate to serum osmolarity of 300–320 mOsm. The half life is 0.16 hour but is efficacious up to 1.5–6 hours. Use in caution in renal patients or patients who are volume depleted and/or hypernatremic. Note possible overshoot of ICP when mannitol is discontinued.
  - Hypertonic saline (23%): Typically given as a 30 cc bolus >10 minutes via central access followed by 3% hypertonic saline infusion at 1 mL/kg/hour with goal Na of 150–155. Be careful to not infuse 23% too rapidly as pulmonary edema can occur.

ADDITIONAL TREATMENT
General Measures
- A change in the volume of parenchyma, blood, or CSF can affect ICP. Intravascular component occupies ~10% of the space is easiest to change
- Optimize cerebral perfusion pressure (CPP = MAP – ICP) to 60–110 mm Hg since hypotension worsens clinical outcome
- Head of bed 30–45 degrees
- Treat agitation and pain
- Treat fever with acetaminophen and/or cooling devices (either surface or intravascular). An increase in 1°C increases cerebral metabolism and can increase ICP 5–7%
- Avoid hyper- or hypoglycemia
- Avoid hypotonic solutions (e.g., 0.45 NS or lactated ringers, or dextrose containing solutions) but maintain euvolemia
- Minimize shivering
- Prompt nutritional support
- Prophylactically treat for seizures since seizures can increase metabolic demand and affect outcome
- Keep neck straight and avoid jugular vein compression

Additional Therapies
- Hyperventilation to $PaCO_2$ of 25–30 mm Hg can reduce CBF by 3%. If actively herniating and on mechanical ventilation, disconnect patient from ventilation and manually bag. Effective but brief benefit, longer-term deleterious.
- Barbiturates: Pentobarbital at 5–20 mg/kg bolus followed by 1–4 mg/kg/hour titration can reduce metabolic demand and thus decrease ICP. Use with caution in patients with cardiac/respiratory compromise, ileus, infection, or hypotension. Monitor patients with EEG when in coma. Goal pentobarbital level is 3–5 mg%.
- Induced hypothermia to 32–34°C can reduce cerebral oxygen metabolism and reduce inflammation.
- Paralytics can reduce metabolic demand but carry risk of intensive care unit (ICU) myopathy/neuropathy.
- Lidocaine (1.5 mg/kg IVP) prior to endotracheal intubation to blunt the rise in ICP.
- Steroids (dexamethasone 6–10 mg IV) have been shown effective in vasogenic cerebral edema.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Pain/agitation control as needed with narcotics, sedatives, seizure prophylaxis, control nausea, and vomiting.

SURGERY/OTHER PROCEDURES
Early neurosurgical consultation is necessary in cases of increased ICP. Mortality with medical management alone 50–80%. Surgical decompression (i.e., frontotemporoparietal bone hemicraniectomy) may be an option for malignant cerebral edema in select patients with large infarcts. Patients are selected on the basis of age, timing of surgery, and neuroimaging findings. Flap should be 12 cm in diameter and also includes duraplasty. Additionally, debulking surgery may be an option for tumors. Consider placement of pressure monitoring devices and CSF drainage.

IN-PATIENT CONSIDERATIONS
Admission Criteria
ICU admission with signs of increased ICP. Discharge will be based on stabilization and continuous management of the underlying cause.

IV Fluids
IV fluids to prevent hypovolemia.

Nursing
- Serial neurological examinations are necessary
- Cardiac and respiratory monitoring
- Strict ins and outs must be maintained

Discharge Criteria
Discharge depends on causation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patients should have follow up after discharge with appropriate departments.

Patient Monitoring
Serial neurological examinations are necessary. Additionally, arterial lines, Swan–Ganz catheters, ICP monitoring devices, and/or central venous catheters may be necessary.

DIET
Nutritional support via NG or PEG tube.

PATIENT EDUCATION
ICU is necessary for monitoring patients with signs of increased ICP.

PROGNOSIS
- Depends on the etiology, course, and severity.
- Poorer prognostic indicators: Increased ICP despite aggressive medical therapy, hypothalamic dysfunction (diabetes insipidus), unstable blood pressure. Neuroimaging loss of basal cisterns or collapse of ventricular system, progressive cerebral edema.

COMPLICATIONS
- Monitor for complications of prolonged bedrest and malnutrition: Serial duplex scans for DVTs. Prophylaxis for DVTs if not contraindicated. Serial chest x-rays for pneumonia, especially if intubated. Nutritional markers.
- PT and OT when able.

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See Also (Topic, Algorithm, Electronic Media Element)
- Brain herniation syndromes
- Increased intracranial pressure
- Hydrocephalus

CODES

ICD9
- 348.4 Compression of brain
- 377.01 Papilledema associated with increased intracranial pressure

CLINICAL PEARLS
- Recognizing signs and symptoms of increased intracranial pressure can prevent secondary brain injury.
- Once recognized, general measures and medical measures can be used to lower ICP. Neurosurgical consultation is indicated for possible decompressive or debulking surgery and also for ICP monitoring device.

INTELLECTUAL DISABILITY

Marc J. Tassé, PhD

BASICS

ALERT
Terminology "intellectual disability" has replaced the previous term "mental retardation." DSM-5 is expected to adopt intellectual disability as current terminology.

DESCRIPTION
Intellectual disability is defined as a disability characterized by significant deficits in both intellectual functioning and adaptive behavior which originates before the person is 18 years old. Intellectual disability is a life-long condition (2).

EPIDEMIOLOGY
Incidence
- Incidence of intellectual disability is difficult to ascertain. Below are incidence rates for genetic syndromes associated with intellectual disability:
  - Down syndrome: 1 in 700 births
  - Fragile X: 1 in 4,000 boys and 1 in 7,000 girls
  - Williams syndrome: 1 in 7,500
  - Angelman syndrome: 1 in 20,000 births
  - Prader–Willi syndrome: 1 in 25,000 births

Prevalence
- Approximately 1% of the population (1)

RISK FACTORS
- Risk factors are multifaceted and can be categorized according to 2 groupings:
  - Biomedical: Chromosomal disorders, single-gene disorders, syndromes, metabolic disorders, cerebral dysgenesis, maternal illnesses, parental age, prematurity, birth complications/injury, neonatal disorders, traumatic brain injury, malnutrition, meningoencephalitis, infections, toxins, seizure disorder, degenerative disorder
  - Social/behavioral: Poverty, maternal nutrition, trauma, lack of prenatal care, impoverished child–caregiver interactions, social deprivation, maternal drug/alcohol use, child abuse/neglect

Genetics
- Screening should be considered for genetic and metabolic syndromes frequently associated with intellectual disability.
  - Down/trisomy 21
  - Fragile X
  - Phenylketonuria (done at birth)
  - Williams
  - Prader–Willi
  - Angelman

GENERAL PREVENTION
- Prevention of the many etiologies associated with intellectual disability will vary by type.
  - Genetic: Prenatal screening of parents and genetic counseling
  - Social/behavioral: Improved public health/education regarding alcohol/drug consumption during pregnancy, improved prenatal maternal and infant/child nutrition
  - Toxins/teratogens: Regulation to reduce exposure to mercury, lead, pesticides, etc.
  - Infectious: Immunization against rubella which prevents intellectual disability associated with congenital rubella, precautions against other prenatal infections (e.g., meningitis)

PATHOPHYSIOLOGY
- Pre-natal and peri-natal causes of intellectual disability that result in more severe intellectual disability are often noticeable at birth or early on during childhood development. There may be associated dysmorphic features (e.g., macrocephaly, almond-shaped eyes, hypotonia, etc.) or significantly delayed developmental milestones (e.g., sucking, feeding, crawling, talking, etc.). With milder forms of intellectual disability, the identification and diagnosis may not occur until the child enters pre-school or elementary school.

ETIOLOGY
- Intellectual disability is a condition that is diagnosed based entirely on the individual's intellectual and adaptive functioning. Hence, etiology is diverse and often multifactorial, including:
  - Prenatal: Genetic or chromosomal disorders, metabolic disorders, trauma or injury that impacts fetal development, infection/toxins
  - Perinatal: Anoxia, infection
  - Postnatal: Sensory deprivation, nutritional deficiency, environmental toxins/poisons (e.g., lead, mercury, pesticides, etc.), trauma/infection or brain injury
  - 30–40% cases have no known etiology.

COMMONLY ASSOCIATED CONDITIONS
- There are no specific physical features, personality type, or behavioral phenotype associated with intellectual disability. There may exist some for specific etiologies resulting in intellectual disability. A number of other conditions are often associated with intellectual disability, including seizure disorders, autism spectrum disorders, cerebral palsy. Co-morbid psychiatric disorders are more prevalent in persons with intellectual disability than the general population (3).
  - Seizure disorders: 5–10% children with intellectual disability will have a co-occurring seizure disorder; up to 50% when neurological impairments co-occur (e.g., cerebral palsy).
  - 60–75% of persons with an autism spectrum disorder also present with intellectual disability.
  - More than 60% of persons with cerebral palsy also have an intellectual disability.
  - Among persons with intellectual disability: Mild intellectual impairments = 15% have autism, 6% cerebral palsy, and 10% a seizure disorder; percentage of co-morbidity increases substantially as intellectual deficits increase. In persons with IQ <50 = 30–40% have autism, 25–50% have cerebral palsy, and 25–50% have a seizure disorder.
  - 40–50% of persons with intellectual disability will be diagnosed with a co-morbid psychiatric disorder. The entire range of psychiatric disorders found in DSM can co-occur in persons with intellectual disability. There is no protective factor associated with low IQ. However, psychiatric symptoms and signs might be expressed differently and be more difficult to diagnose with lower IQ.

DIAGNOSIS

HISTORY
Family history is conducted in effort to identify possible etiology of intellectual disability. Identify other family members who might have a developmental disability or genetic disorder. Establish age of onset for significant deficits in intellectual and adaptive functioning.

PHYSICAL EXAM
- Diagnosis may be made at birth secondary to identifiable genetic disorder (e.g., Down syndrome, Prader–Willi syndrome, etc.). Usual physical exam procedure is needed with special accommodations depending on etiology and co-existence of associated conditions. There are no specific physical features associated with intellectual disability. The physical exam is important to identify possible underlying causes of intellectual disability and the presence of secondary health conditions.
  - The lower the IQ, the higher the rate of concomitant neurological, neuromuscular, cardiovascular, sensory conditions.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- No established protocol to diagnose intellectual disability
  - Electrolytes, BUN, fasting blood sugars, CBC/differential, ammonia, uric acid, urinary ketones, calcium, magnesium, phosphate, copper, ceruloplasmin, viral titers, lead
  - Thyroid function tests
  - Arterial blood gases

Follow-up & special considerations
- Genetic consultation: Fragile X
- Down syndrome: Celiac disease, thyroid function

Imaging
Initial approach
- No established imaging protocol for diagnosing intellectual disability
  - Presence of micro- or macrocephaly

Diagnostic Procedures/Other
- Testing of intellectual functioning and adaptive behavior
- Assessment of individual support needs – for intervention planning

Pathological Findings
Depends on underlying condition

DIFFERENTIAL DIAGNOSIS
- There is no exclusionary criterion for a diagnosis of intellectual disability. Other childhood disorders that might be present but in the absence of significant intellectual and adaptive deficits:
  - Learning disabilities
  - Communication disorders
  - Autism spectrum disorders
  - If age of onset after age 18 years – another diagnosis may be more pertinent

TREATMENT

MEDICATION

First Line

- No established medications exist to treat intellectual disability. Medications are often prescribed to treat co-occurring behavioral or psychiatric problems.
  - – Medication side-effects and interaction effects may differ from general population especially as IQ decreases and in association with co-morbid neurological/genetic disorders.

ADDITIONAL TREATMENT

General Measures

- Interdisciplinary intervention approach is most conducive to effective treatment approaches.
- Determine etiology and structure treatment based upon known etiology.
- Early intervention and intensive early childhood education can help mitigate cognitive impairments, teach needed adaptive skills, and improve educational and social outcomes.

Issues for Referral

- Behavior support
  - – Presence of challenging behaviors
- Psychiatric services
  - – More susceptible than general population to presence of psychiatric disorders. Depression and anxiety disorders more prevalent in this population.
- State/Medicaid services
  - – May necessitate paid services/supports for school/learning, independent living, employment, and health maintenance.

Additional Therapies

- Occupational therapy, physical therapy, and speech-language therapy, as needed

SURGERY/OTHER PROCEDURES

No surgeries or other procedures for intellectual disability per se. Surgeries may be warranted depending on the etiology.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Hospitalization may be required for co-occurring secondary health conditions.

Discharge Criteria

Will require instructions using concrete terms and use of repetition. Request person repeat in own words to ascertain their comprehension of instructions and explanations. Stress, novel situations, unknown, will exacerbate behavior and reduce coping ability.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

There is a need for concrete information and repetition to ensure that care recommendation, medication dosages, etc., are well understood by the person with intellectual disability. May need more intensive follow-up support than typically developing individuals or linkages with community providers that can ensure support in the home or community.

Patient Monitoring

Frequency and intensity of needed patient monitoring and supervision will be dependent on level of cognitive and adaptive functioning.

DIET

No special diet is recommended unless the intellectual disability is associated to a specific metabolic disorder (e.g., *phenylketonuria*) or Prader–Willi syndrome. Some individuals with intellectual disability may be more susceptible to celiac disease and may require a gluten-free diet.

PATIENT EDUCATION

- Patient education may necessitate alternative modes of communication or the use of assistive devices, depending on their mode of communication. Using multimodal communication and reminders (e.g., written words and pictures) will generally work best. Using multiple exemplars will facilitate knowledge acquisition and transfer. Generalizing from one situation to a novel situation is particularly challenging for persons with intellectual disability and should not be assumed.
  - – Persons with an intellectual disability have a tendency to acquiesce and mask their disability and lack of understanding. Asking them if they understand physician instructions may often be met with an affirmative even when nothing has been understood. Asking the person to repeat instructions in their own words is really the only way of ensuring their level of understanding.

PROGNOSIS

- Prognosis will vary depending on etiology, severity of intellectual and adaptive deficits and associated secondary conditions.
  - – Many adults with mild intellectual disability will live independently, learn to drive, lead long healthy lives, and be physically indistinguishable from persons without an intellectual disability. With appropriate education they can achieve a reading/writing level up to the equivalent of 6th grade (1).
  - – Individuals with more severe or profound deficits will require life-long supports and services. Although they do not need to live in an institutional-type setting, they will need supervised living arrangements and supports for their everyday needs.

COMPLICATIONS

- No medical or neurological complications based solely on having intellectual disability. Many complications may be more socially related to having intellectual disability.
  - – More often the victim of exploitation, abuse, or crime. More gullible and naïve which may lead to being taken advantage of by others. Difficulty expressing abstract notions such as pain, understanding and reporting symptoms or medication side-effects.

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CODES

ICD9

- 315.9 Unspecified delay in development
- 319 Unspecified intellectual disabilities
- 758.0 Down's syndrome

CLINICAL PEARLS

- No single cause of intellectual disability.
- Complex and varied clinical profile across individuals with intellectual disability.
- Can learn but may need frequent repetitions and information presented in a concrete format.
- 85% of persons have mild deficits and can achieve relatively high level of independence and self-sufficiency.
- More susceptible to psychiatric disorders than general population.

LAMBERT–EATON MYASTHENIC SYNDROME

W. David Arnold, MD

BASICS

DESCRIPTION

- Lambert–Eaton myasthenic syndrome (LEMS) is a chronic autoimmune neuromuscular disorder that leads to abnormal neuromuscular junction transmission.

EPIDEMIOLOGY

- Incidence
  - LEMS is a rare disorder with an estimated annual incidence of 0.17 per million.
- Prevalence
  - Prevalence has been estimated at 2.5 per million.

RISK FACTORS

- Smoking
- Small cell lung cancer
- Age

PATHOPHYSIOLOGY

- Symptoms of weakness and autonomic dysfunction are related to impaired presynaptic nerve terminal release of acetylcholine and diminished acetylcholine stimulation of nicotinic and muscarinic receptors.

ETIOLOGY

- Paraneoplastic and non-paraneoplastic LEMS are related to an autoimmune response against the presynaptic nerve terminal affecting calcium ion influx and quantal release of acetylcholine. Most patients have autoantibodies against presynaptic voltage-gated calcium channels.
- Most patients with paraneoplastic LEMS have tumors that express functional calcium channels, and antibodies formed against these channels may cross-react with similar presynaptic nerve terminal voltage-gated calcium channels.
- The inciting events that trigger autoimmunity in non-paraneoplastic LEMS are unclear.

COMMONLY ASSOCIATED CONDITIONS

- Two thirds of cases occur in the setting of neoplasm.
- Small cell lung cancer is associated with 90% of paraneoplastic cases, and in patients with small cell lung cancer, 3% will develop clinical and electrodiagnostic features consistent with LEMS.
- Other cancers including other lung cancers, lymphoma, prostate cancer, thymoma, neuroblastoma, and cervical cancer are occasionally associated.
- Other paraneoplastic processes (e.g., cerebellar degeneration, encephalomyelitis, neuropathy) commonly occur concurrently.

DIAGNOSIS

HISTORY

- Usually patients present with slowly progressive proximal lower limb-predominant muscle weakness. Autonomic symptoms including dry mouth, blurred vision, impotence, constipation, and difficulties with urination are frequently noted.

PHYSICAL EXAM

- Pertinent findings include proximally predominant weakness and reduced or absent reflexes. An inconsistently present but pathognomonic feature is facilitation or normalization of reflexes following brief isometric exercise.
- Mild ocular and bulbar weakness may be present. Up to one third of patients have ptosis, but ocular symptoms are not usually a prominent presenting feature.
- Sensory, cerebellar, and cognitive function are normal unless other coexistent paraneoplastic processes are present.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Investigation for paraneoplastic antibodies should be performed. Antibodies to peripheral P/Q-type voltage-gated calcium channels are present in at least 85% of patients and help support the diagnosis.

Follow-up & special considerations

- Investigation for coexistent paraneoplastic or autoimmune disorders should be considered as indicated clinically.
- SOX (SRY-related HMG box) antibodies are seen in association with LEMS associated with small cell lung cancer. Efforts are underway to refine testing for clinical use to aid in the detection of paraneoplastic cases.

Imaging

Initial approach

- Diligent screening with imaging modalities (plain films, CT, or MRI) for neoplasm should occur in all patients (1)[C].

Follow-up & special considerations

- If imaging is unrevealing, bronchoscopy should be considered in patients at high risk for lung cancer.
- PET imaging may have additive screening value in select high-risk cases (1)[C].
- If initial neoplastic screening is negative, periodic surveillance should occur for up to 5 years following diagnosis.

Diagnostic Procedures/Other

- Electrodiagnostic testing is helpful to confirm the presence of a presynaptic neuromuscular transmission defect and to exclude other mimicking conditions.
- Electrodiagnostic procedures include standard sensory and motor nerve conduction studies, low frequency (2–5 Hz) repetitive nerve stimulation, maximal compound muscle action potential (CMAP) response at rest and following 10 seconds of isometric exercise, and needle electrode electromyography. Occasionally, high-frequency (20–50 Hz) repetitive nerve stimulation and single fiber electromyography may be helpful.
- Typical findings include reduced CMAP amplitudes on motor nerve conduction studies, CMAP amplitude decrement during slow-frequency (2–5 Hz) stimulation, and CMAP amplitude increment during high-frequency (20–50 Hz) stimulation or following 10 seconds of isometric exercise. Sensory responses are normal. Needle electromyography may be normal or demonstrate unstable, small-amplitude, short-duration motor unit action potentials mimicking myopathy. Single fiber electromyography reveals increased single muscle fiber action potential jitter and prominent blocking.
- Electrodiagnostic criteria includes CMAP increment of 60% in 3 muscles or 300% in 1 muscle during high-frequency repetitive nerve stimulation or following 10 seconds of isometric exercise (2)[C].

DIFFERENTIAL DIAGNOSIS

- Myopathies including inflammatory, hereditary, and toxic etiologies
- Neuromuscular junction disorders other than LEMS (myasthenia gravis, botulism, congenital myasthenic syndrome)
- Neuropathies with features of proximal weakness particularly Guillain–Barré Syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

TREATMENT

MEDICATION

- Treatment includes strategies targeting associated neoplasm, symptomatic management to improve efficiency of neuromuscular transmission, and immunomodulatory agents to suppress autoimmunity. The primary focus of treatment in paraneoplastic cases is treatment of the underlying neoplastic process.

First Line

- Pyridostigmine, an anticholinesterase inhibitor, may be used with or without 3,4,-diaminopyridine (3,4-DAP). Dosages range from 30 to 120 mg q3–6h. A typical dosing schedule is 60 mg q4–6h. Side effects related to cholinergic action are common and include abdominal cramps, diarrhea, and blurred vision.
- 3,4-DAP is a potassium-channel antagonist that is significantly more efficacious due to its presynaptic mechanism of action (3)[A]. In the USA, it is only available on a compassionate-use basis and is not FDA approved. Dosages range between 15 and 100 mg daily divided t.i.d to q.i.d. Side effects include paresthesias and seizures. 3,4-DAP should be used cautiously in individuals with a history of seizures.
- 3,4-DAP and pyridostigmine are usually used in combination and may have a synergistic effect.
- Chronic nonspecific immunomodulatory treatments are usually necessary. Corticosteroids and steroid-sparing agents including azathioprine and cyclosporine should be considered in patients non-responsive to symptomatic agents alone.
- Rescue therapies are indicated in patients with severe or quickly progressing weakness. Intravenous immunoglobulin (IVIG) has demonstrated efficacy (3)[A]. Although less well studied, plasma exchange may also be used. Both treatments provide rapid but transient improvement, and repeated treatments are occasionally needed.

Second Line

- Other immunomodulatory treatments that may be considered include rituximab and mycophenolate mofetil.

ADDITIONAL TREATMENT

General Measures

- In patients with paraneoplastic LEMS, treatment of associated neoplasm is the primary aim. Chemotherapy is the first-line treatment of small cell lung cancer and may have immunomodulatory effects.
- Agents for bone health such as calcium, vitamin D, and bisphosphonates should be used when chronic steroid treatment is necessary.
- Antibiotic *Pneumocystis jiroveci* pneumonia prophylaxis should be prescribed when appropriate.

Issues for Referral

- Oncology referral is necessary when LEMS is associated with an underlying tumor.

Additional Therapies

- Physical and occupational therapies are helpful to improve and maintain mobility and independence with activities of daily living.

SURGERY/OTHER PROCEDURES

- Surgical resection may result in improvement of autoimmunity in localized cases.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Only rarely is LEMS associated with respiratory compromise, but monitoring of pulmonary parameters is appropriate, particularly in severe or rapidly progressive cases.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Close monitoring is necessary, particularly when immunomodulatory treatments are used.

Patient Monitoring

- Routine

DIET

- Patients treated with corticosteroids should be instructed to follow a low-salt, low-calorie diet.

PATIENT EDUCATION

- Information with regard to LEMS and support groups is available through the National Institute of Neurological Disorders and Stroke. Address: NIH Neurological Institute, P.O. Box 5801, Bethesda, MD 20824. Phone: (800)-352-9424; website: http://www.ninds.nih.gov/

PROGNOSIS

- In patients with neoplasm, prognosis is related to that of the cancer.
- Prognosis of small cell lung cancer is better in patients with associated LEMS compared with patients without LEMS.
- In non-paraneoplastic LEMS, most patients respond to symptomatic and immunomodulatory treatments, but chronic treatment is usually necessary.

COMPLICATIONS

- Immunomodulatory treatments increase risk of infection and tumor growth.
- Corticosteroid-related complications are usually dependent on treatment dose and duration and may include weight gain, hypertension, hyperlipidemia, osteopenia/osteoporosis, hyperglycemia/diabetes, cataracts, and avascular necrosis.
- Steroid-sparing agents should be used when possible.

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See Also (Topic, Algorithm, Electronic Media Element)

- Myasthenia gravis
- Paraneoplastic neurological syndromes

CODES

ICD9

358.1 Myasthenic syndromes in diseases classified elsewhere

CLINICAL PEARLS

- LEMS is a chronic autoimmune neuromuscular disorder that causes proximal weakness, autonomic symptoms, and diminished reflexes.
- Approximately one half of patients have associated neoplasm, usually small cell lung cancer.
- Development of LEMS may precede identifiable cancer, and screening up to 5 years after diagnosis may be necessary.
- Treatment is comprised of strategies directed at cancer treatment, symptomatic management, and usually immunomodulation.

LEPROUS NEUROPATHY

Adam D. Quick, MD

BASICS

DESCRIPTION

Leprosy is an infectious disease that mainly affects the skin, the peripheral nerves, the mucosa of the upper respiratory tract, and the eyes. Leprous neuropathy is the most common type of peripheral neuropathy worldwide. It is caused by direct bacterial infiltration of small-diameter peripheral nerves.

EPIDEMIOLOGY

Leprosy is indigenous to Hawaii and portions of Florida, Louisiana, and Texas in the US. It is also seen in immigrants from India, Southeast Asia, and central Africa.

- Incidence/Prevalence
  - Prevalence of 0.9 million cases worldwide in 1996. It has been gradually but steadily declining over several decades.
  - Prevalence exceeds 10 per 1,000 in endemic areas such as Asia and Africa.
  - 144 new cases in the US in 1995. The majority of leprosy cases diagnosed in the US are in immigrants from leprosy-endemic countries.
- Race
  - No racial predilection known
- Age
  - Leprosy can present at any age but is rare in infancy.
- Sex
  - Equal in children but 2:1 male preponderance in adults

RISK FACTORS

Exposure to nasal discharge of individuals infected with leprosy.

Genetics

There is evidence that HLA-associated genes influence the type of leprosy an individual develops.

ETIOLOGY

The etiologic agent is *Mycobacterium leprae*, an acid-fast bacillus that grows best at 30°C (86°F), which explains its predilection for skin and peripheral nerves. Leprosy is transmitted via transfer of bacteria in nasal discharge of infected individuals to the respiratory tract of susceptible individuals, followed by hematogenous dissemination. The intensity of the cell-mediated immune response to the bacteria correlates with the type of disease expression. Patients with an intense cellular immune response develop disease types toward the tuberculoid end of the spectrum. Little or no cellular immune response is associated with development of lepromatous leprosy.

DIAGNOSIS

- Indeterminate leprosy (initial infection)
- Solitary hypopigmented macule, which may resolve (about 75%) or persist to progress to one of the other types of leprosy.
- Classification of leprosy types is that of a continuous spectrum based on clinicopathologic features: Lepromatous, borderline lepromatous, borderline, borderline tuberculoid, and tuberculoid.
- Lepromatous leprosy
  - Multiple symmetric skin lesions affecting face (especially cheeks and nose), limbs, and buttocks, initially macular and evolving into plaques and nodules, typically fairly symmetric. Lesions centers are convex and indurated, and margins are ill defined.
  - Nasal congestions and epistaxis
  - Ocular: Pain, photophobia, loss of vision, glaucoma
  - Testicular: Sterility, impotence, gynecomastia
  - Sensory loss (especially pain, temperature) in distal limbs (palms and soles spared), pinnae of the ears, breasts, buttocks
  - Nerve root enlargement, especially superficial nerves such as the greater auricular in the neck, ulnar, peroneal as it passes around the fibula, superficial radial, median
  - Motor involvement is late: Amyotrophy, claw hand, foot drop
  - Reflexes preserved
  - Cranial nerve involvement: Preferentially V and VII (eye closure and perioral musculature)
  - Lucio reaction or phenomenon, a type of necrotizing vasculitis that can occur in lepromatous disease with high mortality
- Tuberculoid leprosy
  - Sharply marginated erythematous or hypopigmented macules or plaques that are solitary and asymmetric, occurring in the trunk, buttocks, and face. Tuberculoid leprosy lesions exhibit earlier sensory loss compared with lepromatous lesions.
  - Nerve enlargement occurs early and involves nerves contiguous to skin lesions.
  - Neuritic pain
  - Muscle atrophy, especially in the intrinsic hand muscles
  - Resorption of phalanges (late)
- Borderline leprosy
  - Skins lesions vary in number and character depending on whether the case is more toward the tuberculoid or lepromatous end of the spectrum.
  - Nerve involvement may precede skin lesions in this type, with segmental enlargement and tenderness of nerve trunks.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- ELISA to serum antibody to phenolic glycolipid I, a capsular antigen of *M. leprae*, is positive in most patients with multibacillary disease (lepromatous or borderline lepromatous) and often negative in patients with paucibacillary forms of the disease (tuberculous or borderline tuberculous).
- Diagnosis is generally made from demonstration of acid-fast bacteria from smears from affected skin or nasal mucosa.

Diagnostic Procedures/Other

- Dermal scraping or slit-skin biopsy is sent for acid-fast stain or, alternatively, the Ziehl–Neelsen stain to identify *M. leprae*. In tuberculoid leprosy, noncaseating granulomas are present and bacilli often are scant or absent. In lepromatous leprosy, a diffuse granulomatous reaction is present, often with many demonstrable bacilli.
- Nerve biopsy is not usually necessary to make a diagnosis of leprous neuropathy, except in rare cases of isolated nerve involvement.
- Nerve conduction studies/electromyography are helpful to document neuropathy and delineate pattern of involvement.

DIFFERENTIAL DIAGNOSIS

- Leprosy should be considered in presentations with the combination of a skin rash and peripheral neuropathy. The differential also includes the broad differential of peripheral neuropathy.
  - Lupus erythematosus
  - Lupus vulgaris
  - Sarcoidosis
  - Yaws
  - Dermal leishmaniasis other causes of leprosy

TREATMENT

MEDICATION

- Dapsone (diaphenylsulfone), a folate antagonist, is the primary therapy.
- The regimen recommended by the US Public Health Service Hospital Long Hansen's Disease Center in Louisiana is given below. These recommendations differ from the World Health Organization (WHO) recommendations, which include a broader regimen because of concerns of dapsone resistance.

US Public Health Service Hospital Long Hansen's Disease Center in Louisiana Regimen

- Paucibacillary disease (tuberculoid end of spectrum)
  - Dapsone 100 mg po daily
  - Rifampin 600 mg daily
  - Duration 1 year
  - Multibacillary disease (lepromatous end of spectrum)
  - Dapsone 100 mg po daily
  - Rifampin 600 mg po daily
  - Clofazimine 50 mg po daily
  - Duration 2 years

WHO-Recommended MDT Regimens

- Multibacillary leprosy
  - Rifampicin 600 mg once per month
  - Dapsone 100 mg daily
  - Clofazimine 300 mg once per month and 50 mg daily
  - Duration 12 months
- Paucibacillary leprosy
  - Rifampicin 600 mg once per month
  - Dapsone 100 mg daily
  - Duration 6 months
- Single skin lesion paucibacillary leprosy
  - For adults the standard regimen is a single dose of:
    - Rifampicin 600 mg
    - Ofloxacin 400 mg
    - Minocycline 100 mg
  - Thalidomide is the best therapy for erythema nodosum leprosum.
- Contraindications
  - All medications are contraindicated in patients with a known history of hypersensitivity reactions.
  - Clofazimine and thalidomide are not safe for use during pregnancy.
- Precautions
  - Adverse effects of dapsone are relatively uncommon but include hemolysis, agranulocytosis, hepatitis, and severe exfoliative dermatitis.
  - Clofazimine may cause reddish discoloration of the skin, diarrhea, and abdominal pain.
  - Patients may actually have a worsening of their neuropathy or rash when treatment is initiated due to several types of reactions (see Patient Monitoring).

ADDITIONAL TREATMENT

General Measures

Treatment is given to eradicate the bacteria and to prevent secondary immune reactions that might cause further injury to the nerves. Patients should be evaluated by an ophthalmologist for ophthalmologic manifestations that might threaten vision. Family members should be evaluated for leprosy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Patients should be counseled about the risks of inadvertent injury, such as severe burns to areas rendered insensate by peripheral neuropathy. Insensate limbs should be protected by good footwear, and patients should be warned about the risk of burns.
- Adjunctive treatment
  - N/A

SURGERY/OTHER PROCEDURES

Occasionally release of contractures and nerve and tendon transplants can improve function. Plastic surgery may be useful to correct or improve facial or other deformities.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Not generally required except in severe reactions to treatment (see Patient Monitoring).

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patients with leprosy must be followed closely for several types of adverse reactions to treatment.
  - Leprae type 1 reaction (reversal reaction) is an acute immunologically mediated inflammatory reaction seen in about 50% of patients with borderline leprosy in the first year of therapy. It is manifested as swelling and worsening of skin lesions and of peripheral nerves. Nerve pathology shows inflammation with granulomata and vasculitic changes. Prednisone at an initial dose of 60 mg/day is recommended, with treatment required for several months or more and taper guided by clinical response.
  - Leprae type 2 reaction (erythema nodosum leprosum) is a reaction that occurs in approximately 50% of patients with lepromatous leprosy during the first year of treatment and is attributed to immunologic reaction to massive death of *M. leprae* bacilli (Arthus reaction with deposition of immunoglobulin/complement in skin vessels). This leads to the development of multiple tender skin nodules, as well as fever, arthritis, iridocyclitis, edema, and new peripheral nerve injury in an acute mononeuritis multiplex pattern. Prednisone is also used to treat this reaction. Thalidomide 100–300 mg qhs is useful if prednisone does not quell the reaction.

PATIENT EDUCATION

- Centers for Disease Control. Website: www.cdc.gov/ncidod/dastlr/TB/TB_Hansen.htm
- World Health Organization information on the eradication of leprosy. Website: http://www.who.int/lep/disease/disease.htm

PROGNOSIS

In most patients with lepromatous leprosy, skin lesions typically resolve over months to several years. The peripheral neuropathy may improve, but this depends on the degree of damage present at the time of initiation of treatment. In tuberculoid leprosy, the skin lesions may improve or remain unchanged, and sensory loss often is permanent.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Hansen's disease

CODES

ICD9

- 030.1 Tuberculoid leprosy [type T]
- 030.8 Other specified leprosy
- 030.9 Leprosy, unspecified

LESCH–NYHAN DISEASE

H. A. Jinnah, MD, PhD

BASICS

DESCRIPTION

- Lesch–Nyhan disease (LND) is an inherited metabolic disease characterized by overproduction of uric acid and a characteristic neurobehavioral syndrome.
- The overproduction of uric acid frequently leads to hyperuricemia, gouty arthritis, and kidney stones composed of uric acid.
- The neurobehavioral syndrome consists of severe motor handicap, moderate intellectual disability, and recurrent self-injurious behavior [1–3].

EPIDEMIOLOGY

- Incidence
  - LND occurs in all ethnic groups with an incidence of 1 per 380,000 births.
  - Virtually all cases are males.
  - It is estimated that there are fewer than 1,000 cases in the USA.
- Genetics
  - The disorder is caused by mutations of the *HPRT1* gene on the X-chromosome, with >400 different mutations reported.
  - Inheritance is X-linked and recessive; therefore, female heterozygous carriers are asymptomatic, but their male offspring have a 50% risk of having the disease.
  - Sporadic cases also occur.

GENERAL PREVENTION

- Because there are no effective treatments for LND, prevention is of paramount importance. Any female relative of a patient with LND should be counseled with regard to her risk of producing an affected child.
- Genetic tests are available for both carrier testing and prenatal diagnosis to guide family planning decisions.

PATHOPHYSIOLOGY

- The *HPRT1* gene encodes hypoxanthine guanine phosphoribosyltransferase, an enzyme responsible for recycling the purine bases hypoxanthine and guanine into purine nucleotides.
- In LND, the rate of purine biosynthesis is increased, causing high levels of uric acid in the blood and urine. Precipitation of uric acid in the joints causes gout, whereas precipitation in the kidneys causes kidney stones.
- The pathogenesis of the neurobehavioral features is unknown, but is thought to be due to abnormal development of the basal ganglia.

ETIOLOGY

- The disorder is caused by mutations of the *HPRT1* gene on the X-chromosome.

COMMONLY ASSOCIATED CONDITIONS

- Macrocytic anemia
- Growth retardation
- Dysphagia

DIAGNOSIS

HISTORY

- Most patients present with a history of developmental delay in the first year of life.
- Abnormal movements resembling dystonic cerebral palsy emerge by 4 years of age.
- Although most patients present in a manner resembling cerebral palsy, a few present, instead, with renal failure due to nephrolithiasis or with gout during childhood.

PHYSICAL EXAM

- The physical exam may show scarring or disfigurement of the fingers, hands, face, lips, or other body parts from self-injurious biting or hitting.
- The neurological exam is dominated by generalized dystonia, sometimes with choreoathetosis and spasticity.
- Most patients use arm splints, mittens, and other devices to prevent self-injury. These should be removed only with great caution, and they should be replaced immediately, as self-injury can be immediate and extreme.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum uric acid
- 24-hour urinary uric acid

Follow-up & special considerations

- Evidence for overproduction of uric acid is a helpful clue, but it is not sufficient for definitive diagnosis because it is not specific for LND.
- Diagnosis requires demonstration of a mutation in the *HPRT1* gene.
- Alternatively, diagnosis can be made by demonstration of reduced HPRT enzymatic activity in blood cells or fibroblasts.
- Prenatal testing is possible in the first trimester via chorionic villus sampling.

Imaging

Initial approach

- Imaging studies of the brain may show mild, diffuse volume loss, but are largely unrevealing.
- Ultrasound and CT of the kidneys and urogenital system may reveal stones.

Pathological Findings

- There is no consistent histopathology in the brain.
- Kidneys often show stones and/or signs of chronic inflammation.

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis for developmental delay includes a large number of inherited or acquired disorders.
- Furthermore, the differential diagnosis for self-injurious behavior also is broad and includes severe intellectual disability, autism, and several other genetic syndromes.
- Hyperuricemia is unusual in children, often signifying a metabolic or lymphoproliferative disorder, or the effect of a medication.

TREATMENT

MEDICATION

First Line

- Allopurinol

Second Line

- Febuxostat

ADDITIONAL TREATMENT

General Measures

- Prevention of kidney stones requires an inhibitor of xanthine oxidase (either allopurinol or febuxostat) to reduce the formation of uric acid combined with generous hydration at all times to flush excess purines from the body.
- There are no consistently effective therapies for the behavioral features. Prevention of self-hitting usually requires physical devices such as arm splints, mittens, or hand straps. Dental extraction often is required to prevent self-biting. Behavioral therapy can be helpful to reduce self-injurious behaviors, but is rarely sufficient on its own. Medications sometimes helpful for reducing self-injury include gabapentin, carbamazepine, or benzodiazepines.
- There are no consistently effective treatments for the motor disorder, although benzodiazepines often are used to reduce muscle tone.

Issues for Referral

- Referral to a center with special expertise in the disorder is essential to help the family cope with recurrent self-injurious behavior and other difficult behaviors, and to monitor for the many complications that may occur, such as nephrolithiasis.

Additional Therapies

- Wheelchairs must be customized by covering all potentially dangerous parts within reach. Comfortable devices to prevent self-injury usually are required in the wheelchair and sleeping environment.

SURGERY/OTHER PROCEDURES

- Patients with LND may undergo most routine surgical procedures with standard anesthetic agents.

IN-PATIENT CONSIDERATIONS

Nursing

- Devices used for the prevention of self-injury should not be removed without permission of the patient or family, and they should be replaced as soon as possible.
- These protective devices, sometimes, are mistaken for restraints, leading to proposals that they should be removed for compliance with regulatory restrictions against use of restraints. Removal of the protective devices is ill advised, as serious injury, such as eye gouging leading to blindness, may occur instantaneously.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Regular follow-up is needed to guard against nephrolithiasis and renal failure.
- Stones may arise even in well-hydrated patients taking allopurinol.

DIET

- Patients may eat a regular diet, although many have sufficiently severe dysphagia that a gastrostomy tube is required for adequate nutrition.

PATIENT EDUCATION

- www.lesch-nyhan.org.
- Lesch–Nyhan Syndrome Children's Research Foundation, 210 South Green Bay Road, Lake Forest IL, 60045.
- Emedicine entry for Lesch-Nyhan syndrome. Website: www.emed.com/neuro/topic630.htm

PROGNOSIS

- Although the condition is not progressive or degenerative, few patients survive beyond 40 years of age.
- Most succumb to complications of renal failure or aspiration.
- A significant proportion experience sudden death of undetermined cause.

REFERENCES

1. Jinnah HA, Visser JE, Harris JC, et al. Lesch-Nyhan Disease International Study Group. The motor disorder of Lesch-Nyhan disease. *Brain* 2006; 129:1201–1217.
2. Jinnah HA, Ceballos-Picot I, Torres RJ, et al. Lesch-Nyhan Disease International Study Group. Attenuated variants of Lesch-Nyhan disease. *Brain* 2010;133:671–689.
3. McCarthy GT, Green EM, Ogunbona O, et al. A population study of Lesch–Nyhan disease in the UK. *Dev Med Child Neurol* 2011;53:34–39.

ADDITIONAL READING

- www.lesch-nyhan.org

CODES

ICD9

277.2 Other disorders of purine and pyrimidine metabolism

CLINICAL PEARLS

- Punishment of difficult behaviors, including self-injury, is not effective. Paradoxically, punishment increases these behaviors.
- Renal stones may develop despite adequate allopurinol treatment and hydration. Stone analysis may reveal xanthine stones instead of uric acid, necessitating a reduction in allopurinol doses.
- Attenuated variants may occur with mutations in the *HPRT1* gene, where some features of the full syndrome are absent or unusually mild.

LEUKODYSTROPHIES

Deborah L. Renaud, MD

BASICS

DESCRIPTION

Leukodystrophies are inherited disorders of central myelination resulting in the confluent destruction or abnormal formation of cerebral white matter. Despite substantial progress in our understanding of inherited white matter disorders in recent years, ~50% of children and adults with white matter abnormalities do not have a specific diagnosis in spite of extensive investigations to rule out well-defined leukodystrophies.

EPIDEMIOLOGY

- Incidence
  - Alexander's disease: rare
  - Canavan's disease: rare, 1 in 10,000 in Ashkenazi Jews (prior to routine carrier testing)
  - Megalencephalic leukoencephalopathy with subcortical cysts: rare
- Metachromatic leukodystrophy: 1 in 40,000
- Krabbe's leukodystrophy: 1 in 100,000
- X-linked adrenoleukodystrophy (ALD): 1 in 20,000 males
- Pelizaeus–Merzbacher disease: 1 in 100,000
- Vanishing white matter disease: rare

RISK FACTORS

There are no known environmental risk factors.

Genetics

- The leukodystrophies are inherited in an autosomal recessive pattern with the exception of Alexander's disease (autosomal dominant) and the X-linked recessive conditions (X-linked ALD and Pelizaeus–Merzbacher), which affect males more severely.

GENERAL PREVENTION

- Carrier testing and prenatal diagnosis may be available in some cases.

ETIOLOGY

- Alexander's disease: *de novo* mutation in glial fibrillary acidic protein (GFAP) gene
- Canavan's disease: mutations in aspartoacylase gene
- Megalencephalic leukoencephalopathy with subcortical cysts: mutations in the *MLC1* and *HEPACAM* genes
- Metachromatic leukodystrophy: arylsulfatase A deficiency, multiple sulfatase deficiency, and saposin (activator protein) deficiency
- Krabbe's leukodystrophy: galactocerebrosidase deficiency
- X-linked ALD: deficiency of peroxisomal membrane transporter (ALDP);
- Pelizaeus–Merzbacher disease: deficient formation of proteolipid protein (PLP) in the central nervous system
- Vanishing white matter disease: mutations in 1 of the 5 subunits of the translation initiation factor eIF2B

COMMONLY ASSOCIATED CONDITIONS

In addition to leukodystrophy:

- Metachromatic leukodystrophy: peripheral neuropathy, optic atrophy, and gallbladder disease
- Krabbe's leukodystrophy: peripheral neuropathy, and vision loss
- X-linked ALD: Addison's (adrenal insufficiency)
- Pelizaeus–Merzbacher disease: rotatory nystagmus
- Vanishing white matter disease: Adult females may develop premature ovarian failure.

DIAGNOSIS

HISTORY

- Alexander's disease
  - Infantile: macrocephaly, psychomotor regression, seizures, and spasticity
  - Juvenile: slower development of bulbar signs, ataxia, and spasticity with relative preservation of intelligence
  - Adult onset: heterogeneous, may mimic relapsing–remitting multiple sclerosis
- Canavan's disease
  - Infantile: macrocephaly, hypotonia, developmental delay → seizures and spasticity
  - Congenital: marked hypotonia, lethargy, dysphagia, and early death
  - Juvenile: onset after 5 years of cerebellar dysfunction, cognitive decline → spasticity and optic atrophy
- Megalencephalic leukoencephalopathy with subcortical cysts
  - Macrocephaly prior to 1 year of age.
  - Early development is normal with eventual development of ataxia, spasticity, and slow deterioration in motor functions.
  - Intelligence remains relatively spared.
  - Seizures may develop.
- Metachromatic leukodystrophy
  - Late infantile: initial hypotonia → progressive hypertonia, ataxia, intellectual regression, painful peripheral neuropathy, and optic atrophy
  - Juvenile: school difficulties, incontinence, and gait clumsiness → extrapyramidal features, hypertonia, intellectual deterioration, and pseudobulbar palsy
  - Adult onset: initial neuropsychiatric symptoms with progressive frontal dementia → gait disorder, peripheral neuropathy → hypertonia, optic atrophy, spastic tetraparesis, and bulbar dysfunction
- Krabbe's leukodystrophy
  - Infantile: early irritability/hypersensitivity to stimuli → marked hypertonia, loss of vision and hearing, and peripheral neuropathy
  - Juvenile and adult forms: mental deterioration, pyramidal signs, visual loss, and peripheral neuropathy
- X-linked ALD

6 clinical phenotypes have been recognized for this condition:

- Childhood cerebral ALD
- Adolescent and adult-onset cerebral ALD
- Amyeloneuropathy (AMN)
- Addison's only
- Asymptomatic/presymptomatic
- The childhood cerebral form and amyeloneuropathy are the most common. The childhood cerebral form presents initially with behavioral changes and school difficulties at 2–10 years of age, followed by progressive neurologic dysfunction, vision loss, and adrenal insufficiency. The adolescent and adult-onset cerebral phenotypes have similar features to the childhood cerebral disease but a latter age of onset. Amyeloneuropathy presents in the second to fourth decade of life as progressive spastic paraparesis. Up to half of these patients may develop cerebral symptoms, and two thirds develop adrenal insufficiency. Addison's alone may be present in 10–20% of ALD patients, with a high risk of developing neurologic symptoms later. Patients may remain asymptomatic for decades. Up to 50% of female carriers develop AMN. Different clinical phenotypes can occur within the same family.
- Pelizaeus–Merzbacher disease
  - Classic: rotatory eye movements and hypotonia → very slowly progressive involuntary movements and spasticity
  - Connatal: onset at birth with severe features and more rapid progression; may have intractable seizures
  - X-linked spastic paraparesis
- Vanishing white matter disease
  - Onset from infancy to adulthood
  - Chronic progressive cerebellar ataxia, spasticity, optic atrophy, and mild mental decline
  - Episodes of rapid deterioration following febrile illnesses and minor head trauma

PHYSICAL EXAM

- Onset of cognitive decline, spasticity, and visual changes in a previously normal person should lead to consideration of leukodystrophy

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Alexander's disease: mutation analysis of *GFAP* gene
- Canavan's disease: elevated urinary excretion of *N*-acetylaspartic acid (NAA) in organic acids; decreased aspartoacylase enzyme activity; and DNA mutation analysis
- Megalencephalic leukoencephalopathy with subcortical cysts: DNA mutation analysis
- Metachromatic leukodystrophy: arylsulfatase A assay on WBCs or fibroblasts; sulfatides in the urine; and DNA mutation analysis
- Krabbe's leukodystrophy: galactocerebrosidase assay in WBCs or fibroblasts; and mutation analysis
- X-linked ALD: accumulation of very-long-chain fatty acids (VLCFA) in blood; DNA mutation analysis
- Pelizaeus–Merzbacher disease: mutations or duplication of the PLP gene If negative, consider testing for mutations in the gap junction *A12* gene
- Vanishing white matter disease: mutation analysis of 5 subunits of eIF2B

Imaging

Initial approach

- MRI is the study of choice for the evaluation of leukodystrophy:
- Alexander's disease: extensive frontal, dominant, white matter abnormalities
- Canavan's disease: diffuse hypodensity of white matter and increased NAA peak on magnetic resonance spectroscopy
- Megalencephalic leukoencephalopathy with subcortical cysts: diffusely abnormal; mildly swollen white matter with subcortical cysts in the anterotemporal region and often in the frontotemporal region
- Metachromatic leukodystrophy: periventricular white matter abnormalities evolve into more extensive, symmetric involvement of the subcortical white matter
- Krabbe's leukodystrophy: extensive white matter involvement precedes diffuse cerebral atrophy; may be normal early in the course of the disease
- X-linked ALD: symmetric parietooccipital white matter lesions; less commonly, bifrontal
- Pelizaeus–Merzbacher disease: severe reduction or absence of myelin
- Vanishing white matter disease: diffusely abnormal white matter that vanishes over time and is replaced by CSF

Diagnostic Procedures/Other

- Alexander's disease: histologic finding of Rosenthal's fibers on brain biopsy is diagnostic but has been replaced by mutation analysis
- Metachromatic leukodystrophy: nerve conduction studies to assess for peripheral neuropathy; ultrasound to assess for accumulation of sulfatides in gallbladder wall
- Krabbe's leukodystrophy: nerve conduction studies to assess for peripheral neuropathy
- X-linked ALD: adrenal function testing in patients with all forms of this disease

DIFFERENTIAL DIAGNOSIS

- Multiple sclerosis
- Acute disseminated encephalomyelitis
- CNS vasculitis
- Toxic leukoencephalopathies (e.g., cyclosporine, methotrexate)
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
- Multiple subcortical infarctions
- Disorders of vitamin B_{12} and folate metabolism
- White matter abnormalities associated with other metabolic conditions, including organic acidurias, aminoacidopathies, and mitochondrial disorders

TREATMENT

MEDICATION

First Line

- No effective drug therapies are available.

Second Line

- Alternative drugs
  - Lorenzo's oil has been given to patients with X-linked ALD for more than 2 decades since it was initially shown to normalize plasma VLCFAs. Recent studies, however, have demonstrated no beneficial effects of Lorenzo's oil on the natural course of the neurologic disease. Significant side effects, including elevated liver enzymes and thrombocytopenia, are frequently observed.

ADDITIONAL TREATMENT

General Measures

- Supportive therapy
  - Nutritional support
  - Treatment for spasticity
  - Anti-epileptic medications

Issues for Referral

- Palliative care team

Additional Therapies

- Symptomatic treatment
  - Bone marrow transplantation may result in long-term stabilization and, sometimes, improvement in clinical symptoms when performed early in cerebral X-linked ALD, the juvenile and adult-onset forms of metachromatic leukodystrophy, and Krabbe's disease. Once neurologic symptoms have progressed beyond the early stages, bone marrow transplantation has not been shown to alter the natural course of these diseases.
- Adjunctive treatment
  - Patients with ALD and amyeloneuropathy should be treated for adrenal insufficiency as required.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- None proven effective

SURGERY/OTHER PROCEDURES

- G-tube for feeding

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Presymptomatic boys with X-ALD should be monitored with serial MRI and neuropsychologic assessments to detect early indications of cerebral disease and need for bone marrow transplantation.

DIET

- No specific dietary changes have been found to slow the neurologic progression.

PATIENT EDUCATION

- Genetic counseling should be provided to patients and their families. Presymptomatic testing of siblings may be offered for some conditions in view of the potential benefit of early bone marrow transplantation.
- United Leukodystrophy Foundation. Website: www.ulf.org

PROGNOSIS

Rate of progression of symptoms is dependent upon the age of onset and characteristics of each individual leukodystrophy.

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See Also (Topic, Algorithm, Electronic Media Element)

- Leukoencephalopathies
- Metabolic white matter diseases

CODES

ICD9

330.0 Leukodystrophy

CLINICAL PEARLS

- Leukodystrophies present with cognitive decline, spasticity and visual changes associated with bilaterally symmetric, confluent white matter changes on MRI scan of the brain.

LYME DISEASE, NEUROLOGICAL COMPLICATIONS (LYME NEUROBORRELIOSIS)

David S. Younger, MD

BASICS

DESCRIPTION

- Lyme neuroborreliosis (LNB) is the preferred term for the neurologic complications of Lyme disease. *Borrelia burgdorferi* (hereafter referred to as *B. Burgdorferi*) is the vector of Lyme disease in North America.
- Peripheral nervous system (PNS) manifestations result from involvement of large-caliber peripheral nerves and present as painful meningoradiculoneuritis, mononeuritis multiplex (MNM), distal polyneuropathy (DPN), cranial neuritis, and painful small fiber neuropathy.
- Central nervous system (CNS) manifestations result from involvement of the brain and spinal cord and present as meningitis, meningoencephalitis, and encephalopathy.
- Autonomic nervous system (ANS) manifestations result from autonomic neuropathy and ganglioneuritis and present as orthostatic intolerance (OI) and postural orthostatic tachycardia syndrome (POTS).

EPIDEMIOLOGY

Incidence

Lyme disease is the most common vector-borne disease in the US. Tick-borne spirochetosis affects up to 20,000 persons annually. Incidence in the US of 1 in 2,719 individuals; rate higher in hyper-endemic areas of the northeast. Ranges from <.01 cases per 100,000 persons in Montana to 74 cases per 100,000 in Connecticut.

Prevalence

- The nervous system is thought to be involved in 12–15% of untreated infected individuals.
- Race, age, and gender: The vast majority of affected patients are white, children <15 years and adults >30 years, of equal gender.

RISK FACTORS

- The responsible spirochete is transmitted exclusively by the bite of infected hard-shelled *Ixodes* ticks.
- Residence in, or visitation to, endemic areas during spring and summer is crucial in determining the likelihood of contracting Lyme disease.

Genetics

N/A

GENERAL PREVENTION

Insect repellents, careful tick checks of the body, avoidance of high grass, and other commonsense practices in the outdoors can prevent tick attachment and subsequent infection.

PATHOPHYSIOLOGY

- The mechanisms of LNB are, however, not well understood.
  - Tick-bite meningoradiculoneuritis: Paresthesia, radicular pain, and facial and named nerve paralysis 2–6 weeks after erythema chronicum migrans (EM or ECM) rash, with CSF pleocytosis, electrophysiological and histopathological evidence of inflammatory neuropathy typified by pericapillary cuffing without vessel necrosis.
  - DPN and MNM with minimally abnormal sural nerve histopathology of mild axonopathy and secondary demyelination.

ETIOLOGY

- *B. burgdorferi* in North America
- *B. Afzelii*, *B. Garinii*, *B. burgdorferi*, and occasionally others species of *Borrelia* in Europe

COMMONLY ASSOCIATED CONDITIONS

- Dermatologic: EM, borrelial lymphocytoma, acrodermatitis chronica atrophicans
- Cardiac: Acute high-grade atrioventricular conduction defect, carditis
- Rheumatologic: Joint swelling, oligoarticular arthritis

DIAGNOSIS

- Lymphocytic meningitis and radiculoneuritis
  - In about 10% of patients, the organism can be cultured from CSF and intrathecal antibody production is demonstrated in over 90%.
  - Clinically indistinguishable from viral meningitis.
  - CSF shows lymphocytic pleocytosis, mild protein elevation, normal glucose content.
  - Symptoms are usually self-limited and resolve more quickly with antibiotics.
  - Radicular involvement is similarly common and mimics mechanical monoradiculopathy, plexopathy, MNM, and disseminated polyneuropathy similar to Guillain–Barrè syndrome (GBS); however, electrodiagnostic studies do not show typical demyelinating features and CSF does not show albuminocytologic dissociation.
- Cranial neuritis: The facial nerve is the most commonly involved and may be affected bilaterally.
- Peripheral neuropathy: In patients with acute and indolent PNS involvement, electrodiagnostic studies show multifocal abnormalities with primary axonal and secondary demyelinating features.
- CNS involvement includes extra- and intra-axial disease and CNS dysfunction without obvious CNS lesions. Lyme encephalomyelitis is a focal inflammatory disorder of the brain and spinal cord parenchyma that occurs in about 0.1% of patients with untreated *B. burgdorferi* infection. Lyme encephalopathy shows mild confusion, memory disturbance, cognitive impairments, and significant deficits on neuropsychological and mini-mental status testing.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Serology: Paired-acute and convalescent-phase serum samples, diagnostic levels of IgM and IgG antibodies in CSF, and isolation of *B. burgdorferi* from CSF are all recommended by the Centers for Disease Control and Prevention. Sensitivity and specificity of the serological diagnosis of Lyme disease has not been determined in any given cohort.
- First-tier: Screening ELISA. During the early phase of the exposure, serological testing may be uninformative or falsely negative.
- Second-tier confirmatory Lyme Western blots (WB): IgG and IgM should be obtained with borderline and reactive first-tier test results. The Lyme IgM WB response is the first to appear after initial exposure to *B. burgdorferi* and comprises specific and nonspecific bands. This is followed by the Lyme IgG WB response of specific and nonspecific band reactivity months later.

Imaging

Initial approach

- MRI of the brain and spinal cord should be considered in all patients with LNB employing T1- and T2-weighted sequences to quantify the brain structural integrity via white matter (WM) abnormalities and gray matter (GM) atrophy and to ascertain the presence of disease-related lesions. Conventional MRI shows subcortical WM lesions indistinguishable from multiple sclerosis (MS) in T2 and fluid-attenuated inversion recovery imaging.
- Multiparametric magnetization transfer and diffusion tensor MRI shows that multiple brain and spinal cord T1- and T2-weighted abnormalities seen on conventional MR are not associated with structural damage, distinguishing them from MS lesions.

Follow-up & special considerations

Nuclear medicine cerebral perfusion with single photon emission computerized tomography reveals various patterns of reversible cortical hypoperfusion in LNB. Similar findings are noted in Lyme encephalopathy.

Diagnostic Procedures/Other

- EMG-NCS
- Consider autonomic testing
- Lumbar CSF analysis
- Consider biopsy of cutaneous nerve
- Skin biopsy for epidermal nerve fiber study

DIFFERENTIAL DIAGNOSIS

- Acute cranial neuritis
  - Bell palsy
  - GBS, Miller Fisher syndrome
  - Neurosarcoidosis
- Acute Lyme radiculoneuritis
  - Varicella zoster virus – Post Herpetic neuralgia
  - CMV and Epstein–Barr virus infection
  - Neurosarcoidosis
  - Lumbosacral radiculoplexus neuropathy
  - Nonsystemic vasculitic neuropathy
  - Amyotrophic lateral sclerosis

- Acute Lyme meningitis and meningoencephalitis
  - Viral meningitis and meningoencephalitis
- Chronic Lyme radiculoneuropathy
  - Amyotrophic lateral sclerosis
  - Idiopathic sensory polyneuropathy
  - Degenerative spine disease
- Lyme encephalopathy
  - Toxic-metabolic encephalopathy
  - Early Alzheimer disease
  - Neurosyphilis
- Subacute and chronic Lyme encephalomyelitis
  - MS
  - Post viral encephalomyelitis

TREATMENT

MEDICATION

Once the diagnosis of LNB is made, antibiotic therapy should commence. For LNB with objective brain and spinal cord CNS involvement, there is good evidence that parenteral antibiotics including ceftriaxone, cefotaxime, and penicillin are safe and effective. For LNB without brain or spinal cord involvement, there is good evidence that oral doxycycline is probably safe and effective but this medication should not be used in children under the age of 8 or in pregnant women.

First Line

- Recommendations of the Quality Standards Subcommittee of the American Academy of Neurology include treatment with parenteral antibiotics for syndromes associated with meningitis, encephalomyelitis, encephalopathy, and any neurologic syndrome with CSF pleocytosis. Similarly, severe neuropathic disease syndromes, particularly those deemed oral antibiotic treatment failures, warrant treatment with parenteral therapy including peripheral nerve radiculopathy, diffuse neuropathy, MNM, and cranial neuropathy.
- Oral adult regimen: Doxycycline 100–200 mg b.i.d.
- Oral pediatric regimen in ≥8 year olds: Doxycycline 4–8 mg/kg/day in divided doses, max 200 mg/dose
- Parenteral adult regimen: Ceftriaxone 2 g IV daily
- Parenteral pediatric regimen: Ceftriaxone 50–75 mg/kg/day in 1 dose; max 2 g

Second Line

- Oral adult regimen (when doxycycline contraindicated): Amoxicillin 500 mg t.i.d.
- Oral pediatric regimen (when doxycycline contraindicated): Amoxicillin 50 mg/kg/day in 3 divided doses; max 500 mg/dose
- Parenteral adult regimen: Cefotaxime 2 g IV q8h
- Parenteral pediatric regimen: Cefotaxime 150–200 mg/kg/day in 3–4 divided doses; max 6 g/day

ADDITIONAL TREATMENT

General Measures

The therapeutic goal of LNB treatment is optimization of the general health of the patient, recognition of factors that might preclude a prompt recovery such as concomitant illness, tick borne co-infections, and coexisting medical conditions. Once a therapeutic course of antibiotics is completed, consideration should be given to treatment of the post-infectious autoimmune nervous system sequelae. For example, a therapeutic course of intravenous immune globulin (IVIG) may be considered in patients with clinical, electrodiagnostic and pathologically-proven inflammatory and demyelinating neuropathy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Neuropathic pain control for painful peripheral neuropathy
  - Fludrocortisone for symptomatic OI
  - Beta blockers for symptomatic POTS
- Adjunctive treatment
  - Physical therapy for limb weakness
  - Cognitive rehabilitation for patients with memory disturbance

IN-PATIENT CONSIDERATIONS

Admission Criteria

Outpatient management is generally the rule with admission for patients with significant progressive neurologic deficits.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Serial two-tier Lyme serology. There is no obvious role for repeat CSF analysis unless clinically warranted.
- Follow-up neuropsychological testing to document improved cognition.
- Brain neuroimaging often does not improve but functional imaging does.
- Serial electrodiagnostic studies, autonomic neurophysiological studies, and punch skin biopsy for epidermal nerve fiber (ENF) analysis parallel clinical improvement.

PATIENT EDUCATION

Tick avoidance: Beware of high grass, brush, woods in endemic areas in spring/summer

PROGNOSIS

- In acute Lyme radiculoneuropathy, radicular pain often improves over hours to days of IV antibiotic administration, whereas sensory and motor deficits generally resolve completely over weeks to a few months.
- The prognosis for facial and other cranial nerve palsies is excellent.
- In acute and chronic Lyme encephalomyelitis, neurologic function improves, but residual deficits are common.
- In chronic Lyme radiculoneuropathy, symptoms resolve more slowly than in acute Lyme neuropathy over many months, usually with mild residual deficits.
- The outcome is better in Lyme encephalopathy than encephalomyelitis. Improvement in symptoms is slow, beginning 2–3 months after completion of antibiotic therapy and continuing for 6–9 months.

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CODES

ICD9

- 088.81 Lyme disease
- 320.7 Meningitis in other bacterial diseases classified elsewhere
- 322.9 Meningitis, unspecified

MALIGNANT HYPERTHERMIA

Miriam Anixter, MD

BASICS

DESCRIPTION

- Malignant hyperthermia (MH) is a condition characterized by elevated calcium concentration in the sarcoplasm after exposure to triggering agents, causing an uncontrolled increase in muscle metabolism.

EPIDEMIOLOGY

- Incidence
  - 10.2–13.3 episodes per million hospital discharges (1)
- Prevalence
  - The prevalence of the MH-susceptible phenotype has been estimated to be as high as 1:3,000 individuals (2).

RISK FACTORS

- MH is almost exclusively caused by exposure to triggering agents including all potent inhalational anesthetics, such as sevoflurane and desflurane, and the depolarizing neuromuscular blocker succinylcholine. MH-susceptible patients may not have an episode with their first exposure to a triggering anesthetic; 50% of patients may have had 2 or more uneventful general anesthetics. Triggering and severity of an episode may be ameliorated by mild hypothermia (consistent with the comparatively greater incidence in children as mild hypothermia is less common during pediatric anesthesia).
- Stress has clearly been shown to be a trigger in the porcine model of MH, but evidence for this factor is weak in humans. Nonetheless, it has been standard practice to reduce stress in MH-susceptible patients with careful premedication before surgery. There are several case reports of individuals with exercise or heat intolerance who had MH susceptibility demonstrated by halothane–caffeine contracture testing.
- MH episodes are more commonly diagnosed in males (1,2).

Pregnancy Considerations

- MH-susceptible women may carry infants to term. There are anecdotal reports of MH episodes occurring during the stress of delivery in hot weather.
- Epidural analgesia can be given to MH-susceptible patients. Therefore, modern anesthetic techniques can theoretically reduce the risk of MH during delivery.

Genetics

- The genetics of MH are characterized as autosomal dominant with variable penetrance. Between 20% and 70% of MH-susceptible patients have a genetic mutation in the ryanodine receptor. The MH phenotype may be dependent on other proteins that modulate the ryanodine receptor or calcium reuptake (2).

GENERAL PREVENTION

- Patients who have a family history of MH susceptibility, or are themselves MH susceptible, should not be exposed to triggering agents.
- Anesthesia ventilators used on these patients should be flushed according to manufacturer specifications to avoid inadvertent administration of residual potent inhaled anesthetics.

PATHOPHYSIOLOGY

- Increased muscle metabolism during an MH episode increases CO_2 production as aerobic metabolism increases in muscle, and lactic acid produced by muscular anaerobic metabolism is neutralized. Metabolic and respiratory acidosis results. In spontaneously breathing patients, tachypnea will be noted; in ventilated patients, increases in end-tidal CO_2 occur despite increasing minute ventilation.
- Skeletal muscle rigidity may be caused by uncontrolled stimulation of actin–myosin cross-bridge cycling by increased intracellular Ca^{2+} and by muscle temperature $>43.5^{\circ}C$, which causes irreversible contraction. The rigidity of MH is not affected by neuromuscular blockade.
- Hyperthermia associated with MH is secondary to muscle hypermetabolism and depends on both the ability to dissipate heat produced and the rapidity of definitive treatment.
- Tachycardia and hypertension may be caused directly by hypercarbia, and indirectly by hypercarbic stimulation of catecholamine release. High concentrations of catecholamines, hypercarbia, and cutaneous vasodilatation lead to flushed, diaphoretic skin.
- Local hyperthermia, acidosis, and depletion of adenosine triphosphate (ATP) cause increased membrane permeability and release of potassium by the hypermetabolic muscle. Hyperkalemia leads to arrhythmias, decreased cardiac output, and potential cardiac arrest.
- Muscle hypermetabolism, decreased energy stores, local temperature rise, and decreased perfusion lead to rhabdomyolysis.
- Pulmonary and cerebral edema and disseminated intravascular coagulation (DIC) are associated with severe or untreated MH (2).

ETIOLOGY

- The ryanodine receptor is the calcium-release channel from the sarcoplasmic reticulum (SR). Release of calcium from the SR normally occurs after depolarization via an action potential. Subsequent calcium release into the myoplasm allows actin–myosin cross-bridge cycling (contraction), which is terminated by calcium reuptake into the SR (relaxation). Abnormal stimulation of calcium release by triggering agents causes continuous cross-bridge cycling and consumption of energy stores, both by the contraction apparatus and by sarcoplasmic ATPase (2).

COMMONLY ASSOCIATED CONDITIONS

- Many physicians suspect an increased incidence of MH susceptibility in patients with myopathies. The King–Denborough syndrome is a dysmorphic complex associated with an increased risk of MH. The majority of patients with central core disease are susceptible to MH.
- Duchenne's and Becker muscular dystrophy have been inconsistently associated with MH episodes. These individuals may have acute hyperkalemic arrests and rhabdomyolysis after the administration of succinylcholine secondary to extrajunctional acetylcholine receptors and dystrophin-poor muscle fragility. In addition, dystrophin-poor muscle may have abnormal resting calcium levels, increased calcium release, and impaired calcium-reuptake mechanisms at baseline; the increase of calcium release by inhaled agents may lead to exacerbation of chronic rhabdomyolysis and increased metabolism. The routine use of inhalational anesthetics in these individuals is controversial. If potent inhaled anesthetics are given, careful monitoring of metabolism with end-tidal CO_2 and minute ventilation and of muscle injury with serum potassium and urinary myoglobin is prudent.
- The evidence for association of MH susceptibility with other myopathies is limited, but is suspected due to the abnormal calcium regulation in these conditions (2).

DIAGNOSIS

HISTORY

- An immediate history of exposure to triggering agents is usually present. Some individuals may have past history remarkable for muscle cramps/weakness, or heat intolerance. Unusual metabolic events not meeting the definition of MH may have occurred during previous anesthetics. A history of an MH episode in a family member may only be elicited after the event (3)[B].

PHYSICAL EXAM

- The first sign may be masseter muscle spasm during succinylcholine administration; this may be severe enough to prevent intubation.
  - Approximately 50% of patients with masseter spasm after succinylcholine administration are found to be MH susceptible. When presented with a patient with masseter spasm after succinylcholine administration, consideration should be given to aborting the anesthetic. If the anesthetic is continued with nontriggering drugs, then consideration should be given to what must be done to facilitate early diagnosis and treatment in the event MH develops.
- Other common signs are hypercarbia, rapid increase in temperature, tachycardia, and cola-colored urine (if rhabdomyolysis has occurred) (2,3)[B].

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Arterial and venous blood gases, serum potassium/other electrolytes, urinalysis, baseline creatine kinase (CK), clotting studies, and creatinine.
- The characteristic metabolic and respiratory acidosis secondary to muscle hypermetabolism, along with signs of muscle breakdown and resolution with dantrolene, favor diagnosis of MH.
  - If urine dipstick test is positive for blood, then obtain microscopic analysis for RBCs and quantitative analysis for myoglobin.
  - Increased $paCO_2$ will be seen, reflected by increased end-tidal CO_2 if this is accurately monitored. A reverse gradient between arterial CO_2 and end-tidal CO_2 will be present, reflecting muscle hypermetabolism.
  - An increased gap between venous pO_2 and arterial pO_2 will also be present, due to increased oxygen extraction by muscle.

Follow-up & special considerations

- Repeat CK 12–24 hours later and until value returns to baseline. Repeat other abnormal labs at intervals to guide treatment (2)[B].

Diagnostic Procedures/Other

- The halothane–caffeine contracture test is the only approved diagnostic test for susceptibility to MH. It is available in 4 centers in the USA in 2011, and requires 1 g of fresh muscle. Although the test is very sensitive, it lacks specificity. Therefore, the index patient should undergo contracture testing to maximize the predictive value for other family members.
  - Testing should be delayed at least 3–6 months after an MH episode.
- Genetic testing may be performed in families with a known mutation associated with MH; ideally, the MH status of the proband is confirmed with contracture testing to improve yield. If a family has a known mutation, screening of other family members can be performed (4)[B].

DIFFERENTIAL DIAGNOSIS

- Sepsis, thyrotoxic crisis, pheochromocytoma, metastatic carcinoid, serotonin syndrome, neuroleptic malignant syndrome, inadequate ventilation, light anesthesia, cocaine intoxication, iatrogenic overheating, central fever, and anaphylactoid reactions

TREATMENT

MEDICATION

First Line

- Dantrolene sodium inhibits Ca^{2+} release from the SR. The dose in the acute period is 2.5 mg/kg IV push, repeated until the signs of MH are reversed (may require up to 10 mg/kg), then 1 mg/kg every 6 hours for 24–36 hours.
- Side effects include muscle weakness, drowsiness, nausea, and phlebitis. Respiratory compromise is uncommon without preexisting or concurrent causes of muscle weakness.
- Precautions
  - Dantrolene is an antiarrhythmic, increasing atrial and ventricular refractory periods and increasing action potential duration. Administration of dantrolene in the presence of calcium channel blockers may cause hyperkalemia and profound depression of cardiac contractility, but administration for a suspected MH episode should not be held for this reason.

ADDITIONAL TREATMENT

General Measures

- The definitive treatment of a known or suspected MH episode is administration of dantrolene as soon as possible and immediate discontinuation of triggering agents. Ventilation with high-flow O_2 through the anesthesia ventilator should be sufficient, as the concentration of inhalational agent in this ventilator will be less than that in the patient.
- Symptomatic Treatment
  - Standard treatment of hyperkalemic dysrhythmias should be initiated. Hyperventilation to approach normocarbia, and bicarbonate or tris(hydroxymethyl)-aminomethane (THAM) administration for initial treatment of the metabolic and respiratory acidosis should be titrated. Hyperthermia should be treated with surface cooling, gastric and intraperitoneal lavage, ice packs in the axillae and groin, and intravascular administration of cold solution. Treatment should be continued until the core temperature is <38.5.
  - Aggressive hydration to prevent myoglobin-induced renal failure should be started and monitored by urine output and central venous pressure (CVP).
  - If urine pH is low, consider alkalinization (2,5)[B].

SURGERY/OTHER PROCEDURES

When an episode occurs during surgery, the procedure should be terminated as soon as possible.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Patients transferred should be treated based on the above guidelines.

Admission Criteria

- Patients should be closely monitored until all vital signs and laboratory parameters have been normal for 24 hours. Speed of recovery is dependent on severity of the episode, rapidity of treatment, and development of other sequelae.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- CK measurements are recommended 6, 12, and 24 hours after the initial episode; CK often peaks 24–36 hours after treatment of MH. CK values >20,000 are almost always associated with an MH episode or other severe myopathy (2)[B].

PATIENT EDUCATION

- Patients who have an MH episode should be counseled regarding the seriousness and heritability of their condition and should wear a "Med-alert" bracelet to inform other health-care professionals. First-degree relatives should be considered susceptible (2)[B].

PROGNOSIS

- Administration of dantrolene and cessation of triggering agents halts the syndrome. Hyperkalemia, associated arrhythmias, and respiratory/metabolic acidosis typically resolve. If rhabdomyolysis was extensive, there may be muscle pain and weakness for weeks to months after resolution of acute MH (2)[B].

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4. http://medical.mhaus.org/PubData/PDFs/dx_testing_options.pdf
5. http://medical.mhaus.org/PubData/PDFs/treatmentposter.pdf

ADDITIONAL READING

- The Malignant Hyperthermia Association of the United States. Phone: 203-847-0407, website www.mhaus.org, 24-hour hotline 800-MH-HYPER

CODES

ICD9

995.86 Malignant hyperthermia

CLINICAL PEARLS

- MH is a rare but serious illness triggered in susceptible individuals by all potent inhaled anesthetic agents and succinylcholine.
- Definitive treatment requires immediate discontinuation of triggering agents, administration of dantrolene, and supportive therapy. The mortality of MH is high when untreated or treated late in its course.
- Counseling of family members regarding their potential susceptibility is a priority.

M

McARDLE'S DISEASE (MYOPHOSPHOYLASE DEFICIENCY, GLYCOGENOSIS TYPE V)

Adam D. Quick, MD

BASICS

DESCRIPTION

McArdle's disease is a metabolic myopathy caused by an inherited deficit of the enzyme myophosphorylase.

EPIDEMIOLOGY

- Incidence
  - This is a genetic disorder present from birth. However, individual variability in severity and symptom onset exists. Most patients experience problems in childhood, but adult onset is not unusual.
  - A distinct variant occurs with severe generalized weakness soon after birth.
- Prevalence
  - Limited data has been published, but it is a rare disorder estimated to be present in 1:100,000 to 1:350,000, depending on the population studied.

RISK FACTORS

- Women may be more severely affected and, possibly, more likely to have respiratory muscle involvement according to some series.
- Sedentary lifestyle is associated with more profound symptoms.

Genetics

- McArdle's is inherited in an autosomal recessive manner. The *PYGM* gene codes for myophosphorylase and has been mapped to chromosome 11q13. Multiple mutations have been described that are population specific. The most common in North America is pArg50X. There is no clear genotype–phenotype correlation for the various mutations.
- Occasionally, heterozygote individuals may be symptomatic.

PATHOPHYSIOLOGY

- Myophosphorylase initiates breakdown of glycogen by removing 1,4-glucosyl residues from outer branches of the glycogen molecule. This liberates glucose-1-phosphate which is converted into glucose-6-phosphate which undergoes glycolysis.
- This limitation in the ability to generate glucose from glycogen reduces the capacity for anaerobic glycolysis needed for isometric exercise and blocks aerobic glycogen use with the resultant shortage in pyruvate and thus acetyl-CoA needed for the Kreb's cycle. Oxidative phosphorylation is reduced and exercise above ~50% of VO_2 max is impaired.
- Ultimately, the consequence is that patients with McArdle's disease are unable to utilize muscle glycogen stores.
- Pathophysiology of the contractures and myoglobinuria seen in McArdle's patients is not completely understood.

ETIOLOGY

- McArdle's disease is caused by lack of the enzyme myophosphorylase.

COMMONLY ASSOCIATED CONDITIONS

- Rhabdomyolysis and myoglobinuria
- Vitamin B6 deficiency
- Gout—due to accelerated degradation of muscle purine nucleotides.

DIAGNOSIS

HISTORY

- Patients typically present with symptoms of exercise intolerance and early fatigue, myalgias, cramps (technically these are contractures), myoglobinuria, muscle stiffness, and, sometimes, fixed weakness affecting proximal muscles as the disease progresses.
- Myoglobinuria and muscle swelling may occur following vigorous exercise.
- Symptoms improve with rest and are often precipitated by either brief, intense, isometric exercises such as lifting heavy objects, or less intense but sustained aerobic exercise such as jogging or biking.
- Symptoms may be less severe after ingestion of carbohydrates.
- A characteristic feature is the "second wind" phenomenon. This is a marked improvement in tolerance of aerobic exercise after a brief rest following the initial onset of muscle pain.
  - The cause of this phenomenon is attributed to vasodilatation within the muscle increasing availability of circulating glucose and to enhanced utilization of fatty acids.
- McArdle's disease is generally not life threatening and most patients self-limit the amount and intensity of exercise to avoid severe muscle pain.
- The severity of symptoms can be highly variable between individuals.
- Many patients diagnosed as adults recall myalgias and early fatigability during their school-age years.

PHYSICAL EXAM

- Physical exam may reveal mild muscle wasting predominantly in the paraspinal, periscapular, and proximal upper limb muscles.
- Mild weakness can be present in the axial and limb girdle muscles most often in patients >40 years of age.
- Muscle hypertrophy has also been described involving the deltoids, biceps, calves, and thighs in some patient series.
- Due to poor exercise tolerance, many individuals are overweight or obese.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum CK is elevated in most patients even at rest (>200 in almost all affected individuals and >1000 in ~50%).
- Forearm exercise test: A needle is placed in an antecubital vein and baseline serum ammonia and lactate levels are drawn. The patient is asked to perform repetitive maximal grip strength for 1.5 seconds over the course of 1 minute. Following the exercise, venous blood samples are re-drawn and tested for lactate and ammonia concentrations at 1, 2, 4, 6, and 10 minutes. In normal individuals, venous lactate levels should increase 3- to 5-fold. In patients with myophosphorylase deficiency, lactate levels do not increase. The ammonia level is used as a control to ensure that the subject has exercised adequately.
- Electromyography in McArdle's disease demonstrates myotonic potentials, fibrillations, and positive sharp waves in about half of the patients.
- Muscle biopsy is often used to make the diagnosis. This may reveal focal areas of subsarcolemal and intermyofibrillar accumulations of glycogen. Histochemical staining for myophosphorylase shows no activity in most cases. However, if there are significant numbers of regenerating fibers, false positive results due to the presence of fetal isozyme immunologically different from mature myophosphorylase can occur. This explains the importance of not obtaining muscle biopsy immediately following rhabdomyolysis.
- Diagnosis can be confirmed genetically by sequencing the *PYGM* gene for mutations. However, screening for the most common pArg50X and pGly205Ser mutations is more cost effective in North American populations (1,2)[A].

Imaging

Initial approach

- Clinical imaging studies are not useful in diagnosis.
- Research-based studies using P-31 magnetic resonance spectroscopy demonstrate significantly lower concentrations of ATP and phosphocreatine in patients than in healthy controls following submaximal isometric calf exercise.

Pathological Findings

- Refer to muscle biopsy results noted above.

DIFFERENTIAL DIAGNOSIS

- Other metabolic myopathies including enzyme deficiencies of carbohydrate metabolism:
  - Phosphofructokinase
  - Phosphorylase b kinase
  - Phosphoglycerate kinase
  - Phosphoglyceromutase
  - Lactate dehydrogenase
  - β-enolase
  - Debrancher enzyme
- Lipid metabolism:
  - Carnitine palmitoyltransferase II
- Purine metabolism
  - Myoadenylate deaminase
- Other diseases with muscle involvement, such as: mitochondrial myopathies, hyper- or hypothyroidism, and hypoparathyroidism
- Somatoform disorders
- Dystrophinopathies

TREATMENT

MEDICATION

First Line

- No effective gene- or enzyme-replacement therapy is yet available although viral vectors have transiently restored myophosphorylase activity in sheep.

Second Line

- Several small studies have assessed various pharmacologic interventions including administration of gentamycin, dantrolene, D-ribose, glucagon, verapamil, high- and low-dose creatine, oral branched-chain amino acids, ACE inhibitors, and vitamin B6, all without substantial benefit (3)[A].
- Because 80% of the total body pool of vitamin B6 is in skeletal muscle bound to myophophorylase, supplementation of B6 can be important in preventing deficiency.

ADDITIONAL TREATMENT

General Measures

- Aerobic exercise training in a supervised and moderated fashion can yield a significant improvement in work capacity. Examples include brisk walking and light cycling.
- Isometric/anaerobic exercises should be avoided as these are more likely to provoke rhabdomyolysis.
- Ingestion of sucrose or glucose prior to planned exercise can improve tolerance as can teach strategies to achieve a "second wind."

Issues for Referral

- Any child with characteristic symptoms particularly causing poor performance in gym classes or extracurricular sports should be considered for referral to a neurologist and not be simply attributed to "growing pains."

Additional Therapies

- Use of statin medications may increase the likelihood of rhabdomyolysis in patients with McArdle's disease and should be used cautiously under close supervision.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- In general, admission is only needed in cases of rhabdomyolysis for fluid resuscitation and temporary dialysis if needed.

ONGOING CARE

DIET

- A diet high in complex carbohydrates can ensure that sufficient blood glucose is always available.
- Ingestion of 30–40 g of simple carbohydrate immediately preceding exercise.

PATIENT EDUCATION

- Patients should be educated about the need to avoid strenuous isometric and vigorous aerobic exercises.
- Muscular Dystrophy Association is a good resource for information: www.mdausa.org

Pregnancy Considerations

- Vaginal delivery is likely a better option than C-section to prevent any potential problems associated with anesthesia.

PROGNOSIS

- Individuals with McArdle's disease can live a normal life span but are at risk for obesity, vitamin B6 deficiency, and recurrent episodes of rhabdomyolysis and subsequent acute renal failure.

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See Also (Topic, Algorithm, Electronic Media Element)

- Muscle cramps and pain
- Metabolic myopathy
- Rhabdomyolysis

CODES

ICD9

271.0 Glycogenosis

CLINICAL PEARLS

- One of the most common metabolic myopathies to cause recurrent myoglobinuria.
- "Second wind" phenomenon is highly suggestive of the diagnosis.
- Supervised aerobic training can yield significant improvement in exercise capacity and isometric/anaerobic exercises should be avoided.

MÉNIÈRE SYNDROME

John G. Oas, MD

BASICS

DESCRIPTION

Ménière syndrome (MS) is a peripheral vestibular disorder characterized by symptoms and signs without a defined pathogenesis. Symptoms of otogenic distress include unilateral hearing loss with tinnitus *and* attacks of objective vertigo. Signs include documented fluctuation (loss – recovery – loss) of low-frequency sensorineural (SN) hearing with greatly diminished speech recognition and eventually a unilateral loss of peripheral vestibular function ipsilateral to the hearing loss.

EPIDEMIOLOGY

- Age: Mean age of onset is 42–46 with a wide distribution rarely in children or elderly
- Sex: No preponderance

Incidence

15 cases per 100,000

Prevalence

200 cases per 100,000

RISK FACTORS

- Migraine
- Trauma (labyrinthine concussion, acoustic trauma, temporal bone fracture)
- Systemic illness (autoimmune inner ear disease, Cogan's syndrome, polyarteritis nodosa)
- Infection (syphilis, alpha-human herpesviridae)
- Neoplasia (macroglobulinemia, leukemia, von Hippel–Lindau disease)

Pregnancy Considerations

Pregnancy is neither protective nor preventive. The use of daily diuretics in pregnancy is not advised (Category C) unless the disorder is poorly controlled and use of the medication has provided benefit in the past.

Genetics

Familial clusters have been described yet exclusion from migraine was not performed.

PATHOPHYSIOLOGY

No definitive pathophysiology

ETIOLOGY

Described by Prosper Ménière in 1861, no defined etiology has emerged[1]; thus, its designation as a syndrome rather than a disease. The syndrome may have several separate etiologies, with symptoms and signs merely the expression of labyrinthine distress and destruction. Leading candidates for pathogenesis include alpha-human herpesviridae infection of the temporal bone, labyrinthine trauma, and autoimmune disorders of the endolymphatic sac. Syphilis has been implicated as a possible cause. Rarely an endolymphatic sac tumor (papillotubular neoplasia) causes Ménière syndrome.

DIAGNOSIS

HISTORY

According to the 1995 guidelines[4], the three major symptoms are vertigo, hearing loss, and tinnitus. Vertigo criteria include recurrent, well-defined episodes of spinning or rotation, lasting from 20 minutes to 24 hours, accompanied by nystagmus during the vertigo attacks, commonly accompanied by nausea and vomiting but no neurologic symptoms. Hearing loss criteria include audiometrically documented SN hearing deficits; must fluctuate; progress over time. Tinnitus criteria include variable, low pitched, and louder during attacks, unilateral on the affected side, subjective type (examiner cannot hear the sound). Diagnosis can be specified from possible to certain: *Possible* – vertigo without hearing loss; or SN hearing loss, fluctuating or fixed, with disequilibrium without vertigo. *Probable* – one definitive episode of vertigo with hearing loss on at least one occasion with tinnitus or aural fullness in the designated ear. *Definite* – two or more episodes of vertigo with hearing loss on at least one occasion with tinnitus or aural fullness in the designated ear. *Certain* – meeting definite specification with histopathology confirmation. Proper diagnosis requires careful exclusion of common competing etiologies, especially vestibular migraine (migraine-associated vertigo, migrainous vertigo, migraine vestibulopathy) and recurrent vestibular ganglionitis (viral labyrinthitis, vestibular neuronitis). The diagnosis of Ménière syndrome becomes more defined as the disorder progresses to produce losses of hearing and peripheral vestibular function. Early, when destruction to the labyrinth is minor, spontaneous remission is common. The simultaneous appearance of bilateral signs and symptoms with rapid deterioration in bilateral hearing loss and tinnitus strongly implicates a diagnosis of autoimmune inner ear disease rather than Ménière syndrome. Lack of hearing loss despite multiple recurrent attacks of vertigo suggests recurrent vestibular ganglionitis, unless temporally associated with migraine headache, meeting International Headache Society classification, where a diagnosis of vestibular migraine is more likely. Tumarkin's otolithic catastrophes (rare in definite Ménière syndrome) are extremely brief attacks that throw the patient downward without any loss of consciousness and without the perception of falling. Lermoyez's phenomenon is a transient recovery of hearing loss after a vertigo event.

PHYSICAL EXAM

Generally normal except during an attack; later in course may have hearing loss.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

None. Exclusionary tests for autoimmune disease and syphilis are advised prior to considering vestibular ablative treatment.

Imaging

Initial approach

None. Both high-resolution (3T or higher) MRI of brain and internal auditory canals with or without contrast and high-resolution thin-slice CT imaging of the temporal bone are advised to exclude structural pathology.

Diagnostic Procedures/Other

- Audiogram (pure tone threshold audiometry, speech recognition or word discrimination score): When repeated many times during the course of the disease, this test provides the most diagnostic certainty. A fluctuating SN hearing loss (pure tone threshold reduction of more than 15 dB) occurs in the lowest frequencies (250–2,000 Hz) early in the course of the disorder. Also reductions in speech or word recognition scores (% words correctly heard) are worse than predicted by the degree of tone threshold reduction. This loss stops fluctuating with progression to profound SN hearing loss across all frequencies late in the course of the disorder.
- Electrocochleography (ECochG): An audiometric electrophysiological test that is a poor screening procedure because of less than optimal sensitivity and selectivity. An elevated ratio of the summating potential to action potential of the auditory evoked response is considered positive. This is helpful in situations where other tests have failed to clarify the diagnosis.
- Vestibular testing (caloric tests, videonystagmography, rotational chair tests): During a vertigo event, videonystagmography can document the nystagmus necessary for the diagnosis, but it is difficult to arrange such testing on demand in a sickened patient. Interictally, videonystagmography can identify the nystagmus of either a recovering peripheral vestibular loss (fast component directed toward the ear involved) or an uncompensated peripheral loss (fast component directed away from the ear involved). A peripheral loss can be documented by caloric testing (alternating bithermal water irrigations) later in the course. Rotational chair testing must support the videonystagmography findings or caloric testing to confirm a unilateral loss of peripheral vestibular function. It is most helpful to identify bilateral peripheral losses (relative contraindication) prior to vestibular ablative treatment measures.

Pathological Findings

Endolymphatic hydrops should be considered only as a histologic marker rather than a cause.

DIFFERENTIAL DIAGNOSIS
Early in the course of Ménière syndrome, when episodic vertigo may be the only symptom, many inner ear and neurologic disorders can also cause episodic vertigo, including vestibular migraine[2], recurrent vestibular ganglionitis[3], benign paroxysmal positional vertigo, sporadic and familial episodic ataxia, vertebrobasilar ischemic disease, eighth nerve root entry zone neurovascular compression, symptomatic Arnold–Chiari malformation, hyperviscosity syndromes, endolymphatic sac tumor, brainstem neoplasia, epilepsy, and otosyphilis. Tumarkin's otolithic catastrophes can be confused with myoclonic-astatic epilepsy (rare in adults).

TREATMENT

MEDICATION
First Line
- All medications are used off-label (FDA specifications) and are either empirical or symptomatic. None are curative.
- Symptomatic control of the vertigo event: Sublingual Ativan (generic formulations of lorazepam are not useful for SL usage) at the start of each episode allows for the rapid parenteral absorption of a benzodiazepine and reduction in the intensity of the vertigo event. The dose should be titrated to the lowest effective dose.
- Symptomatic control of nausea and vomiting: Rectal administration of an antiemetic medication (promethazine, prochlorperazine) should be used to prevent the risks of esophageal rupture, dehydration, and electrolyte depletion from protracted vomiting. The dose should be titrated until the lowest effective dose is established.
- Diuretics: This approach as medical treatment is universal. Avoid loop diuretics (furosemide, etc.) due to ototoxicity risk to the opposite ear.
- Antivirals: Treatment with daily doses of antiviral medication with proven efficacy against the alpha-human herpesviridae, implicated in the pathogenesis of some cases with Ménière syndrome, is not universal. Acyclovir 400 mg twice daily, famciclovir 250 mg twice daily, or valacyclovir (prodrug of acyclovir) 1,000 mg once daily are taken for 1 year in the same manner as used in genital herpes simplex virus suppression.

Second Line
Betahistine: Of varying efficacy with conflicting results from multiple trials conducted worldwide. It is not a FDA-approved pharmaceutical and must be provided by a compounding pharmacy in the US. Dosing should be titrated over several days from 16 to 48 mg every 6 hours. If no effect is seen within a couple of weeks, benefit is unlikely.

ADDITIONAL TREATMENT
General Measures
Vestibular rehabilitation physical therapy is advised whenever an uncompensated peripheral vestibular loss develops or after vestibular ablative treatment.

Additional Therapies
See Complementary and Alternative Therapies.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
A 1,000 mg daily maximum sodium-restricted diet prior to considering vestibular ablative treatment measures. Allergy desensitization and dietary restriction from allergens in cases with comorbid allergies.

SURGERY/OTHER PROCEDURES
- Endolymphatic sac decompression/shunting: This surgical approach is often considered in medically refractive cases where vestibular ablative treatment measures are contraindicated or not contemplated. There is no consensus among neurotological surgeons regarding its use in the control of episodic vertigo.
- Intratympanic gentamicin: This intervention requires a myringotomy with local anesthesia. Several protocols have shown good (80–95%) efficacy in vertigo cessation. Hearing loss is a complication and increases significantly with the number and frequency of the dosage, especially in older patients. This is the most popular among the vestibular ablative treatment measures.
- Selective vestibular nerve section: Used in cases where intratympanic gentamicin has failed to control the episodic vertigo and hearing preservation is desired. This procedure has the highest efficacy of all vestibular ablative treatments with the lowest risk to hearing loss as a near term result of the intervention. However, it cannot control the process of eventual hearing destruction and chronic tinnitus. The procedure results in a permanent peripheral vestibular loss.
- Transmastoid labyrinthectomy: Used when intratympanic gentamicin has failed to control episodic vertigo. Craniotomy is not required, and there are fewer perioperative complications. Both hearing and vestibular function are irreparably lost, and tinnitus does not resolve with this procedure.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Hospital admission is advised when the course suggests alternative diagnoses, for control of autonomic symptoms, for rehydration or electrolyte repletion, or when surgical vestibular ablative treatment requires medical stabilization.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Serial audiograms document fluctuations in hearing essential to establish the diagnosis. Vertigo diaries to assess symptomatic management and determine the timing of vestibular ablative treatment. Regular office visits to monitor the effects of medical management and to assess the development of uncompensated vestibular peripheral loss.

DIET
Nutritional counseling for a low-sodium diet.

PATIENT EDUCATION
Emphasize lack of pathophysiology to confirm the cause and the absence of a cure, and provide hope that remissions are common.

PROGNOSIS
Remission of varying duration is common in most cases. Atypical presentations can evolve into more typical symptoms and signs over time. Cure is not possible, and treatments do not alter the highly variable progression to varying degrees of permanent hearing loss, constant tinnitus, and peripheral vestibular loss. The disease may progress to involve both ears. Vestibular ablative treatments can achieve up to 95% cessation of vertigo events but usually result in a permanent peripheral vestibular loss and do not prevent progression of hearing loss nor resolve the tinnitus.

COMPLICATIONS
Hearing loss

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See Also (Topic, Algorithm, Electronic Media Element)
- Vestibular migraine
- Vestibular ganglionitis
- Vertigo
- Vestibular loss
- Tinnitus
- Hearing loss/deafness

CODES

ICD9
386.00 Ménière's disease, unspecified

CLINICAL PEARLS
Treatment is symptomatic, not curative, and mostly empirical. Ultimately vestibular ablative treatment measures may be needed to control the vertigo.

MENINGITIS, ACUTE BACTERIAL

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BASICS

DESCRIPTION

Acute bacterial meningitis (ABM) is an inflammation of the meninges due to bacterial infection, which results in neurologic morbidity and high mortality without appropriate treatment.

EPIDEMIOLOGY

Incidence

- During 2003–2007, among 1670 cases reported, *Streptococcus pneumoniae* was the predominant infective species (58.0%), followed by *S. agalactiae* (Group B Streptococci [GBS]; 18.1%), *Neisseria meningitidis* (13.9%), *Haemophilus influenzae* (6.7%), and *Listeria monocytogenes* (3.4%).
- An estimated 4,100 cases and 500 deaths from ABM annually in the U.S. during 2003–2007.
- According to CDC, the incidence of ABM dropped by 31% from 2 to 1.38 cases per 100,000 between 1998 and 2007.
  - The average age increased to 41.9 years.
  - The incidence was highest among blacks and children under 2 months old.

Prevalence

- Sex: Males and females are equally affected.
- The risk of meningitis has decreased among young children with the success of pneumococcal and Hib conjugate vaccines.

RISK FACTORS

- Cases of ABM are generally sporadic, though close contact may play a role in some cases.
- College students living in dormitories, military personnel and children in childcare facilities.
- People working with domestic animals, ranchers, dairy farmers for *Listeria meningitis*.
- Children under age 2 who have not received Hib vaccine are at risk of ABM from Hib.
- Other risk factors may include the following:
  - Closed head injury with skull fracture or disruption of the cribriform plate.
    - Parameningeal infections such as sinusitis, chronic otitis, and mastoiditis.
    - Anatomic defects (pilonidal sinuses, meningomyeloceles, meningeal disruption).
    - Sickle cell anemia and splenectomy—meningitis due to encapsulated organisms.

Pregnancy Considerations

Pregnant women are at an increased risk of *Listeria meningitis*. The unborn baby of a pregnant woman with listeriosis is also at risk.

Genetics

Complement deficiency is a risk factor for meningococcal disease.

GENERAL PREVENTION

- There are three different types of vaccines that offer protection against many of the common strains of *H. influenzae*, type B (Hib), *N. meningitidis*, and *S. pneumoniae*
  - Hib vaccine, routine childhood immunization.
  - Meningococcal vaccine (MCV4), first dose at 11–12 years old with booster at 16 years; also recommended for high-risk children aged 2–10.
  - Pneumococcal vaccine (PCV-13 for children and PPSV in adults), part of routine childhood immunizations. Also for ages >65, young people with chronic health problems, immunocompromised, and those who smoke or have asthma.
- Close contacts of patient with meningococcal meningitis may need prophylaxis with
  - Rifampin 600 mg PO b.i.d. or
  - Ciprofloxacin 500 mg PO one dose or
  - Ceftriaxone 250 mg IM one dose

PATHOPHYSIOLOGY

- ABM pathogens generally colonize the nasopharyngeal mucosa of the host, enter the intravascular space, cross the blood–brain barrier, and multiply aggressively in the CSF.
- There is a paucity of antibody and complement in the CSF, resulting in inefficient phagocytosis of the bacteria. Cytokines contribute to brain edema and elevated intracranial pressure.
- Inflammatory reaction and immune response to the invading bacterial pathogen result in the manifestations and complications of ABM rather than from direct bacteria-induced tissue injury.

ETIOLOGY

- The most common pathogens responsible for ABM vary by age group. Among neonates, group B streptococcus (*S. agalactiae*) is most common. While *H. influenzae* type B (Hib) was formerly the most common among children of ages 1 month to 4 years, widespread use of the Hib vaccine has dramatically reduced the incidence of this pathogen; *S. pneumoniae* (pneumococcus) and *N. meningitidis* (meningococcus) are now the predominant pathogens in this age group. In older children (5–18 years) and adults, pneumococcus and meningococcus are most common, while pneumococcus, *L. monocytogenes*, and Gram-negative bacilli are most common in adults >50 years of age.
- Some patients with neurosurgery, head trauma, or CSF shunt are at risk for ABM from *Staphylococcus aureus*, coagulase-negative staphylococcus, Gram-negative bacilli (including Pseudomonas), as well as pneumococcus.

DIAGNOSIS

HISTORY

- Symptoms may include fever, headache, stiff neck, confusion, delirium, seizures, nausea, vomiting, and photophobia.
- Classic clinical triad of meningitis is fever, headache, and nuchal rigidity.

PHYSICAL EXAM

Some of the findings that may be present include nuchal rigidity, Kernig's sign, Brudzinski's sign, focal neurological signs, papilledema, skin rash (maculopapular, petechial, or purpuric).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Initial lab tests comprise routine cell counts, chemistries and Gram's stain/culture of CSF; baseline blood work: CBC and differential, blood cultures, serum electrolytes and glucose, liver function tests, and an HIV test.

Follow-up & special considerations

Follow-up of cultures and antimicrobial susceptibility tests is critical to assure that adequate therapy is being delivered.

Imaging

Initial approach

- Adult patients who should undergo CT head before lumbar puncture (LP) include (B-II):
  - Immunocompromised hosts
  - History of CNS disease
  - New onset seizure
  - Papilledema
  - Abnormal level of consciousness
  - Focal neurological deficit
- If no mass effect is seen on imaging, immediate lumbar puncture should be done.

Follow-up & special considerations

If new neurological symptoms or signs develop, repeat imaging might be obtained.

Diagnostic Procedures/Other

CSF obtained by LP is the most important and accurate diagnostic tool. Opening pressure, Gram stain (A-III), CSF culture, protein, glucose, and cell count/differential should be done. Latex agglutination for bacterial antigens may be useful if the patient has had prior antibiotic therapy (B-III). Gram stain is useful for tailoring antibiotic therapy. Prior antibiotic therapy may make it difficult to interpret.

Pathological Findings

Opening pressure is typically elevated. In 80% of cases, the organism is visible on Gram stain. There is usually a neutrophilic pleocytosis (>1,000 WBC cells/mm^3). CSF protein is almost always elevated, and hypoglycorrhachia is common. CSF may rarely be normal, especially in neonates, immunocompromised patients, or very early in the course of disease.

DIFFERENTIAL DIAGNOSIS

- Infectious etiologies: Meningitis (viral, fungal, mycobacterial), encephalitis, brain abscess, primary HIV infection)
- Noninfectious etiologies:
  - Benign or malignant brain tumor
  - Cerebrovascular accident
  - Sarcoidosis, systemic lupus erythematosus, Wegener's granulomatosis, CNS vasculitis
  - Arachnoiditis
  - Migraine
  - Drugs, including NSAIDs, OKT3, and trimethoprim/sulfamethoxazole

TREATMENT

MEDICATION

First Line

- Empiric antibiotics (A-III)
  - Age <1 month: Ampicillin plus cefotaxime or aminoglycoside (to be dosed for age in days)
  - Age 1–23 months: Third generation cephalosporin (TGC) such as cefotaxime or ceftriaxone plus vancomycin (dosed for age)
  - Age 2 to <50 years: TGC such as cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h plus vancomycin 15 mg/kg IV q12h
  - Age 50 and above: Ampicillin 2 g IV q4h plus a third-generation cephalosporin such as cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h plus vancomycin 15 mg/kg IV q12h
  - Patients with impaired cellular immunity: Ampicillin 2 g IV q4h plus ceftazidime 2 g IV q8h +/− vancomycin 15 mg/kg IV q12h
  - Associated basilar skull fracture: TGC such as cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h plus vancomycin 15 mg/kg IV q12h
  - Patients with penetrating head trauma, neurosurgical patients, or with a CSF shunt: Vancomycin 15 mg/kg IV q12h plus ceftazidime 2 g IV q8h or cefepime 2 g IV q8h or meropenem 2 g IV q8h
- Contraindications: History of allergic reaction

Second Line

Alternative drugs—space is too limited to list alternative regimens for each pathogen; infectious disease consultation is recommended.

ADDITIONAL TREATMENT

General Measures

- Antibiotic therapy should initially be directed at the most likely pathogens, then tailored specifically to available Gram stain and culture data. Infectious disease (ID) specialists should be consulted, as antibiotic resistance patterns, especially of *S. pneumoniae* and Hib, vary widely by region.
- In infants and children with ABM due to known or suspected Hib, dexamethasone needs to be started 10–20 minutes prior to antibiotics (A-I).
- In adults with suspected or proven pneumococcal meningitis, dexamethasone is recommended 10–20 minutes before, or at least concomitant with, first dose of antibiotics (A-I).
- Adjunctive dexamethasone is unlikely to improve outcome in infants, children, and adults who have already received antibiotics (A-I).

Issues for Referral

ID consultation is recommended.

Additional Therapies

- Close monitoring is essential, and many patients may need endotracheal intubation for airway protection. Dexamethasone, hyperosmolar agents, or hyperventilation may be needed to treat elevated intracranial pressure.
- Physical therapy for rehabilitation if any focal neurological deficits develop.
- Symptomatic treatment includes management of fevers, antiepileptic drugs for secondary seizures, analgesics for headache, and hydration.

SURGERY/OTHER PROCEDURES

Intraventricular and intrathecal antibiotics are occasionally necessary in CSF shunt infections that are difficult to eradicate or in patients who cannot tolerate surgical removal of device (A-III).

IN-PATIENT CONSIDERATIONS

Initial Stabilization

ABM is an emergency; diagnostic workup and therapy should be initiated without delay.

Admission Criteria

- Patients are admitted for parenteral antibiotics and careful monitoring.
- Duration of therapy is typically 7 days for Hib and *N. meningitidis*, 10–14 days for *S. pneumoniae*, 14–21 days for GBS, 21 days for Gram-negative bacilli, and 21 days or more for *L. monocytogenes*.

Nursing

Close monitoring for neurological decline or changes in mental status is important.

Discharge Criteria

Most ABM patients are hospitalized for the duration of therapy with rare exceptions.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Once hemodynamically and neurologically stable, close monitoring is not indicated.
- Repeat CSF analysis is not required if the patient has responded to antimicrobial therapy.
- Repeat CSF analysis should be performed if:
  - No improvement after 48 hours of appropriate antimicrobial therapy (A-III)
  - Pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains, also treated with dexamethasone
  - Neonate with meningitis due to Gram-negative bacilli to document CSF sterilization to determine duration of antimicrobial therapy (A-III)

PATIENT EDUCATION

- Information is available on NIH MedlinePlus:
  - http://www.nlm.nih.gov/medlineplus/meningitis.html
  - http://www.nlm.nih.gov/medlineplus/tutorials/meningitis/htm/index.htm

PROGNOSIS

Overall morbidity in adults in 1995 was 25%. In another recent study, 61% of children had developmental delay and neurologic sequelae after Gram-negative bacillary meningitis. These two reports emphasize the need for the rapid diagnosis and treatment with appropriate antibiotics in patients suspected of having ABM. Despite appropriate therapy, in many of these patients there will be high morbidity and a variety of neurologic sequelae. Many will require physical and occupational therapy after their illness, and some will have significant neurologic deficits.

COMPLICATIONS

- There is significant mortality associated with bacterial meningitis even with treatment.
- Neurological complications include seizures, impaired mental status and cognition, focal deficits, cerebral edema/increased intracranial pressure, and sensorineural hearing loss.

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See Also (Topic, Algorithm, Electronic Media Element)

- Viral meningitis
- Aseptic meningitis
- Meningoencephalitis and cryptococcal

CODES

ICD9

- 027.0 Listeriosis
- 320.7 Meningitis in other bacterial diseases classified elsewhere
- 320.9 Meningitis due to unspecified bacterium

CLINICAL PEARLS

Acute bacterial meningitis is a medical emergency; evaluation and therapy should be initiated without delay. Prompt administration of empiric antibiotics is critical to minimize neurologic morbidity and mortality.

MENINGITIS, ASEPTIC

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BASICS

DESCRIPTION
Aseptic meningitis syndrome is the clinical syndrome of findings (signs, symptoms, and laboratory abnormalities) consistent with meningitis but with negative Gram stain and culture of the CSF.

EPIDEMIOLOGY
Incidence
- Estimated to be around 5–15 cases per 100,000 per year in the UK.
  - Seasonal variation exists for certain viral causes (enterovirus and arbovirus are more common in the summer, lymphocytic choriomeningitis virus [LCMV] in the fall/winter, and mumps in winter/spring).

RISK FACTORS
Dependent on exposure to infected individuals, animal/insect vectors, and medications, as well as vaccination history and level of immunosuppression.

GENERAL PREVENTION
Good hand hygiene and safer sex practices are always important.

PATHOPHYSIOLOGY
- For infectious diseases, entrance into the CSF is the common step, triggering the inflammatory response. Means of entering the CSF can be various, and include:
  - Enteroviruses invade hematogenously.
  - Mumps, measles, Cytomegalovirus (CMV), and Epstein–Barr virus (EBV) are carried by leukocytes.
  - Polio, herpes simplex virus (HSV), and varicella zoster virus (VZV) travel through nerves.

ETIOLOGY
- Viral infection is the most common cause with enteroviruses (e.g., echovirus, coxsackie, and polio) being identified as the source about 75% of the time. Other common viruses include arboviruses (in the US, the most common arboviruses are California virus, Saint Louis Encephalitis virus, Eastern equine encephalitis virus, Western equine encephalitis virus, Venezuelan equine encephalitis virus, West Nile virus, and Colorado tick fever virus), HIV, HSV-2, LCMV, and mumps.
  - Less frequent viral causes include CMV, EBV, VZV, HSV-1, adenovirus, and rabies virus.
- Differential diagnosis for non-viral causes includes partially treated bacterial meningitis, epidural/subdural abscess, tuberculosis, syphilis, leptospirosis, and Lyme disease.
  - Less frequent non-viral causes include fungal infections, parasites, malignancy, procedure-related, and autoimmune disease (such as systemic lupus erythematosus).
  - Drug-induced aseptic meningitis is a diagnosis of exclusion. Most cases of this have been associated with NSAIDs, antibiotics (trimethoprim/sulfamethoxazole primarily), and antibody therapies (including IVIG, and monoclonal antibodies such as muromonab-CD3).

DIAGNOSIS

HISTORY
- Patients typically complain of acute onset of fever, headache, neck stiffness, nausea, and vomiting. Seizures may be a less common presenting symptom due to meningitis. The differential diagnosis can be altered by exposure to sick contacts, TB, rodents, and insect/tick bites. Sexual history, travel, previous vaccinations, medication use, and weight loss are all relevant.
  - Fatigue may be present, but altered mental status is more consistent with encephalitis.

PHYSICAL EXAM
Particular attention should be paid to meningismus, photophobia, focal neurologic deficits, altered mental status, and fever. Rash is associated with meningococcal infection, primary HIV infection, syphilis, and Rocky Mountain spotted fever. Lymphadenopathy can be a sign of HIV or malignancy. West Nile virus can cause a flaccid paralysis. Genital ulcers raise suspicion for HSV-2 infection and syphilis.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
CBC with differential, chemistries, liver function tests, 2 sets of blood cultures, and HIV antibody with confirmatory Western Blot (if indicated).

Follow-up & special considerations
Other tests that may be useful based on history and physical exam include quantitative HIV RNA PCR (viral load), RPR, HSV PCR, PPD or interferon gamma release assay for TB, and PCR/antigens/serologies for other viral, bacterial, fungal, and protozoan pathogens. Occasionally, paired acute and convalescent serologies can be helpful in diagnosing the etiology of infectious meningitis.

Imaging
Initial approach
Head CT is indicated if the patient is immunocompromised, has a history of CNS disease or seizure within the past week, or displays papilledema, focal neurologic deficit, or altered mental status.

Follow-up & special considerations
In cases of suspected bacterial meningitis, antibiotics should not be delayed if lumbar puncture (LP) or head CT cannot be performed immediately.

Diagnostic Procedures/Other
- LP is key to establishing the diagnosis. Opening pressure should be recorded, and fluid tested for cell count and differential, protein, glucose, gram stain, and culture for bacteria, viruses, and fungi. Aseptic meningitis CSF typically has a WBC over 500 with lymphocytic predominance, protein less than 80, and normal glucose, and no organisms seen on gram stain. CSF can have a neutrophil predominance within the first 48 hours of symptoms.
- Based on clinical suspicion, further CSF testing can be performed. This can be facilitated by saving at least one tube of CSF for such testing.

DIFFERENTIAL DIAGNOSIS
- Infectious
  - Bacterial meningitis which may be partially treated
  - Viral meningitis
  - Viral encephalitis
  - Fungal, mycobacterial, or parasitic meningitis
  - Parameningeal infection, including abscess
- Non-infectious
  - Metastatic disease
  - Lymphoma/leukemia
  - Craniopharyngioma
  - Neurosurgical procedure
  - Intrathecal injection/medication
  - Sarcoid
  - Systemic lupus erythematosus
  - Drug-induced aseptic meningitis
  - Seizure
  - Migraine

TREATMENT

MEDICATION

First Line

- Symptomatic therapy
- IV acyclovir 10 mg/kg q8h (for normal renal function, should be dose adjusted for decreased renal function). This can be transitioned to oral for a 10–14 day course if positive for HSV or if high suspicion.
- Empiric antibacterials until bacterial meningitis has been sufficiently ruled out. There is no one test or CSF parameter that can definitively rule out bacterial infection. The threshold should be low for the administration of empiric antibacterials. The immunosuppressed, elderly, and those who may have partially treated bacterial meningitis need to be treated empirically with antibiotics on presentation.
- Treat other pathogens and consider stopping potentially offending medications.

ADDITIONAL TREATMENT

General Measures

As needed, give supportive care with hydration and monitor for complications secondary to LP.

Issues for Referral

If the patient does not improve symptomatically and testing is negative, the differential diagnosis should be broadened and referral considered.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

As warranted for relief of pain, fever, and other symptoms.

SURGERY/OTHER PROCEDURES

No indications for surgical procedures.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Blood cultures, LP, and antibiotics are the highest priority.

Admission Criteria

Based on severity of symptoms and the need to continue antibiotics until CSF cultures are negative for bacterial meningitis.

IV Fluids

Hydration to be given per clinical status.

Nursing

No specific nursing concerns.

Discharge Criteria

Once symptoms are improved and plan established for antiviral and antibacterial medications.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- If no specific etiology has been found, can consider repeat serologies as an outpatient to complete the diagnostic work-up.

Patient Monitoring

Lab monitoring per protocol for any course of antibiotics given.

DIET

Advance as tolerated by patient.

PATIENT EDUCATION

The CDC offers more information about meningitis at www.cdc.gov/meningitis/index.html.

PROGNOSIS

Aseptic meningitis is typically a self-limited disease with good prognosis.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Acute bacterial meningitis
- Encephalitis

CODES

ICD9

- 047.9 Unspecified viral meningitis
- 320.9 Meningitis due to unspecified bacterium
- 322.9 Meningitis, unspecified

CLINICAL PEARLS

The differential diagnosis of aseptic meningitis is broad, and taking a complete history of risk factors can help guide the laboratory work-up.

MENINGOENCEPHALITIS, CRYPTOCOCCAL

Julian J. Goodman, MD
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BASICS

DESCRIPTION
- Invasive fungal infection of the central nervous system by *Cryptococcus* species
- Most common cause of fungal meningitis

EPIDEMIOLOGY
- Incidence
  - Nearly 1 million cases worldwide annually
    - 0.4–1.3 per 100,000 general population per year
    - 2–100 per 1,000 patients with AIDS per year
    - 2.8 per 100 transplant recipients

RISK FACTORS
- Immunocompromise, T-cell immune defects
  - HIV/AIDS, more so with CD4 <100 cells/μL
  - Solid organ transplantation
  - Corticosteroid use
  - Liver cirrhosis

Genetics
- No known specific contributing genetic factors

GENERAL PREVENTION
- Avoidance of environments with risk of aerosolized bird droppings
- Use of N95 masks and gloves, as well as hand hygiene with soil exposures

PATHOPHYSIOLOGY
- Initial exposure
  - Yeast inhaled and can remain dormant in pulmonary lymph nodes
- Proliferation/dissemination
  - Usually in the setting of impaired cell-mediated immunity
  - Yeast replicate in pulmonary tissues and migrate to extrapulmonary sites
  - High predilection for CNS
  - High CSF levels of dopamine serve as substrate for melanin production that may protect *Cryptococcus* from host defenses
  - *Cryptococcus* produces mannitol, which can contribute to cerebral edema

ETIOLOGY
- *Cryptococcus* species
  - Spherical yeast with thick capsule
  - Found in soil; bird droppings
  - 4 serotypes: A and D are species *neoformans* and B and C are *gattii*
  - *C. gattii* can be associated with infection of immunocompetent hosts

COMMONLY ASSOCIATED CONDITIONS
- Immunocompromised states
  - HIV/AIDS
  - Solid organ transplantation
  - Malignancy
  - Corticosteroid therapy
  - Liver cirrhosis

DIAGNOSIS

HISTORY
- Meningitis
  - Headache, fever, lethargy, altered mental status; presentation can be variable
  - Infrequent nuchal rigidity early in the course; more common later
  - Generally subacute in nature; waxing and waning course
- Pulmonary symptoms
  - Many patients have concomitant respiratory infection with dyspnea and cough
- Other organ systems
  - Infection can cause skin lesions/cellulitis, ocular symptoms, myositis, arthritis; *Cryptococcus* can infect any organ system
- Immune compromise
  - Nearly all patients with cryptococcosis have impaired cell-mediated immunity

ALERT
Patients with cryptococcosis of any site should be evaluated for meningoencephalitis

PHYSICAL EXAM
- General appearance
  - Rapid assessment of patient's stability and need for resuscitation
- Pulmonary examination
  - Abnormal breath sounds may indicate presence of pneumonia
- Neurologic examination
  - Evaluation for cranial nerve palsies, mental status, and signs of elevated intracranial pressure (ICP)
- Skin examination
  - Disseminated disease can result in molluscum contagiosum-like lesions (small, pearly, umbilicated)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests
- CSF studies
  - Cell count, differential, protein, glucose, Gram stain, India ink stain, and culture
  - Protein normal-to-elevated
  - Glucose low-to-normal
  - Cell count generally low (0–50 cells/mm^3 with HIV, 20–200 cells/mm^3 without HIV)
    - Often mononuclear cell predominant
  - Organisms may be missed on Gram stain; capsule usually visualized with India Ink
  - Culture is gold standard
- *Cryptococcus* polysaccharide antigen (PPV 87–98%) (1)[B]
  - Available from CSF and serum samples
  - Titer generally corresponds with organism burden
  - There may be false positives (generally low titer, <1:8) with infection from *Trichosporon beigelii* or *Capnocytophaga canimorsus*
- Cultures
  - CSF, blood
  - May be present in sputum, urine
  - *Cryptococcus* grows on routine culture media

Follow-up & special considerations
- HIV testing
  - T-cell subsets and viral load if positive

Imaging

Initial approach
- CT head to rule out space-occupying lesions prior to lumbar puncture
- Chest x-ray or CT if signs/symptoms of pulmonary disease

Follow-up & special considerations
- Further imaging may be necessary to evaluate for hydrocephalus

Diagnostic Procedures/Other
- Lumbar puncture
  - Opening pressure must be measured and recorded; can be significantly elevated (>20 cm H_2O in 70% of patients with HIV)
  - Serial lumbar puncture/pressure evaluation as detailed in treatment section
  - Laboratory testing as above

Pathological Findings
- Yeast forms seen in tissue
  - Positive staining with mucicarmine

DIFFERENTIAL DIAGNOSIS
- Bacterial meningitis
- Viral/aseptic meningitis
- Other fungal meningitis (*Histoplasma*, *Aspergillus*, etc.)
- Toxoplasmosis
- Syphilis
- Progressive multifocal leukoencephalopathy
- Tuberculosis meningitis
- CNS malignancy (lymphoma, primary tumor, metastatic disease, etc)
- Vasculitis
- Sarcoidosis

TREATMENT

MEDICATION

First Line
- Immunocompromised patients
  - Induction with amphotericin B deoxycholate 0.7–1 mg/kg IV daily or liposomal amphotericin B 3–4 mg/kg IV daily or amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO 4 times daily for 2 weeks
  - Consolidation with fluconazole 400–800 mg PO daily for at least 8 weeks
  - Maintenance with fluconazole 200–400 mg PO daily

– Adverse effects of amphotericin formulations include infusion-related reactions with fevers, chills, rigors, and arryhthmias. Serious adverse effects include renal failure which may be permanent, neurotoxicity including seizures and encephalopathy, nausea and vomiting, hyper/hypokalemia, hypomagnesemia, and hypocalcemia
– Adverse effects of flucytosine include myelosuppression, colitis, and hepatotoxicity; serum levels need to be followed with goal 100–125 μg/mL and dosage should be adjusted based on renal function
– Adverse effects of fluconazole include hepatotoxicity and drug interactions

- Immunocompetent patients
  – Induction with agents as above for at least 4 weeks
  – Consolidation with fluconazole 400 mg PO daily for 8 weeks
  – Maintenance with fluconazole 200 mg PO daily for 6–12 months (2)[A]

Second Line

- Amphotericin without flucytosine may be used but is inferior and has increased risk of relapse
- Itraconazole may be used in place of fluconazole
- Voriconazole and posaconazole have been used in case reports, but have not been evaluated in clinical trials
- Echinocandins (anidulafungin, caspofungin, micafungin, etc) have no activity against *Cryptococcus* species and should not be used

Pregnancy Considerations

Therapy as above, but fluconazole should be avoided during the first trimester and used judiciously during the last 2 trimestersRisk of immune reconstitution inflammatory syndrome in postpartum period

ADDITIONAL TREATMENT

General Measures

- Decrease in overall level of immunosuppression

Issues for Referral

- All patients should be seen by an Infectious Disease specialist
- Periodic visits every 2–3 months to assess efficacy of therapy, immune status, and duration of maintenance therapy

Additional Therapies

- Immune reconstitution inflammatory syndrome (IRIS)
  – With increased ICP, consider corticosteroids (0.5–1 mg/kg daily prednisone equivalent)
  – 2–6 week taper with close follow-up
- Antiretroviral therapy in HIV patients
  – Initiate 2–10 weeks after starting appropriate antifungal therapy
  – Continue maintenance therapy until CD4 count is >100 cells/μL and HIV viral load undetectable for ≥3 months with no less than 12 months of therapy
  – Reinstitute maintenance therapy if CD4 count decreases to <100 cells/μL

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Supportive care

SURGERY/OTHER PROCEDURES

- ***Elevated ICP***
  – If CSF pressure ≥25 cm H_2O, pressure should be relieved by drainage with LP to reduce by 50% or to ≤20 cm H_2O
  – If CSF pressure is persistently elevated, repeat LP daily; consider lumbar drain or ventriculostomy placement
  – Significantly improved outcomes when guidelines followed with respect to ICP monitoring (NNT = 2.5) (3)[C]

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Rapid assessment of sepsis
  – Broad-spectrum antimicrobials pending definitive diagnosis

Admission Criteria

- All patients with suspected cryptococcal meningitis should be admitted for further workup and initiation of therapy

IV Fluids

- Fluid replacement if septic as well as treatment with amphotericin
- Close monitoring of electrolytes as amphotericin can cause hyperkalemia, hypokalemia, hypocalcemia, and hypomagnesemia

Nursing

- Frequent checks of neurologic status

Discharge Criteria

- Stabilization of ICP
- Sterilization of CSF cultures

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Serial lumbar puncture with culture and antigen
  – Every 2 weeks after diagnosis; induction therapy should be continued until sterilization of CSF
  – More frequent if concerned about elevated ICP or potential microbiologic failure
  – There is no clear association with change in serum antigen titer and clinical course

DIET

- No specific dietary restrictions

PATIENT EDUCATION

- Medication compliance should be emphasized as well as avoidance of further exposures

PROGNOSIS

- 6 to 12-month mortality
  – 10–25% in developed countries
  – Nearly 100% in undeveloped countries
  – Poor prognostic factors include strongly positive India ink examination, high antigen titer (>1:1024), poor CSF inflammatory response (<20 WBC/μL), altered sensorium, and abnormal brain imaging

COMPLICATIONS

- Long-term neurologic sequelae related to elevated ICP

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See Also (Topic, Algorithm, Electronic Media Element)

- Syphilis, neurological complications
- AIDS focal brain lesions
- AIDS neurologic complications
- Progressive multifocal leukoencephalopathy

CODES

ICD9

- 117.5 Cryptococcosis
- 321.0 Cryptococcal meningitis

CLINICAL PEARLS

- Life-threatening fungal infection, primarily of immunocompromised patients
- Lengthy therapy with induction, consolidation, and maintenance phases
- Management of ICP is paramount to avoiding neurologic sequelae

M

MITOCHONDRIAL DISORDER

Chang-Yong Tsao, MD, FAAN, FAAP

BASICS

DESCRIPTION

Mitochondrial diseases are clinically and genetically heterogeneous diseases associated with primary mitochondrial respiratory chain dysfunction. Neurologic, systemic, or a combination of both manifestations can be seen in the disorders.

EPIDEMIOLOGY

- Incidence
  - The incidence for most mitochondrial diseases is unknown.
- Prevalence
  - The prevalence of all mitochondrial DNA (mtDNA) disease has been estimated to be 1 in 8,500.

RISK FACTORS

Azidothymidine (AZT) treatment for AIDS may induce mtDNA depletion. Exposure to methyl-phenyltetrahydropyridine (MPTP) can cause brain respiratory chain complex I defect and a Parkinsonian syndrome.

Genetics

Genetically inherited mitochondrial diseases may result from defects of mtDNA or nuclear DNA. Nuclear DNA defects are inherited in either autosomal recessive or autosomal dominant manner. mtDNA defects are transmitted by maternal inheritance. Maternal inheritance is transmitted from the mother to all of her sons and daughters, but only her daughters can pass the mutation to their children. The clinical manifestations are determined by the threshold effect (phenotype occurs when the content of mutated mtDNA reaches a certain percentage, for example, the threshold may be 60–70% in chronic progressive external ophthalmoplegia and mitotic segregation (the contents of mutated mtDNA are changed randomly during cell division).

GENERAL PREVENTION

- During surgery, halothane or other halogenated anesthetic drugs and succinylcholine should be avoided to prevent malignant hyperthermia when mitochondrial diseases are suspected.
- Chloramphenicol and tetracycline are inhibitors of mitochondrial protein synthesis; barbiturates can inhibit the respiratory chain; and valproic acid can sequestrate carnitine. These medications should be avoided.

PATHOPHYSIOLOGY

- Mitochondrial respiratory chain is the common final pathway for aerobic metabolism, which is responsible for the ATP production for metabolism. When respiratory chain dysfunctions interfere with energy production, multiple organs and tissues, especially those highly dependent on aerobic metabolism, such as brain, heart, and muscles, are affected.

ETIOLOGY

The causes of mitochondrial disorders can be due to nuclear DNA defects of the mitochondrial respiratory chain, including mutations in the structural genes, assembly genes, translation factors, or those associated with mtDNA deletions or depletions, or coenzyme Q10 deficiency. They can also be due to mtDNA defects, which include sporadic large-scale deletions or duplications, point mutations affecting structural genes and synthetic genes, as well as defects of communication between both genomes, which consist of autosomal-dominant multiple mtDNA deletions and autosomal-recessive mtDNA depletion.

COMMONLY ASSOCIATED CONDITIONS

- Reye's syndrome: Associated with generalized mitochondrial dysfunction, often seen with influenza or varicella and aspirin treatment.
- Aging: Associated with an increase in mtDNA mutations and a decrease in mitochondrial respiratory chain function.
- Parkinson's disease: Complex I defect in substantia nigra has been shown.
- Huntington's disease: Defects of complex II, III, and IV in caudate nucleus have been reported.
- Alzheimer's disease: Complex IV and pyruvate dehydrogenase defects have been described in the brain.

DIAGNOSIS

HISTORY

The clinical features that may suggest mitochondrial diseases include developmental delay, hypotonia, microcephaly, depression, dementia, mental retardation, stroke, central hypoventilation, short stature, seizures, ataxia, migraine headache, sensorineural deafness, exercise intolerance, cardiomyopathy, cardiac arrhythmia, peripheral neuropathy, renal tubulopathy, hepatopathy, pancytopenia, sideroblastic anemia, pancreatic insufficiency, diabetes mellitus or other endocrinopathies, movement disorders, gastrointestinal disorders such as malabsorption, myoglobinuria, and multiple lipomas.

PHYSICAL EXAM

Sensorineural deafness, ptosis, ophthalmoplegia, optic atrophy, pigmentary retinopathy, cataract, muscle weakness, hypotonia, peripheral neuropathy, microcephaly, ataxia, multiple lipomas, and mental retardation may be seen.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Elevated serum or CSF lactate, associated with lactate/pyruvate ratio >20, strongly suggests respiratory chain defects. However, normal serum or CSF lactate with lactate/pyruvate ratio <20 does not exclude respiratory chain defects.

Follow-up & special considerations

Electromyography and nerve conduction studies may detect myopathy and neuropathy. EEG may show focal or generalized spikes or focal or generalized slowing.

Imaging

Initial approach

- Brain MRI or CT may show basal ganglia calcification in mitochondrial diseases. MRI may also reveal multifocal, hyperintense T_2 signal in the cortex of cerebrum, cerebellum, or subjacent white matter, which is not confined to a single vascular territory, especially in the posterior temporal and occipital areas in mitochondrial encephalomyopathy, lactic acidosis, stroke-like syndrome (MELAS). The increased inorganic phosphate-to-phosphocreatine ratio has been shown in the muscle of mitochondrial myopathy patients.

Follow-up & special considerations

- Cerebral and cerebellar atrophy may be seen.

Diagnostic Procedures/Other

- Muscle and skin biopsy may be useful for diagnosis. Molecular genetic studies may be performed for most common mtDNA point mutations, and most can be done with blood samples; however, muscle may be needed to detect mtDNA deletions or depletions (1–3)[A].

Pathological Findings

- Muscle biopsy may reveal ragged red fibers, which represent proliferation of subsarcolemmal mitochondria, and *cytochrome c* oxidase-negative muscle fibers, which indicate mitochondrial diseases.

DIFFERENTIAL DIAGNOSIS

The following mitochondrial disorders need to be differentiated from other diseases:

- Chronic progressive external ophthalmoplegia: Myasthenia gravis, oculopharyngeal muscular dystrophy, and thyroid oculomyopathy
- MELAS: Viral encephalitis, brain tumor, and stroke
- Myoclonic epilepsy and ragged red fibers syndrome: Lafora body disease, progressive myoclonic epilepsy of Unverricht–Lundborg type, and neuronal ceroid lipofuscinosis
- Leber hereditary optic neuropathy: Optic neuritis, alcohol–tobacco amblyopia, multiple sclerosis, and anterior ischemic optic neuropathy

TREATMENT

MEDICATION

First Line

Treatment of mitochondrial disorders is supportive (4)[A].

Second Line

Same as above

ADDITIONAL TREATMENT

General Measures

- Because mitochondria are virtually present in all organs and systems, mitochondrial diseases often affect multiple organs and systems. If this disease is suspected, audiograms may detect progressive sensorineural deafness. ECG may be needed for the diagnosis of cardiomyopathy. Brain MRI may reveal basal ganglia calcification, progressive cerebral or cerebellar atrophy, or other abnormalities.

Issues for Referral

- Referral to multiple specialties such as neurology, cardiology, gastroenterology, ophthalmology, endocrinology, hematology, nephrology, genetics, psychiatry, surgery, ENT, physical therapy, and respiratory therapy.

Additional Therapies

- Seizures may benefit from anticonvulsant treatment; migraine headache requires appropriate medications.
- Diabetes mellitus or other endocrine abnormalities should be treated if present.
- Sensorineural deafness may require hearing aids.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Moderate aerobic exercise may be useful; prolonged fasting and overexertion should be avoided.
- Optimal nutritional support is also needed.

SURGERY/OTHER PROCEDURES

- For ptosis due to mitochondrial diseases, surgery to elevate upper eyelids to improve vision may be needed. Intraocular lens replacement may be needed for some patients with mitochondrial respiratory chain disorders.
- For severe cardiac conduction defects, cardiac pacemaker implantation may be lifesaving.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- With stroke, prolonged seizures, respiratory distress, malnutrition, and severe cardiac defects, patients need to be stabilized as in-patients.

Admission Criteria

- Patients are sometimes admitted for muscle biopsy when significant sedation is required or for severe complications of these illnesses.

IV Fluids

- With severe malnutrition and respiratory distress, IV fluids may be needed.

Nursing

- With acute stroke, status epilepticus, and severe cardiac defect, in-patient nursing care is needed.

Discharge Criteria

- After seizures are under good control, respiratory distress, stroke, or cardiac condition stabilized with stable vital signs, then patients can be discharged.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients require regular follow-up every 6 months for multi-organ involvements.

Patient Monitoring

During clinical follow-up, patients need to be monitored for muscle weakness, cardiac disturbance, intestinal dysfunction, hepatocellular dysfunction, renal tubulopathy, visual loss or retinitis pigmentosa, pancytopenia, anemia, exocrine pancreatic dysfunction, hyperglycemia, hypocalcemia, and growth hormone or sex hormone abnormalities.

DIET

- Antidiabetic diet is indicated for patients with diabetes mellitus.

PATIENT EDUCATION

- Patients with mitochondrial diseases can be referred to the lay organization, United Mitochondrial Disease Foundation, P.O. Box 1151, Monroeville, PA 15146-1151. Phone/fax 412-856-1297, email: 74743.2705@compuserve.com; http://biochemgen.ucsd.edu/umdf; and another website: http://www.gen.emory.edu/mitomap.html.

GeneReviews: http://www.genetests.org

PROGNOSIS

Prognosis of mitochondrial diseases varies tremendously from mild to severe, especially for mtDNA disease because the level of mutant mtDNA in the organs may increase or decrease with time. The clinical course may be static, or rapidly or slowly progressive.

COMPLICATIONS

- Valproate treatment in Alper's syndrome may precipitate hepatic failure.
- Aminoglycoside treatment may induce non-syndromic sensorineural deafness in mtDNA 155A >G mutation.

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See Also (Topic, Algorithm, Electronic Media Element)

- Mitochondrial cytopathy

CODES

ICD9

- 277.87 Disorders of mitochondrial metabolism
- 277.89 Other specified disorders of metabolism

CLINICAL PEARLS

- Mitochondrial disorders result from respiratory chain dysfunctions and often affect multiple organs and systems.
- Both nuclear and mitochondrial DNA mutations have been implicated in mitochondrial disorders.
- Only supportive treatments and no curative treatments so far are available.

MUCOLIPIDOSES AND GLYCOPROTEINOSES

Jennifer Werely, MD
David S. Younger, MD

BASICS

DESCRIPTION

- Mucolipidoses are inherited autosomal-recessive lysosomal storage diseases affecting the body's ability to carry out the turnover of carbohydrates and lipids in cells. These diseases are characterized by variable storage of mucopolysaccharides, sphingolipids, and/or glycolipids in various tissues, including nerve, liver, muscle, and bone marrow. There are 4 types of mucolipidoses resulting from a wide spectrum of genetic and metabolic defects including Type I (sialidosis), Type II (I-cell disease), Type III (Pseudo-Hurler syndrome), and Type IV. Mucolipidoses have the clinical features of mucopolysaccharidoses and lipidoses; however, mucolipidoses lack the sign of mucopolysachhariduria.
- Glycoproteinoses are autosomal-recessive lysosomal storage diseases with defects in glycoprotein degradation. These include galactosialidosis, fucosidosis, aspartylglycosaminuria, and α- and β-mannosidoses.

EPIDEMIOLOGY

All of the mucolipidoses and glycoproteinoses are rare disorders.

- The following have a predilection for a particular subgroup of the population:
  - Mucolipidosis Type I (sialidosis Type 1): Italians
  - Mucolipidosis Type II (I-cell disease): French Canadians
  - Mucolipidosis Type IV: Ashkenazi Jews (heterozygote frequency 1/100)
  - Galactosialidosis (Juvenille Form): Japanese
  - Fucosidosis: Italians and the Mexican-Indian population of New Mexico and Colorado
  - Aspartylglucosaminuria: Finnish

RISK FACTORS

Genetics

All the disorders are autosomal recessive; therefore, males and females are equally affected. Carrier detection and prenatal testing are available.

DIAGNOSIS

- Mucolipidosis Type I (sialidosis, 2 types)
  - Sialidosis Type 1: Cherry-red spot myoclonus variant, a milder form of disease. Onset after age 10 with progressive visual loss, namely night blindness associated with a cherry red spot and nonpigmentary retinal degeneration. Patients can have both myoclonus and generalized seizures. No dysmorphic facial features and normal intelligence.
  - Sialidosis Type 2: A more severe congenital form characterized by dysmorphic features, hepatosplenomegaly, corneal opacifications, dysostosis multiplex, hydrops fetalis, ascites, and pericardial effusion. Type 2 is rapidly fatal.
- Mucolipidosis Type II (I-cell disease): Most common of the mucolipidoses with characteristics similar to Hurler's syndrome. However, with Mucolipidosis Type II, features are present at birth, and there is a more rapid progression with absence of mucopolysaccharidiuria. Characteristics include hypotonia, coarse facial features, ginigival hyperplasia, congenital hip dislocations, and tight/thick skin.
- Mucolipidosis Type III (Pseudo-Hurler syndrome, a milder form of Mucolipidosis Type II): Onset occurs after 2 years of age with a slowly progressive course. 50% of patients have a learning disability or mild mental retardation. Characteristics include stiffness of the hands and shoulders with subsequent claw hand deformity, scoliosis, dysostosis multiplex, coarse facial features, and carpal tunnel syndrome with the ophthalmologic triad of corneal clouding, retinopathy and hyperopic astigmatism. Many features are similar to mild to moderately severe Hurler's syndrome without mucopolysaccharidiuria.
- Mucolipidosis Type IV: Presents with severe psychomotor retardation with peak developmental level of 12–15 months by 3–4 years of age. Characteristics include corneal opacification and pigmentary degeneration of the retina leading to visual failure soon after birth. Distinguishing feature includes no skeletal deformities or visceromegaly.
- Galactosialidosis (infantile and juvenile/adult onset):
  - Infantile form may present with hydrops fetalis, coarse facies, and skeletal changes.
  - The juvenile form characteristics include coarse facies, dysostosis multiplex, conjunctival telangiectasias, angiokeratoma, corneal clouding, macular cherry red spot, hearing loss, mental retardation, and seizures.
- Fucosidosis: Onset during the first year of life to early childhood with progressive psychomotor retardation, spastic quadriplegia, and decerebrate posturing. Characteristics include enlarged salivary glands, excessive sweating, seizures, deafness, hepatosplenomegaly, coarse facial features, dysostosis multiplex, recurrent infections, and angiokeratoma.
- α-Mannosidosis: Onset during the first year of life to early childhood with progressive mental retardation, hepatosplenomegaly, coarse facial features, dysostosis multiplex, recurrent infections, deafness, lenticular, and corneal opacities.
- β-Mannosidosis: Onset after the first few months of life with developmental regression, mild facial dysmorphism, hearing loss, and recurrent infections.
- Aspartylglycosaminuria: Presents with recurrent infections and diarrhea noted during the first year of life. Mental deterioration starting between age 5 and 15 with an IQ <40 by 15 years of age, severe behavioral disturbances, coarse facial features, lenticular opacities, skeletal dysplasia, and mitral insufficiency.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- Bone x-rays to look for skeletal dysplasia
- Mucolipidosis Type IV: MRI—hypoplastic corpus callosum and may have delayed myelination.
- Fucosidosis: MRI—increased signal in white matter and globus pallidus with increased intensity on T1-weighted images and decreased intensity on T2-weighted and FLAIR imaging. Putamen with increased intensity on T2-weighted imaging.

Other Diagnostic Testing

Excessive excretion of oligosaccharides is found in urine. Specific diagnosis is suspected on clinical grounds and confirmed by enzymatic testing.

- Mucolipidosis Type I: Glycoprotein acid α-neuraminidase enzymatic deficiency
- Mucolipidosis Type II: Multiple lysosomal enzymes due to deficiency of UDP-*N*-acetylglucosamine: lysosomal enzyme *N*-acetylglucosamine phosphotransferase
- Mucolipidosis Type III: Same as Mucolipidosis Type II
- Mucolipidosis Type IV: Ganglioside sialidase, patients are achlorhydric with a secondary elevation in serum gastrin
- Galactosialidosis: Combined β-galactosidase and α-neuraminidase deficiency
- Fucosidosis: α-L-Fucosidase
- α-Mannosidosis: α-Mannosidase
- β-Mannosidosis: β-Mannosidase
- Aspartylglycosaminuria: Aspartylglycosaminidase

DIFFERENTIAL DIAGNOSIS

Other degenerative disorders

TREATMENT

MEDICATION

No specific drug treatment is available.

ADDITIONAL TREATMENT

General Measures

Bone marrow transplantation for mucolipidosis type II, fucosidosis, α-mannosidosis, and aspartylglycosaminuria is experimental.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - Treatment is directed toward complications of the disease.
- Adjunctive Treatment
  - Physical therapy may improve quality of life.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are usually admitted for evaluation and treatment of the complications of their disease.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patient follow-up is guided by the predicted course and potential complications of the disease.

PATIENT EDUCATION

- National Tay–Sachs and Allied Diseases Association, 2001 Beacon St., Ste. 204, Brighton, MA 02135; phone 800-90-NTSAD.
- ML4 Foundation, 714 E. 17th St., Brooklyn, New York 11230. Phone 718-434-5067.

PROGNOSIS

- Mucolipidosis Type I
  - Sialidosis Type 1: Survival into middle age without dementia but with a devastating and virtually untreatable myoclonus.
  - Sialidosis Type 2: Death in infancy in the congenital form with survival to the second decade in milder forms.
- Mucolipidosis Type II: Cardiorespiratory complications usually lead to death in early childhood.
- Mucolipidosis Type III: Survival into adulthood is possible.
- Mucolipidosis Type IV: Few patients survive beyond their teenage years. A milder variant has been reported.
- Galactosialidosis: Early death to survival into adulthood.
- Fucosidosis: Severe form with death in the first decade; however, in milder forms, survival into the third decade.
- α-Mannosidosis: Infantile onset with rapid progression and death between 3 and 12 years of age. Later-onset disease more slowly progressive with survival into adulthood.
- β-Mannosidosis: Severe form with death by 15 months of age. Milder forms with survival into adulthood.
- Aspartylglycosaminuria: Survival to adulthood.

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CODES

ICD9

- 271.8 Other specified disorders of carbohydrate transport and metabolism
- 272.7 Lipidoses

M

MUCOPOLYSACCHARIDOSES

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David S. Younger, MD

BASICS

DESCRIPTION

Mucopolysaccharidoses (MPS) are chronic and progressive multisystem disorders caused by deficiency of lysosomal enzymes that degrade mucopolysaccharides with resultant marked lysosomal accumulation of one or a combination of the following: dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. This accumulation results in cell, tissue, and organ dysfunction. 10 known enzyme deficiencies give rise to 6 disorders. Residual enzymatic activity correlates with clinical course of disease as illustrated by the variable phenotypes due to L-iduronidase deficiency in Hurler's and Scheie's syndromes. In contrast, Sanfilippo's syndrome can result from 4 distinct enzyme deficiencies, all of which result in the accumulation of heparan sulfate. Neurologic symptoms are a prominent feature of some MPSs and occur to some degree in all. Profound mental retardation, which is characteristic of MPS I H, severe MPS II, and all subtypes of MPS III, may be absent in other MPS.

EPIDEMIOLOGY

- Incidence/Prevalence
  - A study of MPS in the Netherlands reported an incidence of 1.19 cases per 100,000 births for MPS I; 1.16 cases per 100,000 births for MPS IIIA; and 0.67 cases per 100,000 births (1.30 cases per 100,000 male births) for MPS II. Incidence of type IVA is estimated at 1 case per 200,000 births. Type IVB is rare, as are types VI and VII.
- Race
  - MPS is diagnosed in patients from many ethnic/racial backgrounds.
- Age
  - See Signs and Symptoms, below.
- Sex
  - Because of X-linked inheritance, patients with Hunter's syndrome are male.

ETIOLOGY

Genetics

- Inheritance is autosomal recessive except for Hunter's syndrome (MPS II), which is X-linked.
- Prenatal diagnosis by enzyme determination following chorionic villus biopsy or amniocentesis is available.

DIAGNOSIS

- Hurler's syndrome or MPS I H: Developmental delay apparent by 12–24 months of age. Psychomotor retardation characterized by a maximum functional age of 2–4 years followed by progressive deterioration. Corneal clouding, dysostosis multiplex (constellation of radiographic abnormalities), hepatosplenomegaly, and heart disease
- Scheie's syndrome or MPS I S: Normal intelligence. Corneal clouding, stiff joints, and aortic valve disease
- Hurler–Scheie compound or MPS I H/S: Intermediate between MPS I H and MPS I S.
- Severe Hunter's syndrome or severe MPS II: Onset of disease occurs between 2 and 4 years of age. Progressive psychomotor retardation, dysostosis multiplex, hepatosplenomegaly, respiratory disease, and heart disease.
- Mild Hunter's syndrome or mild MPS II: Normal intelligence. Short stature, heart disease.
- Sanfilippo's syndrome types A, B, C, and D or MPS III types A, B, C, and D: Onset of disease between 2 and 6 years of age. Severe CNS involvement with mild somatic disease. Profound mental retardation and hyperactivity with aggressive behavior. Mild hepatosplenomegaly in young patients
- Morquio's syndrome types A and B or MPS IV types A and B: Normal intelligence, spondyloepiphyseal dysplasia (which is specific to this disorder), and corneal clouding
- Maroteaux–Lamy syndrome or MPS VI: Normal intelligence, dysostosis multiplex, corneal opacities, and heart disease
- Sly's syndrome or MPS VII: Wide spectrum of severity with mental retardation in severe form and normal intelligence in mild form. If present, mental retardation is evident by 3 years of age. Dysostosis multiplex and hepatosplenomegaly

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

Bone x-rays to look for skeletal dysplasia.

- In Hunter's syndrome, x-rays may be used to detect dysostosis multiplex, and specifically:
  - Abnormal thickness of all bones
  - Thickened ribs with abnormal shape (Martin et al. 2008)

Diagnostic Procedures/Other

- MPS may be diagnosed by finding excessive urinary excretion of mucopolysaccharide degradation products. The diagnosis is confirmed by measuring specific enzymatic activity in serum, leukocytes, or fibroblasts. Patients with MPS have $<10\%$ and often $<1\%$ of residual enzymatic activity. Newborn screening programs derives from the ability of effective therapy in the form of enzyme replacement or substrate reduction therapy and bone marrow transplantation that may improve long-term outcome, as discussed further.
- MPS I H, I S, and I H-S: α-L-iduronidase deficiency
- Severe and mild MPS II: Iduronate sulfatase deficiency
- MPS III type A: Heparan *N*-sulfatase deficiency
- MPS III type B: α-*N*-acetylglucosaminidase deficiency
- MPS III type C: *N*-acetyl transferase deficiency
- MPS III type D: α-*N*-acetylglucosaminide-6-sulfatase deficiency
- MPS IV type A: Galactose 6-sulfatase deficiency
- MPS IV type B: β-Galactosidase deficiency
- MPS VI: Galactosamine-4-sulfatase (arylsulfatase B) deficiency
- MPS VII: β-Glucuronidase deficiency

DIFFERENTIAL DIAGNOSIS

Other degenerative disorders.

TREATMENT

MEDICATION

- Enzyme replacement therapy (ERT) with α-L-iduronidase (Laronidase) for Mps I
- ERT with human iduronate-2-sulfatase (idursulfase) to treat MPS II
- ERT with recombinant human *N*-acetylgalactosamine-4-sulphatase to treat MPS VI
- Substrate reduction therapy using flavonoids, such as daidzein and kaempferol, has been implicated in decreasing GAG accumulation in MPS III

ADDITIONAL TREATMENT

General Measures

- The chronic and progressive course of the MPS warrants periodic evaluation for potential complications, the management of which may improve quality of life. Evaluations should be performed in the following areas: neurologic, cardiovascular, respiratory (including evaluation for obstructive sleep apnea), and joint function.
- Neurologic complications and possible medical and surgical interventions are presented in more detail. It is important to note that patients with MPS I, II, IV, and VI may be at high risk for anesthetic complications because of atlantoaxial instability and presence of a narrowed airway.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - Progressive communicating hydrocephalus due to failure of reabsorption of CSF in the arachnoid granulations may be seen in MPS I H, MPS II, severe, and MPS VI. Ventriculoperitoneal shunt placement may be indicated.
  - Corneal clouding leading to significant visual impairment can occur in MPS I, MPS IV, MPS VI, and MPS VII. Consider corneal transplant.
  - Glaucoma may develop in patients with MPS I and MPS VI.
  - Screening for conductive and sensorineural hearing loss in all patients with MPS. Deafness has been attributed to 3 causes: Frequent middle ear infections, deformity of the ossicles, and probable abnormalities of the inner ear. Hearing aids and myringotomy tubes may improve hearing.
  - Development of carpal tunnel syndrome in all MPS patients except those with MPS III and VII. Surgical nerve decompression may be indicated.
  - Seizures may develop in patients with severe MPS II and MPS III. Antiepileptic medication should be used to control seizures.
  - C1–C2 subluxation/cord compression as a result of a narrowed spinal canal and storage within the meninges (pachymeningitis cervicalis) in patients with MPS IH, MPS IV, MPS VI, and MPS VII. Occipitocervical fusion and laminectomy may be required.
- Adjunctive Treatment
  - Range of motion exercises may help preserve joint function.

SURGERY/OTHER PROCEDURES

Bone marrow transplant (BMT) for patients with MPS I, MPS IV, MPS VI, and MPS VII may lessen visceral and joint symptoms and improve quality of life. BMT can stabilize the CNS in MPS I. BMT performed in patients with MPS 1 H prior to 24 months of age with a Mental Developmental Index >70 can result in continued cognitive development and prolonged survival. Results of BMT for MPS II and MPS III are unsatisfactory.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are generally admitted for evaluation and treatment of the neurologic, cardiovascular, and respiratory complications of their disorder.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be periodically evaluated for complications of their disorder as described in the management section.

PATIENT EDUCATION

- National Mucopolysaccharidosis Society, 17 Kraemer St., Hicksville, NY 11801. Phone 516-931-6338.

PROGNOSIS

Death is usually due to heart failure, but may be secondary to respiratory failure in MPS II or cervical cord compression in patients with MPS IV.

- MPS I H: Death by 10 years of age.
- MPS I S: Normal life span.
- MPS I H–S: Intermediate between I H and I S.
- Severe MPS II: Death between 10 and 15 years of age.
- Mild MPS II: Survival to adulthood and beyond.
- MPS III: Death in teens or early adulthood.
- MPS IV: Patients with severe disease may not survive beyond their 20s.
- MPS VI: Survival to teens in severe form, adulthood in mild form.
- MPS VII: Wide spectrum including hydrops fetalis and survival to adulthood.

ADDITIONAL READING

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CODES

ICD9

277.5 Mucopolysaccharidosis

M

MULTIPLE SYSTEM ATROPHY

Selena Nicholas-Bublick, MD, MHS
Lawrence W. Elmer, MD, PhD

BASICS

DESCRIPTION

- Multiple system atrophy (MSA) belongs to a family of disorders termed α-synucleinopathies which include idiopathic Parkinson's disease (IPD) and dementia with Lewy bodies. Whereas in these latter disorders the histological hallmark of α-synuclein inclusions are found in the cytoplasm, axons, and dendrites of neurons, in MSA the abnormal α-synuclein inclusions are found within the cytoplasm of glial cells in the CNS. These groups of disorders share common clinical features and may initially appear very similar, but with time MSA patients develop a characteristic constellation of symptoms. Two main subtypes are described on the basis of whether the most predominant clinical features include cerebellar dysfunction or parkinsonism. A patient with MSA may be considered as having possible, probable, or definite MSA based on the criteria outlined in the second consensus statement on the diagnosis of MSA (1).
- MSA-P: This designation is given to those patients who present with predominantly parkinsonian features (bradykinesia, rigidity, postural instability, and/or rest tremor). This syndrome is notoriously difficult to distinguish from IPD at initial evaluation; however, in contrast to IPD, a sustained and robust benefit is not achieved from treatment with conventional anti-parkinsonian therapies.
- MSA-C: Cerebellar dysfunction is the major clinical feature of this subtype and may be manifested through one or more of the following: Ataxia of limb movement, ataxia of gait and speech, dysrhythmia, dysdiadochokinesia, titubation, impaired check response, eye movement abnormalities including nystagmus, square-wave jerks, overshoot/undershoot dysmetria, saccadic pursuits, and slowed pursuits. Bulbar symptoms may also develop, increasing the risk of dysphagia.
- Autonomic dysfunction is a required criterion for both subtypes and may include: Otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure (BP) decline. The severity of orthostatic BP decline differs between possible or probable MSA with the latter requiring a decrease of BP within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic.
- Older literature described patients with combinations of the above clinical findings as three separate syndromes: Striatonigral degeneration, olivopontocerebellar atrophy, and Shy–Drager syndrome. This terminology for classification of MSA is now obsolete.

EPIDEMIOLOGY

Prevalence

- The prevalence of MSA has been estimated at 2–5 per 100,000 in the general population. Incidence in individuals past the age of 50 may approach 3/100,000 (2).
  - *Race:* No known ethnic predilection has been noted; however, the phenotype with more predominant parkinsonism features (MSA-P) appears more commonly in the Western Hemisphere and MSA-C appears to be the more frequent phenotype in the Eastern Hemisphere (3).
  - *Age:* The mean age of onset is around the early to mid-fifties, slightly earlier than idiopathic PD.
  - *Sex:* No clear difference in gender shown.

PATHOPHYSIOLOGY

Neuropathological changes in MSA include α-synuclein positive glial cytoplasmic inclusions (GCIs) and widespread neurodegeneration of the cerebral white matter including, but not limited to the following structures: The pons, medulla, putamen, substantia nigra pars compacta, cerebellum, and preganglionic autonomic structures (4).

ETIOLOGY

There are no clear genetic or environmental causes of MSA. The cerebellar variant must be distinguished from hereditary multiple system degenerations (Machado–Joseph disease [*SCA3*] and occasionally *SCA1* and *SCA2* mutations).

DIAGNOSIS

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Bloodwork: There are no specific blood tests to diagnose MSA, but the following tests should be considered to identify potential secondary causes of parkinsonism: Thyroid function tests, serum vitamin E, B12 and ceruloplasmin levels, and 24-hour urine copper excretion.

Imaging

Initial approach

- Functional neuroimaging by PET and SPECT scanning using markers for neuronal activity (fluorodeoxyglucose), dopaminergic terminals (β-CIT, DTBZ, and others) and dopamine receptors (IBZD) may distinguish MSA from idiopathic PD, but does not distinguish MSA from other parkinsonism syndromes such as PSP. These methods are not widely implemented.
- There is evidence to suggest that MRI imaging can assist in the diagnosis of MSA. Brain MRI imaging may reveal changes in imaging intensity and/or atrophy in the putamen, cerebellum and/or brainstem. Some investigators are attempting to define MRI rating scales in order to help diagnose and follow the progression of MSA; however, at this time these are not widely used (5). MRI imaging may also reveal evidence of other causes of parkinsonism such as vascular insults, mass lesions, calcium or iron deposition in the striatum, and cortical atrophy patterns suggestive of other dementing illnesses.

Diagnostic Procedures/Other

Routine studies of autonomic function may distinguish MSA from cases of primary autonomic failure. Cardiac imaging studies visualizing the autonomic innervation of the heart using a SPECT ligand has consistently distinguished MSA from IPD with autonomic involvement.

DIFFERENTIAL DIAGNOSIS

- Idiopathic Parkinson's disease
- Dementia with Lewy bodies
- Corticobasal ganglionic degeneration
- Progressive supranuclear palsy
- Hereditary ataxias

Signs and Symptoms

Differentiating MSA in its early stages from other akinetic-rigid syndromes such as IPD is difficult, even for specialists. The clinical diagnosis relies on the development of distinct signs and symptoms, none of which are unique to MSA. However, consensus criteria have been developed which allow for some degree of confidence in making the diagnosis in an adult who presents with a sporadic progressive disease onset (1). The criteria are as follows.

POSSIBLE MSA

This includes parkinsonism or a cerebellar syndrome and at least one feature suggesting autonomic dysfunction. At least one additional feature from Table 1 should be present. For either phenotype, a Babinski sign with hyperreflexia or stridor may count as an additional feature.

Table 1

Additional Features Required for the Diagnosis of Possible MSA

Possible MSA-C
• Rapidly progressive parkinsonism
• Postural instability within 3 years of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within 5 years of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum
Possible MSA-P
• Parkinsonism (bradykinesia and rigidity)
• Poor response to levodopa
• Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET

FDG, [^{18}F]fluorodeoxyglucose.
From Reference (1).

Table 2

Items That May Indicate Autonomic Failure

- Unexplained urinary urgency or frequency
- Incomplete bladder emptying
- Erectile dysfunction in males
- Significant orthostatic BP decline

From Reference (1).

Probable MSA

Parkinsonism meeting the criteria for possible MSA-C or MSA-P in association with autonomic failure involving urinary incontinence or an orthostatic decrease of BP within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic. Notice the stricter criteria for orthostatic BP in this category.

Definite MSA

- Pathological confirmation of neurodegenerative changes in striatonigral or olivopontocerebellar structures in association with abundant GCIs.
- Other associated clinical features that support the diagnosis of MSA include: Orofacial dystonia, anterocollis, camptocormia and/or Pisa syndrome, contractures of and/or cold hands and feet, inspiratory sighs, severe dysphonia and/or dysarthria, pathologic laughter or crying and a jerky, myoclonic postural/action tremor. Clinical features that should cue the clinician to consider other neurodegenerative disorders include: Classic pill rolling rest tremor, significant neuropathy, unexplained hallucinations, age >75 years old, relatives with ataxia or parkinsonian syndromes, dementia, and/or suspicious white matter lesions on brain imaging.

TREATMENT

MEDICATION

First Line

- Rarely, extrapyramidal symptoms seen in MSA may respond to carbidopa/levodopa, sometimes requiring supratherapeutic (i.e., >600–800 mg levodopa per day) doses. Anticholinergic agents and amantadine may also be of limited usefulness. Responses are usually minimal and short-lived.
- Orthostatic hypotension may be treated with increased salt intake, fludrocortisone (0.1–0.4 mg/day in two divided doses), midodrine (5–10 mg up to 3×/day), and/or pyridostigmine (30–60 mg up to 3×/day-off label use).
- Urinary incontinence may be treated with peripheral anticholinergic therapy (oxybutinin 5–10 mg at bedtime, and other formulations). Constipation is treated with advancing doses of fiber supplements, stool softeners, fruit and vegetable preparations, and/or lactulose.
- The ataxia seen in MSA sometimes responds to clonazepam 0.5–1.0 mg at bedtime.
- Antidepressants, especially SSRI agents, have helped in cases of depression associated with the progression of this illness.
- Contraindications: Individuals with a history of congestive heart failure and/or renal insufficiency should not be prescribed a high salt diet and should be carefully monitored if given a volume expanding agent such as fludrocortisone.
- Precautions: Severe *hypertension* can result from aggressive treatment with volume expanding or vasoactive therapies. Monitor BP carefully during titration of these agents.

ADDITIONAL TREATMENT

General Measures

There is no effective treatment for MSA. Management is aimed at alleviating consequences of the motor and autonomic changes.

Additional Therapies

The extrapyramidal symptoms of bradykinesia and resultant loss of mobility may be overcome by the use of 4-wheeled walkers, but the tendency of patients with MSA, especially MSA-C to fall usually limits the effective duration of this intervention. Percutaneous endoscopic gastrostomy (PEG) may be performed to provide life-sustaining nutrition. Dysarthria/dysphagia may benefit from speech pathology intervention.

SURGERY/OTHER PROCEDURES

Patients with MSA are at risk of vocal cord abductor paralysis (VCAP). VCAP involves dysfunction of the vocal cords that worsens during sleep and may result in sudden death. Definite diagnosis is through fiberoptic laryngoscopy and treatment options include nasal CPAP, laryngosurgery for glottal opening, botulinum toxin injection, and tracheostomy for severe cases. At this time no definite treatment paradigm exists (6).

IN-PATIENT CONSIDERATIONS

Admission Criteria

MSA is usually managed in an outpatient setting. Rarely, concomitant illnesses, especially aspiration pneumonia, can lead to an acute exacerbation of MSA symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility.

ONGOING CARE

PATIENT MONITORING

Like other parkinsonism syndromes, the progression of MSA is relentless and refractory to most common treatment modalities, resulting in death within an average of 6–9 years after time of symptom onset. Patients are monitored in the outpatient setting, usually at 4–6 month intervals. Judicious use of antidepressant medications and timely discussion of PEG tube placement are recommended to assist patients and their families prepare for future decline.

PATIENT EDUCATION

The postural instability characteristic of MSA prevents the use of ambulatory exercise, although stretching and strengthening exercises in a sitting position may be useful. Aquatic therapy with close supervision may help forestall some of the immobility issues associated with this illness. Speech therapy is useful for speech and swallowing disturbances. Frequently, patients continue to be classified as IPD patients, confounding their understanding and expectations of treatment options and prognosis.

PROGNOSIS

Due to its progressive nature, the symptoms of MSA always worsen with time. Over time, the limited responsiveness of MSA patients to dopaminergic therapy typically deteriorates. Death usually occurs as a consequence of cardiac arrhythmia or aspiration pneumonia.

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CODES

ICD9

333.0 Other degenerative diseases of the basal ganglia

CLINICAL PEARLS

"PD with autonomic insufficiency equals MSA" is no longer true (see chapter on "Parkinson's Disease"), but poor response to levodopa and/or early gait and balance disturbance–think "Possible MSA" and refer to a specialist early!

MUSCULAR DYSTROPHY, CONGENITAL

Chang-Yong Tsao, MD, FAAN, FAAP

BASICS

DESCRIPTION

Congenital muscular dystrophies (CMD) refer to a group of rare heterogeneous muscle diseases presenting in the neonatal period or early infancy (<6 months) with diffuse muscle weakness and atrophy, hypotonia with or without joint contractures, variable brain abnormalities and mental retardation, and dystrophic changes in the muscle. Included in the congenital muscular dystrophies are those associated with α-dystroglycan glycosylation defects (Fukuyama CMD, Walker–Warburg syndrome (WWS), muscle–eye–brain disease, Fukutin-related protein CMD, defects in integren-α_7, defects in laminin-α_2 (merosin), defects in collagen VI, defects in nuclear protein lamin A/C, and defects in a protein of endoplasmic reticulum selenoprotein N1.

EPIDEMIOLOGY

- Incidence
  - The incidence of all CMD varies from 1/21,500 to 1/16,000. Merosin-deficient CMD comprises 50% of CMD. The incidence of Fukuyama CMD is 1.92–3.68/100,000 in Japan; that of laminin-α_2–positive CMD is 1/60,000. The incidence of Bethlem myopathy is 0.5/100,000 and that of Ullrich's CMD 0.1/100,000. Incidences of other types of CMD are unknown.
- Prevalence
  - The prevalence varies from 0.68 to 2.5 per 100,000.

RISK FACTORS

Fukuyama CMD is seen in Japan and Taiwan, and is rare in other areas. Muscle–eye–brain disease is described most often in Finland.

Genetics

- All of the CMD are autosomal-recessive diseases with the exception of autosomal-dominant inheritance in lamin A/C-related CMD and both autosomal-dominant and autosomal-recessive inheritance in collagen VI-related CMD.

GENERAL PREVENTION

- Acetaminophen may prevent fever and febrile seizures associated with some CMDs.
- Influenza vaccine may prevent respiratory illness and acute worsening muscle weakness.

PATHOPHYSIOLOGY

- Mutations of multiple genes responsible for structural proteins of extracelluar matrix, defects in glycosylation, proteins of endoplasmic reticulum, and proteins of nuclear envelope cause muscle weakness, hypotonia, dystrophic process, and, in some patients, brain and eye anomalies as well.

ETIOLOGY

- Laminin-α_2 (merosin)–deficient CMD is linked to chromosome 6q22–23 (gene product: merosin). Fukuyama CMD is linked to chromosome 9q31–q33 (gene product: fukutin). Muscle–eye–brain disease is linked to chromosome 1p32–p34 (gene product: POMGNT1, glycosyltransferase). Integrin-α_7–deficient CMD is linked to chromosome 12q13 (gene product: α_7 integrin). Rigid spine CMD is linked to chromosome 1p35–36 (gene product: selenoprotein N1). Ullrich CMD 1–2 is linked to chromosome 21q2 (gene product: collagen VI A1–2); Ullrich CMD 3 is linked to chromosome 2q3 (gene product: collagen VI A3). WWS is linked to chromosome 19q13.3 (gene product: fukutin related protein), chromosome 22q12 (gene product: LARGE protein), chromosome 9q34.1 (gene product: protein *O*-mannosyltransferase 1, POMT1), chromosome 14q24.3 (gene product: protein *O*-mannosyltransferase 2, POMT2). Muscle–eye–brain disease is linked to chromosome 1p34 (gene product: protein *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase: POMGNT1). Fukutin-related protein CMD is linked to chromosome 19q13.3 (gene product: FKRP).

COMMONLY ASSOCIATED CONDITIONS

- Forebrain abnormalities including cobblestone lissencephaly and mental retardation are seen in Fukuyama CMD, muscle–eye–brain disease, WWS, and FKRP-related CMD.
- Cerebral white matter abnormalities are also frequently seen in Fukuyama CMD, muscle–eye–brain disease, WWS, laminin-α_2 (merosin)–deficient CMD, and FKRP-related CMD.
- Eye abnormalities are present in muscle–eye–brain disease and WWS.
- Seizures and epilepsy may occur in Fukuyama CMD, WWS, muscle–eye–brain disease, and laminin-α_2 (merosin) –deficient CMD.
- Early spine contractures, rigidity, and scoliosis are seen in rigid spine CMD.
- Distal joint laxity is seen in all types of Ullrich's CMD.
- Cardiac involvement is reported in Fukuyama CMD, FKRP-related CMD, lamin A/C-related CMD, laminin-α_2 (merosin)–deficient CMD, and rigid spine CMD.

DIAGNOSIS

HISTORY

- In all types of congenital muscular dystrophies, there are generalized hypotonia, diffuse muscle weakness and atrophy, variable early and multiple joint contractures, and onset from birth or the first few months of life.
- Seizures and epilepsy are also reported in Fukuyama congenital muscular dystrophy, muscle–eye–brain disease, WWS, and laminin-α_2 (merosin)–deficient CMD.

PHYSICAL EXAM

- In the classical form of merosin-positive CMD, there are no ophthalmologic abnormalities and the patients are usually mentally normal. Congenital hip dislocation or subluxation is frequently seen. In merosin-deficient CMD, no abnormal ophthalmologic findings are demonstrated, but severe weakness with inability to ambulate independently is present in complete merosin deficiency.
- Fukuyama CMD typically comprises of severe CMD, mental retardation, and mild cobblestone lissencephaly.
- Muscle–eye–brain disease reveals CMD, mental retardation, retinal hypoplasia, and cobblestone lissencephaly.
- In WWS, CMD, severe mental retardation, retinal abnormalities, and severe cobblestone lissencephaly are present.
- Although mental retardation is seen in Fukuyama congenital muscular dystrophy, muscle–eye–brain disease, and WWS, marked eye abnormalities are present in muscle–eye–brain disease and WWS but not in Fukuyama CMD. FKRP-related CMD is without eye and brain abnormalities; LARGE-related CMD is associated with mental retardation and variable eye and brain abnormalities.
- In rigid spine CMD, hypotonia, stable or slowly progressive weakness, poor head control, early spinal rigidity, scoliosis, and early respiratory insufficiency are noted. Delayed motor milestones and mental retardation have been reported in integrin-α_7–deficient congenital muscular dystrophy. Distal joint laxity is seen in all Ullrich CMDs, and spine rigidity is also reported in Ullrich CMD 1 and 2.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum creatine kinase may be mildly to moderately increased in all CMDs.
- EMG shows myopathic changes in most patients with CMD.
- EEG may show epileptiform discharges when seizures or epilepsy occur.

Follow-up & special considerations

- Muscle biopsy reveals dystrophic changes and increased connective tissue in the majority of CMDs.

Imaging

Initial approach

Brain MRI demonstrates a variety of congenital brain abnormalities, including polymicrogyria, pachygyria, cobblestone lissencephaly, and diffuse or patchy prolonged T1 and T2 signals in cerebral white matter in Fukuyama CMD, WWS, muscle–eye–brain disease, and laminin-α_2 (merosin) –deficient CMD. Brain MRI is normal in laminin-α_2 (merosin)-positive CMD and all other CMD.

Follow-up & special considerations

- White matter changes may regress over time.

Diagnostic Procedures/Other

- Muscle biopsy may show dystrophic changes or nonspecific myopathy.
- Muscle or blood molecular genetic testing for gene mutations may establish the diagnosis of different CMD subtypes (1)[A].

Pathological Findings

- Complete or partial muscle and skin laminin-α_2 (merosin) deficiency is detected in laminin-α_2 (merosin)–deficient CMD by immunohistological staining. Secondary partial laminin-α_2 deficiency and α-dystroglycan deficiency are shown in Fukuyama CMD, FKRP- and LARGE-related CMD, WWS, and muscle–eye–brain disease (1)[A].
- Normal laminin-α_2 (merosin) is seen in the muscles of classic or pure form of CMD, WWS, rigid spine CMD, integrin-α_7–deficient CMD, and other CMDs (1)[A].

DIFFERENTIAL DIAGNOSIS

- Mitochondrial encephalomyopathy
- Congenital myopathies
- Congenital myasthenic syndrome
- Congenital myotonic dystrophy
- Metabolic myopathies

TREATMENT

MEDICATION

First Line

Currently, no specific treatment or cure is present for all types of CMD (1,2)[A].

ADDITIONAL TREATMENT

General Measures

- Respiratory therapy and use of cough device, treatment of pulmonary infection or respiratory distress may be important.

Issues for Referral

- Individual multidisciplinary specialty approaches are needed to improve quality and longevity of patients.

Additional Therapies

- Passive stretching to improve contractures, night splints, and serial plaster casts may be useful. Body brace may be used to slow scoliosis.
- Speech and language, physical, and occupational therapies may be needed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Antiepileptic drugs are needed to treat seizures and epilepsy.
- Antispasticity drugs such as baclofen, diazepam, dantrolene, or botulinum toxin injection often reduce spasticity of the extremities.

SURGERY/OTHER PROCEDURES

- Tenotomies, tendon transfer, and tendon lengthening may be necessary for some patients to help in standing and ambulation.
- Progressive scoliosis may require spinal fusion to preserve pulmonary function and respiratory failure.
- Those with severe cardiac conduction defects may need pacemaker placement to prevent sudden death.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Patients with respiratory distress or status epilepticus need to be stabilized before admission.

Admission Criteria

- Patients are admitted for diagnostic evaluations and treatments such as muscle biopsy, brain MRI, and speech, occupational, and physical therapies.

IV Fluids

- Patients with status epilepticus or respiratory distress may need IV fluids.

Nursing

- Patients with status epilepticus or respiratory distress may need nursing care in PICU.

Discharge Criteria

- Patient may be discharged when vital signs have stabilized and there are no prolonged seizures.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients will need multispecialty clinic follow-up every few months for associated problems.

Patient Monitoring

Patients should be followed regularly for seizure control, joint contractures, scoliosis, nutritional, cardiac, pulmonary monitoring, and other supportive treatments.

DIET

- Low-salt diet may be needed for patients with cardiomyopathy and congestive heart failure.

PATIENT EDUCATION

In general, all types of CMDs are rare diseases and the patients need to be referred to muscular dystrophy association clinics or multiple specialty clinics for education and proper care.

PROGNOSIS

- Most patients with laminin-α_2–positive CMD die of respiratory failure during the second decade of life.
- Patients with complete laminin-α_2–deficient CMD can sit but never walk, and rarely may die of respiratory failure during infancy; those with partial laminin-α_2–deficiency can walk independently.
- In Fukuyama CMD patients, only some can stand at age 4, and a few rare patients can walk a few steps. Most die of respiratory failure by age 20.
- Patients with WWS usually die in the first few months of life.
- Those with muscle–eye–brain disease usually can sit and walk. Most can live to age 10–30.
- Patients with rigid spine CMD may develop early life-threatening respiratory insufficiency due to progressive weakness, spinal rigidity, and scoliosis. They require frequent respiratory therapy and may benefit from scoliosis surgical treatment such as timely spinal fusion.
- Lamin A/C-related CMD may have progressive muscle weakness with loss of ambulation in the first decade.
- FKRP-related CMD, LARGE-related CMD, Ullrich CMD and integrin-α_7–deficient CMD have slow clinical course.

COMPLICATIONS

- Patients may have progressive weakness and pneumonia; cardiac failure may result due to dilated cardiomyopathy.

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See Also (Topic, Algorithm, Electronic Media Element)

- Muscular dystrophy

CODES

ICD9

359.0 Congenital hereditary muscular dystrophy

CLINICAL PEARLS

- CMD is a rare congenital muscular dystrophy;
- Different genes are associated with CMD;
- Brain, eye, and other organs may also be affected.

MUSCULAR DYSTROPHY, DUCHENNE AND BECKER

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BASICS

DESCRIPTION

- Duchenne's muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD) are genetic disorders of muscle usually diagnosed during childhood. Both disorders are caused by recessive mutations in the dystrophin gene on the X chromosome.
- Natural history:
  - DMD usually results in clinical manifestations by age 2 or 3, and is diagnosed around age 5. Untreated patients require a wheelchair before age 13, with death occurring at a mean age of 19.
  - BMD usually manifests later, and many patients remain ambulatory into adulthood. Mean survival is into the fifth decade.
  - Multidisciplinary support and corticosteroid treatment significantly improve the prognosis, with DMD patients surviving into their fourth decade with a course more typical of BMD.
- Weakness involves proximal more than distal muscles, and lower more than upper extremities.
- Female carriers may also be affected, usually with a less severe phenotype than in males.
- Systems affected: Musculoskeletal, cardiovascular, central nervous systems
- Synonyms: "Dystrophinopathy" is a blanket term that encompasses DMD, BMD, and intermediate phenotypes.

EPIDEMIOLOGY

- Incidence
  - DMD: 1 per 3,600–6,000 live male births
  - BMD: 1 per 16,000–33,000 live male births
- Prevalence
  - 1.3–1.8 per 10,000 males, ages 5–24

RISK FACTORS

- See Genetics

Genetics

- The gene for dystrophin is located on Xp21.2, and is the largest known human gene. The gene product is 470 kilodaltons. Mutations are inherited in an X-linked recessive fashion, such that almost all affected patients are male.
- Severity of disease expression in carrier females relates to the proportion of active X chromosomes with mutant alleles, according to the Lyon hypothesis.
- 70% of cases are inherited from the mother; 30% are new mutations.
- DMD is caused by mutations (deletions, duplications, or point mutations), which disrupt the reading frame and result in absent dystrophin on muscle biopsy.
- Mutations in BMD preserve the reading frame of the gene, resulting in partial production of a gene product of abnormal size or function. Muscle biopsies in BMD show decreased dystrophin.

GENERAL PREVENTION

- Genetic counseling

PATHOPHYSIOLOGY

- Dystrophin is part of a cytosolic protein complex which anchors the muscle contractile machinery to the muscle cell membrane. Absent or dysfunctional dystrophin results in structural damage to the sarcolemma with contractions. Other possible mechanisms by which dystrophin deficiency might result in muscle damage include disrupted muscle blood flow or calcium regulation, and degradation of dystrophin-associated proteins at the sarcolemma.
- Fibrous tissue accumulation within muscles causes hypertrophy, usually most prominent in the calves, and may be the first clinical sign of disease.
- Dystrophin deficiency in cardiac muscle leads to dilated cardiomyopathy, congestive heart failure, and arrhythmias.
- Weakness of axial musculature leads to scoliosis with resulting compromise of lung volumes. This exacerbates respiratory failure related to diaphragmatic and intercostal weakness.

ETIOLOGY

- See Genetics.

COMMONLY ASSOCIATED CONDITIONS

- Musculoskeletal: bony fractures (20% of DMD patients), contractures, scoliosis
- Neuropsychiatric: Non-progressive cognitive dysfunction, depression
- Cardiac: Cardiomyopathy present in >90% of DMD and 60–70% of BMD
- Gastrointestinal: Dysmotility, volvulus, megacolon, cramping

DIAGNOSIS

HISTORY

- Normal birth history. Weakness begins in early life for DMD and is progressive. Patients have difficulty running, climbing stairs, and jumping, and fall frequently. Toe-walking often brings the patient to medical attention. There may be cognitive impairment, although this is not universal and is rarely the presenting manifestation.

PHYSICAL EXAM

- Musculoskeletal: Scoliosis, calf hypertrophy, contractures, weakness (proximal more than distal, lower more than upper extremities)
- Gowers' sign: In rising from the floor the patient braces their arms on the thighs to push the torso erect.
- Gait: Waddling, with tendency to walk on toes.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum creatinine kinase (CK) is typically 10–20 times the normal value in DMD, but is normal or up to 3 times the normal in BMD. CK peaks around age 2 and gradually decreases over time.
- Genetic testing for dystrophin mutations is mandatory for diagnosis, even if muscle biopsy is consistent with DMD (1)[A].

Follow-up & special considerations

- Elevated serum alanine and aspartate aminotransferase levels reflect damaged muscle, not hepatic pathology.

Imaging

Initial approach

- Plain films are mandatory in the evaluation of scoliosis, and may also detect cardiomegaly.

Follow-up & special considerations

- Patients with scoliosis should be referred to an orthopedic specialist for management.

Diagnostic Procedures/Other

- ECG shows tall, right, precordial R waves and increased R/S ratio, and deep Q waves in leads I, aVL, and lateral precordial leads.
- Electromyography is seldom necessary in DMD patients with a typical phenotype and elevated CK. However, it is sometimes useful, especially in older patients with BMD, to demonstrate the myopathic origin of the weakness
- Muscle biopsy is almost never needed for diagnosis in routine cases.

Pathological Findings

- Muscle biopsy shows fiber-size variation, degeneration/necrotic and regenerating fibers, and marked endomysial fibrosis.

DIFFERENTIAL DIAGNOSIS

- Other muscular dystrophies: Limb girdle (with multiple subtypes), facioscapulohumeral, Emery–Dreifuss, congenital
- Congenital myopathies
- Mitochondrial myopathies

TREATMENT

MEDICATION

First Line

- Glucocorticoids are the only agents shown to delay loss of strength in DMD (1,3)[A].
  - Prednisone: Standard dose is 0.75 mg/kg daily, although other dosing schedules have been used and are being studied (1)[B].
  - Treatment increases strength for 3–6 months, prolongs ambulation by 2–5 years, and improves limb and pulmonary function.
  - Prednisolone and deflazacort (not approved in the USA) are commonly used in other countries.
  - Patients derive maximum benefit from glucocorticoids during the plateau phase when they are no longer gaining motor skills but have not yet started to decline (1)[A].
  - Non-ambulatory patients may also benefit in maintenance of cardiac and pulmonary function and in prevention of scoliosis (1)[B].
  - Adverse effects of long-term steroid therapy (weight gain, glucose intolerance, hypertension, bone demineralization, etc.) require vigilant monitoring (1)[A].

Second Line

- Oxandrolone, an anabolic steroid, has limited efficacy data (4)[C].

ADDITIONAL TREATMENT

General Measures

- Patients benefit from multidisciplinary care involving neuromuscular specialists, cardiologists, pulmonologists, geneticists, physiatrists, orthopedists, and primary care physicians, as well as physical, occupational, respiratory, and speech therapists, and social workers (2)[A].

Issues for Referral

- Patients should be referred to a muscular dystrophy center for ongoing care (2)[A].

Additional Therapies

- Patients may benefit from a number of other treatments at various stages of disease, including noninvasive ventilation, scoliosis surgery, and treatment of cardiac complications.
- Nocturnal noninvasive ventilation with bilevel positive airway pressure and assistive cough devices improve survival (2)[A].

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Massage therapy can be utilized.
- Coenzyme Q10, carnitine, glutamine, arginine, fish oil, vitamin E, and green-tea extract are all used, but there is a lack of supporting evidence or expert consensus.

SURGERY/OTHER PROCEDURES

- Surgery may be useful to correct scoliosis.
- Gastrostomy feeding tubes and tracheostomy tubes may be utilized in late disease to improve respiratory and nutritional status.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- DMD and BMD are managed in the outpatient setting, with hospitalization necessary only for respiratory distress, cardiac complications, or surgical procedures.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients should be followed in a multidisciplinary muscular dystrophy clinic.

Patient Monitoring

- Patients should be clinically screened for scoliosis at every visit while ambulatory, and non-ambulatory patients should be screened with annual plain films for scoliosis of less than 20 degrees, and semiannual studies for greater degrees of scoliosis (2)[C].
- Respiratory parameters, such as forced vital capacity and pulse oximetry, should be followed closely in non-ambulatory patients (2)[B].
- ECG and cardiac ultrasound should be performed by age 6 and should be repeated every 2 years until age 10, when the frequency changes to annual (2)[C].
- Bone density studies should be performed at least yearly in patients on corticosteroids to monitor bone health (2)[C].

DIET

- Patients are at risk for malnutrition and osteoporosis, and thus may benefit from protein, calorie, calcium, and vitamin supplementation.
- Patients on corticosteroids need dietary regulation to limit weight gain and cushingoid side effects.

PATIENT EDUCATION

- Patients should be educated regarding prognosis, including the risks and benefits of interventions such as glucocorticoids, noninvasive ventilation, and scoliosis surgery.
- Patients and their families should be offered genetic counseling.

PROGNOSIS

- DMD: Untreated patients die during the second decade. Patients treated with glucocorticoids and multidisciplinary care may live into the fourth decade.
- BMD: Untreated patients generally live into adulthood. Glucocorticoids extend life expectancy, but this is not well-defined.

COMPLICATIONS

- Scoliosis, fractures, respiratory insufficiency, cardiomyopathy, cardiac arrhythmia.
- Adverse effects of glucocorticoid therapy: Obesity, glucose intolerance, hypertension, bone demineralization

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Muscular dystrophy, congenital
- Muscular dystrophy, fascioscapulohumeral
- Muscular dystrophy, myotonic dystrophy
- Myopathy, congenital
- Myopathy, metabolic

CODES

ICD9

359.1 Hereditary progressive muscular dystrophy

CLINICAL PEARLS

- DMD is an X-linked recessive disorder caused by mutations in the dystrophin gene, and involves progressive muscular weakness, loss of ambulation, and death in the second decade for untreated patients.
- Treatment with glucocorticoids slows disease progression and extends life expectancy.
- Common complications include scoliosis, respiratory insufficiency, cardiomyopathy, and cardiac arrhythmia. Multidisciplinary care is essential in managing these complications.
- BMD is also caused by mutations in the dystrophin gene, but carries a milder phenotype and more benign prognosis.

MUSCULAR DYSTROPHY, FACIOSCAPULOHUMERAL

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BASICS

DESCRIPTION

- Facioscapulohumeral muscular dystrophy (FSHD) is a chronic progressive myopathy characterized by weakness that is, at least initially, restricted to the facial and shoulder girdle muscles. Although the clinical presentation is typical in the majority of cases, there is some heterogeneity both in the pattern and severity of muscular weakness; some patients may be asymptomatic, while up to 20% may become wheelchair-bound.

EPIDEMIOLOGY

- Prevalence
  - 1 in 20,000, making it the third most common dystrophy after Duchenne's and myotonic dystrophy.

RISK FACTORS

Pregnancy Considerations

- Approximately 30% may experience a worsening of symptoms during pregnancy.
- Patients should be cautioned that proximal lower extremity weakness may increase fall risk.
- There is no clear evidence of increased fetal loss in patients with FSHD.

Genetics

- At least 95% of individuals with FSHD (Type 1) have a deletion of a critical number of 3.3-kb DNA tandem repeat units, known as D4Z4, on the long arm of chromosome 4 (4q35). Individuals with FSHD have 1–10 repeats, whereas normal individuals have 11 or more.
- The other 5% of patients (FSHD Type 2) have a clinically indistinguishable phenotype, but have a normal number of tandem repeats. These individuals have loss of DNA-methylation and heterochromatin markers at the D4Z4 repeat, similar to those seen in FSHD 1. However, whereas in FSHD1 the contraction of the repeat is thought to cause the chromatin changes, the primary genetic defect leading to chromatin changes in FSHD2 is yet to be determined.

PATHOPHYSIOLOGY

- Multiple hypotheses have been examined to explain how contraction of a critical number of D4Z4 repeats results in FSHD. Strong evidence now suggests that expression of the gene *DUX4*, usually silenced in somatic cells, results in FSHD.

  A loss of a critical number of D4Z4 repeats results in a change in the chromatin structure from a transcriptionally inactive (heterochromatic) to a transcriptionally active (euchromatic) state. This in turn allows the transcription of a gene, *DUX4*, from within the distal D4Z4 unit that is normally not expressed. However, stable transcripts occur only when the D4Z4 contraction occurs on 1 of 2 sequence variants (A or B) just distal to the repeats. Only the A variant contains a polyadenylation sequence (polyA) that is critical in stabilizing mRNA. Transfection experiments have shown that *DUX4* can induce apoptosis and interfere with myogenesis.

COMMONLY ASSOCIATED CONDITIONS

- Retinal telangiectasias are common on retinal fluorescein angiography. However, symptomatic retinal disease, consisting of an exudative retinopathy (Coat's disease) is rare.
- Atrial conduction abnormalities including atrial tachycardia, and mild conduction delay occur frequently, but are asymptomatic. High-grade atrioventricular block requiring a pacemaker is unusual and suggests an alternative diagnosis such as myotonic dystrophy, or rarely, Emery–Dreifuss muscular dystrophy.
- High-frequency deafness appears to be a frequent accompanying feature, and is usually mild. As with retinal vascular disease, symptomatic patients typically have severe, infantile-onset FSHD.
- Some patients, usually those with severe infantile-onset FSHD, may suffer from mental retardation and seizures.
- Symptomatic respiratory involvement occurs in ~1% of patients, typically in those confined to wheelchairs who have progressive kyphoscoliosis or in severely affected infantile-onset disease.

DIAGNOSIS

HISTORY

- Close attention to specific features of the history, inheritance pattern, and to the pattern of muscle weakness is important.
- The presence of slowly progressive facial weakness, scapular winging, and proximal upper extremity weakness sparing the deltoids is characteristic of FSHD. Side-to-side asymmetry of weakness is often a prominent feature.
- Most patients present during the second decade with slowly progressive proximal upper extremity weakness and are usually unaware of facial weakness. However, on specific inquiry a history of sleeping with eyes open, inability to whistle, or difficulty drinking with a straw is usually elicitable. The most frequent presenting symptom is difficulty with reaching overhead due to periscapular muscle weakness.

PHYSICAL EXAM

- Facial weakness is prominent in most patients (e.g., an inability to bury the eyelashes fully, pout the lips, or whistle, and dimples may be noted at the corners of the mouth with resultant reduction in facial expressivity). Extraocular and bulbar muscles are characteristically spared. The pectoral muscles are often atrophic, leading to axillary creasing; the clavicular angle is flattened. The scapula is prominent and deviates outward and upward on shoulder abduction and elevation. The deltoid is spared, but the biceps and triceps are often affected. This, in combination with relative preservation of the forearm muscles, gives the arm a distinctive "Popeye" appearance.
- Frequently, there is prominent abdominal muscle weakness with an exaggerated lumbar lordosis, and a deviation of the umbilicus in the vertical direction (usually upward) upon attempting a sit-up (Beevor's sign). This is a feature uncommon in other myopathies. Initially, lower extremity involvement is mild and typically restricted to distal muscles, particularly the anterior tibial compartment. However, as the disease progresses, patients usually develop hip-girdle as well as knee extensor and flexor weakness.
- Disease progression is typically descending, starting in the facial and scapular–fixator muscles and later involving the upper arm, distal lower extremity, and hip-girdle muscles. Most patients relate a slow, steady progression, although some patients describe a stuttering course with periods of slow or no progression interrupted by periods of more rapid loss of muscle strength.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum creatine kinase (CK) may be elevated 3–5 times the normal; levels higher than this are atypical and might suggest alternative causes (e.g., certain limb-girdle syndromes, or less commonly, an inflammatory myopathy).

Diagnostic Procedures/Other

- Needle electromyography (EMG) is typically myopathic, with increased insertional activity, but otherwise without specific features.
- The availability of a sensitive and specific molecular diagnostic test precludes the need for diagnostic muscle biopsy in most cases of suspected FSHD. Muscle biopsy should only be performed when molecular testing is negative.
- Accurate molecular diagnosis, performed on blood leukocyte DNA, has a sensitivity and specificity of ≥95%. The test employs a DNA probe that detects, after restriction enzymes digestion, restriction fragments on 4q35 that contain the 3.3-kb repeat units. Unaffected individuals have 2 4q35 alleles >50-kb in size; patients with FSHD will have 1 allele between 10 and 38 kb in size. Although testing for FSHD1 described above is widely available, clinical diagnostic testing for FSHD2 is only available on a research basis. Genetic Testing:
  - Athena Diagnostics, 377 Plantation St., Worcester, MA 01605. Website www.AthenaDiagnostics.com.
  - University of Iowa Hospitals and Clinics, Department of Pathology, Microbiology Laboratory, 200 Hawkins Dr., Boyd Tower 6004 GH, Iowa City, IA 52242-1182; contact Beth Alden: beth-alden@uiowa.edu.
  - See www.genetests.org for complete listing of all diagnostic laboratories.

Pathological Findings
- Muscle biopsy findings are myopathic, with a variable degree of perivascular inflammatory infiltrate, but otherwise nonspecific.
- Muscle biopsy in individuals with negative DNA testing serves to exclude other myopathic conditions.

DIFFERENTIAL DIAGNOSIS
- This includes myopathic and neurogenic causes.
- Idiopathic brachial plexopathy: A prominent history of acute onset of severe shoulder and/or neck pain, followed by weakness and atrophy of shoulder girdle muscles; usually differentiates idiopathic brachial plexopathy from FSHD
- Spinal muscular atrophy syndromes may rarely present with a scapuloperoneal distribution of weakness (e.g., Davidenkow's syndrome). Differentiation on clinical grounds may be difficult, but needle EMG will show characteristic neurogenic changes.
- Atypical presentations of inflammatory myopathies (e.g., polymyositis) are suggested by marked neck flexor weakness. Patients with FSHD usually have relative sparing of the neck flexors while the neck extensors may be quite weak.
- Other dystrophies (e.g., limb-girdle dystrophy): Patients with limb-girdle dystrophies may have significant scapular winging resembling FSHD although typically with only minimal facial weakness. Emery–Dreifuss muscular dystrophy, an X-linked condition, has a scapuloperoneal distribution of weakness resembling FSHD. However, unlike FSHD, they also have prominent contractures, minimal facial involvement, and a characteristic cardiac rhythm disturbance (atrial standstill).
- Myotonic dystrophy presents with marked facial weakness and distal limb weakness, but without characteristic scapular involvement. Clinical examination will usually demonstrate myotonia, confirmed by needle EMG study.

TREATMENT

MEDICATION
There are no specific pharmacologic interventions proven to slow or reverse disease progression.
- Chronic pain is a common complaint in FSHD involving the shoulders, neck, and back and may require treatment with tricyclic antidepressants or other medications used to treat chronic musculoskeletal pain.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Supportive interventions include ankle–foot orthoses for foot drop and various forms of knee bracing. Several bracing techniques have been devised to improve shoulder mobility with variable success. In general, such bracing has to be tight-fitting, making it impractical for prolonged daily use.
- Physical therapy is of benefit to maintain range of motion and prevent joint contractures. The role of exercise in FSHD has not been fully studied. In general, a low- to moderate-intensity exercise program is felt to be safe in FSHD.

ADDITIONAL TREATMENT
General Measures
Treatment is largely symptomatic.

Additional Therapies
- Surgical fixation of the scapula to the chest wall improves shoulder range of motion but can be associated with a number of complications if not performed by experienced surgeons. Careful consideration of residual muscle strength, rate of disease progression, and the presence of fixed range-of-motion limitation of the shoulder joint should be made before considering this surgical procedure.

IN-PATIENT CONSIDERATIONS
Admission Criteria
- Admission is generally not required except for rare cardiac or respiratory complications.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Follow-up at 6- to 12-month intervals is a reasonable approach depending on disease severity and rate of progression.

Patient Monitoring
- In patients susceptible to respiratory muscle weakness, monitoring of respiratory parameters is advisable, and screening for symptoms of nocturnal hypoventilation (e.g., morning headaches, daytime somnolence).
- Screen for retinal vascular disease by indirect ophthalmoscopy. Early detection and treatment of significant retinal vascular disease can prevent the development of exudation, retinal detachment, and loss of vision.

Pediatric Considerations
- In infantile-onset FSHD:
  - Screen for hearing loss: Undetected severe hearing loss can delay language development.

DIET
- There are no proven dietary recommendations.

PATIENT EDUCATION
- MDA; 3300 East Summit Dr., Tucson, AZ 85718-3208. Website http://www.MDAUSA.org.
- FSH Society Inc.; 3 Westwood Rd., Lexington MA 02420. Website http://www.fshsociety.org.
- Fields Center for FSHD research, University of Rochester Medical Center, Rochester, NY: http://www.urmc.rochester.edu/fields-center/

PROGNOSIS
- Because of the slow progression of FSHD, most individuals adapt remarkably well to their disabilities and remain relatively functional. However, ~20% of patients become nonambulatory. Lifespan is shortened in rare patients in whom progressive respiratory muscle weakness develops.

COMPLICATIONS
- In rare cases (1%), respiratory embarrassment may occur and may require non-invasive or invasive ventilator support.

ADDITIONAL READING

- De Greef JC, Lemmers RJLF, Camano P, et al. Clinical features of facioscapulohumeral muscular dystrophy 2. *Neurol* 2010;75:1548–1554.
- Tawil R, Van der Maarel S. Facioscapulohumeral muscular dystrophy. *Muscle Nerve* 2006;34:1–15.
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- Van der Maarel SM, Tawil R, Tapscott SJ. Facioscapulohumeral muscular dystrophy and DUX4: breaking the silence. *Trends Molecular Medicine* 2011;17:252–258.

CODES

ICD9
- 359.1 Hereditary progressive muscular dystrophy
- 728.87 Muscle weakness (generalized)

CLINICAL PEARLS
- Consider FSHD whenever a patient presents with a combination of asymmetric scapular winging and facial weakness.
- Beevor's sign: Among the dystrophies, a positive Beevor's sign is seen almost exclusively in FSHD.
- Typical FSHD shoulder profile: Forward sloping of shoulders, flattened clavicles, axillary creases (pectoral muscle atrophy) and strong deltoids.

MUSCULAR DYSTROPHY, MYOTONIC DYSTROPHY

Bakri H. Elsheikh, MBBS, FRCP

BASICS

DESCRIPTION

- Myotonic dystrophy (MD) is an autosomal-dominant inherited, multisystem disorder characterized by slowly progressive muscle weakness and wasting associated with myotonia and abnormalities of many other organ systems.
- In addition to the skeletal muscles, it affects the heart, eyes, smooth muscles, CNS, and endocrine system.
- There are 2 genetically distinct forms:
  - Myotonic Dystrophy type 1 (DM1), also known as 'Steinert's disease'.
  - Myotonic Dystrophy type 2 (DM2), also known as proximal myotonic myopathy (PROMM)

EPIDEMIOLOGY

- Incidence
  - It is the most common adult muscular dystrophy with an estimated incidence of 1 per 8,000 live births. Higher incidence is reported in specific regions, such as Quebec (1 per 500).
- Prevalence
  - Estimated for DM1 at 3–5 per 100,000
  - DM2 appears to have a lower prevalence than DM1, but this could be related to under diagnosis.

RISK FACTORS

- Positive family history.

Genetics

- DM1 and DM2 are autosomal dominant disorders.
- DM1 is caused by an expansion of CTG trinucleotide repeats in the untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19 q13.3
  - Healthy individuals have 5–37 CTG repeats.
  - Affected individuals have 50–4,000 CTG repeats
  - Individuals with 38–49 repeats are asymptomatic but at risk of having children with pathologically larger repeats.
  - Babies with congenital myotonic dystrophy have >750 repeats.
- DM2 is caused by an expansion of CCTG repeats in the untranslated region of the zinc finger protein-9 (*ZNF9*) gene on chromosome 3q21.3
- Healthy individuals have <75 repeats.
- Affected individuals have 75–11,000 repeats.
- Anticipation is a phenomenon of increased disease severity and earlier age of onset in subsequent generations.
- It occurs in DM1 but less evident in DM2

PATHOPHYSIOLOGY

- Toxic gain of function of the mutant RNA is the likely disease mechanism leading to this multisystem disorder.
- Aggregates of the mutant mRNA retained in the nucleus appear to exert a toxic effect on the cells by disabling RNA-binding proteins such as the muscle-blind proteins.
- This results in abnormal splicing of other pre-mRNA transcripts from various target organs such as chloride ion channel, insulin receptor, cardiac troponin and tau protein, resulting in the multiple system manifestations.

ETIOLOGY

- See above (Genetics and Pathophysiology).

COMMONLY ASSOCIATED CONDITIONS

- Cardiac
  - Cardiac conduction defects
  - Tachyarrythmia
    - Atrial flutter/fibrillation
    - Supraventricular tachycardia
    - Ventricular tachycardia
- Sudden cardiac death
- Cardiomyopathy may occur.
- Gastrointestinal
  - Dysphagia/esophageal dysmotility
  - Constipation
  - Colonic hypomotility/megacolon
  - Intestinal pseudo-obstruction
  - Gallstones
- Respiratory
  - Aspiration pneumonia
  - Alveolar hypoventilation
  - Pulmonary hypertension
- Sleep
  - Excess daytime somnolence
  - Sleep apnea
  - Periodic limb movements in sleep
- Eyes
  - Posterior sub-capsular cataract
- Endocrine
  - Testicular atrophy and infertility
  - Menstrual irregularities
  - Insulin resistance
  - Thyroid disease
- Neurobehavioral
  - Personality traits.
    - Obsessive-compulsive
    - Passive-aggressive
    - Avoidant
  - Anxiety and depression are often seen
  - Frontal–parietal lobe cognitive impairment has been documented on formal testing.
  - Mental retardation (congenital form)
- Skeletal and skin
  - Frontal bossing and high arched palate
  - Pilomatrixomata and epitheliomas can occur, especially on the scalp

DIAGNOSIS

HISTORY

- MD can present at any age including infancy.
  - Classic DM1 patients symptoms starts in late teens up to age 50 whereas DM2 patients' symptoms tend to start in the third decade.
- Patients have a slowly progressive weakness and atrophy of the facial, jaw, and distal limb muscles.
  - Proximal muscles are usually preserved until a later stage in DM1.
- Myotonia is the delay of muscle relaxation after contraction. Although usually present, it is rarely disabling. Occasionally, it interferes with daily activities such as ability to use tools.
- DM2 patients similarly present with weakness, myotonia, and share most of the extramuscular manifestations of DM1; however, they tend to have an early and prominent proximal muscle weakness. Involvement of the facial muscles is infrequent.
- Muscle pain is more prominent in DM2.
- Infants with congenital myotonic dystrophy have severe facial muscle weakness, hypotonia, feeding difficulties, mental retardation, and respiratory failure. Clues to the diagnosis come from examining the mother. There are no reports of congenital form in the DM2 type.

PHYSICAL EXAM

- Frontal baldness
- Ptosis
- Hatchet face
- Temporalis and masseter muscles atrophy
- Thinning of the neck muscles
- Myotonia
  - Elicited by percussion of the thenar eminence or forearm posterior (wrist extensor) muscles or by release after sustained handgrip
  - Repetitive contractions diminish the myotonia.
- Weakness
  - Neck flexor weakness, early in DM1 and DM2
  - Distal predominant in DM1 with early involvement of the distal forearm and ankle dorsiflexor muscles
  - Proximal predominant in DM2 with early involvement of the hip flexors and elbow extensors

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Molecular genetic testing, the gold standard test for establishing the diagnosis, detects mutations in nearly 100% of affected individuals.
- Serum creatine kinase (CK) is usually normal or mildly elevated.
- EMG usually reveals normal sensory and motor nerve conduction studies. Needle EMG demonstrates myotonic discharges, fibrillation potentials, and myopathic motor unit potentials. The latter can be difficult to appreciate because of the myotonic discharges.
- In DM2 patients electrical myotonia is described in 90%; thus, sampling of multiple muscles is important.

Follow-up & special considerations

- ECG may show cardiac conduction defects.
- Pulmonary function test may show restrictive thoracic disorder. Supine and sitting forced vital capacity measurements help detect diaphragm weakness.

Imaging

Initial approach

- Brain MRI often shows mild atrophy and subcortical white matter changes.

Pathological Findings

- Muscle biopsy, seldom needed, reveals nonspecific features including muscle fiber variability, numerous internal nuclei, type 2 fiber atrophy, and nuclear clumps.

DIFFERENTIAL DIAGNOSIS

- Non-dystrophic myotonic disorders
- Neuromyotonia (Isaac's syndrome)
- Inclusion body myositis (IBM)
- Distal myopathies.
- Limb girdle muscular dystrophies.

TREATMENT

MEDICATION

First Line

- There is no cure or therapy to stop progression or increase muscle strength.
- Myotonia rarely requires treatment; however, if disabling or bothersome, Mexiletine or phenytoin can be considered.

Second Line

- Quinine and procainamide are effective agents to treat myotonia but should be avoided because they can impair cardiac conduction and prolong the PR interval.

ADDITIONAL TREATMENT

General Measures

- Only supportive care and symptomatic treatment is available.

Issues for Referral

- Cardiology, if abnormal EKG or symptomatic
- Sleep specialist if symptoms of sleep apnea
- Ophthalmology for cataract
- Speech therapy for swallow evaluation

Additional Therapies

- Bilevel positive airway pressure (Bi-Pap) and modafinil are effective in reducing excess daytime somnolence
- Physical and occupational therapy
- Ankle–foot orthosis for foot drop

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Pulmonary hygiene, incentive spirometry, and cough and deep breathing exercises.

- Children with congenital myotonic dystrophy require intervention if developmental delay and/or mental retardation exists.

SURGERY/OTHER PROCEDURES

- Cataract may require excision
- Cardiac pacemaker and or defibrillator implantation

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- ECG annually with low threshold for cardiology referral if symptomatic or abnormal ECG. Additional studies including echocardiography, 24-hour Holter monitor, and EP studies are needed in some patients. Cardiac pacemaker and/or defibrillator implantation is required in some patients.
- Patients should be screened for sleep complaints and referred for polysomnography and sleep evaluation when appropriate.
- Ophthalmic examination every year to detect cataracts.
- Serial forced vital capacity measurement

PATIENT EDUCATION

- Genetic counseling is recommended for all considering reproduction, especially when the affected person is female due to the risk of congenital myotonic dystrophy.
- Muscular Dystrophy Association (MDA) website: http://www.mdausa.org/disease/dm.html

PROGNOSIS

- Life expectancy is reduced; the median age of death is ~60 years.
- The most common causes of death are cardiac and respiratory.

COMPLICATIONS

- Cardiac
- Respiratory

ADDITIONAL READING

- Annane D, Moore DH, Miller RG. Psychostimulants for hypersomnia (excessive daytime sleepiness) in myotonic dystrophy. *Coch Datab Syst Rev* 2011;2.
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See Also (Topic, Algorithm, Electronic Media Element)

- Steinert's disease and PROMM

CODES

ICD9

359.21 Myotonic muscular dystrophy

CLINICAL PEARLS

- Myotonic dystrophy is the most common adult muscular dystrophy.
- It is not a muscle disease but a multisystem disorder.
- Despite the lack of cure, proper screening and management can possibly reduce morbidity/mortality.

MYASTHENIA GRAVIS

Noor A. Pirzada, MD

BASICS

DESCRIPTION

- Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies directed against the postsynaptic receptors at the neuromuscular junction (NMJ) including the acetylcholine receptor (AchR) and the muscle-specific kinase (MuSK) receptor. Its main feature is muscular weakness which often fluctuates, worsening with activity and improving with rest. The muscle weakness has a distinctive pattern with the ocular and bulbar muscles being the most commonly affected.
- Congenital MG is a rare nonimmunologic form due to genetic defects at presynaptic, synaptic, or postsynaptic locations in the NMJ. It usually manifests soon after birth or in early life.

EPIDEMIOLOGY

Incidence

- Incidence is 1–9 per million.
- Age of onset is bimodal for both men and women. Peak incidence for women is between 20–24 and 70–75 years. Men have peak rates between 30–34 and 70–74 years. In the early disease onset group female-to-male ratio is 7:3 while in the late onset group gender ratio is 1:1.

Prevalence

Prevalence is 25–142 per million.

RISK FACTORS

Many medications worsen preexisting MG but D-penicillamine and α-interferon can cause MG.

Genetics

MG is not transmitted by Mendelian inheritance. There is a moderate association with human leukocyte antigens (HLAs) B8, A1, and DRw3.

PATHOPHYSIOLOGY

Normally with repetitive muscle contraction the quanta of acetylcholine (Ach) released from the presynaptic nerve terminal decreases but the end plate potential (EPP) stays above the threshold required to cause muscle depolarization ("safety factor") and muscle weakness does not occur. In MG because of loss of AchRs the decrease in Ach quanta causes the EPP to fall below threshold leading to failure of muscle depolarization and muscle weakness.

ETIOLOGY

MG is an autoimmune disease of the NMJ with production of antibodies directed against postsynaptic receptors in the NMJ. About 70% of patients have thymic hyperplasia, while 20% have thymomas. Muscle-like (myoid) cells in the thymus express the AchR antigen. A breakdown in immune tolerance to self-antigens occurs within the gland, initiates antibody production to the AchR antigen expressed on its cells which leads to impaired transmission at the NMJ.

COMMONLY ASSOCIATED CONDITIONS

- Graves disease and autoimmune thyroiditis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyositis
- Aplastic anemia

DIAGNOSIS

HISTORY

The ocular muscles are most commonly involved; ptosis and diplopia are the initial symptoms in 70% of cases, and present in 90% of cases at some time. Bulbar muscle weakness with dysphagia and dysarthria, is the initial presentation in 15% of patients with eventual involvement in 70–80% of cases. Presentation as limb weakness is seen in only 15%. With severe disease, diaphragm and chest muscles weakness may cause respiratory insufficiency (myasthenic crisis). Weakness is fluctuating, usually mildest in morning and worsening with activity.

PHYSICAL EXAM

- Ptosis and ocular muscle weakness, often asymmetric, is seen in most patients. Medial rectus is most frequently affected. Weakness of eye closure is common. Nasal and slurred voice, jaw weakness, and neck flexor weakness occur. In limbs deltoid, triceps, wrist and finger extensors, and ankle dorsiflexors more frequently involved.
  - Assess muscle strength repetitively during maximum effort and then after rest to demonstrate fluctuation
  - MG that is confined to the eyes for 2 years or more is called ocular MG. When symptoms spread beyond the eye muscles it is classified as generalized MG

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum AchR antibodies occur in >90% of patients with generalized MG and in 50–70% with ocular myasthenia. MuSK antibodies are positive in 40% of patients who are AChR antibody-negative. The anti-striated muscle Ab occurs in 70–80% of MG patients with thymoma but is also positive in 30% of MG patients without thymoma.
- Thyroid function tests should be performed to rule out associated autoimmune thyroid disease, as myasthenic patients respond best to treatment in the euthyroid state.
- Systemic infections are a common cause of exacerbations and should be ruled out.

Imaging

CT scan/MRI of the chest is done to rule out thymoma.

Diagnostic Procedures/Other

- Edrophonium hydrochloride (Tensilon) test: Tensilon prevents the breakdown of Ach at the NMJ and improves muscle weakness in myasthenic patients. Tensilon is preferred for diagnostic testing as it can be given intravenously, and has rapid onset (30 seconds) and a short duration of action (about 5 minutes). The test is considered positive when there is unequivocal improvement in an objectively weak muscle. A fractionated test is performed in which 2 mg are given initially, and two further doses of 4 mg are then given at 5-minute intervals if required.
- EMG and nerve conduction: Repetitive nerve stimulation and single-fiber EMG demonstrate defective transmission at the NMJ.

Pathological Findings

- There is marked hyperplasia of the medulla of the thymus in the majority of cases characterized by lymphoid follicles with active germinal centers.
  - Two forms of thymic tumors occur, one composed of histiocytic cells and the other predominantly lymphocytic and considered to be lymphosarcomatous.

DIFFERENTIAL DIAGNOSIS

Patients presenting with ocular or bulbar involvement may be misdiagnosed with stroke, motor neuron disease, multiple sclerosis, or cranial nerve palsies. Patients with acute generalized weakness can be misdiagnosed with botulism or Guillain–Barre syndrome. Diseases characterized by excessive fatigability like Lambert–Eaton myasthenic syndrome or fibromyalgia may be misdiagnosed as MG.

TREATMENT

MEDICATION

First Line

- The drugs used depend on extent of the disease and on how quickly a therapeutic effect is needed.
- Cholinesterase inhibitors: Prevent breakdown of Ach allowing it to accumulate at the NMJ. Pyridostigmine (Mestinon) is preferred because of its long duration of action (4–6 hours). It is available in 60-mg tablets and is started in a dose of 30 mg t.i.d. and increased according to response. It provides symptomatic treatment only. Mestinon may be the only treatment required for ocular myasthenia, but immunosuppressive drugs must be added in generalized MG. This is the first-line treatment for pregnant patients.

- Corticosteroids: Prednisone is most often used, in a dose of 1.5–2 mg/kg/day. More than 75% of patients show improvement within 2 weeks and are then switched to an alternate-day schedule. The dose is slowly reduced over many months to the lowest dose necessary to maintain improvement; 25% of patients show a transient initial worsening when prednisone is started, and this requires an increase in the dose of Mestinon or, in more severe cases, plasmapheresis. Prednisone is the immunosuppressive agent of choice during pregnancy.

Second Line

- Cyclosporine: A useful alternative if steroids are contraindicated or cause unacceptable side effects. The dose is 5–6 mg/kg/day given in two divided doses 12 hours apart. The dose is adjusted to maintain a trough of serum cyclosporine concentration of 75–150 ng/mL. Improvement is seen within 1–2 months after starting the drug. Monitor urea and creatinine due to potential for nephrotoxicity. Blood pressure may rise and need appropriate treatment.
- Azathioprine: It provides relief of symptoms in most patients, but its effect is delayed by 4–8 months. It is usually started in a dose of 50 mg/day and increased weekly by 50 mg to a total of 150–200 mg/day. It is indicated in patients who do not respond to corticosteroids or require large doses that are producing severe side effects.
- It can cause leukopenia and hepatitis and this requires regular monitoring of CBC and liver function tests. An idiosyncratic reaction with flu-like symptoms can occur in the first 2 weeks of treatment and requires discontinuation of the drug.
- Mycophenolate mofetil: It can be used as an alternative to prednisone when it is not effective or very large doses are required. Improvement usually occurs within the first 3 months of treatment. The dose is 1–2 g/day in two divided doses. The major side effect is diarrhea but at higher doses it can cause leukopenia. An association with progressive multifocal leukoencephalopathy has been reported.
- Cyclosporine, azathioprine, and mycophenolate cannot be used during pregnancy.

ADDITIONAL TREATMENT

- Plasmapheresis provides the most rapid therapeutic benefit and is the treatment of choice for severe generalized disease and respiratory embarrassment. A typical protocol consists of removing 2–3 L of plasma three times a week for a total of 5–6 exchanges. Improvement is usually seen within 48 hours of the first exchange.
- Intravenous immunoglobulin (IVIG) also produces improvement in MG. It can be used for patients in crisis who are refractory to treatment with plasmapheresis and steroids or if plasmapheresis is contraindicated. Effects are seen within a week. The dose is 400 mg/kg/day for 5 days. IVIG and plasmapheresis have been used during pregnancy for acute management of severe exacerbations.

SURGERY/OTHER PROCEDURES

Elective thymectomy is recommended for all MG patients with thymomas due to the potential for local and metastatic spread. Prior to thymectomy, effective immunosuppressive treatment must be used to render the patient asymptomatic as this greatly reduces postoperative morbidity and mortality. For patients without thymomas the role of thymectomy is not as clear. In young patients (<50 years) without thymoma surgery can be considered as an option to increase the chances of improvement and remission with immunosuppressive treatment. Clinical data suggest that thymectomy does not benefit MuSK antibody-positive patients.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

In an acute exacerbation, respiratory function should be monitored closely with forced vital capacity (FVC) and negative inspiratory force (NIF) measurements every 4 hours. FVC of <1 L and an NIF of less than −20 are indications for elective intubation. The patient's medications should be screened for drugs that can exacerbate myasthenia, and these should be discontinued or changed whenever possible. Such drugs include aminoglycoside antibiotics, beta-blockers, calcium channel blockers, quinidine, etc.

Admission Criteria

Most patients with MG can be treated on an outpatient basis. Patients with rapidly progressive weakness or with respiratory insufficiency should be admitted to an intensive care unit setting until they show improvement in weakness and respiratory function.

Discharge Criteria

Patients can be discharged once respiratory function tests and clinical examination show that breathing is stable, there is no significant swallowing difficulty and ambulation is safe.

ONGOING CARE

PATIENT MONITORING

- Patients discharged from the hospital should be seen in the clinic in 2–4 weeks and once stable can follow up at intervals of 4–6 months.
  - Periodic laboratory tests are usually required to monitor side effects of medications, such as LFT, CBC for azathioprine or BUN, creatinine for cyclosporine.

DIET

If bulbar symptoms occur during an exacerbation oral intake should be stopped and once swallowing improves with treatment a normal diet can be resumed.

PATIENT EDUCATION

Exacerbations of the disease can be caused by systemic infections; patients should therefore see their physician promptly if they experience symptoms such as fever, productive cough, etc.

PROGNOSIS

If MG remains confined to ocular muscle 2 years or longer, there is little chance it will generalize. In generalized MG complete relief of symptoms or marked improvement occurs in >75% of patients with immunosuppressive treatment; some improvement occurs in the rest. With prompt, appropriate treatment most patients in a crisis survive. With optimum treatment the majority of patients lead normal lives.

COMPLICATIONS

- Aspiration from involvement of bulbar muscles with dysphagia
- Respiratory failure due to involvement of respiratory muscles

ADDITIONAL READING

- Batocchi AP, et al. Therapeutic apheresis in myasthenia gravis. *Ther Apher* 2000;4(4):275–279.
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See Also (Topic, Algorithm, Electronic Media Element)

- Lambert–Eaton syndrome

CODES

ICD9

- 358.00 Myasthenia gravis without (acute) exacerbation
- 728.87 Muscle weakness (generalized)

CLINICAL PEARLS

- MG is characterized by fluctuating fatigable weakness of ocular, oropharyngeal, axial, and/or limb muscles. Sensations and reflexes are normal.
- Pyridostigmine improves symptoms and can be used as the sole therapy in ocular myasthenia. Generalized MG requires immunosuppression.
- Thymectomy is indicated for presence of thymoma and can be considered in young patients without thymoma, to improve response to immunosuppressive medications.

MYOADENYLATE DEAMINASE DEFICIENCY

David S. Younger, MD

BASICS

DESCRIPTION

Myoadenylate deaminase (mAMPD) deficiency is a clinically diverse disorder of skeletal muscle adenosine triphosphate (ATP) catabolism due predominantly to inherited defects in the *AMPD1* gene. Most individuals with this metabolic derangement are asymptomatic, while others are grouped according to clinical, biochemical, and molecular criteria. Exertional myalgia and intolerance without other clinical complications typically characterize symptomatic, inherited, mAMPD deficiency. Acquired and coincidental mAMPD deficiencies are both secondary to a wide variety of other definable clinical diseases but differ in molecular criteria.

EPIDEMIOLOGY

Common, with an incidence of ~2% in the entire Caucasian and African-American populations.

- Age
  - Most individuals are asymptomatic. Affected individuals can present as young as 18 months of age and up to age 76. Most commonly, clinical features have appeared in more than half of all reported cases in the teenage and young-adult years.
- Sex
  - Affects both males and females consistent with the location of the *AMPD1* gene on the short arm of chromosome 1 (p13-p21). The inheritance follows an autosomal-recessive pattern.
- Race
  - Prevalent in Caucasians and African Americans, but rare in Japanese owing to the apparent absence of a common mutation found in the former populations.

RISK FACTORS

Other than inheritance of *AMPD1* mutant alleles, additional risk factors related to symptomatic inherited mAMPD deficiency, although suspected, have not been identified.

Pregnancy Considerations

A normal pregnancy, labor, and delivery without complications have been reported in a woman with symptomatic inherited mAMPD deficiency.

ETIOLOGY

All individuals with inherited forms of mAMPD deficiency have identified defects in the *AMPD1* gene. Independent of grouping, the predominant mutant allele in Caucasians and African Americans is defined by double C–T transitions at nucleotide +34 and +143 in the *AMPD1* open reading frame. The former is the dysfunctional mutation and results in a Q12X nonsense codon and premature termination of mAMPD polypeptide translation. Prevalence of the common *AMPD1* mutant allele in Caucasian sample groups (10–14%) is sufficient to account for the combined incidence of all forms of mAMPD deficiency in this population. Other rare mutations have also been identified that result in single amino acid substitutions (Q156H in Caucasians and R388W and R425H in Japanese). Individuals with acquired mAMPD deficiency are simple heterozygotes for *AMPD1* mutations in which pathology related to the associated disorder reduces *AMPD1* expression from the normal allele into the deficient range.

COMMONLY ASSOCIATED CONDITIONS

Coincidental inherited and acquired mAMPD deficiencies have been reported secondary to a wide variety of other definable clinical disorders too numerous to list. The relationship of mAMPD deficiency to clinical involvement in most of these individuals is unknown and may simply reflect the prevalence of *AMPD1* mutations in the general population. Consequently, the number of associated disorders in these 2 groups of mAMPD-deficient individuals should not be limited to those already described. Notably, clinical symptoms can be more severe than either condition alone when a coincidental inherited mAMPD deficiency is combined with another defect in energy metabolism (termed "double trouble"). In addition, clinical symptoms have been observed in patients with documented multiple partial defects in energy metabolism (including *AMPD1*), a condition referred to as synergistic heterozygosity.

DIAGNOSIS

Symptomatic inherited mAMPD deficiency presents with diffuse symptoms that can include exercise intolerance, fatigue, muscle aches, and pain. This form of the disease is generally not progressive, although some individuals do experience more persistent symptoms over time. Exercise-induced myoglobinuria has been exceptionally reported. Limb muscles, particularly lower ones, are most symptomatic. Cranial, trunk, and respiratory muscles are spared. Even in symptomatic patients, clinical weakness is unusual. Clinical complications of coincidental inherited and acquired mAMPD deficiency are generally defined by the associated disorders that are typically more severe.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Serum creatine kinase (CK) level may be slightly elevated. Electromyography (EMG) is often normal, but may reveal small-amplitude, short-duration, motor unit potentials in symptomatic proximal muscles. Serum uric acid elevation has been described. A blunted venous ammonia response during ischemic forearm exercise provides a relatively noninvasive and sensitive diagnostic test for mAMPD deficiency. However, the subject has to perform enough work to prevent a false-negative diagnosis. Adequate effort should produce a concurrent rise in venous lactate of 2.5–4 mmol/L (~20–35 mg/dL). If mAMPD deficiency is indicated, the diagnosis can be confirmed from muscle biopsy material using enzymatic assay or histochemical stain.

Diagnostic Procedures/Other

Polymerase chain reaction (PCR)-based tests are available to identify the C34T mutation in genomic DNA from fresh whole blood.

DIFFERENTIAL DIAGNOSIS

- Symptomatic inherited mAMPD deficiency
- Exertional myalgia (undefined)
- Fibromyalgia

TREATMENT

MEDICATION

No medications are currently available for symptomatic inherited mAMPD deficiency.

ADDITIONAL TREATMENT

General Measures

Individuals with symptomatic inherited mAMPD deficiency tend to adopt a more sedentary lifestyle in response to their exertional myalgia. However, mild to moderate exercise should be encouraged in these patients as it may promote exercise tolerance. Management of coincidental inherited and acquired mAMPD deficiencies is dictated by treatments appropriate for the associated disorder.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - There is no reliable treatment available for individuals with symptomatic inherited mAMPD deficiency. Oral administration of 5-carbon sugars, such as ribose and xylitol, reportedly have minimized exertional myalgia in some individuals with symptomatic mAMPD deficiency, whereas this strategy has been ineffective for others. These sugars are reasonably well tolerated at doses of 15–20 g/day without significant side effects. Treatment of coincidental inherited and acquired mAMPD deficiencies follows courses appropriate for the associated disorder.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Individuals with symptomatic inherited mAMPD deficiency may seek follow-up if they perceive a change in their generally diffuse symptoms or become frustrated with their modified lifestyle. Monitoring of those with coincidental inherited and acquired mAMPD deficiencies will be dictated by the associated disorder.

PATIENT EDUCATION

- The Muscular Dystrophy Association maintains a website related to mAMPD deficiency: http://www.mdausa.orgjdisease/mad.html.

PROGNOSIS

Although symptomatic inherited mAMPD deficiency is generally not progressive, some individuals experience a worsening of symptoms, such as cramping and pain even at rest. Emotional issues can also develop over time due to patient or physician frustration arising from a lack of reliable treatment. The course and prognosis of coincidental inherited and acquired mAMPD deficiencies should be dictated by the associated disorder.

ADDITIONAL READING

- Fishbein WN, Armbrustmacher WV, Griffin JL. Myoadenylate deaminase deficiency: a new disease of muscle. *Science* 1978;200:545–548.
- Younger DS, Hirano M, DiMauro S. Metabolic myopathies. Chapter 12. In: DS Younger, ed., *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2005.

See Also (Topic, Algorithm, Electronic Media Element)

- MDD
- MADD
- Muscle adenylate deaminase deficiency
- Muscle adenylic acid deaminase deficiency
- Muscle adenosine monophosphate deaminase deficiency

CODES

ICD9

277.2 Other disorders of purine and pyrimidine metabolism

MYOCLONUS

David S. Younger, MD

BASICS

DESCRIPTION

Myoclonus is a brief, sudden, muscle jerk. It is caused by either active muscle contractions (positive myoclonus) or a brief interruption of tonic muscle activity (negative myoclonus), as is seen in asterixis. It may involve the face, trunk, or extremities.

EPIDEMIOLOGY

Myoclonus is considered a common movement disorder. Myoclonus is not a disease entity in itself, but can be a sign of a wide variety of different illnesses. For this reason, its epidemiology is largely unknown.

- Race
  - – No study has demonstrated any ethnic predominance.
- Age
  - – Myoclonus may occur at any age, and there is no predisposition for any specific age group.
- Sex
  - – Males and females are equally affected.

RISK FACTORS

Myoclonus is a physiologic manifestation that can be caused by a long list of associated neurologic illnesses. Essential myoclonus is familial (autosomal dominant); thus, a positive family history predisposes to the condition. Cortical or spinal cord lesions may produce myoclonus. Degenerative diseases such as Creutzfeldt–Jakob disease, Alzheimer's disease, multiple system atrophy, or corticobasal ganglionic degeneration are associated with myoclonus. Metabolic derangement secondary to liver or renal failure and toxins such as bismuth can cause myoclonic jerks.

Pregnancy Considerations

Pregnancy in itself is not associated with myoclonus.

ETIOLOGY

Myoclonus can occur as a result of a wide variety of disorders. An etiologic classification is summarized as follows:

- Physiologic myoclonus refers to muscle jerks occurring in normal subjects. Examples include hiccups or nocturnal myoclonus.
- Essential myoclonus is usually inherited in an autosomal-dominant fashion and is not associated with any other underlying or progressive illness. As with essential tremor, it is often very responsive to ethanol.
- Epileptic myoclonus is often associated with generalized-onset seizures such as juvenile myoclonic epilepsy of Janz.
- Secondary myoclonus refers to a condition in which myoclonus is a manifestation of an underlying neurologic disease. In some of these conditions, myoclonus is the major neurologic manifestation such as in Lance–Adams syndrome (due to cerebral anoxia), bismuth poisoning, or renal failure.
- Hyperexplexia (exaggerated startle syndrome) presents with myoclonus due to an exaggerated startle response to an external stimulus.
- Psychogenic myoclonus represents a voluntary muscle jerk.

COMMONLY ASSOCIATED CONDITIONS

Cortical, brainstem, or spinal cord lesions such as tumors, arteriovenous malformations, encephalitis, ischemia (as in palatal myoclonus), or inflammation

- Progressive myoclonic epilepsies, epilepsia partialis continua, juvenile myoclonic epilepsy, and other childhood myoclonic epilepsies
- Spinocerebellar degeneration
- Basal ganglia degenerations such as multiple system atrophy, corticobasal ganglionic degeneration, and Parkinson's disease
- Dementias such as Creutzfeldt–Jakob disease and Alzheimer's disease
- Encephalitides such as subacute sclerosing panencephalitis, herpes simplex encephalitis, and others
- Metabolic derangements such a hepatic and renal disease, hyponatremia, hypoglycemia, and mitochondrial encephalomyopathies
- Toxic encephalopathies such a bismuth, heavy metal, methyl bromide poisoning, or medications such a levodopa or serotonin reuptake inhibitors
- Posthypoxic encephalopathy (Lance–Adams syndrome).
- Startle syndromes (hyperexplexia).

DIAGNOSIS

Myoclonus may affect 1 or 2 adjacent body parts (focal or segmental myoclonus), different noncontiguous body parts (multifocal myoclonus), or the entire body (generalized myoclonus). It may be present at rest, while maintaining a posture, or when a particular movement is performed (action myoclonus). Reflex myoclonus can be triggered by visual, auditory or somesthetic stimuli, such as pinpricking or flicking the fingers or toes. Negative myoclonus consists of a short interruption of tonic muscle activity (asterixis). Asterixis is usually multifocal. When axial muscles are affected the patient experiences postural lapses that manifest in a bouncy, unsteady gait.

DIAGNOSTIC TESTS AND INTERPRETATION

Diagnostic Procedures/Other

Electrodiagnostic studies

- Electromyography (EMG) recordings from involved muscles may sometimes be helpful in characterizing the myoclonus.
- EEG can distinguish cortical from brainstem myoclonus, which has no preceding cortical discharge.
- Somatosensory evoked potentials show an enlarged P25/N33 component in cortical myoclonus, and a cortical correlate may be back-averaged in the simultaneously recording EEG.
- The presence of a Bereitschafts potential prior to the EMG discharge on the back-averaged EEG suggests the possibility of psychogenic myoclonus.

DIFFERENTIAL DIAGNOSIS

- Tics: In contrast to myoclonus, tics are voluntarily suppressible and are often associated with a premonitory feeling of urgency prior to the tic and a sense of relief afterwards.
- Chorea: Consists of quick jerk-like movements, which are in a continuous flow
- Tremor: Tends to be repetitive, whereas myoclonus has a sudden, definable onset and end
- Dystonia: Consists of often painful twisting and turning movements that cause abnormal postures

TREATMENT

MEDICATION
Aside from the symptomatic medications discussed, amelioration of myoclonus depends largely on treating the underlying cause for the myoclonic syndrome.

ADDITIONAL TREATMENT
General Measures
The most important measure is to correctly subclassify myoclonus and treat the underlying disease process. Essential myoclonus like essential tremor responds to small doses of alcohol (e.g., a glass of red wine), a feature that is not found in other types of myoclonus.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Symptomatic Treatment
  - Myoclonus secondary to cortical lesions and epileptic myoclonus respond best to valproate, clonazepam, or a combination of these. Piracetam has also been shown to be effective in the treatment of myoclonus; however, it is not readily available in the USA at this time. Primidone has been tried successfully as well. In several cases, combinations of the above medications are needed. Negative myoclonus is much more resistant to treatment than positive myoclonus. The abovementioned medications may be tried, but are much less effective. Clonazepam appears to be most effective for brainstem myoclonus. *N*-acetylcysteine has been shown to be beneficial in the symptomatic treatment of myoclonus in the Unverricht–Lundborg disease. Occasionally, serotonin reuptake inhibitors may be helpful. β-blockers may be helpful in essential myoclonus. A combination of 5-hydroxytryptophan and carbidopa has been found to be successful in the treatment of Lance–Adams syndrome (postanoxic myoclonus).

SURGERY/OTHER PROCEDURES
Myoclonus is generally treated successfully with medications, and surgical treatment is rarely recommended. However, there are reports of successful surgical management of myoclonus. Spinal myoclonus may respond to removal of a compressive lesion in or adjacent to the spinal cord. A recent study demonstrated alleviation of hereditary essential myoclonus by neurostimulation of the ventral intermediate thalamic nucleus. Older studies show improvement of myoclonus with destructive lesions of the lateral ventral nucleus of the thalamus.

IN-PATIENT CONSIDERATIONS
Admission Criteria
The criteria for admission depend, in general, on the underlying disease and not the myoclonus itself. However, rarely, action myoclonus or negative myoclonus of the lower extremities can be so severe as to affect patient's ability to walk or feed themselves, which may necessitate hospitalization.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Patients should be followed on an individualized basis, depending on the severity of the myoclonus. The underlying disorder that causes the myoclonic syndrome dictates the frequency of follow-up and the need for hospitalization.

PATIENT EDUCATION
Support groups for myoclonus:
- Moving Forward, 2934 Glenmore Ave., Kettering, OH 45409. Phone 513-293-0409.
- Myoclonus Research Foundation (MRF), 200 Old Palisade Rd., Suite 17D, Fort Lee, NJ 07024. Phone: 201-585-8114, website www.research@myoclonus.com.

PROGNOSIS
In general, the prognosis depends on the underlying disorder that causes the myoclonic syndrome. Myoclonus itself does not tend to cause complications, unless associated with seizures, which may lead to hypoxia, aspiration, or traumatic injuries.

ADDITIONAL READING

- Shibasaki H. Electrophysiologic studies of myoclonus. *Muscle Nerve* 1988;11:899–907.
- Snodgrass SR. Myoclonus: Analysis of monoamine, GABA, and other systems. *FASEB J* 1990;4: 2775–2788.
- Tabbal SD, Pullman SL. Neurophysiology of clinical motor control. Chapter 4. In: Younger DS, ed. *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2005.

See Also (Topic, Algorithm, Electronic Media Element)
- Jerks
- Lightning-fast movements
- Involuntary movements
- Tremor

CODES

ICD9
- 306.0 Musculoskeletal malfunction arising from mental factors
- 333.2 Myoclonus
- 345.10 Generalized convulsive epilepsy, without mention of intractable epilepsy

MYOPATHY, CONGENITAL

David S. Younger, MD

BASICS

DESCRIPTION

The congenital myopathies are nonprogressive myopathies of the neonatal period with weakness and hypotonia of varying severity. Common congenital myopathies are initially referred to as those with obvious structural abnormalities, including central core disease, nemaline rod myopathy, and myotubular myopathy. There are also uncommon forms of congenital myopathies, including multicore myopathy, fingerprint body myopathy, congenital fiber type disproportion, and protein surplus myopathies due to accumulation of abnormal proteins, such as desmin-related myopathies and actinopathies.

EPIDEMIOLOGY

Incidence of nemaline myopathy is 0.02 in 1,000 live births. Incidence of other congenital myopathies is unknown.

- Race
  - No ethnic predilection is noted.
- Age
  - Onset mostly at birth or in the first few months; recently, adult onset has been reported in some patients.
- Sex
  - Both sexes are equally affected.

ETIOLOGY

- Myotubular myopathy or centronuclear myopathy comprise 3 disorders due to mutation in the *MTM1* gene. They are inherited is an X-linked recessive (XR) manner in neonatal cases, autosomal-recessive (AR) in late infantile and early childhood cases, and autosomal-dominant (AD) in late childhood cases. The estimated occurrence is 1 in 50,000 newborn boys.
- Nemaline rod myopathy has 6 clinical forms that occur in infancy, childhood, and adulthood, and 3 congenital forms, termed typical, severe, and intermediate, all with considerable overlap. 5 distinct genes encode protein components of thin muscle filaments, mutations within which cause nemaline rod myopathy, with transmission in mainly AD and AR fashion.
- Central core disease is usually transmitted in an AD fashion with linkage to chromosome 19q12–13. The protein encoded by this gene is the calcium release channel of the sarcoplasmic reticulum, and mutations of the gene have been found in families with malignant hyperthermia and central core disease. However, it can also be a sporadic disease.
- Multicore disease is a clinically heterogeneous entity with 4 distinct phenotypes, a classical form accounts for three-fourths of affected patients and presents with neonatal hypotonia, delayed motor development and axial weakness leading to scoliosis and respiratory involvement, with associated pelvic and facial weakness, cardiomyopathy, short stature, failure to thrive, marfanoid habitus, and slow progression through adolescence and adulthood. A moderate form presents with hand involvement and characteristic distal upper limb weakness and joint laxity. An antenatal form is associated with arthrogyposis multiplex congenital and joint contractures at birth due to poor fetal movement often with doliocephaly, nasal root, oblique palpebral fissures, high arched palate, low-set ears, short neck, and clinodactyly. The disorder occurs with AR and rarely AD inheritance. Molecular genetic testing reveals disease-causing mutations in the selenoprotein N1 and ryanodine receptor in up to one half of patients.

COMMONLY ASSOCIATED CONDITIONS

- Malignant hyperthermia, especially with central core disease and multicore disease
- Skeletal abnormalities including congenital hip dislocation, scoliosis, clubfoot
- Ophthalmoplegia, ptosis, especially with myotubular myopathy
- Respiratory failure, especially with myotubular myopathy, multicore disease, nemaline rod myopathy, and desmin-related myopathies
- Seizures, especially with myotubular myopathy
- Cardiomyopathy, especially with myotubular myopathy, nemaline rod myopathy, and desmin-related myopathies
- Exercise intolerance, especially with desmin-related myopathies
- Mental retardation, especially fingerprint body myopathy
- Gastroesophageal reflux

DIAGNOSIS

- Most patients with congenital myopathy present with generalized hypotonia, delayed motor milestones, and generalized muscle weakness and atrophy.
  - Respiratory failure, ptosis, or ophthalmoplegia may be seen.
  - Slender body habitus, long narrow face, and skeletal abnormalities such as clubfoot, congenital hip dislocation, and kyphoscoliosis are often noted.
  - However, some patients with congenital myopathies can be asymptomatic or only present with mild muscle weakness. Occasionally, cardiomyopathy is seen in the patients with nemaline rod myopathy and myotubular myopathy.
  - Mental impairment is reported in fingerprint myopathy.
- Desmin-related myopathies, a newly recognized group of disorders, may present in late adolescence or adulthood, with scapuloperoneal or distal muscle weakness, and some patients may also have respiratory insufficiency, cardiomyopathy, and cardiac arrhythmia.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Serum creatine kinase (CK) is normal or mildly increased.
- Electromyography (EMG) shows either normal or myopathic features.
- Nerve conduction studies are normal; repetitive nerve stimulation is normal.

Imaging

Sonographic, CT, or MRI studies of muscles are not useful to recognize specific congenital myopathy.

Diagnostic Procedures/Other

Muscle biopsy is necessary to diagnose specific congenital myopathy. In myotubular myopathy, central nuclei are detected in many muscle fibers. In nemaline myopathy, characteristic red or purple, rod-shaped structures, so-called nemaline bodies, are noted against the blue–green myofibrillar background of the modified Gomori's trichrome stain. In central core disease, well-circumscribed central areas or cores are noted usually extending along the entire length of the muscle fiber, with decreased staining reactions for oxidative enzymes and phosphorylase. The minicores of multicore disease are recognized as small zones of sarcoplasmic reticulum disorganization and diminished oxidative activity that correlates with type 1 and 2 fibers, with variable immunoreactivity to anti-titin, desmin, crystalline antibodies, heat shock protein 27, and filamin in core lesions.

DIFFERENTIAL DIAGNOSIS
- Spinal muscular atrophy
- Congenital muscular dystrophy
- Congenital myotonic dystrophy
- Pompe's disease
- Debranching enzyme disease
- Mitochondrial myopathy
- Carnitine deficiency
- Congenital peripheral polyneuropathy
- Congenital myasthenic syndrome

TREATMENT

MEDICATION
No specific drugs are available for any type of congenital myopathies.
- Contraindications
  - Because malignant hyperthermia is associated with central core and multicore myopathies, these patients should avoid halothane or other halogenated anesthetic agents and succinylcholine, which may precipitate malignant hyperthermia.
- Precautions
  - Patients should wear medical alert bracelet or necklace indicating their risk of malignant hyperthermia associated with anesthesia.

ADDITIONAL TREATMENT
General Measures
In general, only supportive treatment is available for all types of congenital myopathies.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Symptomatic Treatment
  - Ankle–foot orthoses may be needed for footdrop.
  - Back bracing may help scoliosis.
  - Respiratory support or gastrostomy feeding may be necessary in respiratory failure or gastroesophageal reflux.
- Adjunctive Treatment
  - Physical therapy is often needed to prevent joint contractures.
  - Wheelchair may be needed.

SURGERY/OTHER PROCEDURES
Associated congenital hip dislocation, scoliosis, or clubfeet may require surgical treatment.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Patients may be admitted for muscle biopsy for diagnosis and surgical treatment of scoliosis, gastrostomy tube placement, and then discharged to home.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Patients should be followed regularly for respiratory insufficiency, cardiomyopathy, or cardiac arrhythmia if present in some congenital myopathies, and the need of braces, physical therapy, nutritional support, or scoliosis treatment.

PATIENT EDUCATION
Because all types of congenital myopathies are rare, the patients should be referred to the Muscular Dystrophy Association clinics for care, education, and support: Muscular Dystrophy Association, 3300 E. Sunrise Dr., Tucson, AZ 85718-3208. Phone: 1-800-572-1717, website www.mdausa.org.

PROGNOSIS
- Central core disease is usually mild, nonprogressive, but with rare exceptions.
- Nemaline myopathy may run mild to severely progressive course with some fatal outcome, especially those with neonatal onset.
- Myotubular myopathy may also run mild to severely progressive course, even fatal outcome, especially with neonatal onset.
- Congenital fiber-type disproportion usually has mild, nonprogressive course.
- Desmin-related myopathies may be fatal in the infancy or early childhood due to respiratory failure.

ADDITIONAL READING

- Ferreiro A, Fardeau M. 80th ENMC International Workshop on MultiMinicore disease: 1st International MmD Workshop. *Neuromuscul Disord* 2000;12:60–68.
- Laporte J, Kress W, Mandel JL. Diagnosis of X-linked myotubular myopathy by detection of myotubularin. *Ann Neurol* 2001;50:42–46.
- Ryan MM, Schnell C, Strickland CD, et al. Nemaline myopathy: a clinical study of 143 cases. *Ann Neurol* 2001;50:312–320.
- Younger DS, Bonilla E, Tanji K. Muscle pathology. Chapter 5. In: Younger DS, ed., *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2005.

See Also (Topic, Algorithm, Electronic Media Element)
- Myopathy

CODES

ICD9
359.0 Congenital hereditary muscular dystrophy

MYOPATHY, METABOLIC

David S. Younger, MD

BASICS

DESCRIPTION

Metabolic myopathies are a group of muscle disorders stemming from defective energy utilization due to abnormalities in glycogen, lipid, purine, or mitochondrial metabolism.

EPIDEMIOLOGY

- Incidence/Prevalence
  - Rare. Prevalence rates between 1:40,000 and 1:1,000,000 for each individual disorder. However, collectively they are not uncommon.
- Race
  - No known difference.
- Age
  - Age of onset varies from infancy through middle age.
- Sex
  - No known difference except for the 2 X-linked disorders of carbohydrate metabolism.

RISK FACTORS

Genetics

Inheritance patterns vary by disease. Most disorders are autosomal recessive. Others follow X-linked, mitochondrial, or, rarely, autosomal-dominant modes of transmission.

ETIOLOGY

Skeletal muscle is highly energy dependent and uses three major sources of adenosine triphosphate (ATP): High-energy phosphate compounds such as phosphocreatine; glycogen; and fatty acids. The intensity and length of exertion determines which energy source is used:

- At rest—fatty acids
- During exercise
  - First few minutes—high-energy phosphate compounds
  - Minutes to an hour—glycogen
  - Hours—fatty acids

COMMONLY ASSOCIATED CONDITIONS

The following conditions occur with some of the metabolic myopathies:

- Disorders of carbohydrate metabolism: Hepatomegaly, cardiomyopathy, ketotic hypoglycemia, and anemia
- Disorders of lipid metabolism: Cardiomyopathy, cirrhosis, and hypoketotic hypoglycemia
- Disorders of mitochondrial function: Deafness, neuropathy, retinopathy, seizures, and stroke

DIAGNOSIS

Enzyme deficiencies present with signs and symptoms that are dynamic, static, or both. Most diseases have a usual manner of presentation. They are listed below by their presenting signs and symptoms, energy metabolism pathway, and mode of inheritance.

Dynamic Signs and Symptoms

- Cramps/myalgias, fatigue, reversible weakness, myoglobinuria
  - Carbohydrate metabolism
    - Myophosphorylase (MyoP)—autosomal recessive (AR)
    - Phosphofructokinase (PFK)—AR
    - Phosphorylase b kinase (PBK)—AR and X-linked recessive (XR)
    - Phosphoglycerate kinase (PGK)—XR
    - Phosphoglycerate mutase (PGM)—AR
    - Lactate dehydrogenase (LDH)—AR
    - β-Enolase—AR
  - Lipid metabolism
    - Carnitine palmitoyl transferase II (CPT II)—AR
    - Very-long-chain acyl-CoA dehydrogenase (VLCAD)—AR
    - Short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD)—AR
  - Purine metabolism
    - Myoadenylate deaminase deficiency (MADD)—AR
  - Mitochondrial disorders
    - Multiple—mitochondrial inheritance (Mito)

Static Signs and Symptoms

- Progressive, proximal weakness
  - Carbohydrate metabolism
    - Acid maltase (AMD)—AR
    - Debrancher enzyme—AR
    - Brancher enzyme—AR
    - Aldolase A—AR
  - Lipid metabolism
    - Carnitine transporter—AR
    - Medium-chain acyl-CoA dehydrogenase (MCAD)—AR
    - Long-chain acyl-CoA dehydrogenase (LCAD)—AR
  - Mitochondrial disorders—Mito

Both Dynamic and Static Signs and Symptoms

- Carbohydrate metabolism: MyoP, PFK, PBK, debrancher
- Lipid metabolism: VLCAD, LCAD, SCHAD, TP
- Mitochondrial: Mitochondrial DNA-depletion myopathy—AR

Clues to Metabolic Pathway Affected

- Carbohydrate metabolism
  - "Second wind" phenomenon—when muscle symptoms develop, a brief rest results in improved exercise tolerance
  - Symptoms are associated with brief, vigorous, isometric exercise such as squatting or lifting a heavy weight, or with short-duration, vigorous aerobic activity such as sprinting 100–800 m.
- Lipid metabolism
  - Symptom onset associated with fasting, illness, cold, or anesthesia
  - Onset of symptoms with prolonged (4–12 hours) exertion
  - Episodes mimicking a Reye's-like syndrome or coma
  - Family history of sudden infant death syndrome
- Mitochondrial
- Multisystem involvement
- CNS and/or peripheral nervous system involvement
  - Ptosis, external ophthalmoplegia

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Serum—creatine kinase (CK), lactate, pyruvate, LDH, free and total carnitine, ammonia ($NH3^{+}$), liver transaminases (including GGT), potassium, phosphate, calcium, and creatinine
- Urine—myoglobin, ketones, organic/dicarboxylic acids, and acylglycines
- CSF—lactate, pyruvate, protein, and amino acids

Imaging

Phosphorous MR spectroscopy is in use at research facilities.

Diagnostic Procedures/Other

- Nerve conduction studies—exclude acquired demyelinating polyneuropathies.
- Repetitive nerve stimulation—excludes neuromuscular junction disorders in cases with ptosis or ophthalmoplegia.
- Needle electromyography (EMG)—confirms myopathy with findings of abnormal spontaneous activity (fibrillation potentials and positive sharp waves) and/or short-duration, low-amplitude motor units that recruit early seen in some cases. EMG is often normal in metabolic myopathies without permanent weakness.
- ECG and echocardiography—evaluate symptomatic cardiac involvement and exclude presymptomatic disease.

- Forearm exercise test (FET)—a useful screening tool for carbohydrate and purine metabolism disorders. Collect baseline CK, pyruvate, lactate, and ammonia ($NH3^+$) levels.
  - Have the patient squeeze a ball or hand dynamometer vigorously for 1 minute, intermittently squeezing for 3 seconds and relaxing for 1 second.
  - Draw blood samples for lactate and $NH3^+$ at 1, 2, 4, 6, and 10 minutes after exercise. All blood samples should be placed on ice.
  - Interpretation of FET results
    - In normal subjects, both the lactate and $NH3^+$ levels should rise at least 2.5- to 5-fold within 1–4 minutes (lactate) and 2–6 minutes ($NH3^+$) after exercise.
    - In disorders of carbohydrate metabolism, lactate levels should not rise or be blunted (<2-fold elevation), while $NH3^+$ levels should rise normally, by at least 2.5-fold.
    - In disorders of purine metabolism, such as myoadenylate deaminase deficiency, the rise in $NH3^+$ levels is blunted, while the lactate response is normal, at least a 2.5-fold rise.
    - If both the lactate and $NH3^+$ levels do not rise by at least 2.5-fold, this suggests inadequate effort and the test should be repeated.
- Open muscle biopsy—allows sampling of the muscle for histologic review, histochemical analysis, biochemical assays, and genetic analysis. Biceps and quadriceps muscles are the most commonly sampled muscles.
- Carbohydrate metabolism
  - Histology—vacuoles and accumulation of glycogen staining positive with periodic acid-Schiff (PAS) stain.
  - Histochemical—diminished or absent staining for the enzyme on the muscle tissue sections in myophosphorylase, phosphofructokinase, or acid maltase deficiencies.
  - Biochemical—quantitative enzyme-function assays can be performed on muscle tissue.
  - Commercial testing is available for deficiencies of all the glycolytic defects (AMD, debrancher, brancher, MyoP, PFK, PBK, PGK, PGM, and LDH) except aldolase A and β-enolase.
  - Mutation analysis—genetic testing is available commercially for the most common mutations causing myophosphorylase deficiency (McArdle's disease).
- Lipid metabolism
  - Histology—vacuoles and accumulation of glycogen staining positive with oil-red-O (ORO) stain.
  - Biochemical—commercially available assays can be performed on muscle tissue for free and total carnitine levels along with CPT II.
- Mitochondrial metabolism
  - Histology—"ragged red fibers" and diminished muscle staining for oxidative enzymes (NADH, SDH, and COX).
  - Biochemical—analysis for mitochondrial enzyme deficiencies.
  - Mutation analysis—testing is commercially available for some disorders (MELAS, MERRF, NARP, LHON, and KSS/CPEO) via blood and/or muscle tissue. In mitochondrial myopathies, disease-causing mutations may segregate disproportionately with muscle tissue rather than other tissues during embryogenesis. Therefore, mutation analysis on muscle tissue provides a higher diagnostic yield for mitochondrial myopathies.

DIFFERENTIAL DIAGNOSIS

- Other myopathies—include endocrine, drug-induced, and inflammatory myopathies
- Muscular dystrophies
- Fibromyalgia
- Polymyalgia rheumatica

TREATMENT

MEDICATION

No medical regimen is yet known.

- Alternative Drugs
  - Some patients with mitochondrial myopathies improve after treatment with coenzyme Q10, 50–100 mg t.i.d., and L-carnitine, 1,000 mg t.i.d., plus an antioxidant vitamin regimen.

ADDITIONAL TREATMENT

General Measures

The major therapeutic goal in metabolic myopathies is avoidance of provocative factors such as brief bursts of exertion for carbohydrate disorders and fasting for disorders of lipid metabolism. In the future, treatment will consist of enzyme replacement and/or genetic therapy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
- Most patients with a metabolic myopathy derive benefit from a low-intensity, graduated exercise program with emphasis on aerobic exercise.
- Dietary modification may benefit some patients. A diet high in protein and fats benefits some patients with carbohydrate metabolism disorders. The obverse is true for disorders of lipid metabolism. These patients benefit from frequent meals and a low-fat, high-carbohydrate diet.
- Adjunctive Treatment
- Co-management of concomitant cardiac, hepatic, and hematologic dysfunction improves quality of life and may be lifesaving. Seizures in mitochondrial disorders usually respond to conventional anticonvulsant drugs. Malignant hyperthermia, especially prevalent in disorders of carnitine processing, responds to dantrolene.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Rhabdomyolysis or episodes of severe weakness warrant admission. Occasionally, patients present with hypoglycemia, seizures, or stroke and require admission.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be seen every 6–12 months to monitor disease progression. These visits also facilitate patient education about advances in care.

PATIENT EDUCATION

- Muscular Dystrophy Association, 3300 E. Sunrise Drive, Tucson, AZ 85718. Phone: 800-572-1717, website www.mdausa.org.
- Distinct patient organizations exist for many of the individual metabolic myopathies and may be found by searching the Internet.

PROGNOSIS

The clinical course and prognosis are highly variable. Influencing factors include the distinct enzyme involved, the percentage reduction in enzymatic activity, the unique compensatory genetic milieu of each patient, and the environment in which these features play out. Some infantile forms of these disorders cause death due to cardiorespiratory failure prior to the first birthday, while adult-onset forms may present late in life with mild symptoms such as myalgias, cramps, and fatigue.

ADDITIONAL READING

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- Younger DS, Hirano M, DiMauro S. Metabolic myopathies. Chapter 12. In: Younger DS, ed. *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams and Wilkens, 2005.

See Also (Topic, Algorithm, Electronic Media Element)

- Myophosphorylase deficiency = McArdle's disease
- Phosphofructokinase deficiency = Tarui's disease
- Infantile form of acid maltase deficiency = Pompe's disease

CODES

ICD9

- 259.9 Unspecified endocrine disorder
- 359.5 Myopathy in endocrine diseases classified elsewhere
- 359.89 Other myopathies

MYOPATHY, TOXIC

Boyd Koffman, MD, PhD

BASICS

DESCRIPTION

Toxic myopathies are potentially reversible muscle disorders due to myotoxicity of prescribed or illicit drugs. Suspicion of a toxic myopathy is increased when there is temporal association of drug use prior to symptom onset, absence of preexisting neuromuscular symptoms, and improvement of symptoms after withdrawal of suspected toxin. Tentative classification based on the pathogenetic mechanism has been proposed, although knowledge of the mechanism of many toxins is limited. Several authors classify according to whether the myopathy is painful, painless, presence of an associated neuropathy, histopathologic features, drugs of abuse, and focal myopathies.

EPIDEMIOLOGY

- Race, age, and sex are not factors.
- **Incidence**
  - Incidence is unknown for most toxic myopathies, but appears to be common.
  - For statin-induced myopathies, myalgias may occur in 2–7%, weakness and CPK elevation >10-fold the upper limit of normal in 0.1–1.0%, and severe myopathy in 0.8% of cases.
- **Prevalence**
  - Unknown

RISK FACTORS

- Autoimmune or other conditions requiring chronic corticosteroid treatment
- Alcoholism
- Illicit drug use
- Use of dietary supplements
- Prescribed medications
  - Neuroleptics
  - Antiepileptics
  - Intramuscular injections
  - HMG-CoA reductase inhibitors (statins)
  - High-dose corticosteroid use
    - Acute (with or without neuromuscular blocking agents or sepsis)
    - Chronic

Genetics

- Statin-induced myopathies: Genetic polymorphisms of several proteins have been reported:
  - Cytochrome P450
  - Uridine diphosphate (UDP)-glucuronosyl-transferase-1 (UGT1)
  - Solute-carrier organic transporter (SLCO) family
  - The second enzyme of CoQ biosynthesis (*COQ2* gene)

GENERAL PREVENTION

ALERT

The incidence of rhabdomyolysis is increased when statins are combined with other drugs, especially simvastatin and:

- Amiodarone (FDA Alert posted August 8, 2008, see http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118869.htm)
- Gemfibrozil
- Cyclosporin
- Macrolide antibiotics
- Azole antifungals

Anticipating drug–drug interactions may help prevent statin-induced myotoxicity

ALERT

FDA notified healthcare professionals that it recommends limiting the use of the highest approved dose of the cholesterol-lowering medication simvastatin (80 mg) because of increased risk of muscle damage.
RECOMMENDATION: Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.

PATHOPHYSIOLOGY

The mechanism varies depending on the agent. Syndromes include:

- Myoglobinuria
- Necrotizing myopathy [statins, fibrates, organophosphate poisoning, episolon aminocaproic acid (EACA)]
- Thick–filament-loss mopathy (critical illness neuromyopathy)
- Type II fiber atrophy (corticosteroid myopathy)
- Hypokalemic myopathy (laxatives, thiazide diuretics, mineralocorticoids, lithium)
- Amphiphilic cationic drug (lysosomal) myopathy (chloroquine, amiodarone)
- Impaired protein synthesis (emetine/ipecac poisoning)
- Antimicrotubular myopathy (colchicine, vincristine)
- Inflammatory myopathy (D-penicillamine, statins, interferon-α)
- Fasciitis (eosinophilia myalgia syndrome, toxic oil syndrome)
- Mitochondrial myopathy (zidovudine, fialuridine, germanium)
- Focal myopathies secondary to injections
- Unclassified mechanisms

ETIOLOGY

- Toxic substances may act in several ways
  - Direct action on muscle cells
  - Indirect action on muscles
    - Drug-induced immunologic reaction directed toward muscles
    - Electrolyte disturbances
    - Muscle compression
    - Ischemia

COMMONLY ASSOCIATED CONDITIONS

- Toxic myopathies may be painful or painless
- Potential sequelae of rhabdomyolysis include myoglobinuria and renal failure.

DIAGNOSIS

HISTORY

Myopathic weakness begins after a suitable duration of exposure to a presumed toxin. There is usually no preexisting neuromuscular condition, and symptoms of weakness resolve following removal of the offending agent.

PHYSICAL EXAM

- Myopathic weakness
- Deep tendon reflexes and appreciation of primary sensory modalities are preserved.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Laboratory procedures to consider when a toxic myopathy is suspected should be based on suspicions elicited from the history.

- Serum: Creatine phosphokinase (CPK), aldolase, potassium, serum toxicology screen, ethanol level
- Urine: Myoglobin, urine toxicology screen

Diagnostic Procedures/Other

- Electromyography (EMG)/nerve conduction studies (NCS)—should be considered to exclude an alternate cause of weakness such as demyelinating neuropathy or neuromuscular junction defect. Some agents can cause a neuropathy as well as a myopathy, and NCSs may also be affected. This is the case with the antimicrotubular agents colchicine and vinblastine and, possibly, with chloroquine and amiodarone. EMG is normal in acute corticosteroid myopathy and demonstrates normal insertional and spontaneous activity with short duration and low-amplitude voluntary motor units in chronic corticosteroid myopathy.
- Muscle biopsy—should be done if there is incomplete or no resolution of weakness following removal of the suspected offending toxin, and may be done sooner to exclude causes of weakness other than toxin-induced myopathy.

Pathological Findings
Types of injuries incurred by myofibers or their organelles and identified on muscle biopsy:
- Necrotizing myopathy
- Thick–filament-loss myopathy
- Type II fiber atrophy
- Lysosomal storage (amphiphilic cationic drug) myopathy
- Myofibrillar myopathy
- Antimicrotubular myopathy
- Inflammatory myopathy
- Fasciitis
- Mitochondrial myopathy

DIFFERENTIAL DIAGNOSIS
There should be no other identifiable cause of myopathy present. Differential diagnoses are listed by clinical and pathologic findings and may be listed more than once if more than one mechanism of presentation has been described.

Painful Toxic Myopathies
- Myopathic disorders: Inflammatory myopathy and mitochondrial myopathy
- Medications: D-penicillamine, procainamide, didanosine, germanium, zidovudine; possibly phenytoin, levodopa, cimetidine, leuprolide, propylthiouracil, streptokinase
  - – Cholesterol-lowering agents: HMG-CoA reductase inhibitors (lovastatin, mevastatin, pravastatin)
  - – Fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil)
  - – Nicotinic acid
- Fasciitis: Fascia is connective tissue surrounding the muscle. Inflammation of fascia is fasciitis, and is listed as symptoms of pain from inflammation of the fascia may be difficult to distinguish clinically from muscle pain or myalgia. Inflammation may be detected on muscle biopsy when fascia is included with the biopsy for inspection.
- Eosinophilia–myalgia syndrome
- Toxic (rapeseed) oil syndrome
- Ethanol (acute)
- Etretinate
- Hypervitaminosis E
- Ipecac/emetine

Painless Toxic Myopathies
- Corticosteroids (acute high dose, or chronic)
- Myoglobinuria
  - – Metabolic (ethanol, heroin, lipid-lowering drugs)
  - – Fever, hyperthermia (malignant hyperthermia, malignant neuroleptic syndrome, cocaine, amphetamine, 3,4-methylenedioxymeth-amphetamine, or "ectasy", phencyclidine)
- Direct effect on muscle (succinylcholine, colchicine)
- Hypokalemic myopathy [amphotericin-B, laxatives, licorice (carbenoxolone/glycyrrhizate), lithium, mineralocorticoids, thiazide diuretics, toluene abuse)
- Drug-induced lysosomal storage myopathy, or amphiphilic cationic drug myopathy (perhexiline, amiodarone, clomipramine, imipramine, colchicine, chloroquine, plasmocid, and lovastatin)
- Antimicrotubular myopathy (colchicine, vincristine)
- Toxic focal myopathies
  - – Ethanol (acute)
  - – Intramuscular injections
    - ○ Acute: cephalothin, lidocaine, diazepam
    - ○ Chronic: antibiotics (children), intravenous drug abuse, meperidine, pentazocine, pethidine
- Toxic myopathies associated with drugs of abuse (amphetamines, cocaine, heroin, phencyclidine, or volatile inhalation of toluene or gasoline)

TREATMENT

ADDITIONAL TREATMENT
General Measures
Most cases of toxic myopathy require removal of the potentially offending agent.

Issues for Referral
- Reporting

The U.S. Food and Drug Administration (FDA) encourages voluntary reporting of adverse events, defined as "any undesirable experience associated with the use of a medical product in a patient." A report should be made when use of a medication causes disability or death, requires medical intervention or hospitalization, or may jeopardize a patient.

Reports (see the Internet site http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm) may be submitted via postage-paid MedWatch form; by phone: 1-800-FDA-1088; by Fax: 1-800-FDA-0178; or via Internet (Medwatch online) at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Additional Therapies
- Physical therapy as appropriate
- Occupational therapy as appropriate
- Detoxification (ethanol abuse, drug abuse)

SURGERY/OTHER PROCEDURES
- See EMG/NCS and muscle biopsy, above, under Diagnostic Testing

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Correct impaired renal function
- Electrolyte control
- Monitor vital capacity if dyspneic

Admission Criteria
- Rhabdomyolysis or myoglobinuria—risk of renal failure
- Impaired ambulation
- Impending respiratory failure

IV Fluids
Hydration for hyperthermia and to prevent renal failure in rhabdomyolysis or myoglobinuria

Nursing
- Activity: Consider fall precautions

Discharge Criteria
- Weakness resolving
- CPK normalizing

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
- Clinical observation for improving strength
- Monitor CPK levels and renal function

PATIENT EDUCATION
- Activities—as tolerated
- Provide information to patients about recognition and reporting of symptoms of myopathy during statin therapy.

PROGNOSIS
- Complete or at least partial resolution of symptoms after treatment
- Exception: The nucleoside analogue fialuridine can cause irreversible myotoxicity after incorporation into mitochondrial DNA

COMPLICATIONS
- Falls/injury
- Untreated rhabdomyolysis: Renal failure

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Neuroleptic malignant syndrome
- Malignant hyperthermia

CODES

ICD9
- 359.4 Toxic myopathy
- 359.81 Critical illness myopathy
- 359.89 Other myopathies

CLINICAL PEARLS
- Toxic myopathy is usually a diagnosis of exclusion. Temporal association should be present and fit lab (CPK) and pathology data, including muscle biopsy, if appropriate.

M

NARCOLEPSY

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BASICS

DESCRIPTION

Narcolepsy is a chronic condition that falls into one of two categories. There is narcolepsy with cataplexy and narcolepsy without cataplexy. Narcolepsy with cataplexy is characterized by excessive daytime sleepiness (EDS) and cataplexy which is a sudden loss of either partial or generalized often bilateral muscle tone provoked by strong positive emotion. Narcolepsy without cataplexy is characterized by EDS but no cataplexy. Both types can have other associated features of sleep paralysis, hypnagogic hallucinations, and nocturnal sleep disruption.

EPIDEMIOLOGY

Incidence

- Narcolepsy most commonly begins in the second decade between ages of 10 and 25 years. Most patients will experience symptoms of the disorder before age 30. Excessive sleepiness is usually the first symptom to appear, with cataplexy appearing mostly within a year. Rarely cataplexy can precede the symptom of EDS or occur up to 30 years later.

Prevalence

- Narcolepsy is estimated to occur in 0.03–0.16% of the general population.
- The prevalence of narcolepsy with cataplexy is 15–50 cases per 100,000 people (0.015–0.05%), and the prevalence of narcolepsy without cataplexy is 56 cases per 100,000 people (0.056%).

RISK FACTORS

- Genetic or familial risk
- Slightly higher risk in men than women
- HLA-DQB1*0602 allele is associated with narcolepsy with cataplexy.
- Hypocretin deficiency is also associated with narcolepsy with cataplexy.

Genetics

- The risk of narcolepsy with cataplexy developing in a first-degree relative of a narcoleptic individual is 1–2%. This is 10–40 fold higher risks compared to the general population.
- The concordance rate of monozygotic twins for narcolepsy with cataplexy is 25–31%.
- The HLA-DQB1*0602 gene is associated strongly with narcolepsy with cataplexy. Its prevalence is 95% in the narcoleptic population with cataplexy, 41% in the narcoleptic population without cataplexy, and 18–35% in the general population.

PATHOPHYSIOLOGY

- This is a condition that involves dysregulation of REM sleep.
  - Patients enter into REM sleep quickly after falling sleep.
  - Cataplexy, sleep paralysis, and hypnagogic hallucinations are due to intrusion of REM sleep into the wake state.
- There is an association between HLA-DQB1*0602 and narcolepsy with cataplexy.
  - This is found in 95% of narcoleptics with cataplexy and 41% of those with narcolepsy without cataplexy. This may suggest an autoimmune response as some autoimmune diseases are associated with the HLA haplotypes.
- Dysfunction of the hypothalamic hypocretin system
  - The hypocretinergic system is located in the lateral hypothalamus and has a role in regulation of the sleep–wake cycle.
  - Low CSF concentrations of hypocretin-1 (<110 ng/L) are seen in 94% of narcoleptics with cataplexy. Almost all of these patients also have a positive DQB1*0602.

COMMONLY ASSOCIATED CONDITIONS

- Depression
- REM sleep behavior disorder
- Periodic limb movements of sleep
- Eating disorders
- Obesity
- Obstructive sleep apnea syndrome
- Migraine
- Narcolepsy secondary to medical or neurological illnesses
  - More than 90% of narcolepsy cases are sporadic. Secondary narcolepsy is rare
  - Medical conditions associated with secondary narcolepsy are:
    - Multiple sclerosis
    - Hypothalamic disorders such as Type C Niemann–Pick disease, tumors, cranial trauma, sarcoidosis, neurocysticercosis, and limbic encephalitis
    - Brainstem lesions
    - Head trauma

DIAGNOSIS

HISTORY

- For narcolepsy with cataplexy, the tetrad of symptoms is EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis. Fragmented nocturnal sleep is another common complaint.
  - EDS is the most important complaint made by patients. EDS must be daily for at least 3 months.
  - Cataplexy is characterized by sudden loss of either partial or generalized often bilateral muscle tone provoked by strong positive emotion (e.g., laughing) or by fear or anger. It is the most specific clinical marker of narcolepsy. Cataplexy generally emerges within a year of EDS.
  - Hypnagogic and hypnopompic hallucinations are dream-like experiences occurring in the wake–sleep or sleep–wake transitions, respectively. They occur in 20–65% of narcoleptics and are generally visual or somato-sensorial (i.e., "out of body" sensations).
  - Sleep paralysis is the total incapacity to move which occurs when falling asleep or when in the transition from sleep into wakefulness but awareness is maintained. Sleep paralysis can be accompanied by hallucinations in up to 50% of cases. Episodes last from an average duration of 2 minutes and ends abruptly after mental effort or by means of external sensory stimulation.
  - Fragmented nocturnal sleep: Multiple awakenings and poor sleep quality occur in up to 90% of patients, especially in those over 35 years of age.
  - Of note sleep paralysis, hypnagogic hallucinations, and nocturnal sleep disruption can be seen in normal people and in those with other sleep disorders, so is not specific to narcolepsy.
- Other manifestations of narcolepsy include:
  - Refreshing naps
  - Irresistible sleep attacks
  - Episodes of automatic behaviors
  - Cognitive symptoms such as attention deficits when performing long, monotonous, and repetitive psychomotor tasks.

PHYSICAL EXAM

Typically the physical and neurological exam is normal unless the patient has secondary narcolepsy.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

MRI of the brain may be indicated for secondary narcolepsy.

Diagnostic Procedures/Other

- Polysomnography (PSG) followed by a multiple sleep latency test (MSLT) is the standard diagnostic procedure for narcolepsy.
- PSG is an overnight sleep study that monitors different parameters during sleep (EEG, EOG, EMG, ECG, heart rate, respiratory parameters, and pulse oximetry). This test evaluates for obstructive sleep apnea and movement disorders as the cause of the patient's excessive daytime sleepiness (1)[C].
- MSLT is indicated as part of the evaluation of narcolepsy in order to confirm the diagnosis (2)[A]. A PSG must be done the night before an MSLT. MSLT findings consistent with a diagnosis of narcolepsy are an MSL of 8 minutes and the presence of 2 sleep-onset REM periods. The diagnosis of narcolepsy should be suspect if the patient had less than 360 minutes of total sleep time on the preceding PSG.
  - Discontinuation of all REM sleep-suppressing agents, such as antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, etc.) and CNS stimulants, is recommended for 14 days before the sleep studies (2)[C].
  - The patient must be free of drugs that influence sleep for 15 days (1)[C].
  - The patient should maintain regular sleep–wakefulness schedules documented by sleep diary or actigraphy for at least 7 days before the sleep study (1)[C].
  - Drug screening may be indicated the morning of MLST to ensure sleepiness is not pharmacologically induced (2)[C].
  - 15% of narcoleptics may have a normal or borderline positive MSLT.
- HLA-DQB1*0602 typing
  - 95% of those with narcolepsy with cataplexy are HLA-DQB1*0602 antigen positive. However, the presence of this allele alone is not diagnostic as it is present in up to 35% of the general population.
- Hypocretin-1 in the CNS
  - CSF hypocretin-1 levels below 110 pg/mL are highly specific (99%) and sensitive (87–89%) for narcolepsy cases with cataplexy. HLA-DQB1*0602 typing should precede the measurement of hypocretin-1 levels in the CSF. If HLA-DQB1*0602 is negative, it becomes unnecessary to measure hypocretin levels because there is no reduction of hypocretin-1 in the CSF without HLA-DQB1*0602 positivity in cases of sporadic narcolepsy.

DIFFERENTIAL DIAGNOSIS

- Excessive daytime sleepiness
  - Behaviorally induced insufficient sleep syndrome
  - Depression
  - Hypersomnia due to other sleep disorders such as:
    - Obstructive sleep apnea syndrome
    - Idiopathic hypersomnia
    - Recurrent hypersomnia
    - Circadian rhythm disorder
  - Hypersomnia due to associated medical conditions
  - Hypersomnia associated with drugs or other substances
- Cataplexy
  - Epilepsy
  - Non-epileptic spells
  - Transient ischemic attacks
  - Psychiatric conditions

TREATMENT

MEDICATION

First Line

- Excessive daytime sleepiness
  - Modafinil at 200 mg/day is the recommendation by American Academy of Sleep Medicine. However, split dosing and higher dosing at 400 mg has shown efficacy in studies as well (3)[A].
  - Armodafinil
  - Sodium oxybate (3)[A]
- Cataplexy
  - Sodium oxybate (3)[A]

Second Line

- Excessive daytime sleepiness
  - Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (3)[C]
  - Scheduled naps – combination of regular bedtimes and 2–15-minute regularly scheduled naps reduced daytime sleepiness compared to stimulants alone (3)[C]
- Cataplexy
  - Tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, and reboxetine (3)[C].

ADDITIONAL TREATMENT

General Measures

- Combinations of long- and short-acting forms of stimulants may be indicated and effective for some patients.
- Patients with severe sleepiness should be advised to avoid dangerous activity at home and work. They should not operate motor vehicle until sleepiness is controlled.
- The patient should be assisted by health care providers on occupational and social accommodations for disabilities.
- Treatment of hypersomnias of central origin with methylphenidate or modafinil in children between the ages of 6 and 15 appears to be relatively safe.

Pregnancy Considerations

- Amphetamine, methylphenidate, and modafinil are pregnancy category C.
- Sodium oxybate is pregnancy category B.
- SSRI class is pregnancy category C.

IN-PATIENT CONSIDERATIONS

In-patient care is typically not required unless one is attempting to determine if cataplectic spells are seizures or non-epileptic spells by admission to an epilepsy monitoring unit.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Those patients stable on stimulant medication should be seen at least once a year but preferably every 6 months.
- Patients who fail to respond to adequate doses of stimulant medication should be assessed for insufficient sleep, poor sleep hygiene, circadian rhythm disorders, obstructive sleep apnea, and periodic limb movements of sleep.

PATIENT EDUCATION

Narcolepsy network:
http://www.narcolepsynetwork.org/

PROGNOSIS

Life-long condition

COMPLICATIONS

Use of amphetamines as stimulant can lead to development of tolerance.

REFERENCES

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3. Morgenthaler TI, Kapur VK, Brown T, et al Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep* 2007;30(12):1705–1711.

CODES

ICD9

- 347.00 Narcolepsy without cataplexy
- 347.01 Narcolepsy with cataplexy

CLINICAL PEARLS

- The tetrad of symptoms for narcolepsy with cataplexy are excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis.
- Diagnosis is made by a multiple sleep latency test. This must be proceeded by an overnight polysomnography to rule out other sleep disorders such as obstructive sleep apnea and periodic limb movements of sleep as causes of the excessive daytime sleepiness.
- The standard first-line treatment for excessive daytime sleepiness is modafinil and sodium oxybate.

N

NEUROFIBROMATOSIS TYPE I

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BASICS

DESCRIPTION

- Neurofibromatosis type I (NF1) is a progressive autosomal dominant genetic disorder characterized primarily by various cutaneous manifestations and the tendency to develop tumors of the peripheral and CNS.
- NF1 clinical presentation and severity are extremely variable, even within the same family.
- It was known as Von Recklinghausen's disease in the past.
- The diagnosis of NF1 can be made, using the National Institute of Health criteria, if there are 2 or more of the following:
  - 6 or more café-au-lait spots that are greater than 5 mm in a prepubertal child and greater than 15 mm in diameter in a postpubertal individual.
  - 2 or more neurofibromas or 1 plexiform neurofibroma.
  - 2 or more Lisch nodules (iris hamartomas).
  - Axillary or inguinal freckling.
  - Optic glioma.
  - Distinctive bony lesions including sphenoid dysplasia or thinning of the long-bone cortex with or without pseudoarthrosis.
  - Definitive diagnosis of NF1 in a first degree relative based upon the above criteria.
- Segmental NF1 with involvement of a limited body region can occur.

EPIDEMIOLOGY

Incidence

- Approximately 1 in 3000 live births.

Prevalence

- NF1 is the most common neurocutaneous disorder affecting about 100,000 Americans.
- NF1 has no particular racial, ethnic, or gender predilection.

RISK FACTORS

Having a parent diagnosed with NF1

Genetics

- NF1 is an autosomal dominant genetic disorder characterized by a complete penetrance with variable expression.
- There is 100% penetrance after childhood.
- About 50% of patients have new mutations; the other 50% have a parent with NF1.
- The severity of NF1 is not different between inherited and new mutations.

GENERAL PREVENTION

- There are no interventions that prevent NF1.

PATHOPHYSIOLOGY

- A mutation in the large 60-exon NF1 gene on chromosome 17 q11.2 accounts for most NF1.
- Neurofibromin, the NF1 gene product, controls cellular proliferation and functions as a tumor suppressor gene. It activates GTPase that downregulates the Ras proto-oncogene which plays a role in cell growth and proliferation.
- The absence of neurofibromin leads to increased cell proliferation and tumor formation.
- Neurofibromin is found in many tissues including kidney, brain, spleen, and thymus.

ETIOLOGY

- Inheritance pattern is autosomal dominant.
- Spontaneous new mutations of unknown cause occur in half of the patients.
- Neurofibromin, the gene responsible for NF1, is a tumor suppressor gene located on chromosome 17q11.2. Mutations result in loss of tumor suppressor function of neurofibromin.

COMMONLY ASSOCIATED CONDITIONS

- Hypertension
  - Essential
  - Renal artery stenosis
  - Pheochromocytoma
- Epilepsy
- Malignant peripheral nerve sheath tumors
- CNS tumors
  - Astrocytomas and brainstem gliomas
- Osteopenia
- Learning disabilities in children

DIAGNOSIS

HISTORY

- Careful history regarding an abnormal skin findings, freckles, rapidly or slowly enlarging growths to suggest neurofibromas, visual complains, headaches, seizures, scoliosis, focal neurological complaints, and paresthesias should be sought.
- Careful history should also be obtained regarding learning disabilities, behavioral and growth abnormalities.

PHYSICAL EXAM

- Café-au-lait macules
  - Flat hyperpigmented spots of various sizes and shapes, more often found in the trunk.
- Neurofibromas
  - Most common tumors in NF1.
  - Benign tumors arising from peripheral nerve.
  - Pain might occur in the nerve distribution but can be asymptotic.
- Plexiform neurofibromas
  - 5% lifelong risk of malignant transformation.
  - Cause distortion of involved structures.
  - Often develop in the face.
- Lisch nodules (iris hamartomas)
  - Asymptomatic (no visual symptoms).
- Axillary or inguinal freckling
- Optic glioma
  - The most common CNS tumor in NF1.
  - Can be an incidental finding or patients might present with progressive vision loss and optic atrophy. Pain and proptosis can occur.
- Kyphoscoliosis
- Short stature
- Skeletal anomalies
- Macrocephaly
- Precocious puberty

Pediatric Considerations

- Only half of the children with NF1 and no family history of NF1 meet the NIH criteria for diagnosis of NF1 by age 1. However, most children meet the criteria for diagnosis by age 8.
- The diagnosis of NF1 in a child, whose parent is confirmed to have NF1, only requires the presence of 1 more item of the NIH criteria.
- In children with many café-au-lait spots and no known family history of NF1, the clinician should suspect NF1 and follow the child clinically.
- Children with NF1 might have normal intelligence, but learning disabilities often occur. Also poor social skills, behavioral and personality changes can be seen.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Genetic testing confirms the diagnosis
- Slit lamp examination of the eye helps detect iris hamartomas

Follow-up & special considerations

- Dictated by findings on clinical exam

Imaging

Initial approach

- It is debated at this time whether a brain MRI should be obtained at initial diagnosis.
- Abnormal signals on T2-weighted MRI referred to as "Unidentified Bright Objects" can occur in the optic tracts, basal ganglia, brainstem, cerebellum, and cortex. Their prognostic significance is unknown.
- MRI can help identify bony dysplasia in the cranium and the presence of optic glioma or other tumors.

Follow-up & special considerations

- Should be based upon clinical exam

Diagnostic Procedures/Other

- Should be based upon clinical exam

Pathological Findings

- N/A

DIFFERENTIAL DIAGNOSIS
- Noonan syndrome
- Neurofibromatosis type 2
  - Schwannomatosis
  - Multiple café-au-lait spots
  - McCune–Albright syndrome
  - Congenital generalized fibromatosis
  - Lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth, deafness (LEOPARD) syndrome
  - Legius syndrome

TREATMENT

MEDICATION
First Line
- There is no treatment to cure or halt progression of NF1. The hallmark of current treatment is monitoring and treatment of complications and genetic counseling.
- Pain associated with neurofibromas could benefit from NSAIDs or antiepileptic medication such as gabapentin.
- Seizures, if present, are treated with appropriate antiepileptic drugs.

Second Line
- N/A

ADDITIONAL TREATMENT
General Measures
- Patients benefit from referral to a neurofibromatosis multidisciplinary clinic.

Issues for Referral
- Ophthalmological referral for optic gliomas and vision assessment.
  - Referral to neurosurgeons for possible removal of plexiform neurofibromas or other peripheral or CNS tumors.
  - Referral to spine surgeon for possible correction of scoliosis.
  - Referral to epileptologists for control of seizures.

Additional Therapies
- Patients may need referral to physical, speech, or occupational therapy based upon neurological deficits.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- N/A

SURGERY/OTHER PROCEDURES
- When neurofibromas become very large causing pain or disfigurement, surgical removal should be considered.
  - With skeletal abnormalities including scoliosis, patients may consider seeing a spinal surgeon for spinal fusion.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- N/A

Nursing
- N/A

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Should follow-up yearly with a neurologist and ophthalmologist; follow-up with other specialties based on findings.

Patient Monitoring
- Yearly neurological exams to monitor progression of NF1
- Yearly ophthalmological exams to monitor for optic gliomas
- Regular blood pressure monitoring as hypertension is associated with NF1
- Yearly physical exam with increased attention to skin, skeleton, cardiovascular, and neurological systems
  - Developmental progress in children including height, weight, head circumference, and school progress

DIET
- N/A

PATIENT EDUCATION
- Patients should be offered genetic counseling and explained that if 1 parent has NF1, there is a 50% chance each offspring will have it.
- Prenatal diagnostic testing is available. DNA can be extracted from fetal cells through amniocentesis at 15–18 weeks gestation or chorionic villus sampling at 8–12 weeks gestation
- With severe NF1, prenatal ultrasound may be able to help with diagnosis
- Sources for more information:
  - NINDS: Neurofibromatosis fact sheet. Website: http://www.ninds.nih.gov/disorders/neurofibromatosis/detail_neurofibromatosis.htm
  - Neurofibromatosis, Inc. (NF Inc.), P.O. Box 66884, Chicago, IL 60666. Website: http://www.nfinc.org

PROGNOSIS
- Prognosis of NF1 is difficult to estimate as the disease course is highly variable; however, it is progressive in the majority of patients with a small number having stable symptoms.

COMPLICATIONS
- Disease-associated tumors including neural tumors such as malignant peripheral nerve sheath tumors (neurofibrosarcomas, malignant schwannomas, angiosarcomas), optic gliomas, cerebellar astrocytomas, cerebral gliomas, and brainstem gliomas
- Disease-associated tumors including nonneural malignant tumors such as pheochromocytoma, xantholeukemia and rhabdomyosarcoma
- Disease-associated epilepsy with an overall risk of 2–5% due to abnormalities of the cortex
- Cerebrovascular disease including
  - Stroke due to stenosis or occlusion of major blood vessels, especially in the supraclinoid internal carotid or proximal anterior or middle cerebral arteries with an increased risk of Moyamoya disease
  - Cerebral aneurysms and subarachnoid hemorrhage
- Cognitive deficits can occur along with learning disabilities with an IQ 5 to 10 points lower than the general population.
- Cardiovascular effects may include essential hypertension or hypertension secondary to coarctation of the aorta, pheochromocytoma, or renal artery stenosis
- Respiratory complaints may occur with plexiform neurofibromas of the head and neck with growth into the upper airway. Also, scoliosis associated with NF1 may decrease lung volumes and impair ventilation
- Gastrointestinal disease may include carcinoid tumors in the duodenum near the ampulla of Vater. Also, ganglioneuromatosis may affect the myenteric plexus of NF1 patients causing abdominal pain and constipation.
- Urogenital disease including neurofibromas in the retroperitonium can compress the urinary tract or compress the bladder causing urinary complaints.
- Skeletal disease including scoliosis, kyphosis, and long bone deformation

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- N/A

CODES

ICD9
237.71 Neurofibromatosis, type 1 [von Recklinghausen's disease]

CLINICAL PEARLS
- NF1 is a complex genetic disease that requires a multidisciplinary team approach to the diagnosis and management.
- Despite the absence of specific preventive treatment, some of the disease complications can be prevented by timely intervention.

NEUROFIBROMATOSIS TYPE 2

Matthew L. Bush, MD
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BASICS

DESCRIPTION

- Neurofibromatosis type 2 (NF2) is a highly penetrant autosomal dominant genetic disorder with variable expressivity that is characterized by the development of multiple nervous system tumors. The presence of bilateral vestibular schwannomas is diagnostic of NF2; however, NF2 patients may also develop other cranial nerve schwannomas, spinal schwannomas, meningiomas, and ependymomas. The Manchester criteria diagnoses NF2 in individuals with:
  - Bilateral vestibular schwannomas
  - A first-degree relative with NF2 AND either a unilateral vestibular schwannoma OR any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Unilateral vestibular schwannoma AND any two of: Meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
  - Multiple meningiomas AND unilateral vestibular schwannoma OR any two of: Schwannoma, glioma, neurofibroma, cataract
- Cutaneous manifestation of NF2 occurs in many patients; however, skin lesions are sparse and much less common when compared to NF1. Tumors include cutaneous schwannomas, neuromas, and/or café au lait spots. These lesions may cause persistent neuropathic pain, but less so than the schwannomas associated with schwannomatosis, a distinctly different entity.

EPIDEMIOLOGY

Incidence

The incidence of NF2 is 1 in 25,000 live births, and the disease prevalence is 1 per 60,000. NF2 typically has an early onset, which is typically between 18 and 24 years; however, subtle disease presentation in children may delay diagnosis. Nearly all individuals develop bilateral vestibular schwannomas by the age of 30 years. Genetic mosaicism accounts for 20–30% of NF2 patients without a family history of the disease and one half of patients with NF2 represent acquisition of a new mutation.

Genetics

Genetic testing is available and may be helpful in pre-symptomatic care of patients within families with NF2.

ETIOLOGY

NF2 is due to a germ-line mutation within a tumor suppressor gene, known as neurofibromatosis type 2 (*NF2*), located on chromosome 22q12. This gene encodes a cytoskeletal protein known as merlin or schwannomin and modulates cellular proliferation, adhesion, and motility. Phenotype may vary greatly within families of NF2; however, disease severity appears to be related to the type and location of *NF2* mutation present. A more severe form of the disease has been associated with frameshift or nonsense mutations. Merlin interacts with multiple transcellular receptors and intracellular signaling pathways such as PI3K/Akt, Raf/MEK/ERK, ErbB, and PDGFR and mTOR pathways, which represent potential targets for drug development for NF2 patients.

DIAGNOSIS

HISTORY

- Vestibular schwannomas may be asymptomatic when small; however, the majority of patients experience unilateral auditory and vestibular dysfunction. Tinnitus, sensorineural hearing loss, and chronic disequilibrium are common.
- Meningiomas may present with recurrent headaches and/or seizures. Spinal lesions may lead to chronic pain, focal weakness, and sensory loss. The ocular presentation of posterior subcapsular lens opacities, meningiomas, and retinal hamartomas may result in progressive vision decline and permanent loss.

PHYSICAL EXAM

- Expansion of the tumor within the cerebellopontine angle, or the presence of synchronous cranial nerve schwannomas or meningiomas, may lead to brainstem compression and cranial nerve dysfunction with resultant diplopia, facial hypesthesia, facial paralysis, dysphagia, hoarseness, hydrocephalus, and, potentially, death.
- Mono- and polyneuropathy may also occur in a minority of patients leading to severe muscle wasting. 10% of patients may also experience epilepsy unrelated to tumor burden.

DIAGNOSTIC TESTS AND INTERPRETATION

Audiogram

Speech discrimination scores which are unusually poor when compared to pure tone thresholds may be an early sign of a vestibular schwannoma.

Imaging

Initial approach

MRI of the brain with and without contrast and with thin cuts through the internal auditory canal is the gold standard in evaluation of patients with unilateral auditory and vestibular dysfunction in order to identify enhancing vestibular schwannomas, cranial nerve schwannomas, and meningiomas. A comprehensive spinal MRI with contrast is also useful to evaluate for spinal tumors. Monitoring tumor growth with three-dimensional volumetric analysis may be more sensitive in monitoring small changes of tumor growth over time.

Pathological Findings

Histological features consistent with schwannoma or meningioma

DIFFERENTIAL DIAGNOSIS

Non-NF2-related schwannomas or meningiomas affecting the cranial nerves and/or skull base

TREATMENT

ADDITIONAL TREATMENT

General Measures

The management of NF2 patients is complex due to chronic nature of the disease and the presence of high tumor burden in many patients. These patients are best managed in centers that specialize in the care of NF2 patients and provide multi-disciplinary comprehensive care.

Additional Therapies

- *Serial imaging*: Tumor burden can be monitored with serial MRI over time. NF2-associated vestibular schwannomas exhibit an average growth rate of 1.3 mm/year. Patients that opt for observation should have their first follow-up MRI at 6 months and yearly thereafter. Any change in symptoms should result in repeat imaging.

- *Radiation*: Stereotactic radiation therapy can be used to treat a variety of NF2-associated intracranial tumors in patients that refuse surgery or are unable to safely undergo surgery. Vestibular schwannomas are treated with doses between 12 and 13 Gray (Gy) to 50% isodose line at the periphery of the tumor. Extracranial disease can be treated with stereotactic radiotherapy or external beam radiation. NF2-associated vestibular schwannoma treated with stereotactic radiation has shown tumor control rates of 71–85% with approximately 50% retaining functional hearing at 5 years following treatment. Radiation-associated complication rates are higher in NF2 patients than in those with sporadic tumors. Concern has been raised over the potential of inducing secondary malignancies from radiation in patients with inherent genetic mutations.
- *Chemotherapy*: Although no FDA-approved NF2 chemotherapeutic agents exist, patients with severe disease have been treated with chemotherapeutic agents. Inhibitors directed at the ErbB receptor family, AKT/PI3 kinase signaling pathway, and VEGF have shown evidence of inhibition of NF2 vestibular schwannoma growth. Some agents have shown initial improvement in hearing and tumor size reduction in early trials.

SURGERY/OTHER PROCEDURES

Microsurgery: In order to preserve neurologic and hearing function in NF2 patients, early intervention is indicated. Vestibular schwannoma progression will eventually result in deafness and potentially brainstem compression. The surgical approach is chosen based on the size and location of the tumor, as well as the presence of functional hearing. The suboccipital and middle fossa approaches have hearing preservation rates of 50%. NF2 patients may also undergo auditory brainstem implantation (ABI) at the time of suboccipital or translabyrinthine tumor resection to rehabilitate the loss of hearing. In the event that the cochlear nerve is preserved during tumor resection, cochlear implantation can be performed and offers improved auditory function over ABIs. Bony decompression of the internal auditory canal may also afford an extension of functional hearing in patients that are experiencing disease progression. Surgical management of other NF2-associated tumors is based on the symptoms, as well as the anatomic location. Cranial base and spinal lesions are treated surgically in the situation of progressive neurologic decline.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Typically admitted for surgical resection of NF2 schwannomas or meningiomas

ONGOING CARE

PATIENT MONITORING

- NF2 patients should undergo annual comprehensive neurologic examinations, MRI of the brain with and without contrast, and audiograms. Development of new symptoms should be followed with repeat imaging. Spinal MRI is indicated at the time of development of symptoms. Children with NF2 should undergo frequent surveillance and rehabilitation of sensory deficits. Pre-symptomatic NF2 children should undergo MRI of the brain every 2 years through adolescence. Along with regular ophthalmologic and audiologic exams, individuals with visual and/or hearing loss should receive prompt rehabilitative services.
- Genetic testing should be offered for first-degree relatives of NF2 patients, and genetic counseling should be offered to NF2 patients.

PATIENT EDUCATION

Support groups such as the Acoustic Neuromas Association (www.anausa.org) and the Children's Tumor Foundation (www.ctf.org) provide many educational and social resources for patients and families affected by NF2.

PROGNOSIS

The prognosis of NF2 patients is poor as they face a life of progressive neurologic decline; however, the rate of decline is variable. Progressive cranial base tumor growth can lead to lower cranial nerve dysfunction, which may lead to chronic aspiration, gastrostomy tube dependence, and recurrent pneumonia, and is often the root cause of death. Patients diagnosed from 1970 to 1990 were found to have a 15-year life expectancy from the time of diagnosis. Improved diagnosis and early intervention have improved current life expectancies.

COMPLICATIONS

Loss of hearing, facial nerve paralysis, vestibular dysfunction, and impaired function of other cranial nerves due to tumor compression and/or surgery.

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See Also (Topic, Algorithm, Electronic Media Element)

Neurofibromatosis type 1

CODES

ICD9

- 225.1 Benign neoplasm of cranial nerves
- 225.3 Benign neoplasm of spinal cord
- 237.72 Neurofibromatosis, type 2, acoustic neurofibromatosis

CLINICAL PEARLS

- In the majority of patients with NF2, initial symptoms consist of tinnitus, headache, and hearing loss.
- The typical patient with NF2 will develop bilateral acoustic schwannomas.
- Treatment is surgical resection in most cases, although stereotactic radiosurgery can also be used in selected patients.

N

NEUROLEPTIC MALIGNANT SYNDROME

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BASICS

DESCRIPTION
Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening reaction that occurs in patients who are treated with antipsychotic agents (neuroleptics). It appears that the cause of NMS is dopamine blockade, which would explain why this disorder has also been associated with drugs such as:

- Amoxapine (an antidepressant)
- Antiemetics such as prochlorperazine (Compazine), promethazine (Phenergan), and metoclopramide (Reglan)

EPIDEMIOLOGY
Incidence
- Estimated incidence of NMS ranges from 0.01% to 0.02% of patients treated with neuroleptics. This may not be as prevalent as once thought.
- Reasons for this variability include:
  - Diverse patient populations
  - Different thresholds for diagnosing the disorder
  - Variations in treatment practices
- Incidence of NMS is decreasing due to increased awareness, early detection and treatment, and efforts at prevention.
- Race
  - African Americans may be at higher risk because they have a higher proportion of alleles that code for reduced CYP2D6 enzymatic activity (genetic polymorphisms exist in most of the CYPs).
- Age
  - All ages are affected, although NMS most commonly occurs in adults aged 20–50.
- Sex
  - NMS is more commonly seen in men, but this may be attributed to the fact that men are medicated more frequently and more aggressively with neuroleptics than women.

RISK FACTORS
- Dehydration
- History of prior episodes of NMS
- High doses of neuroleptics
- Intramuscular administration of neuroleptics
- Rapid rate of neuroleptic loading
- Catatonia
- Iron deficiency
- Use of other medications (especially lithium) in conjunction with neuroleptics
- Prolonged use of seclusion/restraints
- Electrolyte disturbances
- Presence of an organic dysfunction
- Presence of a mood disorder

Genetics
Genetic predisposition for developing NMS has been suggested by studies of dopamine D2 receptor gene polymorphisms.

GENERAL PREVENTION
Minimizing unnecessary use of neuroleptics reduces the risk of NMS.

PATHOPHYSIOLOGY
Dopamine D2 receptor antagonists are associated with this disorder, and it is assumed that NMS is caused by dopamine receptor blockade.

ETIOLOGY
- There is still a fair amount of controversy over the etiology of NMS.
- NMS has been conceptualized as a drug-induced form of malignant (potentially fatal) catatonia.
- Studies show that dopamine blockade could lead to hypothalamic dysfunction resulting in:
  - Hyperthermia
  - Labile blood pressure
  - Tachycardia
- Dopamine blockade in the striatum can cause:
  - Tremor
  - Rigidity
  - Rhabdomyolysis (due to prolonged muscular hypertonicity)

DIAGNOSIS

HISTORY
Diagnostic Criteria for NMS
- Recent treatment with neuroleptics (within 7 days before onset)
- Hyperthermia (temperature above 38°C)
- Muscle rigidity
- Exclusion of systemic or neuropsychiatric illness
- And at least three of the following:
  - Change in mental status
  - Change in blood pressure
  - Creatinine phosphokinase (CPK) elevation or myoglobinuria
  - Leukocytosis
  - Metabolic acidosis
  - Tachycardia
  - Diaphoresis or sialorrhea
  - Tremors

PHYSICAL EXAM
- Hyperthermia
- Generalized rigidity (lead pipe)
- Autonomic instability
- Mental status changes
- Profuse diaphoresis

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests (1)[C]
- CPK
- CBC
- Electrolytes, including calcium and magnesium
- Renal and hepatic function tests
- Urinalysis, including urine myoglobin
- Optional tests to be done if appropriate:
  - Arterial blood gas
  - Toxicology screen
  - Coagulation studies
  - Blood cultures

Imaging
Initial approach
CT scan or MRI scan of the head (1)[C]

Diagnostic Procedures/Other
Lumbar puncture to rule out CNS infection (1)[C]

DIFFERENTIAL DIAGNOSIS
- Catatonia
- Serotonin syndrome
- Heat exhaustion and heat stroke
- Malignant hyperthermia
- Delirium – secondary to anticholinergic toxicity
- Withdrawal of antiparkinsonian agents in a patient with Parkinson's disease
- Thyrotoxicosis
- CNS infections
- Drug toxicity: Amphetamines, phencyclidine, cocaine
- Intermittent acute porphyria
- Pheochromocytoma
- Tetany
- Parkinson's disease and other neurologic disorders

TREATMENT

MEDICATION
First Line
- In most cases pharmacologic management is instituted if the course of the syndrome, following neuroleptic discontinuation, fails to improve with supportive measures alone (2)[C].
- Dopamine agonist agents have been shown in some studies to possibly decrease mortality and shorten the course of NMS (1)[C].
- Bromocriptine (Parlodel): A dopamine agonist
  - Usually the starting dose is 2.5 mg PO t.i.d. The dose can be increased by 2.5–7.5 mg daily, up to a daily total of 45 mg in divided doses.
  - Possible side effects include nausea, vomiting, possible exacerbation of psychotic symptoms.
  - Caution should be used when administering to children younger than 15 years of age.

- Amantadine (Symmetrel)
  - Usual adult dose is 200–300 mg PO daily in divided doses
- Sinemet
  - Usual adult dose is 25/250 mg PO t.i.d. or q.i.d.
- Dantrolene (Dantrium)
  - Dantrolene is a muscle relaxant and is specifically recommended for severe hyperthermia. It may be given IV or PO. Initial dose is 1–3 mg/kg IV followed by a total of up to 10 mg/kg/day IV in divided doses or 50–600 mg/day in divided oral doses. Dantrolene may be used in conjunction with bromocriptine if clinically indicated.
  - Dantrolene may cause hepatitis, and liver function needs to be monitored.
- Precautions: Complications include:
  - Rhabdomyolysis
  - Renal failure
  - Aspiration pneumonia
  - Seizures
  - Respiratory or cardiac failure
  - Exacerbation of psychiatric illness following discontinuation of antipsychotic agent or treatment with dopamine agonists
- Benzodiazepines, administered orally or parenterally, have been shown in case reports and through clinical experience to improve symptoms and speed recovery, especially in milder cases (3)[C].
- Lorazepam (Ativan)
  - First dose 1–2 mg IM or IV
  - May be helpful in patients with primarily catatonic symptoms
  - Can give 1–2 mg IM or IV every 4–6 hours if improvement is seen following initial dose

Second Line

- Subcutaneous heparin should be used to prevent pulmonary embolism or deep vein thrombosis.
- Iron deficiency anemia may aggravate NMS. Therefore, iron supplements should be prescribed for patients who are deficient.

ADDITIONAL TREATMENT

General Measures

- The most critical intervention is to discontinue all neuroleptic agents immediately.
- The discontinuation of other medications such as lithium or anticholinergic agents should be considered.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - IV fluids to correct dehydration, hypotension, and electrolyte imbalance
  - A cooling blanket and antipyretics to reduce the temperature
  - If rhabdomyolysis occurs, it is important to hydrate patients and alkalinize the urine to prevent renal failure.
  - Aspiration precautions
  - Maintain good nutrition, as this may minimize rhabdomyolysis
- Adjunctive treatment
  - Dialysis may be necessary if renal failure develops.
  - Electroconvulsive therapy (ECT) has been found to be effective both in treating NMS and the underlying psychiatric condition (3)[C].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Most patients suspected of having NMS should be treated (at least initially) in the medical intensive care unit.

Admission Criteria

Patients may be transferred to a medical or psychiatric inpatient unit once their vital signs are stable, their hydration status and electrolyte imbalance corrected, CPK levels are falling, and there is no evidence of renal failure or cardiorespiratory compromise.

Discharge Criteria

Normalization of vital signs and physical exam

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Follow-up for the condition warranting the NMS-causing agent is urgent.

Patient Monitoring

Patients with NMS should be off neuroleptics for 2 weeks following resolution of the syndrome. Vital signs and CPK levels need to be monitored.

PATIENT EDUCATION

Every patient who has had NMS should be told that he or she is at risk for recurrence if challenged with any dopamine-blocking agent.

PROGNOSIS

- The clinical course of NMS usually lasts 2–14 days, although in the case of long-acting depot antipsychotic agents it may be prolonged up to 30 days.
- Mortality rate is 10–20% from complications listed above. In the absence of these complications the prognosis for full recovery is good.
- Patients who develop NMS are more likely to have a recurrence upon reintroduction of neuroleptic agents. To minimize the risk of a recurrence, several measures may be helpful:
  - Try a neuroleptic from a different chemical class and with a lower D2 affinity, such as an atypical antipsychotic (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole), although all atypical antipsychotics have been associated with the potential to cause NMS (4)[C].
  - Clozapine is currently recommended for patients who need an antipsychotic and have a history of NMS (but the risk for agranulocytosis needs close monitoring with this agent). In addition, clozapine has also been associated with NMS (but less frequently).
  - Consider alternative treatments with lithium, valproate, carbamazepine, or ECT.
  - If an antipsychotic agent is necessary, use the lowest effective dose and increase the dose slowly.
  - Obtain informed consent from the patient and family and discuss at length the risks, benefits, and side effects of treatment. In addition, closely monitor vital signs and CPK levels.

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

Neuroleptic midbrain syndrome

CODES

ICD9

333.92 Neuroleptic malignant syndrome

CLINICAL PEARLS

- NMS is a potentially life-threatening reaction to treatment with a dopamine-blocking agent.
- Fever and rigidity are key exam findings.
- Discontinuation of the offending agent, in the context of hospital-based supportive management, is a primary step in treatment.

NEUROMYELITIS OPTICA (DEVIC'S DISEASE)

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BASICS

DESCRIPTION
- Neuromyelitis optica (NMO), otherwise known as Devic's disease, is an idiopathic, relapsing, inflammatory, and necrotizing disorder of the CNS which preferentially affects the optic nerves and spinal cord.

EPIDEMIOLOGY
Incidence
- Incidence unknown. Limited population studies suggest incidence of 0.05–0.26/100,00 per year.

Age
- Onset usually in 30s and 40s; mean age of onset is 39.

Gender
- Female predominance. Case series suggest an M:F ratio of 1:4–1:9.

Race
- NMO has been described worldwide; more frequent case reports from patients of African and Asian origin.

RISK FACTORS
- Female gender
- Asian/African origin
- Association with thymus tumors/myasthenia gravis and other malignancies (breast, lymphoma)

Genetics
- Familial aggregation of NMO has been reported.
- HLADRB1*03 and HLADR3 alleles have been associated with NMO.

GENERAL PREVENTION
- No known forms of prevention.

PATHOPHYSIOLOGY
- Aquaporin 4 water channels (astrocyte end-feet) targeted by IgG.
- Antibody/complement activation leads to infiltration by eosinophils and neutrophils.
- Vasculocentric deposition of immune complexes.
- Secondary immune-mediated demyelination, neuronal injury, and necrosis.

ETIOLOGY
- Pathogenic role of aquaporin 4 IgG (NMO antibody)
- Malignancy-associated cases may suggest a paraneoplastic component.

COMMONLY ASSOCIATED CONDITIONS
- Recurrent optic neuritis
- Longitudinally extensive transverse myelitis
- Thyroditis
- Sjogren's syndrome
- Systemic lupus erythematosus
- Thymus malignancy with or without myasthenia gravis
- Other malignancies (mainly breast adenocarcinoma, lymphoma)

DIAGNOSIS

HISTORY
- History of optic neuritis and transverse myelitis which may present in a monophasic or relapsing variant
- Optic neuritis
  - Acute (hours to days) onset
  - Central scotoma
  - Ocular pain
  - Unilateral or bilateral
  - Often severe, limited recovery
- Transverse myelitis
  - Acute (hours to days)
  - Symmetric paraparesis/plegia or quadraparesis
  - Sensory loss with level
  - Bladder/bowel involvement
- Temporal pattern
  - Remitting over years, may be monophasic.

PHYSICAL EXAM
- Optic nerve dysfunction
  - Central scotoma with decreased acuity
  - relative afferent pupillary defect
  - Color desaturation
  - Fundoscopic exam: Normal, acute papillitis, or optic disc pallor
- Myelopathy
  - Weakness in legs, arms
  - Over-time weakness will develop definite upper motor neuron signs
  - Sensory loss with a spinal level
- Brainstem dysfunction
  - Extension of high cervical lesions
  - Focal brainstem palsies
  - Respiratory center involvement is possible

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- NMO IgG antibody in serum
  - Sensitivity: 73%
  - Specificity: 91%
- CSF testing
  - Pleocytosis (>50 cells/mm^3, mainly neutrophils)
  - Increased total protein
  - Oligoclonal bands are not common (10–30%)
  - NMO in CSF (if serum negative)

Follow-up & special considerations
- Evoked potential studies tailored to clinical presentation
  - Visual-evoked potentials
  - Somatosensory evoked potentials
- Ocular coherence tomography (OCT)
  - Retinal nerve fiber layer thinning seen with optic neuritis.

Imaging
Initial approach
- MRI of the brain with and without contrast with a focus on optic nerves may show edema, signal abnormality, or enhancement in the optic nerves. Brain lesions typically occur in peri-ependymal regions typically located close to the third ventricle.
- MRI of the cervical and thoracic spine with and without contrast will show lesions that typically are longitudinally extensive (>3 spinal segments). Cervical cord is most commonly affected. Variable degree of necrosis, cavitation, and gadolinium enhancement.

Follow-up & special considerations
- Serial imaging of the cervical and thoracic cord as clinically warranted and to monitor therapy

Diagnostic Procedures/Other
- OCT may be used to follow recovery from optic neuritis and pre-clinical changes.

Pathological Findings
- Pathology rarely pursued due to the location of lesions (spinal cord and optic nerves)
- Post-mortem pathology shows demyelination with astrocyte loss, vasculocentric complement deposition, vascular hyalinization, eosinophil, and neutrophil infiltrates

DIFFERENTIAL DIAGNOSIS
- Multiple sclerosis
- Acute disseminated encephalomyelitis
- Neuro-psychiatric lupus
- B12 deficiency
- Copper deficiency
- CNS vasculitis
- Mitochondrial disease
- Neuro-sarcoidosis
- Sjogren's syndrome
- Spinal cord neoplasm
- HIV/HTLV infections

TREATMENT

MEDICATION
Acute Exacerbations
First Line
- Solumedrol 1 g IV daily for 3–5 days, followed by a prolonged oral tapering dose (1)[C].

Second Line
- For steroid unresponsive patients, plasma exchange (1–1.5 plasma volume per exchange) may be used (2)[C].

Relapse Prevention
First Line
- Azathioprine 2.5–3 mg/kg/day orally + prednisolone 1 mg/kg orally (tapering after months) (3)[C].
- Rituximab 375 mg/m^2 IV weekly for 4 weeks (4,5)[C].

Second Line
- Cyclophosphamide 600–1200 mg/m^2 IV monthly adjusted based on white blood cell count [C].
- Methotrexate 5–25 mg orally weekly [C].
- Mycophenolate mofetil 1–3 g orally daily [C].

ADDITIONAL TREATMENT
General Measures
- Patients should be followed closely for treatment of multiple symptomatic issues. Special attention for patients who have para/tetraplegia should include venous thrombo-embolic disease risk and prevention. Monitoring of respiratory, speech/swallowing function, and bladder/bowel function.

Issues for Referral
- Physical therapy, occupational therapy, and physical medicine/rehabilitation consultation as needed
- Neuro-ophthalmology, low-vision clinic
- Speech/swallow therapy

Additional Therapies
Symptomatic treatment
- Symptomatic treatment should be tailored individually.
- Spasticity: Baclofen (10 mg t.i.d.), tizanidine (4 mg–32 mg div. doses), benzodiazepines, botulinum toxin for more severe cases.
- Bladder dysfunction: Anticholinergics, alpha adrenergic blockers, self catheterization.
- Constipation: Dietary changes, stool softeners.
- Pain syndromes: Gabapentin (300–2400 mg div t.i.d.), selective serotonin reuptake inhibitors, low-dose tricyclic antidepressants.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- N/A

SURGERY/OTHER PROCEDURES
- Intrathecal baclofen test injection and placement of permanent pump for cases that do not respond to PO baclofen.
- Tracheostomy/gastrostomy tube for patients with high cervical/medullary lesions.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Airway protection, endotracheal intubation if needed.
- Hemodynamic monitoring due to blood pressure (BP) and heart rate (HR) fluctuations.

Admission Criteria
- Significant change in disability level requiring placement and inpatient physical therapy.
- Respiratory/swallowing compromise due to new or evolving lesions.

IV Fluids
- Judicious management of IV fluids.

Nursing
- BP, HR, and respiratory monitoring
- Prompt swallow evaluation
- Venous thromboembolism prevention (heparin, enoxaparin)

Discharge Criteria
- Stable neurological exam
- Safe environment for discharge (home care if needed)

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Frequent and close follow-up is needed for the treatment of multiple symptomatic issues, as well as monitoring of disease-modifying therapy.

Patient Monitoring
- Patient should monitor for new or evolving symptoms.

DIET
- As tolerated by swallowing ability

PATIENT EDUCATION
- National Institutes of Health. Website: *www.ninds.nih.gov/disorders/neuromyelitis_optica/neuromyelitis_optica.htm*

PROGNOSIS
- NMO occurs more commonly as a relapsing disorder, but may be monophasic.
- Predictors of a relapsing form include female sex, older age of onset, less severe motor impairment, and long interval between the first and second event.

COMPLICATIONS
- Venous thromboembolic disease
- Pneumonia
- Decubitus ulcers
- Urinary infections and urosepsis

REFERENCES

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CODES

ICD9
341.0 Neuromyelitis optica

CLINICAL PEARLS
- NMO antibodies should be tested for in all patients with longitudinally extensive myelitis of presumed auto-immune origin.
- NMO patients respond poorly to beta-interferons.

NEURONAL CEROID LIPOFUSCINOSES

Eveline C. Traeger, MD

BASICS

DESCRIPTION

- Neuronal ceroid lipofuscinoses (NCL forms 1–10) are a group of neurodegenerative disorders, characterized by progressive dementia, visual loss, epilepsy, and intralysosomal accumulation of a membrane-bound fluorescent lipopigment in neurons and other cells. Signs and symptoms are confined to the CNS.
- NCLs are a clinically and genetically heterogeneous group of disorders. 8 of the 10 forms of NCL have been molecularly characterized and are associated with gene mutations.

EPIDEMIOLOGY

Prevalence

- The NCLs are the most common group of neurodegenerative disorders. 25,000 families in the US are affected with a form of NCL.
- Prevalence is highest in the Scandinavian countries, especially Finland.

RISK FACTORS

Genetics

Autosomal recessive mode of inheritance except for a rare adult-onset variant that is autosomal dominant. Gene identification is available for NCL1, NCL2, NCL3, NCL5, NCL6, NCL7, NCL8, and NCL10. Prenatal diagnosis is available if the proband has a documented enzyme deficiency or a disease-causing mutation.

PATHOPHYSIOLOGY

Apoptosis and dysregulated sphingolipid metabolism.

DIAGNOSIS

HISTORY

- Congenital NCL: Microcephalic at birth with seizures, spasticity, and central apnea.
- Infantile NCL (INCL): Dramatic onset of psychomotor deterioration, seizures, and blindness during the first year of life. The common ocular abnormality is optic atrophy; retinal abnormalities have been reported.
- Late-Infantile NCL (LINCL): Onset between 2 and 5 years of age, with psychomotor deterioration and intractable seizures. Blindness associated with optic atrophy or retinitis pigmentosa. Vegetative state ensues after symptoms have been present for about 1 year.
- Juvenile NCL (JNCL): Onset between 5 and 15 years of age, with either gradual visual loss resulting in blindness within 3–5 years and/or behavioral symptoms. There is macular degeneration, optic atrophy, or retinitis pigmentosa. Some time after the onset of the visual disturbance, motor dysfunction (apraxia and ataxia), seizures, and slow dementia are noted.
- Northern epilepsy (NE): Onset with frequent tonic–clonic seizures between 5 and 10 years of age followed by progressive mental retardation. Visual loss is not a prominent feature.
- Adult NCL (ANCL): Average onset at 30 years, with a steadily progressive dementia and seizures that ultimately become refractory. Vision is not usually affected.

PHYSICAL EXAM

- Progressive cognitive decline.
- Variable visual loss. Funduscopic evaluation may reveal optic atrophy, retinitis pigmentosa, or macular degeneration.
- Progressive motor dysfunction may include spasticity, extra pyramidal symptoms, or ataxia.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- EEG, electroretinogram, visual evoked potentials, and somatosensory evoked potentials may add supportive evidence. Electron microscopic identification of characteristic ultrastructural abnormalities in lymphocytes or tissue biopsy of skin or conjunctiva.
- Histologic inclusions:
  - Granular osmiophilic deposits (GROD) in NCL1, NCL9, NCL10
  - Curvilinear inclusion bodies (CV) in NCL2, NCL6, NCL7, NCL9
  - Fingerprint inclusions (FP) in NCL3, NCL5, NCL6, NCL7
  - Mixed-type inclusions (CV, FP, GROD) in NCL4, NCL8

Imaging

Initial approach

Neuroimaging may reveal cerebral and/or cerebellar atrophy.

Diagnostic Procedures/Other

- Molecular genetic testing for the 8 genes known to be associated with NCL. The following phenotype–genotype correlations should help guide molecular testing:
  - Congenital NCL: NCL10
  - INCL: NCL1
  - LINCL: NCL2 (most common), NCL5 (most common in Finland), NCL1, NCL6, NCL7, NCL8, NCL10
  - JNCL: NCL3 (most common), NCL1, NCL2, NCL9
  - NE: NCL8
  - ANCL: NCL1, NCL3, NCL4, NCL5, NCL10
- Enzyme activity of palmitoyl-protein thiesterase 1 for NCL1, tripeptidyl-peptidase 1 for NCL2, Cathepsin D for NCL10

DIFFERENTIAL DIAGNOSIS

The NCLs are easily distinguished from the other known inherited metabolic neurodegenerative diseases based on physical examination, funduscopic evaluation, and clinical course. It is important to confirm the diagnosis to rule out other neurodegenerative disorders.

TREATMENT

MEDICATION

First Line

No medications are available to reverse the symptoms of these disorders.

ADDITIONAL TREATMENT

General Measures

Patients and their families require emotional support.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Correction of associated visual refractive errors.
  - Antiepileptic drugs should be selected with caution.
  - Psychotropic drugs for treatment of behavior problems.
- Adjunctive treatment
  - Braille training and visual impairment education.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients usually are admitted for evaluation and treatment of the complications of their disease.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patient follow-up is guided by the predicted course and potential complications of the particular disease.

PATIENT EDUCATION

- Batten Disease Support and Research Association, 2600 Parsons Avenue, Columbus, OH 43207. Phone: 800-448-4570.
- Children's Brain Diseases Foundation, 350 Parnassus Avenue, Suite 900, San Francisco, CA 94117. Phone: 415-565-5402.
- National Batten Disease Registry, 1050 Forest Hill Road, Staten Island, NY 10314-6399. Phone: 800-952-9628.

PROGNOSIS

- Congenital NCL: Death soon after birth.
- INCL: Rapid and severe neurologic devastation. Usually fatal before the end of the first decade.
- LINCL: Rapidly progressive. Usually fatal before the end of the first decade.
- JNCL: May remain ambulatory and able to attend school until the late teens, although 25% of patients die in their teens after a more rapidly dementing course with prominent seizures.
- NE: Epileptic seizures decrease after puberty. Slow cognitive decline continues throughout life. Some individuals have lived beyond 60 years of age.
- ANCL: Slow progression. Duration of illness 20–30 years.

ADDITIONAL READING

- Chang CH. Neuronal ceroid lipofuscinoses. http://emedicine.medscape.com/article/1178391.
- Mole SE, Williams RE. Neuronal ceroid-lipofuscinosis. http://www.ncbi.nlm.nih.gov/books/NBK1428/.
- National Center for Biotechnology Information.http://www3.ncbi.nlm.nih.gov.
- OMIM.http://www.ncbi.nlm.nih.gov/omim/204500.

CODES

ICD9

- 330.1 Cerebral lipidoses
- 362.71 Retinal dystrophy in systemic or cerebroretinal lipidoses

CLINICAL PEARLS

- NCL forms 1–10 are clinically and genetically heterogeneous.
- Characterized by progressive dementia, visual loss, and epilepsy.
- Electron microscopy reveals intralysosomal accumulation of a membrane-bound fluorescent lipopigment in neurons and other cells.
- 8 of the 10 forms are molecularly characterized.
- No specific treatment is available.

NEUROPATHY, DIABETIC

Vern C. Juel, MD
Ram Narayan Kaveer Nandigam, MD

BASICS

DESCRIPTION
Diabetes mellitus (DM) is the most frequent cause of peripheral neuropathy in the developed world. The most common type of diabetic neuropathy is a distal, symmetrical polyneuropathy (DSPN) with length-dependent sensory loss, acral dysesthesia, and distal weakness.

EPIDEMIOLOGY
Incidence
1.9 million individuals in the US age >20 years were newly diagnosed with DM in 2010 (1). About 7.5% of these patients had neuropathy at the time of diagnosis.

Prevalence
DM currently affects 8.3% of the overall US population, and 26.9% of people age ≥65 years. About 60–70% of diabetics eventually develop neuropathy (1).

RISK FACTORS
- Chronically poor glycemic control is the most important risk factor for developing DSPN.
- Advanced age, hypertension, elevated triglyceride level, obesity, and smoking are additional risks for DSPN (2).
- Strict glycemic control reduces the risk for developing DSPN.
- Once axonal injury is established, there are no known effective interventions to reverse DSPN.

Pregnancy Considerations
Pregnant women with gestational diabetes are not at increased risk for developing DSPN, unless their hyperglycemia persists beyond 6 weeks postpartum.

Genetics
Aldose reductase gene polymorphisms have been implicated in early onset DSPN.

GENERAL PREVENTION
Strict glycemic control can prevent or slow progression of diabetic polyneuropathy.

PATHOPHYSIOLOGY/ETIOLOGY
- DSPN results from chronic hyperglycemia. Though the precise pathophysiology has not been established, microangiopathy and metabolic abnormalities are the major proposed causes.
- Endoneurial microvascular changes with basement membrane thickening and pericyte degeneration progress to vessel and nerve ischemic injury.
- Metabolic abnormalities include accumulation of advanced glycosylation end products leading to smooth muscle proliferation and capillary atherogenesis. Accumulation of polyol constituents, such as sorbitol and fructose, may ultimately lead to nerve demyelination and axonal injury.
- Oxidative stress with excessive free radical production may lead to lipid peroxidation of nerve membranes.
- Circulating nerve growth factors are also reduced.

COMMONLY ASSOCIATED CONDITIONS
- *Diabetic autonomic neuropathy* may produce postural hypotension with a rapid, invariant pulse and reduced sweating in distal limbs. GI manifestations include gastroparesis, postprandial sweating, and nocturnal diarrhea. Genitourinary manifestations include bladder atony with difficulty initiating micturition, incomplete bladder emptying, and post-void dribbling. Most men experience erectile impotence, but ejaculation is initially unaffected.
- *Diabetic cranial neuropathies* include oculomotor neuropathy with subacute unilateral ptosis and external ophthalmoplegia sparing pupil constrictor function that is often preceded by retrobulbar or hemicranial pain.
- *Compressive mononeuropathies*: Diabetics have increased susceptibility to compression neuropathies, including median neuropathy at the wrist (carpal tunnel syndrome), ulnar neuropathy at the elbow, and peroneal neuropathy at the fibular head.
- *Truncal radiculoneuropathy*: Diabetics may develop subacute thoracic paraspinal, flank, chest wall, or upper abdominal pain, which is generally unilateral, intense, and independent of position or inspiratory movement. Examination may demonstrate abnormal sensation in a radicular or segmental pattern in the thoracic region, occasionally with focal abdominal wall weakness. Recovery occurs over several weeks.
- *Lumbosacral radiculoplexus neuropathy*: This syndrome of painful, asymmetric lower extremity weakness (also called Bruns-Garland syndrome or diabetic amyotrophy) is most often observed in older men with type 2 DM. Severe pain involving the back, hip, buttock, or anterior thigh precedes the development of muscle weakness and atrophy affecting both proximal and distal muscles. Weakness may progress over weeks or months, with later involvement of the contralateral lower extremity. Recovery occurs over months, with the degree of recovery directly related to the severity and distribution of weakness.

DIAGNOSIS

- *Sensory symptoms and signs*: Initial symptoms of DSPN include tingling or burning paresthesias and allodynia in the toes and feet with reduced sensation. Achilles tendon reflexes and vibratory sensation in the toes are often reduced early. Hand numbness and sensory loss may develop later as a consequence of the progression of length-dependent neuropathy or from compressive median or ulnar neuropathies. Abnormal sensation may be perceived on the anterior abdomen due to distal involvement of thoracic nerves. Large-fiber sensory deficits develop later, with distal proprioceptive loss and sensory ataxia. Patients may develop gait unsteadiness with difficulty walking in a dark environment or loss of balance with eyes closed. Neurogenic foot arthropathy (Charcot joint) may develop at the instep. Distal autonomic dysfunction with sweating abnormalities or circulatory instability may be observed in the feet.
- *Motor symptoms and signs*: Distal weakness with reduced strength and bulk for toe extension, foot dorsiflexion, and intrinsic hand muscles may develop with more advanced disease.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- Establish the diagnosis of DM with fasting plasma glucose ≥126 mg/dL, HbA1C ≥6.5%, 2 hour plasma glucose ≥200 mg/dL during an OGTT using 75 g glucose, or random plasma glucose ≥200 mg/dL with classic symptoms of hyperglycemia. Point-of-care A1C assays are currently not sufficiently accurate for diagnostic use.
- *Electrodiagnostic (EDx) studies*: Nerve conduction studies may demonstrate reduced conduction velocity and amplitudes of sensory nerve action potentials and compound muscle action potentials in a length-dependent fashion. Needle electromyography may demonstrate denervation and reinnervation in distal muscles with more advanced disease. EDx studies are particularly useful when a superimposed compression neuropathy is being considered.
- *Quantitative sensory testing* is used to measure vibration and thermal perception thresholds. It is an effective tool to document the evolution of sensory abnormalities in longitudinal evaluations of patients with DSPN. Its use in detection of preclinical neuropathy is unproven.
- *Autonomic studies* are useful in documenting autonomic dysfunction in polyneuropathy. Utilization of a combination of autonomic reflex screening tests including heart rate variability to deep breathing and tilt or orthostatic posture (R-R interval testing) may demonstrate loss of the normal sinus arrhythmia.
- *Skin biopsy* may be considered to demonstrate reduced intra-epidermal nerve fiber density when small-fiber neuropathy is suspected, particularly if autonomic studies are impractical due to confounding medications (e.g. beta-blockers, anticholinergics, SSRIs).

Follow-up & special considerations
Perform the HbA1C test biannually if glycemic control is stable, otherwise quarterly.

Imaging
Not indicated in DSPN.

Diagnostic Procedures/Other
Nerve biopsy in DSPN demonstrates nonspecific findings and is not needed for diagnosis.

Pathological Findings
- Nerve fiber atrophy, loss of myelinated and unmyelinated fibers associated with axonal degeneration and segmental demyelination.
- Vascular abnormalities in endoneurial or epineurial spaces, such as thickening, occlusion, medial sclerosis, and fragmentation of the internal elastica.

DIFFERENTIAL DIAGNOSIS
- Polyneuropathy due to hypothyroidism, paraproteinemia, toxins, nutritional deficiency, idiopathic sensory polyneuropathy, chronic inflammatory demyelinating polyneuropathy
- Primary erythromelalgia

TREATMENT

MEDICATION

Neuropathic pain in DSPN that affects quality of life (QOL) may require treatment. The goal of neuropathic pain treatment is to improve functional measures and QOL. Achieving "zero" pain is not always realistic.

First Line

- Pregabalin (300–600 mg daily) is effective in reducing DSPN-related pain (NNT 5.6) and improves QOL measures. Sedation and weight gain are the most common adverse events (3,5)[A].
- Gabapentin (1,200 mg or more daily) provides significant pain relief (NNT 5.8), with frequent and often tolerable adverse effects including somnolence, dizziness, peripheral edema, and gait disturbance (4,5)[A].
- Duloxetine (60–120 mg daily) and venlafaxine (75–225 mg daily) reduce diabetic neuropathic pain. Minor side effects of nausea, dry mouth, and dizziness are most common (5)[A].
- Tricyclic antidepressants, such as amitriptyline (up to 150 mg daily), desipramine, and imipramine, provide moderate pain relief. Amitriptyline has the best evidence for effectiveness (5)[A].

Second Line

- Sodium valproate reduces pain, but may be associated with weight gain and poor glycemic control (5)[A].
- Opiates, including morphine sulfate, oxycodone, dextromethorphan, and tramadol, are probably effective in reducing pain in DSPN and in improving QOL, though they are associated with significant adverse effects including constipation, medication overuse headache, and tolerance (5)[A].
- Topical capsaicin (0.075% cream and 8% patch) relieves pain in DSPN. Transient local skin irritation is common (5)[A].

Unproven or inefficacious treatments

- Lamotrigine (200–400 mg daily) has no demonstrated efficacy in chronic neuropathic pain.
- Insufficient evidence exists whether vitamin B supplementation is beneficial or harmful.
- Neurostimulation therapies for neuropathic pain are unproven.

ADDITIONAL TREATMENT

General Measures

Meticulous foot care is essential to prevent the development of foot infections, which are difficult to treat and may lead to amputation.

Issues for Referral

- Patients with diabetic autonomic neuropathy should be referred for cardiac investigation before beginning intense physical activity.
- Physical therapy for gait safety may be indicated for patients with sensory ataxia.
- Podiatric referral for foot hygiene, including nail care and callus removal, should be promoted.

Additional Therapies

- Gastroparesis symptoms may improve with dietary changes and prokinetic agents.
- Treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors.

SURGERY/OTHER PROCEDURES

- Surgical treatment of moderate-to-severe carpal tunnel syndrome relieves symptoms significantly better than splinting.
- Decompression surgery for diabetic symmetric distal neuropathy is not recommended.

IN-PATIENT CONSIDERATIONS

Hospital admission is not generally required.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

See above

DIET

Diabetic dietary guidelines are recommended to achieve strict glycemic control.

PATIENT EDUCATION

- Exercise, weight loss, appropriate diet, optimal foot care, and compliance with insulin and/or oral hypoglycemic medications are important for best outcomes.
- Reliable patient education resources are available through the following organizations:
  - National Diabetic Education Program. Website: http://ndep.nih.gov
  - American Diabetes Association. Website: http://www.diabetes.org/living-with-diabetes/complications/neuropathy
  - American Chronic Pain Association. Website: http://www.theacpa.org

PROGNOSIS

Progression of polyneuropathy occurs with chronic hyperglycemia and is not inevitable with good glycemic control.

COMPLICATIONS

- Neuropathic pain in distal limbs
- Sensory loss leading to limb ulcerations, infections, and amputations
- Reduced proprioception with sensory ataxia and falls
- Susceptibility to compression neuropathies

REFERENCES

1. U.S. Department of Health and Human Services CDCP. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011.
2. Tesfaye S, Chaturvedi N, Eaton SEM, et al. Vascular risk factors and diabetic neuropathy. *N Eng J Med* 2005;352:341–350.
3. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews*, 2009.
4. Moore RA, Wiffen PJ, Derry S, et al. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews*, 2011.
5. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy. *Neurology* 2011;76: 1758–1765.

CODES

ICD9

- 250.60 Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
- 250.61 Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
- 250.62 Diabetes with neurological manifestations, type II or unspecified type, uncontrolled

CLINICAL PEARLS

- Distal, symmetrical polyneuropathy (DSPN) is a common complication of diabetes mellitus.
- Strict glycemic control is the best measure to prevent development of DSPN.
- Effective neuropathic pain management may improve function and quality of life.

NEUROPATHY, HEREDITARY

Zarife Sahenk, MD, PhD

BASICS

DESCRIPTION

Hereditary neuropathies are a clinically and genetically heterogeneous group in which an accurate genetic diagnosis is increasingly possible with the exciting new developments in diagnostic methods of disease-specific CHIPS, exome sequencing, and whole-genome sequencing. Most common hereditary motor sensory neuropathies (HMSN) fall under the category of Charcot–Marie–Tooth (CMT) disease characterized by muscle wasting, weakness, and sensory loss, usually most severe distally. Less common hereditary neuropathies include hereditary sensory and autonomic neuropathies/hereditary sensory neuropathies (HSAN/HSN), distal hereditary motor neuropathies (dHMN), familial amyloid polyneuropathy, disorders of lipid/mitochondria metabolism, ataxia with neuropathy syndromes, and rare miscellaneous conditions. The major classification of CMT is done according to the mode of inheritance [autosomal dominant (AD), autosomal recessive (AR), or X-linked] and the principal pathology/electrophysiology [demyelinating (CMT1) or axonal (CMT2)]. Severely affected infants are classified as having congenital hypomyelinating neuropathies (CHN) or Dejerine–Sottas disease (DSD), previously labeled as AR type HSMNIII and currently as CMT3. Many of these patients are now known to have *de novo* AD neuropathies. Most common form CMT1 refers to AD demyelinating form, while CMT2 refers to AD or AR axonal form. CMT4 group includes cases resembling CMT1, CMT3, or CMT2 phenotype but is inherited only in an AR mode. Subtypes (CMT1A, CMT2A, etc.) are used to mark specific genetic causes of each of the large categories. Although this classification offers some practical considerations, it is far from being perfect because of the diversity in phenotypes and inheritance patterns and overlap of CMT with HSANs and dHMNs.

EPIDEMIOLOGY

Incidence

CMT disease is the commonest inherited neuromuscular disorder affecting at least 1 in 2,500. Duplication of CMT1A locus is the most prevalent mutation found in CMT1. In the US, approximately 90% of CMT cases are either AD- or X-linked, whereas in countries with high rate of consanguineous marriages, AR CMT constitutes about 40% of CMT cases. CMT1 is reported as more common than CMT2; however, the true prevalence of CMT2 is unknown as more than 60% of the genes remain to be unidentified.

RISK FACTORS

Pregnancy Considerations

The rate of obstetric complications in CMT patients is similar to the general population. Exacerbation of CMT (increasing weakness) was reported in 1/3 of patients in at least one pregnancy as a temporary worsening (35%) or persistent disability (65%).

Genetics

New mutations responsible for different forms of CMT are being discovered at a rapid pace. Most common AD CMT1 and X-linked dominant CMT subtypes are listed below in descending order of frequency:

- CMT1A is caused by a 1.4 Mb duplication on chromosome 17p11.2–12 encompassing the peripheral myelin protein gene *PMP22* (70% of all CMT mutations). Sporadic cases occur in about 10% of CMT1A. Other mutations in *PMP22* are associated with a wider spectrum of phenotypes, including classical CMT1A and more severe early-onset CMT. Deletion of the same gene causes the reciprocal disorder, hereditary neuropathy with pressure palsies (HNPP).
- CMTX1, the second commonest form of CMT, is an X-linked dominant disorder, secondary to mutations in the gap junction B1 (*GJB1*) encoding connexin 32 (Cx32). Female carriers have milder phenotype compared to affected males.
- CMT1B, comprising about 10% of AD CMT1, results from mutations in *MPZ*.
- CMT1C, comprising <1% of AD CMT1, is caused by mutations in *LITAF* (lipopolysaccharide-induced tumor necrosis factor). *LITAF* patients frequently present with classic CMT1 phenotype.
- CMT1D results from mutations in *EGR2* (early growth response 2) gene, comprising <1% of AD CMT1. *EGR2* is a transcriptional factor involved in the regulation of myelination. *EGR2* patients usually have a more severe classical CMT1 or CHN/DSD phenotype.
- So far, 3 distinct phenotypes have emerged from the AD CMT2 population, which should provide guidance for genetic testing. Most common phenotype is the classical CMT2, caused by mutations in 5 genes [*MFN2*, *MPZ*, *NEFL*, *AARS*, and *GDAP1*].
- CMT2A is caused by mutations in *MFN2* which represents about 20% of all AD CMT2 cases. Patients more commonly present with severe childhood-onset disease than the classical CMT2 phenotype. About 20% of reported cases have *de novo* mutations.
- CMT2E is caused by mutations in *NEFL*; some patients have slow motor conduction velocities in CMT1 range with early-onset severe disease.
- CMT2I is caused by mutations in *MPZ* presenting with classic CMT2 phenotype; CMT2J specifies the phenotype with hearing loss and pupillary abnormalities resulting from *MPZ* mutations.
- CMT2K is caused by mutations in *GDAP1*; usually presents with late-onset CMT2. Pyramidal features can be part of the phenotype (CMT2H).
- The second AD CMT2 phenotype is CMT2 with major sensory impairment and related complications such as ulcerations. Motor involvement occurs later in the course (usually mild). Currently 2 genes are known to cause this phenotype [*SPLTC1* (serine palmitoyltransferase long chain base subunit 1) and *RAB7* (RAS-associated protein RAB7)]. Some patients with *SPLTC* mutations (also classified as having HSAN1), particularly males, develop significant motor involvement, hence justifying consideration under CMT2. The patients with *SPLTC* mutations often have neuropathic pain.
- CMT2B is caused by mutations in *RAB7*. The phenotype is similar to *SPLTC* mutations with the exception of neuropathic pain symptoms.
- The third AD CMT2 phenotype is characterized with major motor involvement affecting predominantly upper limbs (*BSCL2*, *GARS*) or lower limbs (*HSPB1*, *HSPB8*, *BSCL2*, *TRPV4*). *BSCL2* mutations usually cause Silver syndrome (spastic legs and distal amyotrophy of the upper limbs).
- CMT2D is caused by mutations in *GARS* presenting with unilateral or bilateral atrophy and weakness of hand muscles with much later involvement of lower limb muscles.
- CMT2F is caused by mutations in *HSPB1* presenting with lower limb dHMN or classic CMT2.
- Mutations in *TRPV4* (CMT2C) are described causing CMT2 with vocal cord paralysis with respiratory involvement, scapulo-peroneal spinal muscle atrophy, and congenital distal spinal muscle atrophy.
- In general, CMT4 (AR CMT1) cases have early-onset and are more severe than typical patients with AD CMT1.
- CMT4A is caused by mutations in *GDAP1*, presents with severe CMT1 or CMT2 phenotype; vocal cord and diaphragm paralysis have been described.
- CMT4B1 is caused by mutations in *MTMR2*, presents with severe CMT1 phenotype; facial/bulbar involvement has been described.
- CMTB2 is caused by mutations in *MTMR3*, presents with severe CMT1, glaucoma.
- CMT4C is caused by mutations in SH3TC2, presents with severe CMT1, scoliosis.
- CMT4D, confined to Balkan gypsies, is caused by mutations in *NDRG1* and associated with a high prevalence of deafness and tongue atrophy.
- CMT4F is caused by mutations in *PRX* (periaxin), presents with CMT1 phenotype with predominant sensory involvement.
- CMT4J is caused by mutations in *FIG4*, presents with a predominantly motor CMT1 phenotype, can be rapidly progressive.

ETIOLOGY

- Axonal loss in CMT1 correlates with clinical disability even though "demyelinating" pathological features coin this group. Schwann cells mutations exert profound influence on their axonal counterpart. This results in alterations in cytoskeletal components and impaired axonal transport leading to preferential distal axonal loss with a clinical presentation of a length-dependent axonal neuropathy, the "classical CMT phenotype." In CMT2, mutations affecting components of axonal cytoskeleton, axonal transport, mitochondrial function, and protein synthesis or stress response result in primary axonal pathology.

COMMONLY ASSOCIATED CONDITIONS

Essential tremor is present in 1/3 of CMT1, less common in CMT2. Palpable nerve enlargement is seen in 50% of CMT1 cases. Pes cavus and hammertoes are common (not invariable). In rare families with demyelinating phenotype, associated deafness was reported. Occasional CMT2A patients have optic atrophy, brisk reflexes, hearing loss, and cognitive impairment.

DIAGNOSIS

PHYSICAL EXAM

- CMT1: Usually manifests in the first 2 decades with distal muscle weakness and atrophy, more prominent in the lower extremities than upper (latter occurs in about 2/3 of cases), with loss of distal muscle stretch reflexes; the majority is areflexic throughout. An early age of onset of motor impairment is predictive of a more severe course. Most patients have foot deformities and may experience deep foot pain. Sensory complaints are usually absent, decreased vibration with preservation of position sense is common.
- CMT2: The neurological exam findings in classic CMT2 are similar to CMT1, except that the peak age of symptom onset is in later decades (20s–70s) and axonal type electrophysiology. Some CMT2 subtypes may have onset in infancy or later with associated vocal cord and/or diaphragm paralysis, intercostal and laryngeal involvement, and minimal sensory loss.
- CMT3 (CHN/DSD): Should be considered a severe phenotypic variant of CMT1. Onset in infancy or early childhood includes cases with hypotonia at birth with delayed motor milestones. Generalized limb/trunk weakness with prominent large-fiber sensory loss, ataxia, areflexia, and palpable peripheral nerves are common. Skeletal abnormalities, including kyphoscoliosis, pes cavus, and hammertoes, may be prominent.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

The first study performed is usually electromyography/nerve conduction study.

- For CMT1 types (MCV <38 m/s in median or ulnar nerves), characteristic findings are diffusely and equally decreased conduction velocities. The amount of slowing is 60–80%, with absolute values around 20–25 m/s. Such slowing can also be found in asymptomatic individuals.
- CMT2: MCVs are normal or mildly slow (>38 m/s in median or ulnar nerves), sensory nerve action potentials reduced or absent.
- CMT3: Uniform slowing (<20 m/s in arms, <10 m/s in legs).
- HNPP: Focal slowing of conduction velocities and loss in amplitude in relation to compression, may have features of mild generalized demyelinating sensory–motor neuropathy.
- Sural nerve pathology: Nerve biopsy is usually unnecessary for diagnosis, given availability of genetic testing, but is helpful for diagnostic dilemmas. Findings depend upon the type. CMT1 shows many thinly re-myelinated fibers and prominent onion-bulbs, presumably resulting from multiple layers of re-myelination. CMT2 reveals axon loss, occasional Wallerian degeneration, and atrophic axons. CMT3 cases typically show severe loss of myelinated nerve fibers, many thinly myelinated fibers, and prominent onion-bulbs. HNPP is characterized with tomacula formations (focal sausage-like myelin thickening) and loss of myelinated nerve fibers. CMT4B pathology due to *MTMR* mutations is characterized by unique alterations of focally folded myelin.

Imaging

Initial approach

White-matter abnormalities in brain are seen rarely in patients with X-linked CMT, CMT2A, and HNPP. In CMTX cases, transient nonenhancing symmetrical white-matter abnormalities correspond to acute transient ataxia, dysarthria, and weakness.

Follow-up & special considerations

Tests

Well over 30 causative genes have been identified, only about 20% are commercially available for some CMT subclasses. The mode of inheritance, age of onset, clinical features, and electrophysiology should guide the clinician in selecting a candidate gene defect for testing.

DIFFERENTIAL DIAGNOSIS

In sporadic cases or when a reliable family history is unavailable, a broad differential of causes of neuropathy with insidious onset and slowly progressive course such as toxic metabolic and deficiency states should be ruled out. An early onset with slow progression in the absence of sensory symptoms favors a genetic cause.

TREATMENT

MEDICATION

First Line

There is no medical therapy to reverse or slow down the disease process at this time.

ADDITIONAL TREATMENT

General Measures

Physical therapy (low-impact exercises and stretching techniques) is usually beneficial. Many patients benefit from ankle–foot orthosis. Appliances may be useful for hand weakness. Patients with DSD phenotype may require knee–ankle–foot orthosis. Patients should be tested periodically to ensure early diagnosis of possible superimposed diabetes, thyroid dysfunction, or vitamin B12 deficiency.

Additional Therapies

Many patients have musculoskeletal pain, responding to acetaminophen or NSAIDs. Neuropathic pain may respond to tricyclic antidepressants or antiepileptic drugs (such as carbamazepine or gabapentin).

SURGERY/OTHER PROCEDURES

Corrective surgical procedures for foot deformities may help in selected patients.

ONGOING CARE

PATIENT EDUCATION

- http://www.charcot-marie-tooth.org
- http://www.neuropathyassociation.com

PROGNOSIS

CMT neuropathies usually have an insidious onset, slowly progressive course. Patients with a recent history of notable worsening of their disease should be evaluated for the possibility of superimposed acquired autoimmune neuropathies or toxic/metabolic disorders.

COMPLICATIONS

Drugs with known neurotoxic effects, particularly chemotherapeutic agents such as vincristine, taxol, or adriamycin, can cause severe and rapid progression of CMT neuropathy. Monitor patients on such medications closely or switch to less toxic alternatives if possible.

ADDITIONAL READING

- Mendell JR, Sahenk Z. Hereditary motor and sensory neuropathies and giant axonal neuropathy. In Mendell JR, Kissel JT and Cornblath DR, eds. *Diagnosis and management of peripheral nerve disorders*. New York: Oxford University Press, 2001:429–449.
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CODES

ICD9

- 356.1 Peroneal muscular atrophy
- 356.2 Hereditary peripheral neuropathy
- 357.82 Critical illness polyneuropathy

CLINICAL PEARLS

Consider clinical and electrophysiologic features to guide genetic testing in inherited neuropathies.

NEUROPATHY, PERIPHERAL

Glenn A. Mackin, MD, FAAN, FACP

BASICS

DESCRIPTION

Acquired or hereditary disorder of multiple peripheral nerves. Injury to sensory and/or motor axons/neurons, myelin, and/or autonomic fibers.

EPIDEMIOLOGY

Incidence

- Sparse population-based, cause-specific data
- Age: Occurs at all ages

Prevalence

- Overall: 2,400/100,000 (2.4%)
- Elderly: 8,000/100,000 (8%)
- Neuropathy Association (US) estimates 5–10% of US population (30 million) affected

RISK FACTORS

- Genetic mutations: Listed elsewhere
- Habits: Alcohol, poor diet, smoking, HIV risks
- Toxic medications: Amiodarone, bortezomib, chloramphenicol, chloroquine, cisplatin, dapsone, colchicine, cytarabine, disulfiram, docetaxel, ergots, ethambutol, gold, hydralazine, imipramine, indomethacin, isonicotinylhydrazine, linezolid, metronidazole, misonidazole, nitrofurantoin, nucleoside, oxaliplatin, paclitaxel, phenytoin, perhexiline, penicillamine, procainamide, pyridoxine, procarbazine, statins, sulfa, suramin, tacrolimus, thalidomide, vincristine
- Occupational: Acrylamide, allyl chloride, arsenic, biphenyls, cadmium, carbon disulfide, ethylene oxide, dichlorodiphenyltrichloroethane, hexacarbons, lead, mercury, methyl bromide, nitrous oxide, organophosphates, thallium, trichloroethylene, triorthocresyl phosphate, vacor
- Environmental: Cold, vibration, electric injury

Genetics

- HMSN (hereditary motor sensory neuropathy; Charcot–Marie–Tooth disease), many types
  - Autosomal dominant > recessive, X-linked
  - Demyelinating (HMSN-I), axonal (HMSN-II)
- HNPP (hereditary neuropathy with liability to pressure palsies). Entrapment vulnerability
- Hereditary sensory neuropathies (HSN)
- Hereditary sensory autonomic neuropathies
- Familial amyloid polyneuropathy (FAP)
- Leukodystrophies (metachromatic, globoid cell/Krabbe's), lipoprotein disorders (HDL deficiency/Tangier's, abetalipoproteinemia), lysosomal enzyme deficiency (Fabry's)
- Peroxisomal: Adrenomyeloneuropathy
- Porphyrias (acute intermittent, variegate)
- Miscellaneous: Refsum's disease (phytanic acid accumulation), giant axonal neuropathy
- Multisystem: Myotonic dystrophy, Friedrich's ataxia, spinocerebellar degenerations

GENERAL PREVENTION

- Balanced, nutritious diet; blood sugar control
- Avoid excess alcohol, excess B6, above risks

PATHOPHYSIOLOGY

- Axon loss with secondary demyelination
- Primary demyelination, secondary axon loss
- Multifocal neuropathy (immune, compressive)

ETIOLOGY

- Genetic: Multiple identified gene mutations
- Acquired: Commonest acquired neuropathy in Western world is diabetes; worldwide is leprosy

COMMONLY ASSOCIATED CONDITIONS

- Immune-mediated
  - Primary demyelinating diseases
    - Acute inflammatory demyelinating polyneuropathy [AIDP; Guillain–Barré (GBS)]
    - Chronic inflammatory demyelinating polyneuropathy (CIDP)
    - Multifocal motor neuropathy (MMN)
  - Collagen vascular diseases (Behçet's, mixed connective tissue, relapsing polychondritis, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic lupus)
  - Gastrointestinal (celiac, inflammatory bowel)
  - Granulomatosis (sarcoidosis, Wegener's)
  - Vasculitis (connective tissue syndromes, hypersensitivity, systemic necrotizing vasculitis, polyarteritis nodosa, Churg–Strauss, others)
- Infection (HIV, Lyme, leprosy, syphilis)
- Metabolic [diabetes, dyslipidemia, thyroid, malabsorption, malnutrition, porphyria, vitamin deficiencies (B1, B6, B12, E), acromegaly]
- Malignancy (lymphoma, myeloma, infiltrating)
  - Paraneoplastic (sensory neuropathy or neuronopathy, sensory motor neuropathy)
- Multi-organ failure (critical-illness neuropathy)
- Paraproteins [monoclonal gammopathy of undetermined significance (MGUS), myeloma, Castleman's, cryoglobulinemia, POEMS, primary systemic amyloidosis, Waldenstrom's macroglobulinemia]
- Cryptogenic: Incidence approx 50% in elderly

DIAGNOSIS

HISTORY

- Numbness (lost pinprick, vibration, position)
- Dysesthesias (tingling, burning, lancinating)
- Hypersensitivity (heat, cold, touch intolerance)
- Gait ataxia, pseudoathetosis (large fiber loss)
- Muscle weakness, atrophy, and fatigability
- Muscle cramps, fasciculations
- Autonomic dysfunction (hyperhidrosis or anhidrosis; dry skin; dry eyes and mouth; orthostasis; bowel, bladder, sexual dysfunction)
- Cranial nerves (facial numbness, tingling, weakness; diplopia, rarely dysarthria/dysphagia)

PHYSICAL EXAM

- Hyporeflexia, ranging ankles only to areflexia.
- Most acquired polyneuropathies involve slow "dying-back" of axons, resulting in a "fiber-length-dependent" pattern of symmetrical sensory before motor loss starting in the feet. As tingling reaches mid-calves, fingertips start tingling, and so forth.
- Asymmetric or non-length-dependent acquired neuropathies (hands involved before or with feet).
  - Primary demyelinating (e.g., AIDP, CIDP). Diffuse reflex loss, motor predominant signs
  - Mononeuropathies multiplex: Random sensory motor deficits of "named" nerves
- HMSN: Many genotypes, similar phenotypes, variable severity. Pes cavus, hammertoes, foot drop. Diffuse hyporeflexia to areflexia (HMSN-I) vs. relatively preserved reflexes (HMSN-II).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Rational lab testing requires knowing whether neuropathy acute or subacute/chronic, symmetric or multifocal, primarily axonal or demyelinating, and fiber-type specific or mixed sensory motor.
- Among identifiable neuropathies, most likely cause usually is a known or clinically identifiable disease, mutant gene, metabolic (diabetes and prediabetes are the commonest acquired causes), medication toxicity, vitamin deficiency, alcoholism, IV drug abuse, occupational or environmental exposure.
- *Primary tests* (everyone, if not recently done):
  - EMG and nerve conductions (NCS) – essential
  - Blood tests: CBC,CMP, FBS, $HgbA_{Ic}$, TSH, B12, ESR, ANA, SSA, SSB, RF, SPEP/UPEP
- *Secondary tests* (often, specific suspicion or abnormality above): 2-hour glucose tolerance (most important of all), antiendomysial IgA and t-TG (small fiber), methylmalonic acid, B1, B6, SIFE, UIFE, hepatitis B and C, T_4, dsDNA, C3, C4, CH50, Lyme, HIV, RPR; CXR (atypical sensory).
- *Tertiary tests* (uncommon, specific suspicion and/or abnormal lab): ANCA, ACE, cryoglobulins, porphyrins (motor), Vitamin E, lead and mercury (motor), arsenic and thallium (sensory), copper.
- *Quaternary* (rare, specific diseases, genetics):
  - G_{M1} ganglioside Ab: Seen in 60% of MMN. Most helpful if no NCS conduction block
  - Anti-MAG antibody: Seen in 50% of CIDP with IgM MGUS; refractory to immunotherapy
  - Anti-Hu (ANNA-1): Paraneoplastic sensory neuropathy, usually in SCC lung; CXR, CT
  - G_{Q1B} ganglioside: Miller-Fisher variant AIDP
  - Antisulfatide antibody: Sensory neuropathies
  - HMSN panels: HMSN types, CMT-X, HNPP
  - Transthyretin: Amyloid (autosomal dominant, small-fiber sensory–autonomic; organs)

Imaging

Initial approach

- Suspected "pseudo-neuropathic" symptoms from CNS: MRI brain, lumbosacral/cervical spine
- Atypical sensory neuropathy, suspected to be paraneoplastic: CXR, CT chest/abdomen/pelvis

Follow-up & special considerations

- Possible polyradiculoneuropathy (CIDP, infection, cancer): Contrast MRI of spine, CSF
- Plexopathy (inflammatory, infectious, cancer, hypertrophic): MRI brachial/lumbosacral plexus
- Paraprotein: Skeletal survey (plasmacytoma)

Diagnostic Procedures/Other

- EMG/NCS: Indispensable test to characterize axonal vs. demyelinating, acuteness and severity.
- Cutaneous punch biopsy: Verify small-fiber dying-back polyneuropathy. Can stain for amyloid.

- Nerve biopsy [uncommon, mostly sural nerve; sometimes superficial peroneal sensory fascicle when suspect diagnostic material inside nerve (e.g., vasculitis; amyloidosis; tumor, rarely CIDP)].
- CSF: Albuminocytologic dissociation in demyelinating polyneuropathies (few or no WBC, elevated protein in AIDP and CIDP; HIV-related AIDP >50 WBC). CIDP often very high protein (>125–150 mg/dL). Abnormal Lyme PCR, VDRL.
- Quantitative sensory testing: Sensory thresholds for small and large axonal functions.
- Autonomic testing: Quantitative sudomotor axon reflex test, thermoregulatory sweat test, EKG R-R interval, tilt table, Schirmer's.
- Other biopsies: Minor salivary gland (Sjögren's), rectal mucosa or fat pad (amyloid).

DIFFERENTIAL DIAGNOSIS

- *Ask whether polyneuropathy is truly present*. "Pseudo-neuropathic" referred from CNS.
- *Consider time course* (acute over days, AIDP, some toxic neuropathies; subacute over months, some inflammatory and vasculitic; or chronic over years, mostly axonal).
- *Note associated diseases* (diabetes, uremia), *family history* (HMSN, FAP), *habits* and *occupational exposures* (e.g., painters and lead; smelters and arsenic, plastics, and acrylamide; farmers and organophosphates).
- *Consider the anatomic distribution*.
  - *Symmetric "length–dependent," stocking-glove, legs > arms, distal > proximal*: Over 3/4 of neuropathies, most axon loss (Mimics: CIDP, mononeuropathy multiplex).
  - *Proximal ≥ to distal signs, symmetric* (e.g., AIDP/GBS, occasionally CIDP).
  - *Asymmetric, multifocal pattern*. Uncommon. Mononeuropathies multiplex (random lesions affecting "named" nerves, usually vasculitic infarcts, diabetic), inflammatory or infiltrative processes, MMN, HNPP.
- *Ascertain whether paresthesias are present*. "Positive" sensory symptoms (e.g., tingling, burning) often indicate acquired neuropathy. HSN can be dysesthetic, HMSN usually not.
- *Note if symptoms are predominantly sensory or motor*. Most acquired neuropathies are pure sensory or sensory > motor. AIDP, CIDP, HMSN-I, HMSN-II are mainly motor.
- *Painful* (alcohol, amyloid, arsenic, diabetes, uremia, cancer, vasculitis, small fiber).
- *Note diffuse hyporeflexia* (demyelinating polyneuropathies, AIDP, CIDP, HMSN-I).
- *Consider other informative physical findings*.
  - Palpably large peripheral nerves (HMSN-I, amyloid, leprosy, occasionally CIDP).
  - Autonomic (AIDP, porphyria, amyloid, renal).
- *Determine if there is selective but uncommon fiber-type involvement*, narrowing differential.
  - Large sensory neurons/axons (ataxic): Paraneoplastic (SCLC), Sjögren's, toxic (B6), *cis*-platinum, docetaxel, vincristine, vitamin deficiency (B12 or E), idiopathic.
  - Small sensory neurons/axons (often painful): Elderly cryptogenic sensory neuropathy, diabetes, vasculitis, amyloid, arsenic, HIV.
  - Motor neurons/axons: Motor neuron diseases, HMSN-II, demyelinating (MMN, AIDP, CIDP), porphyria, lead, dapsone.
  - Autonomic: Diabetes, amyloid, AIDP, HIV, vincristine, paclitaxel, amiodarone, porphyria, HSAN, idiopathic and paraneoplastic pandysautonomias.
  - *Obtain NCS to determine whether primary process is axonal loss or demyelination*.

TREATMENT

MEDICATION

First Line

- AIDP/GBS: Plasma exchange (PLEX) = IVIg
- CIDP: Steroids, azathioprine, mycophenolate mofetil, cyclosporine; IVIg or PLEX if severe
- Connective tissue: Treat primary condition
- Deficiency states: Appropriate supplement
- Familial amyloid neuropathy: Liver transplant
- MMN: IVIg, cyclophosphamide, rituximab
- Osteosclerotic myeloma: XRT and/or surgery
- MGUS: If mild, monitor; if severe, PLEX, IVIg, immunosuppression (IgM and MAG are refractory)
- Vasculitis: Corticosteroids, cytotoxic agents
- Generic Rx: α-Lipoic acid, acetyl-L-carnitine

ADDITIONAL TREATMENT

General Measures

- Rational, pattern-recognition, cost-effective testing approach. If unusual progression presents or emerges, re-evaluate, consider nerve biopsy.
- Low threshold for consulting neuromuscular diseases specialized neurologist for unexplained neuropathy, especially <age 50, no family history.
- Treatment of cause – if known – may halt or improve neuropathy (e.g., tight diabetes control).
- Immunotherapy for autoimmune neuropathies.
- Effectively treat neuropathic, nociceptive pain.
- Monitor cognition and function on analgesics.
- Limit complications of immunosuppressants.
  - Steroids: Calcium, bisphosphonates, DEXA
  - Immunosuppressants: Monitor LFTs, CBC
- Encourage exercise and well-balanced diet.
- Review "alternative" meds for possible toxins.
- Limit vitamin B6 to <50 mg/day (RDA is 2 mg).
- Frequently inspect insensate feet for trauma.
- Excellent foot and nail care (e.g., diabetics).
- Lubricants to avoid cracking, drying, infection.
- Effective arch supports, customized shoewear.
- AFOs (footdrop) or boots (ankle instability).
- Ambulation aids, visual guidance for ataxia.
- Car hand controls (severe proprioceptive loss).

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Neuropathic pain: Antiepileptics (gabapentin, pregabalin (1)[A], carbamazepine (2)[B]; others), antidepressants (tricyclic, duloxetine (3)[A]), topical agents (lidocaine, capsaicin [B]), mexiletine, clonidine, opioids (off label)
  - Nociceptive pain: Nonsteroidals, tramadol
  - Autonomic: Tears, midodrine, elastic hose
- Adjunctive treatment
  - Depression: Exercise, medication, counseling
  - PT: Flexibility, endurance, range of motion
  - OT: Adaptive aids, splints, home safety
  - Durable goods: AFO, cane, walker, scooter, wheelchair, ramps, grab bars, shower seats

SURGERY/OTHER PROCEDURES

- Nerve biopsy: Biopsy site pain may persist.
- Other biopsies: Skin, minor salivary gland, abdominal fat pad, rectal mucosa, bone marrow.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- AIDP: ICU or high-level monitor, FVC q shift
- Severe: PLEX, IVIg, IV immunosuppression

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Variable, depends on rate of progression.

DIET

Balanced diet. Standard multivitamin.

PATIENT EDUCATION

- Charcot-Marie-Tooth Association, PO Box 105, Glenolden, PA 19036. Phone: 800-606-2682 (US) or 610-499-9264. Website: www.cmtausa.org
- The Neuropathy Association, 60 East 42nd Street, Suite 942, New York, NY 10165. Phone: 212-692-0662. Website: www.neuropathy.org

PROGNOSIS

Quite variable, depending on specific cause

REFERENCES

1. Tölle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: randomized, double-blind study. *Eur J Pain* 2007;12:203–213.
2. Dworkin RH, OConnor AB, Backonia M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132: 237–251.
3. Pritchett YL, McCarberg BH, Watkin JG, et al. Duloxetine for the management of diabetic neuropathic pain. *Pain Med* 2007;8:397–409.

See Also (Topic, Algorithm, Electronic Media Element)

- Neuropathy, polyradiculoneuropathy

CODES

ICD9

- 356.2 Hereditary sensory neuropathy
- 356.9 Unspecified idiopathic peripheral neuropathy
- 357.82 Critical illness polyneuropathy

CLINICAL PEARLS

- NCS second in diagnostic value only to H&P.
- 2-hour glucose tolerance test is high yield in neuropathy diagnosis.
- Commercial gene panels for neuropathy rarely justify cost. Better to selectively order gene tests.
- Surgical releases unproven in polyneuropathy.
- Neuropathic pain is often the biggest problem.

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NEUROPATHY, VASCULITIC

David S. Younger, MD
Adam P. J. Younger

BASICS

DESCRIPTION

Vasculitis is a term that covers a diverse group of disorders in which inflammatory changes destroy blood vessel walls, resulting in ischemia and thrombosis. Peripheral nerve damage occurs when inflammation affects the vasa nervorum supplying individual nerves. This most commonly is part of a systemic illness, although peripheral neuropathy may rarely be the predominant manifestation of vasculitis. The vasculitides are commonly distinguished by their organ system involvement and the size of the blood vessels pathologically affected.

EPIDEMIOLOGY

The exact incidence of vasculitic neuropathy is unknown. In polyarteritis nodosa, which is considered the most common systemic necrotizing vasculitis, approximately 60% of individuals have peripheral nerve involvement, equating to roughly 5 cases per million people.

- Age
  - More common at older ages (mean age of onset 60 years)
- Sex/gender
  - There is no clear sex or racial predominance.

RISK FACTORS

Vasculitis occurs in the setting of connective tissue disease, drugs, infections, and malignancy.

Pregnancy Considerations

There is no known relationship with pregnancy.

ETIOLOGY

Autoimmune disease is the presumed pathologic mechanism, although this remains largely unproven. An inciting antigen is thought to trigger a cascade involving humoral or cellular responses, resulting in leukocyte adherence to the endothelial surface of blood vessel walls. Inflammatory changes then damage the endothelial surface, and the blood vessel may undergo necrosis. The immunologic hypothesis stems from the fact that vasculitides occur with connective tissue diseases, malignancies, and hypersensitivity drug reactions, or in association with infections including syphilis, Lyme disease, *Rickettsia*, HIV, CMV, and *Cryptococcus*.

COMMONLY ASSOCIATED CONDITIONS

Peripheral nerve vasculitis is often part of a wider systemic illness. Other organ manifestations that may occur with peripheral nerve involvement include coronary artery disease (Kawasaki disease), necrotizing glomerulonephritis (Wegener's granulomatosis, microscopic polyangiitis), respiratory tract inflammation and eosinophilia (Churg–Strauss), skin disorders (Henoch–Schönlein purpura, cryoglobulinemia, leukocytoclastic vasculitis), arthritides (rheumatoid arthritis), and polymyalgia rheumatica (temporal arteritis).

DIAGNOSIS

Vasculitic neuropathy typically presents as asymmetric weakness and sensory loss in the distribution of multiple individual nerves. Clinical involvement most commonly occurs in the peroneal and ulnar distributions. Symptoms occur acutely or subacutely, and progress in a stepwise pattern to involve one nerve after another. Pain and dysesthesia are common (50–80%), usually noted at the onset of peripheral nerve damage. Sensory loss and weakness conform to individual peripheral nerves and are typically apparent on neurologic examination. Constitutional symptoms of fever, myalgias/arthralgias, and weight loss are common, and their presence, along with skin, lung, kidney, or joint involvement, should help point to a systemic illness. Besides mononeuritis multiplex, other clinical presentations may occur, including a rapidly progressive, areflexic paralysis resembling Guillain–Barré syndrome, and a slowly progressive, symmetric, distal sensorimotor polyneuropathy. Gradual overlapping involvement of multiple individual peripheral nerves may lead to the appearance of a symmetric distal or generalized sensorimotor polyneuropathy.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Laboratory studies, including CBC, ESR, coagulation panel, serum chemistries, liver function tests, urinalysis, serum protein electrophoresis, rheumatoid factor, antinuclear antibody, extractable nuclear antigen antibodies, serum complements, and cryoglobulins, help to identify more widespread systemic disease. Additional testing, aimed at identifying a vasculitis-related illness, includes HIV, Lyme titer, syphilis serologies, serum angiotensin-converting enzymes, chest x-ray film, cytoplasmic (c) ANCA (Wegener's granulomatosis), and perinuclear (p) ANCA (Churg–Strauss, microvascular polyangiitis). CSF analysis is of limited utility.

Imaging

There are no specific imaging abnormalities.

Diagnostic Procedures/Other

- *Nerve conduction studies* reveal a multifocal sensorimotor axonopathy with reduced amplitude compound motor and sensory nerve action potentials. Sensory changes tend to be more prominent, and the lower extremities are affected more than the upper extremities. Distal latencies and conduction velocities are typically normal. A few reports describe primarily demyelinating features and motor conduction block, which may be apparent in the first week, although subclinical abnormalities in asymptomatic nerves may help with diagnosis in difficult cases.
- *Needle electromyography (EMG)* typically demonstrates active denervation (fibrillations, positive sharp waves) and decreased recruitment patterns most severely affecting the distributions of individual peripheral nerves where weakness is present.
- *Nerve biopsy* is the only means of proving vasculitis of the nerves. The sural and superficial peroneal sensory cutaneous nerves are those most sampled. Biopsy features of vasculitis include microscopic inflammatory cell infiltration of the vessel wall with endothelial cell destruction, fibrinoid necrosis, intimal hyperplasia, and vascular sclerosis; however, adjacent vessels may show perivascular inflammation. Simultaneous muscle biopsy, looking for inflammatory changes in blood vessels supplying small nerve twigs entering muscle, may increase the diagnostic yield compared to nerve biopsy alone.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes diabetic mononeuropathy multiplex and infectious or carcinomatous causes of polyradiculopathy. Autoimmune conditions, such as multifocal acquired demyelinating sensory and motor neuropathy, may also mimic vasculitic mononeuropathy multiplex. Guillain–Barré syndrome should be considered in cases with more acute onset and symmetric neuropathic involvement. Other conditions with a clinical presentation resembling vasculitic neuropathy include Sjögren's-related sensory neuronopathy, amyloidosis neuropathy, sarcoidosis, and toxic neuropathies related to heavy metal exposure (e.g., arsenic, thallium).

TREATMENT

MEDICATION

- *Immunosuppression*: Most authorities commence treatment with an oral regimen of prednisone 1.5 mg/kg daily or a corticosteroid-sparing agent such as azathioprine 2–3 mg/kg daily in pathologically confirmed cases of vasculitic neuropathy, with frequent assessment to gauge response to therapy. Severe unresponsive or progressive peripheral nerve involvement warrants consideration of cyclophosphamide 2 mg/kg PO daily or monthly 500–600 mg/m^2 IV pulse therapy; however, there can be severe life-threatening side effects.
- *Vaso-occlusion*: Antiplatelet therapy with aspirin (81–325 mg daily) may help reduce thromboxane-induced vasoconstriction and platelet activation that is not covered by glucocorticoid administration. Calcium channel blockers may also be helpful.
- Contraindications: Prednisone should be used under supervision in poorly controlled diabetes mellitus or hypertension. All immunosuppressant medications should be used cautiously during pregnancy.
- Precautions: Side effects of long-term prednisone use include weight gain, glucose intolerance, osteoporosis, cataracts, hypertension, acne, and myopathy. Cyclophosphamide may cause hemorrhagic cystitis, bladder and hematologic malignancies, GI symptoms, and alopecia. Azathioprine leads to dose-related bone marrow suppression and anemia.
- Alternative drugs: The immunomodulatory medication IVIg (intravenous immunoglobulin) has been used in patients intolerant of immunosuppressant medication. It is generally given at a dose of 2 g/kg over 5 days/month for 3–6 months. Pretreatment with normal saline, benadryl 50 mg PO, and acetaminophen 650 mg PO is usually ordered. In selected patients with exacerbation of migraine headaches, ketorolac 30 mg IVP (intravenous pyelogram) can be given instead of acetaminophen.

ADDITIONAL TREATMENT

General Measures

The four basic principles of vasculitic neuropathy management are:

- Accurate diagnosis with pathologic confirmation in a peripheral cutaneous nerve specimen followed by removal of any known inciting antigens (drug reaction, infections, malignancy)
- Immunosuppressive or immunomodulatory therapy
- Treatment of vaso-occlusion
- Supportive/adjunctive care

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Neuropathic pain is common. Effective medications include tricyclic antidepressants (amitriptyline, nortriptyline); antiepileptic medications [gabapentin, phenytoin (Dilantin), carbamazepine (Tegretol)]; mexiletine; topical creams (capsaicin, lidocaine); transdermal medications (lidocaine patch, fentanyl patch); and scheduled opioid therapy (methadone). Trials of these various medications can be managed through routine clinic visits, but recalcitrant pain may require management by a pain specialist.
- Adjunctive treatment
  - Physical and occupational therapy assist in maintenance of strength, flexibility, and functional ability in the setting of neurologic impairment from vasculitic neuropathy. Ankle-foot orthoses may be required for footdrop, and splints may be required to stabilize and protect weakened extremities. Once the underlying vasculitis is under control, aggressive physical therapy may be required to hasten strength recovery.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Hospital admission is not commonly required, unless the neuropathy is particularly severe and rapidly progressive.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be seen frequently when there is active vasculitis and when immunosuppressive therapy is initiated. Follow-up should focus on clinical change, adjustment of medications, and monitoring of adverse effects. Blood testing for patients on cyclophosphamide should include a monthly CBC, electrolytes, liver function tests, and urinalysis. Patients on prednisone should be monitored for symptoms of diabetes. Dietary consultation and TB skin testing may be considered before initiating prednisone therapy.

PATIENT EDUCATION

There are no specific therapies, activities, or dietary restrictions related to vasculitis. Nutritional therapists may instruct patients regarding appropriate dietary changes while taking prednisone. Information about peripheral nerve vasculitis is available from the following:

- American Autoimmune Related Diseases Association, Inc. Website: www.aarda.org
- Neuropathy Association. Website: www.neuropathy.org

PROGNOSIS

There are no long-term, prospective studies specific to vasculitic neuropathy. However, 25–50% of patients with systemic vasculitis fail to respond to therapy or may relapse during treatment. In addition, 40% experience drug-related side effects and up to 85% experience disease-related morbidity primarily involving other organ systems. As in most neuropathies associated with significant axonal damage, clinical stabilization and improvement can be expected, although recovery is often protracted and incomplete.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Peripheral nerve vasculitis
- Mononeuritis multiplex

CODES

ICD9

- 355.9 Mononeuritis of unspecified site
- 446.0 Polyarteritis nodosa
- 447.6 Arteritis, unspecified

NONEPILEPTIC SEIZURES

J. Layne Moore, MD, MPH
Sheri L. Cotterman-Hart, MD, PhD

BASICS

DESCRIPTION
- Pseudoseizures are events that look like seizures but present without any EEG evidence of epileptic seizures. They are most often characterized by convulsive activity but may also present with periods of unresponsiveness, staring, or a variety of abnormal behaviors. Almost any type of abnormal behavior may be called seizure and present for evaluation. The events in question are usually not stereotyped (they vary from occurrence to occurrence) and remain refractory to antiepileptic drugs. Unlike epileptic seizures, which are almost always 2 minutes or less in duration, pseudoseizures may go on for many minutes or even hours.
- Usually all prior evaluations have been normal, including EEGs, neuroimaging (MRI, CT head), and neurological examination.

EPIDEMIOLOGY
Incidence
- The overall incidence is unknown but approximately 25–30% of patients who are monitored at a tertiary epilepsy center are diagnosed with pseudoseizures.
- Age: Usually adult
- Race: No predilection
- Sex: 80% women

Prevalence
Unknown

RISK FACTORS
- Patients with lower levels of education are at higher risk.
- Victims of physical, sexual, or emotional abuse.
- Patients with a number of psychiatric diagnoses are at increased risk.

Genetics
No genetic studies

GENERAL PREVENTION
None

PATHOPHYSIOLOGY
Unknown

ETIOLOGY
Unknown

COMMONLY ASSOCIATED CONDITIONS
- Dissociative disorder
- Somatization disorder
- Hypochondriasis
- Conversion disorder

DIAGNOSIS

HISTORY
- Episodes of a wide range of abnormal behaviors including shaking, unresponsiveness, crying, tonic posturing, angry outbursts.
- Episodes often last more than 2 minutes (rare in real epilepsy).
- Fluctuating course with side-to-side head movements, back arching, eye closure, and crying may be reported.

PHYSICAL EXAM
Normal

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests
- CBC, electrolytes
- Prolactin (often elevated in epileptic seizure if obtained in less than 30 minutes after the seizure)

Follow-up & special considerations
None

Imaging
Initial approach
Not indicated

Follow-up & special considerations
Patients are refractory to therapy and may need to be followed up even while seeing a mental health professional after the diagnosis is made via video-EEG monitoring.

Diagnostic Procedures/Other
Awake and sleep EEG, Prolonged Video EEG

Pathological Findings
None

DIFFERENTIAL DIAGNOSIS
- Epilepsy (including frontal lobe epilepsy which is often difficult to see on EEG)
- Syncope with myoclonic jerks afterwards (also called syncopal seizure)
- Syncope
- Tussive syncope
- Malingering
- Nonepileptic myoclonus
- Sleep disorders including narcolepsy, cataplexy, periodic limb movement, nightmares, and might terrors

TREATMENT

MEDICATION

First Line
No medications are indicated but antidepressants are often used.

Second Line
None

ADDITIONAL TREATMENT

General Measures
Patients will ideally be followed by a mental health professional after diagnosis.

Issues for Referral
The mental health professional should be familiar with the concept of pseudoseizures and be willing to work with the patient.

Additional Therapies
None

COMPLEMENTARY AND ALTERNATIVE THERAPIES
None

SURGERY/OTHER PROCEDURES
None

IN-PATIENT CONSIDERATIONS

Initial Stabilization
If inpatient management is required, continuous EEG recording will be necessary to prevent endotracheal tube insertion and medications for medically induced coma.

Admission Criteria
Frequent, uncontrolled events

IV Fluids
Not indicated

Nursing
Seizure precautions as the patient may injure themselves with falls during pseudoseizures.

Discharge Criteria
Control of events

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- The patient should ideally be followed by both mental health professional and a neurologist initially.
- Earlier tapering of anticonvulsants after diagnosis may lead to better outcomes.

Patient Monitoring
Patients will follow up based on the frequency of their events.

DIET
No restrictions

PATIENT EDUCATION
- There are few widely available printed materials for patients.
- The internet has some resources but none of it is evidence-based.

PROGNOSIS
Prognosis is better when the diagnosis is made and treatment is started early. A small number of patients will gradually improve after learning the diagnosis.

COMPLICATIONS
Patients can injure themselves during pseudoseizures and precautions must be observed.

ADDITIONAL READING

- Kanner AM, Parra J, Frey M, et al. Psychiatric and neurologic predictors of psychogenic pseudoseizure outcome. *Neurology* 1999;53:933–938.
- Martlew J, Baker G, Goodfellow L, et al. Behavioural treatments for non-epileptic attack disorder. *Cochrane Database Syst Rev* 2009;(4).

CODES

ICD9
- 300.14 Dissociative identity disorder
- 300.19 Conversion disorder
- 300.81 Somatization disorder

CLINICAL PEARLS

- Also called nonepileptic seizures, nonepileptic attacks, psychogenic seizures.
- May be misdiagnosed for many years.
- Anyone with uncontrolled seizures, for 1 year or more or having failed 2 or more medications, should be evaluated by an epilepsy specialist to make sure the seizures are epileptic.

OPSOCLONUS

Bernd F. Remler, MD

BASICS

DESCRIPTION

Opsoclonus is an acquired, supranuclear eye movement disorder which affects both eyes. It consists of back-to-back saccades (rapid eye movements) in the horizontal, vertical, and torsional planes. It can be continuous or intermittent and is singularly dramatic when the saccades are of large amplitude. The term "saccadomania" has been used to describe this striking ocular motor syndrome. Opsoclonus can occasionally be of very small amplitude and requires careful examination of the eyes for detection. Most patients with opsoclonus also have truncal and appendicular ataxia, multifocal myoclonus, and behavioral/cognitive abnormalities ("opsoclonus–myoclonus syndrome"; "opsoclonus–myoclonus–ataxia syndrome") (1). Myoclonus in children may be very pronounced. Without inspection of the eyes, an erroneous diagnosis of myoclonic epileptic status could be made (2).

EPIDEMIOLOGY

Opsoclonus is a rare disorder. It shows no ethnic or gender preference.

Incidence

- Peak incidence is in young children, young to middle-aged adults, and in older adults correlating with the increased risk of cancer in this age group.
  - The incidence of the pediatric syndrome is 0.18 new cases per million total population per year (3). The incidence in adults is not known.

Prevalence

Not known

RISK FACTORS

None known

Genetics

Autoimmune disorders are more prevalent in family members of opsoclonus patients compared to the general population. Turner's syndrome is associated with an increased prevalence of neuroblastoma with opsoclonus (4). No specific genes predisposing to opsoclonus have been identified.

GENERAL PREVENTION

Not applicable

PATHOPHYSIOLOGY

- Opsoclonus is most commonly seen as a parainfectious disorder and in occult cancer. The presumed underlying mechanism is immune-mediated, but specific neuronal antigens have not been identified. Circulating onconeural autoantibodies (anti-Ri, anti-Hu) are present in a minority of adult patients who have developed opsoclonus in the context of gynecologic cancers. Pediatric patients with the opsoclonus–myoclonus syndrome may show proliferation of intrathecal B and T lymphocyte populations and increased levels of B-cell activating factor (BAFF). Elevated levels of BAFF correlate with the presence of autoantibodies to cerebellar neurons in the CSF (5).
- Functional MRI studies have shown hyperactivity of the fastigial nuclei in the cerebellum, indicating disinhibition. These deep cerebellar nuclei project extensively to saccadic eye movement generators in the brainstem.

ETIOLOGY

Opsoclonus has multiple etiologies which correlate with age. In children, approximately 50% of cases are related to neural crest cell tumors (mostly neuroblastoma). However, only a minority (ca. 3%) of children with neuroblastoma develop opsoclonus–myoclonus (dancing eyes and dancing feet). The majority of adults over the age of 60 presenting with opsoclonus have an occult malignancy (predominantly small-cell lung and breast cancer). Most young adults presenting with opsoclonus are believed to have a parainfectious process. Aside from malignancies and infections, there are case reports of opsoclonus arising in the context of drug toxicity, toxic metabolic states, inborn errors of metabolism, and demyelinating disorders.

- Malignancies: Neuroblastoma, ganglioneuroma, ganglioneuroblastoma, adult esthesioneuroblastoma, small- and large-cell lung, breast, ovarian and endometrial cancer, malignant and benign teratomas, medullary thyroid, renal cell, testicular and pancreatic cancer, malignant melanoma, thymoma, lymphoma of the digestive tract and non-Hodgkin's lymphoma.
- Infections: Epstein–Barr virus, mumps, coxsackie B3, enteroviruses including hand—foot–mouth disease, herpes encephalitis, HIV, hepatitis C, West Nile, parainfluenza, varizella zoster, HHV6, St Louis encephalitis, poststreptococcus group A, spirochetal infections (Lyme, syphilis), hemophilus influenzae, mycoplasma pneumoniae, rickettsial diseases, psittacosis, salmonella, scrub typhus, malaria.
- Drug toxicity and toxins: Diphenhydramine, phenytoin, lithium, amitriptyline, diazepam, cyclosporine after organ transplantation, toluene and neuroleptic use in the context of toluene-induced cerebellar damage, cocaine, organophosphates (diazinon, no longer available for residential use), thallium, strychnine, and chlordecone (no longer manufactured).
- Metabolic disorders: Biotin responsive carboxylase deficiency, hyperosmolar non-ketotic coma, hyperphosphatasemia,
- Other: Celiac disease, following human papilloma virus vaccination, multiple sclerosis, acute disseminated encephalomyelitis.

DIAGNOSIS

HISTORY

The history should screen for possible drug toxicity and symptoms of infectious or neoplastic processes. Patients usually report subacute onset of blurring of vision or frank oscillopsia (the illusion of movement of stationary objects). Additional symptoms correlate with the presence and severity of accompanying myoclonus, cerebellar dysfunction (ataxia, gait instability, dysarthria), and cognitive impairment. Patients may also complain of vertigo and nausea. Children with myoclonus–opsoclonus may have sleep disturbances and pronounced irritability.

PHYSICAL EXAM

Opsoclonus is easily observed, but the uncommon variant of small-amplitude opsoclonus may only be detectable during a slit lamp or fundoscopic examination. Opsoclonus can be either continuous or intermittent. It may be stimulated by gaze shifting and refixation. The frequency of oscillations ranges from 6 to 15 Hz. Opsoclonus usually persists during sleep.

- Cerebellar testing elicits various degrees of truncal and appendicular ataxia.
- Myoclonus is multifocal, spontaneous or movement-induced, and can be subtle or dominating the clinical presentation.
- Cognitive testing may be normal or yield variably severe deficits in attention, memory, frontal lobe, and other cognitive functions. Encephalopathic states are more commonly associated with paraneoplastic opsoclonus and may be severe.

DIAGNOSTIC TESTS AND INTERPRETATION

Initial Work-Up

- Drug levels if toxicity is suspected
- 24-hour urinary catecholamines
- Blood and possible CSF screens for infectious processes (IgG, IgM titers, polymerase chain reaction)
- Imaging for cancer including CT of the chest, abdomen and pelvis, mammography
- Iodine-123 metaiodobenzylguanidine scan for neuroblastoma

Follow-Up

If cancer is suspected and the initial work-up is negative, consider positron emission tomography scanning and onconeuronal antibodies, including anti-Hu (small-cell lung cancer, neuroblastoma) and anti-Ri (breast and ovarian cancer). Presence of these antibodies strongly suggests an underlying malignancy even if the initial work-up was negative. Repeat cancer diagnostics are recommended as delays between the emergence of opsoclonus and tumor detection of up to 1 year have been reported.

Pathological Findings

There are no comprehensive pathologic studies defining the structural correlate of opsoclonus.

DIFFERENTIAL DIAGNOSIS

Ocular Flutter

This acquired eye movement disorder also consists of back-to-back saccadic oscillations of both eyes. In contrast to opsoclonus, however, ocular flutter is not continuous, and the oscillations are restricted to the horizontal plane. Etiologies of both disorders overlap, and they likely represent a pathophysiologic continuum. However, only ocular flutter, but not opsoclonus, has been reported in the following clinical settings: Amyotrophic lateral sclerosis, Miller Fisher and other GQ1b antibody syndromes, intracranial hypertension due to cerebral venous thrombosis, vidarabine toxicity, and the carbohydrate-deficient glycoprotein syndrome type 1a.

TREATMENT

GENERAL MEASURES

- New-onset opsoclonus warrants hospital admission especially when other symptoms such as ataxia, myoclonus, and encephalopathy coexist. The multitude of etiologies requires a diagnostic and therapeutic approach tailored to each patient.
- In paraneoplastic opsoclonus, 2 main strategies are applied: treatment of the underlying malignancy and suppression of the immune response against nervous system targets. In adults, this is usually attempted with corticosteroids, IV immunoglobulin infusions, plasma exchange, and immunoabsorption. None of these methods has been shown to be consistently superior, and therapeutic benefit may remain elusive even if several of these methods are applied.
- Children with neuroblastoma-related opsoclonus–myoclonus respond acutely to adrenocorticotropic hormone (ACTH) or corticosteroids. Long-term management of neuroblastoma is complex and often requires ongoing immune-suppressant treatment, including azathioprine, mycophenolate mofetil, or cyclosporine. Rituximab is increasingly used because of its effect on intrathecal lymphocyte populations (6).
- Postinfectious opsoclonus generally has a benign but sometimes protracted course. Corticosteroids are frequently used in this setting. However, concern about aggravating an underlying infection, particularly in children, may make IV immunoglobulins a better choice. In view of the high rate of spontaneous improvement and unpredictable course of disease, it has not been possible to define the value of immune-modulatory treatment.
- Symptomatic treatment of opsoclonus has been attempted with clonazepam, mysoline, propranolol, baclofen, and thiamine. Gabapentin can be effective in suppressing opsoclonus in the locked-in syndrome.

ONGOING CARE

PROGNOSIS

- Opsoclonus that is not related to neoplastic disease generally has a favorable prognosis. Postinfectious opsoclonus, nonetheless, may require weeks or months to resolve and relapses can occur. Complete recovery is common, but residuals such as mild truncal ataxia might remain.
- Children with neural crest tumors show a high initial response rate to ACTH or prednisone, but ongoing immune-suppressant treatment is usually required. A significant proportion of children show signs of permanent CNS injury and of a progressive encephalopathy presenting with expressive language disturbances, attentional deficits, irritability, and delayed motor and cognitive development. Intercurrent illnesses may provoke recurrences of ataxia and myoclonus.
- Adults with paraneoplastic opsoclonus have the least favorable prognosis, especially when an encephalopathic state coexists. Immune therapies do not show consistent benefit and even responders may be left with permanent cerebellar dysfunction. Occasionally, however, patients may show resolution of opsoclonus after successful tumor removal, and rare patients have improved spontaneously without cancer treatment. Compared to other adult paraneoplastic syndromes, opsoclonus appears to have a somewhat more favorable prognosis.

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8. Koide R, Sakamoto M, Tanaka K, et al. Opsoclonus–myoclonus syndrome during pregnancy. *J Neuroophthalmol* 2004;24:273.

ADDITIONAL READING

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- Wong A. An update on opsoclonus. *Curr Opin Neurol* 2007;20:25–31.

CODES

ICD9

- 333.2 Myoclonus
- 379.59 Other irregularities of eye movements

CLINICAL PEARLS

- Some individuals have the ability to produce horizontal saccadic oscillations at will (voluntary ocular flutter). A very rare person can generate saccades in multiple planes mimicking acquired opsoclonus (multiplanar ocular flutter). However subjects are generally not able to sustain these movements for a few, to maximally 40 seconds.
- Opsoclonus as a benign and transient phenomenon has been described in healthy newborns (term or premature) (7) and pregnant women (8). However, this remains a diagnosis of exclusion.

OPTIC NEURITIS

David S. Younger, MD

BASICS

DESCRIPTION

Optic neuritis refers to inflammatory demyelination of the optic nerve which may be acute, chronic, or subclinical. Acute optic neuritis is most common and is typically characterized by sudden, usually unilateral vision loss that progresses over hours to days. The central visual disturbance may be mild or severe. Many patients notice color desaturation and difficulty seeing in dim illumination. Ninety percent of patients have mild-to-moderate pain in or around the eye, usually worse with eye movement. Neuromyelitis optica (NMO) or Devic's disease, with CNS involvement isolated to the optic nerves and spinal cord, is a variant of multiple sclerosis (MS).

EPIDEMIOLOGY

- Incidence
  - Approximately 6 per 100,000. Peak incidence is in the third and fourth decades.
- Sex
  - The female-to-male ratio is approximately 2:1.

RISK FACTORS

Patients with known MS are at significant risk of optic neuritis.

Pregnancy Considerations

Little is known concerning the relationship between pregnancy and optic neuritis. In patients with MS, there is a diminished risk of new exacerbations including optic neuritis, especially during the third trimester.

ETIOLOGY

Optic neuritis occurs as the initial symptom of MS in 35–62% and is likely a forme fruste of MS in its isolated form.

- Causes of optic neuritis other than MS
  - Viral and parainfectious: Adenovirus, coxsackie, cytomegalovirus, HIV, hepatitis A, Epstein-Barr virus, measles, mumps, rubella, varicella zoster, herpes zoster
  - Post-vaccination
  - Syphilis
  - Lyme neuroborreliosis (*Borreliia burgdorferi*)
  - Tuberculosis
  - *Mycobacterium pneumoniae*
  - Sarcoidosis
  - Vasculitides (systemic lupus erythematosus, Wegener granulomatosis)
  - Autoimmune
  - Sinus infection
  - Bee venom
  - Toxoplasmosis
  - Cat scratch disease

COMMONLY ASSOCIATED CONDITIONS

In patients presenting with isolated optic neuritis, the risk of developing MS is approximately 30% after 5–7 years. In long-term follow-up studies (up to 30 years), 75% of women and 34% of men develop clinically definite MS.

DIAGNOSIS

The diagnosis is suggested by the clinical tempo or visual loss and confirmed by ophthalmologic examination. Central acuity is usually reduced, but 10% of patients have preserved central vision of at least 20/20. Patients who retain normal or near-normal acuity often have reduced color vision and contrast sensitivity out of proportion to central visual disturbance.

- The majority of affected patients have unilateral relative afferent pupillary defect (or Marcus Gunn pupil) that is demonstrable by the swinging flashlight test or subjectively by asking the patient to compare brightness of a light source in the affected and unaffected eyes.
- Central visual field loss or central scotoma accounts for 90% of the visual field defects; however, others also occur including cecocentral, paracentral, arcuate, hemialtitudinal, hemianopic types, as well as peripheral constriction and diffuse suppression. The optic disc may appear normal in retrobulbar optic neuritis in approximately two thirds of patients, inspiring the adage "the patient sees nothing and the physician sees nothing." In anterior optic neuritis (or papillitis), the disc may be swollen. Hemorrhage at the disc margin occurs in less than 6% of patients.
- The optic disc may become pale weeks after the initial episode. Transient reversible neurological dysfunction in response to exercise or exposure to heat is referred to as Uhthoff's symptoms, named after the German ophthalmologist. Uhthoff's symptoms should raise suspicion of, but is not pathognomonic for, MS.
- Patients with NMO present with acute transverse myelitis in association with bilateral optic or retrobulbar neuritis, but incomplete syndromes have been described. A serum immunoglobulin IgG autoantibody (NMO-IgG) serves as a specific marker. It selectively binds to the aquaporin-4 water channel, a component of the dystroglycan protein complex located in astrocytic foot processes at the blood–brain barrier and represents a novel class of autoimmune channelopathy. NMO can be monophasic, relapsing, or progressive but tends to have a poorer prognosis and response to immunomodulation than straightforward MS.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Blood work

The following tests should be considered: CBC/differential, thyroid function tests, vitamin B12 and folate levels, rapid plasma reagin, anti-nuclear antibodies, rheumatoid factor, anti-SSA, anti-SSB, p and c anti neutrophil cytoplasmic antibody, HIV, serum and/or CSF angiotensin-converting enzyme level, Lyme titer, immunofixation, CSF studies including IgG index and synthesis rate, oligoclonal bands, cryptococcal antigen, acid-fast bacillus smear and culture, cytology, and hypercoagulable studies in selected patients (including anticardiolipin antibodies, protein C and S, antithrombin III, activated protein C resistance, factor V Leiden, plasma viscosity, homocysteine, fibrinogen).

Imaging

Lesions in the optic nerve may be detected by gadolinium-enhanced MRI in the first month but not long thereafter and correlates with recovery of visual acuity Subcortical white matter abnormalities on MRI can herald MS or support the concurrent diagnosis thereof, thereby facilitating long-term treatment decisions and counseling.

- CSF testing provides an index of CNS inflammation. They can also add diagnostic certainty wherein pleocytosis, increased immunoglobulin G production, elevated myelin basic protein level, and oligoclonal bands add certainty to the diagnosis of MS; whereas the concomitant expression of the NMO-IgG antibody in serum instead supports NMO.

Diagnostic Procedures/Other

- Visual field testing
  - Confrontational visual field techniques may be used for screening, but are insensitive compared to Goldmann perimeter or automated threshold perimetry.

- Neurophysiologic studies
  - Visual evoked potentials (VEPs) record electrical activity along visual pathways from the optic nerves to the occipital cortex. Bilateral eye testing that result in asymmetric intereye latency prolongation of the P100 response is consistent with unilateral prechiasmatic optic nerve involvement. Pattern reversal stimulus presentation yields more reproducible results. However, flash VEP can be used to confirm visual pathway integrity when the P100 is not seen with pattern VEP. Other disorders that cause VEP disturbance include compressive lesions, congenital optic nerve anomalies, glaucoma, hereditary and toxic optic neuropathy, and papilledema.

DIFFERENTIAL DIAGNOSIS

Numerous infectious and inflammatory disorders can cause optic nerve disturbances including compressive optic neuropathy from intracranial tumors, anterior ischemic optic neuropathy, sinus disease, and radiation-induced optic neuropathy. Patients presenting with bilateral anterior optic neuritis should be evaluated for papilledema. Leber's hereditary optic neuropathy (LHON), a mitochondrial disorder usually causing bilateral central visual loss, may mimic optic neuritis, especially in young men in early stages before the fellow eye is involved.

Optic neuropathies and ophthalmic conditions mimicking optic neuritis are as follows:

- Neuroretinitis
- Big blind spot syndrome
- LHON
- Diabetic papillitis
- Ischemic optic neuropathy
- Central retinal vein occlusion
- Venous stasis retinopathy
- Optic disc drusen
- Central serous retinopathy
- Carcinomatous meningitis
- Infiltrating neoplasm (lymphoma)
- Radiation-induced optic neuropathy
- Paraneoplastic disorder

TREATMENT

MEDICATION

Corticosteroids have long been the cornerstone of therapy for optic neuritis despite conflicting studies of effectiveness.

- 1,000 mg/day of methylprednisolone may be administered as a single daily IV infusion for 3–5 days, followed by a tapering dose of oral prednisone starting at 100 mg for 4 days and then tapering by 10 mg every other day over 2–4 weeks.
- Oral prednisone in conventional doses of 1 mg/kg/day is contraindicated as the sole treatment, although some practitioners are exploring the use of higher doses (2–5 mg/kg/day or more).
- Contraindications: In patients with a suspected infectious etiology, corticosteroids should be withheld until appropriate antibiotic therapy is instituted.
- Precautions: Common adverse events related to high-dose corticosteroid treatment include gastric irritation, insomnia, euphoria, depression, and occasionally psychosis, tachycardia, hypertension, hypokalemia, hyperglycemia, increased appetite, and fluid retention. Pretreatment with an H2 blocker for GI prophylaxis and potassium supplementation should be considered. A single morning dose of corticosteroids may reduce the risk of insomnia. Blood pressure, potassium, and glucose levels should be monitored. Those with diabetes or hypertension require more careful monitoring that often includes the use of sliding-scale insulin. Mild tranquilizers are effective for insomnia.
- Alternative drugs
  - While controlled studies are lacking, some consider treating steroid recalcitrant visual loss with either intravenous immunoglobulin (IVIG) or plasma exchange.

ADDITIONAL TREATMENT

General Measures

The disparity of visual functioning between the two eyes is often sufficient to provoke headache and ocular discomfort. Analgesic agents should be used as necessary. Patching the involved eye for a few days may be helpful if the interocular visual functioning is highly disparate.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - There are currently no approved therapies for the symptomatic complaints associated with optic neuritis. In those who experience Uhthoff's phenomenon, high temperatures should be avoided. Ingestion of ice-cold liquids or the use of cooling devices may also be helpful.
- Adjunctive treatment
  - Formal evaluation by an ophthalmologist is suggested to maximize visual function with refractive techniques and to exclude potentially treatable ophthalmic conditions.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with optic neuritis can be treated with IV corticosteroids in the hospital or at home. Diabetes mellitus and uncontrolled hypertension are comorbidities that may warrant hospitalization.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be reexamined after steroid therapy to exclude a further decline in visual function.

PATIENT EDUCATION

See the chapter on Multiple Sclerosis.

PROGNOSIS

The natural course of acute optic neuritis is variable. Visual deficits typically worsen over a few days to 2 weeks. Most patients then recover rapidly, achieving most of their improvement by 5 weeks. Some continue to recover for up to a year. The mean visual acuity 12 months after the onset is 20/15. Fewer than 10% have visual acuity less than 20/40 at 1 year. Despite recovery of vision to "near normal," most patients are aware of residual visual dysfunction due to deficits in contrast sensitivity, color vision, and depth perception.

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See Also (Topic, Algorithm, Electronic Media Element)

- Inflammatory optic neuropathy
- Retrobulbar optic neuritis
- Optic papillitis

CODES

ICD9

- 377.16 Hereditary optic atrophy
- 377.30 Optic neuritis, unspecified
- 341.0 Neuromyelitis optica

ORTHOSTATIC HYPOTENSION

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BASICS

DESCRIPTION

It is valuable to diagnose variable degrees of autonomic failure that may present as orthostatic intolerance (OI), postural tachycardia syndrome (POTS), or syncope. Orthostatic hypotension (OH) is a dominant feature of severe autonomic failure. The clinician must rely upon the history and observations of patients of any age, from childhood to older age, as autonomic failure can affect all age groups. The history of rapid-onset, short-lived dizziness, and other symptoms upon assuming the upright position that abates and resolves usually over seconds to minutes is suggestive of OH and OI. It is defined as (a) symptoms triggered by standing and relieved in supine position, (b) heart rate increase >30 beats per minutes (bpm) or >120 bpm, and (c) blood pressure is normal or increased. OH is defined as (a) blood pressure fall >20/10 mm Hg for 3 minutes, (b) with or without symptoms of cerebral hypoperfusion, and (c) loss of heart rate increase indicating severe autonomic failure. Neurogenic syncope is triggered by reflex mechanism and may occur with both conditions. The syndrome of POTS is defined as symptoms of OI usually of greater than 6 months' duration, accompanied by a rise in the heart rate of at least 30 bpm or exceeds 120 bpm, within the first 10 minutes of the upright position or upon head-up tilting.

EPIDEMIOLOGY

In the US, 500,000 patients have OI.

- Race
  - N/A
- Age
  - OI may affect all ages. OH is more common in the middle aged and the elderly.
- Sex
  - Female > male; multiple system atrophy (MSA) male > female.

RISK FACTORS

Falls, injury.

Pregnancy Considerations

- OI—generally improvement during pregnancy
- OH—determined by primary diagnosis

Genetics

Unknown, except for familial dysautonomia [Riley–Day syndrome in Ashkenazi Jews on chromosome 9 (q31)].

COMMONLY ASSOCIATED CONDITIONS

- OI
  - Small fiber neuropathy
  - Excessive venous pooling/deconditioning/prolonged bed rest/weightlessness
  - Hypovolemia
  - β-receptor supersensitivity
  - Brainstem dysregulation, Arnold–Chiari malformation
- OH
- Primary autonomic failure
  - Pure autonomic failure (PAF)
  - MSA with parkinsonian, cerebellar, and pyramidal features
  - Acute and subacute pandysautonomia
- Secondary autonomic failure
  - Peripheral autonomic neuropathy (diabetes, amyloidosis)
  - Dopamine-β-hydroxylase (DBH) deficiency
  - Guillain–Barré syndrome
  - Paraneoplastic (Lambert–Eaton syndrome—small cell lung carcinoma)
  - Brain tumors—posterior fossa
  - Autoimmune and collagen disorders (Sjögren's syndrome)
  - Tabes dorsalis
  - HIV infection
  - Familial dysautonomia (Riley–Day)
  - Lyme neuroborreliosis
  - Psychotropic medications in elderly

DIAGNOSIS

- Light-headedness
- Dizziness
- Blurred vision
- Fatigue
- Nausea
- Gastrointestinal symptoms
- Palpitations
- Shortness of breath, hyperventilation, dyspnea
- Headache
- Memory loss (OH in elderly)

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- ECG normal; Holter monitoring shows episodes of sinus tachycardia.
- Standing plasma catecholamines are increased in some OI patients but reduced in OH.
- Reduced adrenocorticotropic hormone and β-endorphin can distinguish OH due to MSA vs. PAF (normal).
- Reduced growth hormone and melatonin in DBH deficiency.
- Screening metabolic, parainfectious, and autoimmune serology.

Imaging

- OI—MRI typically normal.
- OH—MSA—T2-weighted images show putamen hypointensity, olivopontocerebellar atrophy (OPCA). Positron emission tomography shows reduced reuptake of F-dopa in MSA.

Diagnostic Procedures/Other

Diagnosis of autonomic failure is made using a battery of autonomic tests:

- Tilt table testing is done at 60–80 degrees for 5–10 minutes without medications. OI shows sinus tachycardia (>100 bpm) for at least 5 minutes with normal or increased blood pressure. POTS is severe form of OI with orthostatic heart rate >120 bpm. OH shows sustained blood pressure drop >20/10 mm Hg for 3 minutes. Loss of heart rate increment indicates severe autonomic failure. Isoproterenol/nitroprusside infusions are used for evaluation of syncope.
- Heart rate variation to deep breathing and bradycardia/tachycardia ratio during Valsalva maneuver is typically reduced.
- Quantitative sudomotor axon reflex test (QSART)—stimulation of postganglionic sudomotor fibers using iontophoresis of 10% acetylcholine chloride. QSART may be normal in OI but is typically reduced with OH due to peripheral neuropathy.
- Thermoregulatory sweat test—body is covered by alizarin powder and temperature is raised by 1°C. Sweating is indicated by red coloration. Typically, in diabetic neuropathy, sweating is lost in stocking/glove distribution.

DIFFERENTIAL DIAGNOSIS

- Non-neurogenic OI
  - Anxiety
  - Cardiogenic syncope
  - Tachyarrhythmias/bradyarrhythmias
  - Seizures, pseudoseizures
  - Porphyria
  - Pheochromocytoma
  - Anemia
- Non-neurogenic OH
  - Cardiac impairment (myocardial infarction, myocarditis)
  - Impaired cardiac filling/output (e.g., aortic stenosis, cardiomyopathy, heart failure)
  - Nephrogenic (nephropathy, hemodialysis)
  - Blood/plasma loss—hemorrhage, burns, sepsis
  - Fluid/electrolyte loss—vomiting, diarrhea, fluid loss
  - Increased intracranial pressure
  - Drug induced—centrally acting agents that reduce sympathetic activity (clonidine, methyldopa, reserpine, barbiturates, anesthetics)
    - Peripheral—guanethidine, bethanidine
    - α-blockers—prazosin, phenoxybenzamine
    - β-blockers—propranolol, pindolol, timolol, etc.
    - Vasodilators—nitrates, alcohol
    - Diuretics

TREATMENT

MEDICATION

- Orthostatic intolerance
  - Fludrocortisone 0.05 mg PO b.i.d.; weekly increase to 0.1–0.3 mg PO b.i.d
  - 3- to 6-lb weight gain is desirable
  - Side effects: 50% hypokalemia, 50% hypomagnesemia, peripheral edema
  - Sodium chloride (salt tablets): 50 mEq or 1,200 mg PO t.i.d.
  - Side effects: Peripheral edema
  - Propranolol (Inderal) 10–40 mg PO q.i.d.
  - Pindolol (Visken) 2.5–5.0 mg bid to t.i.d.
- Orthostatic hypotension
  - Fludrocortisone (Florinef) 0.05 mg PO b.i.d.; weekly increase to 0.1–0.3 mg PO
  - Side effects: See above
  - Sodium chloride: See above
  - Midodrine (ProAmatine): Starting dose 5 mg t.i.d. up to 40 mg/day, last dose before supper
  - Side effects: Sensation of goose flesh (chills), scalp pruritus, urinary retention, supine hypertension, may increase urinary Na^+ loss
  - Caffeine 250 mg (2 cups) in the morning and 1 cup with meals (postprandial hypotension)
  - Erythropoietin (epoetin alfa) 25–75 mg U/kg IV or SC 3 times weekly (only for severe autonomic failure)
  - Octreotide (somatostatin) 25 μg SC b.i.d. with increase to 100–200 μg t.i.d.
  - Clonidine (Catapres—α_2-agonists) 0.1–0.3 mg given as 0.2–0.8 mg b.i.d. to t.i.d.
  - Indications: Autonomic failure due to efferent sympathetic lesion. Note that patients with peripheral lesion become hypotensive
- Contraindications
  - Fludrocortisone, ProAmatine— congestive heart failure
  - Erythropoietin—hypersensitivity to human albumin
  - Clonidine—caution with β-blockers; tricyclic antidepressants may cause rebound hypertension
- Precautions: Monitor supine hypertension, peripheral edema, and congestive heart failure
- Alternative drugs
  - OI: Disopyramide 150 mg q.i.d. or 300 mg b.i.d.
  - OH: Ephedrine sulfate 12.5–25 mg, PO t.i.d.

ADDITIONAL TREATMENT

General Measures

Treatment of OH includes a combination of volume expansion, pressor agents, and supportive measures.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Liberalize fluid and salt intake.
  - Review all medications to determine if any that might be contributing to orthostasis may be discontinued, especially diuretics, antihypertensive agents, antianginal agents, and antidepressants.
  - Have patient move from supine to sitting and standing positions in gradual stages.
  - Head-up tilt bed—elevation of bed to 20-degree angle activates the renin–angiotensin–aldosterone system and decreases nocturnal diuresis.
  - Elastic body garments (custom-fitted stockings with graded pressure, abdominal binder inflatable, or easy-wraps
- Adjunctive treatment
  - N/A

SURGERY/OTHER PROCEDURES

- Tumor removal
- Brainstem decompression in Arnold–Chiari malformation

IN-PATIENT CONSIDERATIONS

Admission Criteria

Frequent loss of consciousness/improvement of orthostatic tolerance.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- If no improvement of symptoms is there, repeat tilt study on medications.
- Monitor supine hypertension (24-hour BP monitoring might be useful).

DIET

High sodium and 2–2.5 L of fluids; small, more frequent, low-carbohydrate meals.

PATIENT EDUCATION

- Activities
  - Countermaneuvers (squatting, leg crossing, toe raising, marching, bending forward, abdominal contraction); supine exercise (leg lifting, weight pressing), swimming; relaxation. Avoid overheating and straining maneuvers. Schedule activities for the afternoon since the symptoms are typically worse in the morning.
- Organizations
  - The National Dysautonomia Research Foundation, contact person: Linda J. Smith (Email: *ndrf@ndrf.org*, phone: 715-594-3140; fax: 715-594-3140; website: http://www.ndrf.org)

PROGNOSIS

- OI
  - Good prognosis—majority of patients improve over time.
- Orthostatic hypotension
  - Knowing precise diagnosis is important for prognosis
  - Diabetic neuropathy—increased risk for death/arrhythmias
  - MSA survival: 5 years from diagnosis
  - PAF survival >10 years

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- OI
  - Postural orthostatic tachycardia syndrome, orthostatic tachycardia, Da Costa's syndrome, soldier's heart, effort syndrome, mitral valve prolapse syndrome, neurocirculatory asthenia, idiopathic hypovolemia, chronic fatigue syndrome, vasoregulatory asthenia, partial dysautonomia, irritable heart
- Neurally mediated syncope
  - Neurocardiogenic, vasovagal, vasodepressor
- OH
  - MSA: Shy–Drager syndrome, olivopontocerebellar degeneration (OPCA), striatonigral degeneration
  - PAF: Bradbury–Eggleston syndrome

CODES

ICD9

- 458.0 Orthostatic hypotension
- 780.2 Syncope and collapse

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

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BASICS

DESCRIPTION
Paraneoplastic neurological syndromes are a diverse group of diseases characterized by neurological dysfunction in the setting of a remote malignancy secondary to an autoimmune-mediated response. The central, peripheral, and autonomic nervous system may be affected. The presentation often precedes the identification of the underlying malignancy in up to 50% of patients.

EPIDEMIOLOGY
These disorders affect <8% of cancer patients. Tumors commonly involved affecting the central nervous system express neuroendocrine proteins (small cell lung cancer, neuroblastoma), affect organs with immunomodulatory properties (thymoma), or contain neuronal tissue (teratomas). Immunoglobulin producing tumors (plasma cell dyscrasias, B-cell lymphomas) typically affect the peripheral nervous system. Small cell lung cancer has the highest incidence, followed by breast cancer, ovarian cancer, and Hodgkin's disease.

- Race
  - No known racial or ethnic predisposition.
- Age
  - Most patients are >40 years. Paraneoplastic opsoclonus-myoclonus (POM) may occur in very young children and infants with neuroblastoma.
- Sex
  - Reflects the sex distribution of the underlying cancer.

RISK FACTORS
Genetics
No known genetic predisposition.

ETIOLOGY
- Likely an inflammatory, immune-mediated mechanism. Anti-neuronal antibodies in the serum and CSF are detected in a large percentage of patients.
- Antibody mediated: Some antibodies seem to have a direct pathogenic role. Antibodies to cell-surface antigens and the associated disorder may occur with or without cancer. For example, the Lambert–Eaton myasthenic syndrome is due to antibodies directed against voltage-gated calcium channels at the neuromuscular junction. The absence of serum or CSF onconeuronal antibodies does not exclude the diagnosis of paraneoplastic disease.
- T-cell mediated: The T-cell immune response is likely directed against target antigens of the accompanying antibodies.
- A specific area of the nervous system is targeted in each syndrome:
  - Paraneoplastic cerebellar degeneration (PCD)—Purkinje cells
  - POM—brainstem and cerebellum
  - Paraneoplastic limbic encephalitis (PLE)—limbic system
  - Paraneoplastic sensory neuronopathy (PSN)—dorsal root ganglia
  - Lambert–Eaton myasthenia syndrome—presynaptic neuromuscular junction

COMMONLY ASSOCIATED CONDITIONS
The conditions comprise systemic malignancy.

DIAGNOSIS

- Paraneoplastic cerebellar degeneration (PCN)
  - Subacute, progressive pancerebellar dysfunction
  - Gait and limb ataxia
  - Dysarthria and dysphagia
  - Diplopia/nystagmus/oscillopsia
  - Vertigo
- Paraneoplastic opsoclonus myoclonus
  - Involuntary, arrhythmic, conjugate vertical, and horizontal eye movements
  - Diffuse or focal myoclonus of virtually any voluntary muscle
- Paraneoplastic encephalomyelitis and associated paraneoplastic sensory neuronopathy
  - Subacute dementia or delirium
  - Focal or generalized seizures
  - Psychosis
  - Spastic hemiparesis/quadriparesis
  - Cerebellar ataxia
  - Parkinsonism
  - Limb anesthesia/paresthesia
  - Neuropathic pain
  - Sensory ataxia
  - Lower motor neuron weakness, fasciculation, and muscle wasting
  - Dysautonomia

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
- Blood work: A subset of patients has serum antibodies that can be measured:
  - PCD: Anti-Yo (cdr2), anti-Tr, anti-Ri, anti-Hu, antibodies to CRMP5, mGluR1, CV2, PCA2, and ANNA-3
  - POM: A subset of adult patients will have circulating serum and CSF antibodies to neural antigens. Anti-Hu, anti-Ri, and anti-Yo antibodies are found in adults, whereby in children with neuroblastoma antibodies are less frequently detected (occasionally anti-Hu antibodies are detected). Anti-Ri antibody has been found in some female patients with POM and breast or pelvic cancers
  - PEM/PSN: Anti-Hu or ANNA-1
- Antibodies may point to the causal malignancy. Anti-Yo (APCA) is associated with breast, ovarian, and uterine cancer. Anti-Hu (ANNA-1) is associated with small cell cancers and its presence is highly associated with underlying malignancy. Anti-Ri (ANNA-2) is seen in association with breast and lung cancers. Anti-Ma seen in paraneoplastic limbic encephalitis and is associated with testicular cancer. These antibodies are specific but not sensitive.
- Further diagnostic evaluation: Serologic testing to rule out underlying infection (CBC with differential and blood cultures if febrile), toxic-metabolic disorders (sodium, calcium, magnesium, liver, and renal function tests), and vasculitis (ESR, ANA, RF, ENA, and ANCA) should be performed. Serum and urine immunoelectrophoresis, fasting glucose, serum B_{12} level, urine heavy metals, and toxicology screen may also be appropriate.

Imaging
- Neuroimaging is important to rule out alternative causes. Often imaging studies may be normal. After several months, marked diffuse cerebellar atrophy is usually noted in PCD and PET scan may show cerebellar hypometabolism. In limbic encephalitis up to 80% of patients' MRI FLAIR and T2 sequences show hyperintensity of the mesial temporal lobes with PET scan showing hypermetabolism of the temporal lobes. An aggressive search for an underlying malignancy should be undertaken. This may include total body CT, mammogram, liver function tests, bone scan, testicular ultrasound or other tests deemed appropriate by an oncologist. Some have advocated an exploratory laparotomy in patients with anti-Yo (APCA) antibodies, if pelvic imaging and mammography are negative, to search for an occult tumor. Pediatric patients should have testing to detect a thoracic or abdominal neuroblastoma. Patients seropositive for anti-Hu (ANNA-1), bronchoscopy may be indicated even if chest CT or MRI is normal.

Diagnostic Procedures/Other
- Lumbar puncture: After neuroimaging has excluded a mass, CSF should be examined to exclude hemorrhage and infection. Approximately 50% of patients with PCD, POM, and PEM/PSN will have nonspecific inflammatory changes of CSF including a modest increase in protein, CSF lymphocytic pleocytosis, increased IgG index, and the presence of oligoclonal bands.
- PEM/PSN
  - EEG may demonstrate diffuse or asymmetric cerebral slowing and focal or multifocal epileptiform activity.
  - Nerve conduction studies typically show reduced/absent sensory nerve action potentials with relatively preserved compound muscle action potential amplitudes and conduction velocities. EMG may show evidence of muscle denervation.

DIFFERENTIAL DIAGNOSIS

- PCD/POM/PEM/PLE
  - Primary or metastatic tumor of the CNS
  - Toxic/metabolic disorders causing ataxia (5-FU, ARA-C, anticonvulsant medications, lithium, alcohol, vitamin B_{12} or B_1 deficiency, heavy metal poisoning, Wilson's disease, etc.)
  - Brainstem or cerebellar infarct/hemorrhage
  - Infection (bacterial, fungal, or parasitic abscess, encephalitis, PML, CJD)
  - Demyelinating disease
  - Heritable ataxias
  - Toxic or metabolic encephalopathy (diabetic hyperosmolar nonketotic coma, lithium, thallium, amitriptyline overdose, toluene, strychnine)
  - Hydrocephalus
  - Cerebral vasculitis
  - Multiple cerebral infarcts
- PSN
  - Acute or chronic inflammatory demyelinating polyneuropathy (AIDP/CIDP)
  - Monoclonal gammopathy-associated polyneuropathy
  - Diabetic polyneuropathy
  - Vasculitic neuropathy (particularly Sjögren's syndrome)
  - B_{12} deficiency
  - Toxic neuropathies (vitamin B_6 overdose, chlorobiphenyl, thalidomide)
  - Idiopathic subacute sensory neuronopathy

TREATMENT

MEDICATION

Unfortunately, there is no specific therapy for these disorders. There are reports of spontaneous remission or improvement with treatment of the underlying cancer; however, no standard of care has been established. The use of corticosteroids, plasma exchange, intravenous immunoglobulin, cyclophosphamide, and tacrolimus did not substantially modify the neurological outcome of patients whose tumors were successfully treated although there are case reports of an apparent benefit from immunotherapy. The immune responses associated with more severe neurological deficits (Yo, Hu, CRMP5) are also the most refractory to treatment. Patients who received anti-tumor treatment, with or without immunotherapy, lived significantly longer than those who did not. Anti-epileptics are used to control seizures if present.

ADDITIONAL TREATMENT

General Measures

Supportive care is paramount to avoid secondary complications like aspiration pneumonia, decubiti, urinary tract infection, deep venous thrombosis, and injury from falls.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Physical therapy may assist with gait and avoidance of joint contractures.
- Adjunctive treatment
  - No reports available.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission may be required for hydration and evaluation for oncologic workup and exclusion of other neurologic disorders.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

If malignancies are not found on the initial evaluation, periodic reevaluations for malignancy should be conducted.

PROGNOSIS

- In most patients, PCD is permanent and disabling. The disease progresses rapidly over a period of weeks or months and then stabilizes. The prognosis of adult-onset POM is highly variable. Spontaneous remissions or improvement after treatment of the underlying cancer are frequently noted. Many patients suffer residual disability from cerebellar ataxia. Although childhood cases associated with neuroblastoma do remit with corticosteroid therapy, most children are left with permanent neurologic deficits.
- The onset and course of PEM/PSN is usually subacute and progressive. Most patients stabilize with severe neurologic deficits. Remission is extremely rare.
- Interestingly, prolonged survivals even without cancer treatment have been seen in all of these syndromes in patients with pelvic and lung cancers. This suggests that heightened immunity may have a beneficial effect on host defenses to cancer. Although patients may die from progression of their underlying cancers, many die from complications of their neurologic disease.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- PCD: Anti-Yo syndrome
- POM: "Dancing eyes and dancing feet," infantile polymyoclonia
- PEM: Anti-Hu syndrome, paraneoplastic limbic encephalitis
- PSN: Anti-Hu syndrome, subacute sensory neuronopathy

CODES

ICD9

- 331.89 Other cerebral degeneration
- 355.9 Mononeuritis of unspecified site
- 357.3 Polyneuropathy in malignant disease

PARKINSON'S DISEASE (PD)/PD DEMENTIA

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BASICS

DESCRIPTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterized by bradykinesia, rest tremor, and rigidity. As the disease advances, patients may experience gait and balance disturbances as well as nonmotor features including cognitive dysfunction, also known as PD with dementia (PDD). Advances in pharmacological, nonpharmacological and surgical options in the last 2 decades have greatly enhanced our ability to successfully manage PD symptoms for many years, although long-term treatment remains limited as the disease advances and patients exhibit dementia and loss of balance.

EPIDEMIOLOGY

Incidence

Incidence rates of PD vary worldwide with most estimates suggesting 10–20 new cases per 100,000 population annually.

Prevalence

Prevalence rates for PD worldwide vary significantly ranging from <50 to >300/100,000. Since the incidence and prevalence of PD increases with age, rough estimates suggest a prevalence of 1% of people above the age of 65.

RISK FACTORS

- *Race*: PD prevalence appears higher in Europe and North America, with lower rates in Japan, China, and Africa. In addition, prevalence in the USA is lower among blacks than whites. However, differences in sampling methodology preclude conclusive determination of PD risk based on race (5).
- *Age*: Increasing age is the single greatest risk factor for developing PD.
- *Sex*: Most current studies support a greater risk of PD in males; in some cases up to twice as frequent in comparison to females.
- *Environment*: Current theories of pathogenesis (1) are consistent with observational studies demonstrating increased risk of PD in farming communities, exposure to well water and contact with pesticides and herbicides.

Genetics

A number of mutations have been found in familial PD. Some of these mutations include genes encoding alpha-synuclein, leucine-rich repeat kinase 2, and others (2).

GENERAL PREVENTION

- N/A

PATHOPHYSIOLOGY

- Understanding of the pathogenesis of PD has changed dramatically in the last 10 years. The classic pathological features include a significant loss of dopamine neurons in the substantia nigra pars compacta, as well as the hallmark finding of Lewy bodies (eosinophilic intracytoplasmic inclusions containing alpha-synuclein, ubiquitin, and other proteins).
- In the early 2000s, Braak and colleagues published the results of their comprehensive neuropathological survey, examining the entire nervous system of 140 patients who died of PD. Immunocytochemically, they identified aggregates of alpha-synuclein in peripheral, autonomic, olfactory, and enteric nervous system structures, in addition to the CNS.
- This landmark research demonstrated that the earliest pathological manifestation of PD, the development of Lewy bodies and Lewy neurites, appears initially in the olfactory bulb and the plexus of the enteric nervous system. In the brain, the alpha-synuclein pathology appears to ascend the brainstem to the midbrain, eventually involving the substantia nigra, sometimes continuing on to reach the cortex, which correlates with PDD.
- These discoveries altered our understanding of the course of PD and provided a pathologic basis for clinical observations supporting pre-motor features that may be identified in people at risk of developing PD.
- The list of premotor features identified to date includes the following:
  - Constipation
  - Olfactory dysfunction
  - Rapid eye movement (REM) sleep behavior disorder
  - Depression and anxiety

ETIOLOGY

- The cause of PD is felt to be the result of environmental exposure superimposed on a genetic predisposition. Polygenetic factors may be involved, but are still being elucidated.
- A number of genetic mutations have now been discovered that may cause PD. At this time, it is estimated that known genetic mutations may account for approximately 5–15% of cases of PD. The remaining cases are currently considered "idiopathic." It seems likely that more genetic mutations associated with PD will be discovered.

COMMONLY ASSOCIATED CONDITIONS

- N/A

DIAGNOSIS

HISTORY

Motor and Nonmotor Abnormalities

- PD symptoms develop insidiously and, when present initially on the nondominant side, may not be noticed by the patient for months or even years. Without the classic rest tremor, the slowness and awkwardness of movement along with muscle rigidity and aching are frequently considered part of the aging process and the diagnosis is delayed, if not missed entirely.
- Pain may be present, typically reported in large muscle groups such as the shoulder girdle, low back, or hip. One international survey confirmed that shoulder pain was the most common symptom shared by patients prior to their formal diagnosis.
- Loss of olfaction, slowing of GI transit times with resultant constipation, and REM sleep behavior disorder may predate the motor symptoms of PD by a decade or more. Increasingly, these symptoms and others are being recognized as part of the PD complex (see "Pathophysiology").
- Modern diagnostic criteria require the presence of bradykinesia along with rest tremor and/or rigidity. In addition, PD is an asymmetric disorder, usually beginning on one side and remaining worse on that side throughout the course of the illness. In addition, in almost all cases, bradykinesia and rigidity clearly improve with the introduction of dopamine replacement medications [levodopa (LD) or dopamine agonists] at appropriate doses. Postural instability (loss of balance) is a late feature of PD and is not expected at presentation.
- *Supportive prospective diagnostic criteria for a diagnosis of PD:*
  - Unilateral onset
  - Rest tremor present
  - Progressive disorder
  - Persistent asymmetry primarily affecting side of onset
  - Excellent response (70–100%) to LD
  - LD response for ≥5 years
  - Severe LD-induced chorea
  - Clinical course of ≥10 years

Cognitive and Mood Disorders

- Criteria for a diagnosis of PDD have been published (3). These criteria are nearly identical to that for dementia with Lewy bodies (DLB).
- Mood disorders are a common complication of PD with or without dementia, but depression and anxiety are more commonly seen in PDD.
- Hallucinations and delusions are seen frequently in PDD, but the overlap between drug-induced psychosis and that induced by the disease burden makes accurate diagnosis and treatment difficult at times.

PHYSICAL EXAM

Motor Features

- Patients classically present with asymmetric slowness (*bradykinesia*) in movement on the affected side. Typical exam features include reduced amplitude and/or inability to sustain ongoing movements such as finger tapping, open–closing hand, and pronation–supination. In addition, there will typically be micrographia (reduced size of handwriting), which progressively worsens as the patient continues to write. While walking, there may be reduced natural arm swing and shortened stride length on the affected side.
- *Rest tremor* is also asymmetric, when present, and is slower than most other forms of tremor, typically in the range of 3–5 Hz. There may be a "pill-rolling" characteristic with the thumb, index, and middle fingers moving against each other.
- *Rigidity* is part of the early motor symptom triad and may be best described as increased resistance to passive manipulation. Other terms include "lead-pipe" or "cogwheel" rigidity, although the ratcheting sensation is primarily the result of the tremor superimposed on the rigidity.
- *Postural instability* is typically a late manifestation of PD, but may be seen early in the other parkinsonisms [see multiple system atrophy (MSA), progressive supranuclear palsy (PSP)].
- Inability to resist blinking when the examiner taps the glabella (Myerson's sign) is considered suggestive of PD, but this primitive reflex may be seen with other degenerative disorders and/or medical conditions.
- Patients may have masked facies (reduced spontaneous facial movement), hypophonia (reduced voice amplitude), and difficulty initiating movement from a seated to standing position without supporting the movement with their arms.
- Eye movements are typically abnormal due to saccadic pursuits.
- As the disease progresses, symptoms of bradykinesia, rigidity, and/or tremor spread to the contralateral side. In advanced cases, patients develop a stooped posture and increased difficulty maintaining their balance if given a postural challenge. Gait becomes more difficult with "shuffling" and periods of "freezing", during which the initiation of gait is markedly inhibited.

Cognitive and Autonomic Signs

- Autonomic dysfunction with orthostatic hypotension may be present on blood pressure testing.
- PDD is characterized on exam by features common to DLB. Patients may have myoclonus. Cognitive testing demonstrates problems with attention and concentration (serial 7's, spelling WORLD backwards) along with visuospatial dysfunction (drawing intersecting pentagons and/or clock drawing test) usually well before difficulties with orientation or memory become prominent.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Bloodwork: There are no specific blood tests to diagnose PD, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism: Serum vitamin B12 and D levels and thyroid function tests.

Imaging

- DaTscan™ can now be used as an aid in the diagnosis of PD. Single-photon emission computed tomography (SPECT) scanning is utilized to image a ligand that binds to dopamine transporters on dopamine terminals. This provides a visual index of the number of remaining dopamine neurons. It is decreased in PD, as well as in other degenerative parkinsonisms such as MSA and PSP. It is normal in ET, DIP, healthy individuals, and psychogenic parkinsonism. This test should be reserved for those individuals in whom the diagnosis is uncertain.
- There is no evidence to suggest that structural imaging studies (CT, MRI) can assist in the diagnosis of PD. MRI imaging may reveal evidence of other causes of parkinsonism such as vascular insults, mass lesions, calcium or iron deposition in the striatum, atrophy in the posterior fossa suggestive of multiple system atrophies, and cortical atrophy patterns suggestive of other dementing illnesses.

Diagnostic Procedures/Other

- N/A

Pathological Findings

- See "Pathophysiology"

DIFFERENTIAL DIAGNOSIS

- DLB
- Essential tremor
- Drug-induced parkinsonism (e.g., antipsychotics, antiemetics, and other dopamine-blocking agents)
- MSA
- PSP
- Corticobasal degeneration
- NPH
- Vascular parkinsonism

TREATMENT

MEDICATION

A primary goal in the treatment of PD is to provide good motor benefit through the day. This is generally accomplished by restoring dopamine levels as close to normal as possible. This can be accomplished through the use of LD (used in combination with a dopa-decarboxylase inhibitor [DDCI] to prevent peripheral breakdown to dopamine), dopamine agonists, or monoamine-oxidase type B (MAO-B) inhibitors. In addition, catechol-O-methyl transferase (COMT) inhibitors, when combined with LD/DDCI, increase the bioavailability of LD, thereby enhancing brain levels of dopamine. Additional available medications include anticholinergic agents and amantadine. All of these treatments have specific potential benefits and side effects.

Levodopa

- The most effective and widely used treatment option for the motor features of PD is LD (combined with a DDCI). LD is taken up by remaining dopamine neurons, converted to dopamine, and released over time to restore normal stimulation of striatal neurons. However, long-term use of LD is associated with motor fluctuations, such that patients notice benefit for a few hours after LD administration and then experience a "wearing-off" of its effect. In addition, many patients develop twisting, turning chorea movements that typically occur when LD-derived dopamine is peaking in the brain. The usual dose of carbidopa/levodopa (C/L) is 25/100, 3–4 times daily, typically given at 4-hour intervals and apart from meals. A common side effect when initiating LD therapy is nausea, which may be ameliorated by the co-administration of C/L with food at the beginning. Days to weeks later, the medication may be moved to 30–60 minutes prior to meals.
- It has been hypothesized that dyskinesias are the result of nonphysiologic peaks and troughs of dopamine brain concentrations that result from the short serum half-life of LD. The development of dyskinesias correlates with the total dose of LD and, therefore, unnecessarily high doses of LD should be avoided.
- Carbidopa/levodopa (C/L) (brand name Sinemet®, multiple generic formulations) is the preparation that provides the standard of care for people with idiopathic PD. While its use is controversial as a first-line agent due to predictable development of motor fluctuations after prolonged exposure to LD, it is the most efficacious and biologically effective medication available.
- Controlled-release form of C/L (Sinemet CR® or C/L ER) is only 70% bioavailable on average compared to immediate release C/L, and thus there is a tendency to underdose patients when using this formulation.

Dopamine Agonists

Dopamine agonists, such as pramipexole, ropinirole, and rotigotine, are moderately effective in controlling motor features of PD as monotherapy in early disease and as adjuncts to LD in more advanced disease. Large, controlled clinical trials have demonstrated that the initial use of a dopamine agonist to which LD is added when the agonist alone is no longer sufficient delays the development of fluctuations and dyskinesias. However, dopamine agonists are associated with more somnolence (including sudden onset sleep), hallucinations, edema, and impulse control disorders than LD. Because younger PD patients are more likely to develop fluctuations and dyskinesias, the strategy of starting dopaminergic therapy with an agonist and/or an MAO-B inhibitor and then adding LD when necessary may be beneficial in this population (<65 years).

MAO-B Inhibitors

- MAO-B inhibitors (selegiline and rasagiline) provide mild symptomatic benefit as monotherapy in early disease and as adjuncts to LD in more advanced disease. There has been controversy regarding whether this class of agents may slow clinical progression and improve long-term outcome. Both agents are generally well tolerated.

- Selegiline (5–10 mg/d) and rasagiline (Azilect® 0.5–1 mg/d) are both selective MAO-B inhibitors that delay or decrease the breakdown of dopamine in the brain, resulting in symptomatic benefit. Selegiline has been approved for adjunctive therapy in PD along with LD/DDCI therapy while rasagiline has been approved for both monotherapy in early PD and adjunctive therapy in advanced PD.
- A large, controlled, multicenter study was completed in 2009 comparing early versus delayed start of rasagiline as monotherapy for PD. While controversial, the results suggested the possibility that rasagiline slows disease progression in early PD. Further studies are expected.

COMT Inhibitors

- COMT inhibitors are useful as adjuncts to LD/DDCI. The COMT inhibitors reduce the peripheral metabolism of LD, thereby allowing more LD to enter the brain over a longer time. The addition of a COMT inhibitor to a LD/DDCI regimen in a patient with motor fluctuations extends the clinical benefit of each LD administration and reduces "off" time, the time when LD is not providing benefit. The most common COMT inhibitor in use worldwide is entacapone. Tolcapone is a highly effective COMT inhibitor, but it can rarely cause fatal hepatotoxicity and liver function test monitoring is required.
- Tolcapone (Tasmar® 100–200 mg t.i.d.) had the adverse side effect of lethal hepatic damage in several patients worldwide, resulting in a black-box warning on the package insert. There is an absolute requirement for liver function monitoring and, thus, this medication should be prescribed only by specialists familiar with its use and contraindications.
- Entacapone (Comtan® 200 mg with every dose of C/L) has not shown any evidence of hepatic toxicity. A combination pill incorporating carbidopa/LD/entacapone – Stalevo® – is also available with multiple different doses of LD/DDCI along with a fixed dose of 200 mg of entacapone in each tablet.

MISCELLANEOUS

- Anticholinergic agents, such as trihexyphenidyl, benztropine, and others, are generally reserved to ameliorate tremor that has not adequately responded to dopaminergic medications. Side effects include dry mouth, dry eyes, constipation, and cognitive dysfunction. They must be used cautiously in older individuals and avoided in those with dementia.
- Amantadine, initially developed as a treatment for influenza, provides mild benefit as monotherapy in early PD. In more advanced PD, it can reduce dyskinesias and motor fluctuations. Common side effects include hallucinations and confusion. It must be used cautiously in older individuals and those with cognitive impairment.
- Treatment of cognitive and behavioral symptoms in PD and PDD replicates the strategies of similar symptoms in DLB.

ADDITIONAL TREATMENT

General Measures

- Dopaminergic replacement is the mainstay of PD and PDD therapy. However, there is increasing evidence that specialized exercise therapies positively impact the functional capacity of people with PD.
- Management of cognitive and behavioral features of PDD is complicated, involving most, if not all, of the treatments outlined in the chapter on DLB.
- One medication of the cholinesterase inhibitor class, rivastigmine, has been demonstrated in a large, controlled clinical trial to improve cognitive deficits in PD patients with dementia. Other potential benefits of this medication include a reduction of hallucinations, depression, anxiety, and other neuropsychiatric manifestations of PD.
- Hallucinations are usually improved by reducing and/or discontinuing PD medications other than LD. If the LD dose necessary to maintain motor function causes hallucinations, treatment with quetiapine (Seroquel® 12.5–25 mg q.h.s. or b.i.d.) can be considered.
- Depression in PD is extremely common – a recent study demonstrated significant improvement of depression and good tolerability of 2 commonly prescribed agents paroxetine and venlafaxine.
- Other nonmotor features of PD that may require symptomatic treatment include insomnia, anxiety, and constipation.
- Surgical treatment of PD may dramatically improve motor symptoms in PD and reduce side effects of other dopaminergic therapies by allowing significant reductions and/or elimination of those medications. Success of deep brain stimulation (DBS) correlates with careful patient selection by a movement disorder specialist along with high-precision placement of the DBS electrodes by an experienced neurosurgeon.

Issues for Referral

- Patients with atypical symptoms or who fail to respond to conventional therapies and doses of dopaminergic agents may be referred to a movement disorder specialist. Patients experiencing significant side effects from their medications and/or those who have disabling "off" times or dyskinesias may be candidates for DBS surgery.
- Physical and occupational therapists can assess and recommend treatment of mobility issues or difficulties in activities of daily living. Occupational therapists perform driving evaluations in patients at risk of having motor vehicle accidents, especially those in whom visuospatial skills are impaired (PDD).
- Neuropsychologists may determine whether depression and/or anxiety is a confounding component of a PD/PDD patient's presentation.
- Social workers assess caregiver stress and coordinate home health care services. They also address medico-legal issues pertinent to PDD such as driving.
- Referral to geriatric psychiatry, cognitive or movement disorder neurology, or other specialists in dementia is frequently warranted due to the complications of disease progression and medication management seen in patients with PDD.

Additional Therapies

Physical therapy, occupational therapy, and voice therapy play an important therapeutic role in the management of PD patients with disability. Big and Loud® therapy and the Theracycle® have significantly improved disability, especially involving gait and balance, in controlled clinical trials (e.g., 4).

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Co-enzyme Q10 was recently studied as a potential disease-modifying treatment in a large, placebo-controlled clinical trial. While no safety issues emerged, the use of 1,200–2,400 mg/d of CoQ10 demonstrated no evidence of slowing disease progression.

SURGERY/OTHER PROCEDURES

- High-frequency DBS of the subthalamic nucleus or the internal portion of the globus pallidus is an effective treatment to treat most motor symptoms of PD, reducing motor fluctuations and dyskinesias in patients on LD whose clinical symptoms cannot be adequately managed by medications alone. Candidates for DBS are those who experience a meaningful improvement with LD but are unable to adequately sustain the response through the day.
- Another surgical option, intestinal infusion of LD (Duodopa®), using an external pump has also been demonstrated to better maintain LD benefit through the day and reduce dyskinesias.

IN-PATIENT CONSIDERATIONS

Admission Criteria

- PD is usually managed in an outpatient setting. Not uncommonly, concomitant illnesses (e.g., pneumonia, UTI) can lead to an acute exacerbation of PD symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility. Psychosis in the setting of idiopathic PD with excessive dopaminergic medication may precipitate hospitalization and/or institutionalization. If hospitalized, careful attention to dopaminergic dosages and timing of doses is critical to enhance positive outcomes.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patients with idiopathic PD are seen usually 2–3 times per year in an outpatient setting. These visits are typically more frequent when medications are adjusted.
- By its very nature, idiopathic Parkinson's disease (IPD) typically requires steadily increasing doses of medications, for the treatment of dopaminergic deficiency or the side effects of (exogenous) dopaminergic therapy.

- Patients with PDD may need to be seen more frequently, up to 4–6 times per year, due to the additional complications of cognitive and/or behavioral changes superimposed on the motor disturbances.
- Patients with PD and prominent nonmotor symptoms (dysautonomia, sleep disturbances, bowel/bladder disturbances, etc.) may also need to be seen more often or referred to appropriate subspecialists for the management of these symptoms.

DIET

- As dysphagia develops, use of pureed foods may be indicated to avoid aspiration pneumonia. Patients may require PEG tube placement in order to maintain nutritional status.

PATIENT EDUCATION

- Support groups for PD are available locally in many areas of the country. There are several large national organizations that provide educational materials to patients and their families. Numerous internet-based resources are available as well.

PROGNOSIS

Over time, patients with PD may develop gait and balance disturbances leading to falls along with or complicating cognitive and/or behavioral abnormalities. Recent studies suggest that PD without cognitive changes does not shorten lifespan, while dementia shortens lifespan, commonly associated with reduced therapeutic alternatives for the management of motor symptoms and/or institutionalization.

COMPLICATIONS

Dysphagia with resultant aspiration pneumonia and falling are 2 common causes of morbidity and mortality in PD and especially in PDD.

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See Also (Topic, Algorithm, Electronic Media Element)

- DLB
- MSA
- PSP

CODES

ICD9

- 331.82 Dementia with Lewy bodies
- 332.0 Paralysis agitans
- 332.1 Secondary parkinsonism

CLINICAL PEARLS

Hallucinations in drug-induced psychosis or associated with PDD are commonly visual in nature and typically make no sound, in contrast to the auditory hallucinations seen in schizophrenia.

PITUITARY APOPLEXY

John M. McGregor, MD

BASICS

DESCRIPTION

Pituitary apoplexy (PA) is characterized by a combination of hemorrhage, infarction, or necrosis of the pituitary gland resulting in the classic clinical picture of sudden onset of severe headache, nausea, vomiting, neck stiffness, visual loss, ophthalmoplegia, pituitary dysfunction, and altered level of consciousness.

- Most frequently associated with an underlying pituitary adenoma (pituitary tumor apoplexy).
- May be a life-threatening emergency due to intracranial mass effect, extensive subarachnoid hemorrhage (SAH), or to acute glucocorticoid deficiency.

EPIDEMIOLOGY

Incidence

- Incidence of pituitary adenoma is 10 per 1,000,000 per year.
- Reported incidence of PA varies from 0.6% to 10% depending on the inclusion criteria.
- 25% of patients with pituitary adenomas may show asymptomatic or incidental pituitary fossa hemorrhage, not considered PA.
- 2% of patients with pituitary adenoma may have PA.
  - – 45% are from nonsecreting adenomas.
  - – 80% occur in asymptomatic patients or those with undiagnosed adenomas.

RISK FACTORS

- 60–80% are spontaneous events
- Nearly all have an underlying pituitary tumor
- Rarely other precipitating factors:
  - – Pregnancy (Sheehan's Syndrome)
  - – Hypertension
  - – Prolonged hypotension
  - – Major surgery
  - – Previous radiation therapy
  - – Dynamic pituitary gland testing
  - – Coagulopathic state
  - – Initiation or withdrawal of dopamine agonist therapies
  - – Head trauma

Pregnancy Considerations

Sheehan's Syndrome describes pituitary ischemia and/or hemorrhage in the setting of pregnancy, usually associated with severe postpartum blood loss and hypotension.

PATHOPHYSIOLOGY

- Mechanisms are unclear. May be due to a primary hemorrhage event or hemorrhage into an ischemic infarct. Macroadenomas are more at risk than microadenomas. Adenoma tumor vessels have fragmented basal membranes that are more susceptible to hemorrhage. Pituitary tumors are supplied by both hypophyseal portal system and internal carotid system (via meningohypophyseal trunk, inferior and superior hypophyseal arteries).
- Hemorrhage into the local intrasellar contents or generally into the subarachnoid space may lead to meningeal irritation, headache, fever, nausea, vomiting, photophobia, altered levels of consciousness, and symptoms of meningismus or vasospasm.
- Lateral cavernous sinus compression leads to ocular palsies in up to 70% of patients. 50% of these are 3rd cranial nerve deficits.
- Expanding suprasellar hematoma results in decreased visual acuity (70% of patients: Bitemporal hemianopia, field loss or blindness due to optic nerve or chiasm compression), hypothalamic dysfunction, midbrain compression, coma, stroke (arterial compression or vasospasm).
- Acute pituitary damage or increased intrasellar pressure and mass effect leads to impaired pituitary function in 80% of patients at presentation (70% adrenal, 45% thyroidal, 80% gonadal, 20% prolactin) including panhypopituitarism or adrenocortical crisis.

ETIOLOGY

- Nearly always associated with a pituitary adenoma.
  - – Other conditions as detailed in "Risk Factors."

COMMONLY ASSOCIATED CONDITIONS

Pituitary adenoma. See also "Risk Factors."

DIAGNOSIS

HISTORY

- Acute onset of retro-orbital or general headache, may be subacute
- Nausea, vomiting
- Photophobia, neck stiffness
- Double vision, blurring, visual field deficit, blindness
- Altered consciousness, coma
- Acute hypopituitarism, adrenal insufficiency, diabetes insipidus (DI)
- Stroke, hemiparesis
- Hypothalamic dysfunction, temperature imbalance, hemodynamic instability

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- CBC, electrolytes, BUN, creatinine, liver function panel, coagulation panel
- Urine and serum osmolarity
- Serum cortisol, ACTH, prolactin, TSH, T3, T4, FSH, LH, GH, IGF1, testosterone, and estradiol

Follow-up & special considerations

- Monitor serum sodium, fluid balance, I's and O's for possible DI, SIADH
- Follow serum electrolytes, correct/normalize
- Normalize coagulation status if necessary

Imaging

Initial approach

- Head CT scan: Acute blood seen as a hyperdensity within the sella or a suprsellar mass. Evaluates other causes in the differential.
- MRI shows the age and extent of blood, tumor, and the relations to CNS anatomy.
- MRA or CTA evaluate adjacent cerebral vasculature for aneurysms, vasospasm.
- Formal cerebral angiography may be used to help identify cavernous aneurysm, spasm.

Follow-up & special considerations

- Serial head CT scans follow progression or resolution of hemorrhage, evaluate for obstructive or communicating hydrocephalus.
- MRI scans follow extent of resection/decompression postoperatively.

Diagnostic Procedures/Other

- Ophthalmologic evaluation
  - – Visual acuity, visual fields, ocular motility, papilledema should be documented.
- Lumbar puncture may be performed in select cases after a normal head CT scan. Results may show xanthochromia or elevated protein, and RBC. Useful to help rule out meningitis.

Pathological Findings

Pituitary adenoma with hemorrhage is the most likely pathologic finding. Nonsecreting adenoma is the most common tumor type (45%).

DIFFERENTIAL DIAGNOSIS

- Acute SAH, aneurysm, arteriovenous malformation
- Meningitis
- Cavernous sinus thrombosis
- Ophthalmic artery occlusion
- Acute optic neuritis
- Migraine with visual aura
- Ischemic or other hemorrhagic stroke
- Pituitary abscess

TREATMENT

Untreated PA associated in the past with 50% mortality. Patients require urgent evaluation and attention to neurologic, endocrinologic, ophthalmologic, and hemodynamic systemic status.

MEDICATION

First Line

- Support hemodynamic status if needed with fluids and/or pressors.
- Hydrocortisone replacement 100–200 mg IV bolus and q6h. Taper as conditions improve.
- Correct any underlying coagulopathy.
- Observe fluid intake and urinary output, treat with appropriate fluid replacements.
- DDAVP and fluids to manage significant DI.
- Correct any electrolyte imbalance intravenously as necessary.

Second Line

- Additional pituitary hormone replacement
- Dopamine agonist or somatostatin analog therapy for specific tumor pathologies

ADDITIONAL TREATMENT

General Measures

- Intensive care therapy for proper treatment of hemodynamic instability; management of neurologic dysfunction and possible respiratory compromise; monitoring and management of acute hypopituitarism with adrenal cortical insufficiency; acute fluid and electrolyte imbalance secondary to diabetes insipidus, SIADH, and hypocortisolism and ongoing evaluation for neurologic deterioration from stroke, edema, vasospasm, hydrocephalus, etc.
- Recognition of hypothyroid state will help direct medical and anesthesiological management.

Issues for Referral
- Neurosurgical referral for surgical decompression of the optic apparatus, evacuation of hemorrhage, treatment of any hydrocephalus, including external ventricular drainage and/or shunting, long-term follow-up for pituitary tumor
- Endocrinology referral for management of acute hypopituitarism and long-term replacement
- Interventional neuroradiology for diagnostic evaluations of SAH and for therapeutic management of significant vasospasm

Additional Therapies
- Symptomatic treatment including headache management with appropriate analgesia.
- Postoperative management is similar to that for other elective pituitary tumor removal surgery.
- Increased attention to endocrine hypofunction, and to late effects of SAH, mass effect, and stroke.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
- Small tumors or hemorrhages without visual compromise may be managed expectantly with observation and serial imaging studies, and attention to endocrine status.
- Prolactin-secreting tumors may be treated with dopamine agonists without surgery with close evaluation of visual status.
- Stereotactic radiosurgery, stereotactic radiotherapy, or conventional fractionated radiotherapy may be indicated for tumor control.
- May consider medical management of hypersecretion from individual pituitary adenomas depending on the underlying pathology, including dopamine agonists, somatostatin analogs, ketoconazole.

SURGERY/OTHER PROCEDURES
- Indicated for acute pituitary hemorrhage with mass effect, severe visual acuity loss, or persistent or deteriorating visual field deficit. Should be considered urgently in PA and, if possible, involve a neurosurgeon with pituitary surgery expertise.
- Transsphenoidal resection of adenoma and hemorrhage is usual procedure.
- May require formal frontal craniotomy for decompression in rare cases.
- Patient may need surgery for hydrocephalus including external ventricular drain or shunting.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
- Airway considerations in the cases of significant neurologic compromise
- Hemodynamic support with fluids and possibly pressors if indicated
- Hydrocortisone therapy, 100 mg IV bolus and q6h initially
- Treatment of any acute hydrocephalus
- Early consultation with neurointensive care, neurosurgery, neuro-ophthalmology

Admission Criteria
- Any pituitary hemorrhage with symptomatic headache, neurologic compromise, visual field or acuity deficit, hemodynamic instability, or acute endocrinopathy should all be managed as inpatients, likely in the ICU.
- Asymptomatic, subacute, or incidental hemorrhages noted within the pituitary gland on head CT and MRI may be considered for outpatient management and serial imaging.

IV Fluids
Isotonic solutions initially, may be adjusted as needed depending upon severity of hypo- or hypernatremia. Patients may need volume replacement. Ongoing evaluation and management of fluid intake and output necessary with efforts to replace urinary outputs as needed.

Nursing
In addition to hemodynamic and volume status assessments, patients will need hourly neurologic checks with specific attention to level of consciousness, visual acuity and visual fields, and motor function.

Discharge Criteria
Once stabilized from a postoperative standpoint, neurologic function, visual evaluation and from an endocrinologic standpoint including stable on supportive medications, patients may be considered for release to home or inpatient rehabilitation depending on identified needs.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
- Endocrinological, neurosurgical, ophthalmological, and physiatric follow-up is anticipated depending on patient's clinical status.
- 80% of PA patients will require pituitary hormone replacement.

Patient Monitoring
- Endocrinology to follow pituitary status with addition of replacement hormones or hypersecretory tumor suppressive therapy as indicated.
- Ophthalmologic follow-up evaluations of eye motilities, visual acuity, and visual fields for postoperative improvements or deteriorations.
- Neurosurgical evaluations for postoperative care and for follow-up of tumor evaluation.
- Routine MRI imaging to assess tumor for recurrence, progression over time.

PATIENT EDUCATION
- 2% risk of PA with known pituitary adenoma.
- Patients should be counseled regarding the symptoms, and the potential urgent actions required.

PROGNOSIS
- Untreated cases historically had 50% mortality.
- Visual loss improves in 70% of patients, less likely with complete mono- or binocular blindness.
- Ocular motility more likely to recover with treatment (80–90%).
- Recovery of some or all pituitary function in treated patients occurs in 50% of patients.
- Low initial serum prolactin levels are associated with higher intrasellar pressures, and with lower recovery rate of pituitary function.
- Pituitary replacement therapy will be required in 80% of patients in long term.

COMPLICATIONS
Observe for usual complications associated with pituitary surgery including re-hemorrhage, meningitis, visual deterioration, CSF leak, hypopituitarism, diabetes insipidus.

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CODES

ICD9
- 237.0 Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct
- 253.2 Panhypopituitarism
- 253.8 Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin

PLEXOPATHY, BRACHIAL

J. Ned Pruitt II, MD

BASICS

DESCRIPTION

Atraumatic brachial plexopathy is characterized by acute pain and weakness around the shoulder girdle and arm with variable findings of sensory loss, reflex change, and atrophy developing over the next several weeks. The pattern of weakness depends on whether a portion or the whole plexus is involved.

EPIDEMIOLOGY

Incidence

- This is an uncommon disorder occurring at approximately 1.6 per 100,000.
- Age: Most cases occur between the ages of 20 and 55 years, although cases have been reported at all ages.
- Sex: Brachial plexopathy is more common in males with a ratio of 2:1 to 10.5:1 in various studies.
- Race: There seems to be no racial predominance in this disorder.

RISK FACTORS

Traumatic lesions of the plexus are often seen after penetrating wounds or after severe traction on the upper limb with motorcycle or snowmobile accidents.

Genetics

A familial form of recurrent brachial neuritis is inherited in an autosomal dominant manner and is associated with a mutation in the septin (SEPT9) gene. Attacks may be recurrent and are commonly bilateral.

ETIOLOGY

Many precipitating factors have been suggested as the etiologic factor for brachial plexopathy. Antecedent factors associated with development of brachial plexopathy frequently include viral infection, immunization, invasive medical procedures in the axilla or trauma at childbirth. Based on the timing of onset after viral illnesses many investigators have postulated an immune-mediated mechanism. Multifocal mononuclear cell infiltrates have been found in some patients after plexus biopsy.

COMMONLY ASSOCIATED CONDITIONS

- Autoimmune diseases: Systemic lupus erythematosus, giant cell arteritis, polyarteritis nodosa, inflammatory bowel disease
- Infectious diseases: HIV infection, CMV infection, Coxsackie-virus infection, parvovirus, Q fever, infectious mononucleosis, mycoplasma pneumonia, bacterial pneumonia, typhoid, syphilis
- Postimmunization: Tetanus toxoid, immune sera, diptheria, swine flu, recombinant DNA hepatitis B vaccination
- Neoplasia: Hodgkin's disease, neuroblastoma, postradiation
- Hereditary neuropathies: Hereditary neuropathy with liability to pressure palsies

Pregnancy Considerations

Pregnancy and childbirth can be precipitating factors, especially in cases that are familial.

DIAGNOSIS

HISTORY

Acute pain and weakness of the involved shoulder and arm are the most common symptoms.

PHYSICAL EXAM

- The onset of brachial neuritis is often dramatic with acute pain in the shoulder radiating into the neck and into the arm to the level of the elbow. The arm is often held flexed at the elbow and adducted at the shoulder. The pain may be constant for several weeks and may be intermittently painful for long periods. After several days and within a few weeks, weakness develops in the limb and the distribution varies depending on what portion or portions of the plexus are involved. Lesions that involve the entire plexus affect muscles innervated by C5 through T1 and often the arm hangs limp at the patient's side. Sensory loss involves almost the entire arm in those cases.
- Lesions involving the upper trunk produce weakness in the C5 and C6 distribution causing weakness in abduction of the shoulder and flexion of the elbow while the shoulder internally rotates. This has been called the "waiter's tip" posture. Sensory loss occurs over the lateral arm, forearm, and thumb. Involvement of the lower trunk causes weakness in muscles innervated by C8 and T1 roots. Weakness is present in both median nerve and ulnar nerve innervated intrinsic hand muscles and medial wrist flexors. Sensory loss occurs in the medial two fingers, medial hand, and medial forearm.
- Lesions at the level of the cords are most often traumatic. Posterior cord lesions cause weakness in muscles innervated by the axillary and radial nerves. This results in loss of shoulder abduction and elbow and wrist extension. Sensory loss occurs in the posterior lateral aspect of the arm, forearm, and dorsal lateral aspect of the hand. Lateral cord lesions cause weakness in muscles innervated by the musculocutaneous nerve and median nerve muscle supplied by roots C6 and C7. This results in weak pronation of the forearm and flexion of the wrist. In medial cord lesions, muscles innervated by the ulnar nerve and those muscles that receive C8 and T1 via the median nerve are weak. Isolated nerves can be affected as they branch off the plexus (e.g., phrenic nerve involvement causing diaphragmatic weakness or isolated suprascapular nerve involvement causing weakness in the supraspinatus and infraspinatus).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Electromyography (EMG) is very helpful in making the diagnosis and defining the degree of plexus injury. Denervative changes in muscles innervated by two cervical roots and involving at least two peripheral nerves points to the plexus as the site of the lesion. By definition the lesion must be distal to the roots if EMG examination of the cervical paraspinal muscles is normal. Traumatic lesions may cause both plexus lesions and cervical nerve root lesions if the root is avulsed. Spinal fluid studies are usually normal. Occasionally neoplastic lesions may also affect the plexus as well as cervical roots.

Imaging

Initial approach

Plain x-rays of the chest and neck are often very helpful. A lesion at the pulmonary apex with erosion of the first or second rib may be the cause of a lower plexus lesion. Similarly, the presence of a cervical rib or elongated C7 transverse process may explain thoracic outlet syndrome symptoms. MRI and CT imaging with contrast are helpful in finding mass lesions compressing or infiltrating the plexus.

Diagnostic Procedures/Other

Biopsy of the roots/plexus may be helpful in selected cases to rule out neoplasm and other inflammatory disorders.

Pathological Findings
Multifocal mononuclear cell infiltrates can be noted in affected nerves.

DIFFERENTIAL DIAGNOSIS
- Poliomyelitis
- Entrapment neuropathy
- Cervical root syndromes
- Vertebral artery dissection
- Rotator cuff injuries
- Subacromial bursitis

TREATMENT

MEDICATION
First Line
Narcotics are often used for pain control in the acute stages.

ADDITIONAL TREATMENT
General Measures
Management is largely supportive with efforts focusing on pain control and passive and active range of motion exercises for the limb. Corticosteroids do not alter the course of the disease but may be helpful in the acute stage when pain is not relieved with narcotics alone. Prednisone 60 mg/day for a few days with a rapid taper may be useful. IVIG has been helpful in isolated cases when given early in the course of the illness.

Additional Therapies
- Symptomatic management
- Extensive physiotherapy is often needed for many months to maintain range of motion and avoid a frozen shoulder syndrome

SURGERY/OTHER PROCEDURES
Surgery may occasionally be needed to define the lesion's full extent. Intraoperative electrical monitoring of evoked responses may help determine motor root damage. Occasional nerve grafting along with tendon transfers may allow return of function for some patients.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Admission is rarely necessary in this patient population.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Referral to physical medicine and rehabilitation will be necessary in cases with moderate to severe weakness.

Patient Monitoring
Regular visits to insure full range of motion in the joints is recommended.

PROGNOSIS
About one-third of nontraumatic plexus injuries return to normal function in 1 year. Seventy-five percent have full recovery at 2 years and almost all by 4 years. Upper brachial plexus lesions recover more quickly. Weakness in the diaphragm and serratus anterior are often associated with persistent weakness.

COMPLICATIONS
The main complication is a variable degree of permanent weakness of the shoulder and limb.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Acute brachial neuropathy
- Parsonage–Turner syndrome
- Brachial neuritis
- Neuralgic amyotrophy
- Brachial plexus neuropathy

CODES

ICD9
353.0 Brachial plexus lesions

CLINICAL PEARLS
- Brachial plexopathy usually presents with acute pain and progressive, variable weakness of the affected upper extremity.
- EMG and nerve conduction studies are critical for an assessment of the involved portions of the plexus and involvement of distal nerves.

PLEXOPATHY, LUMBOSACRAL

David S. Younger, MD

BASICS

DESCRIPTION

The anatomy of the lumbosacral plexus has been recognized for over a century. Disorders of the lumbosacral plexus are characterized by pain, weakness, loss of stretch reflexes, and variable atrophy of affected muscles along individual nerves or parts of the plexus as demonstrated clinically or by electrodiagnostic studies. The main nerves that arise from the lumbosacral plexus include the iliohypogastric, ilioingunial, genitofemoral, and lateral femoral cutaneous sensory nerves; and the mixed motor and sensory pudendal, femoral, obturator, and sciatic nerves. Inclusively, rami of the lumbar plexus extend from T12 to L5 and those of the sacral plexus extend from L4 to S4. The plexus is supported by 5 lumbar arteries which originate from the abdominal aorta; the deep circumflex artery, which is a branch of the external iliac artery; and the iliolumbar and gluteal branches of the internal iliac artery. Although there is a rich anastomotic blood supply, the middle and distal intrapelvic portions are nonetheless less prone to ischemia.

EPIDEMIOLOGY

- Incidence/Prevalence
  - Lumbosacral plexopathies are less common than brachial plexopathies, in part because the lumbar plexus is less likely to be involved in trauma.
- Race
  - No demonstrated ethnic predominance.
- Age
  - Many etiologies for lumbosacral plexopathy occur in older individuals.
- Sex
  - Lumbosacral plexopathies due to cancer infiltration are more common in women. Radiation-induced lumbosacral plexopathy occurs in women, but is also seen in young men after treatment for testicular cancer.

RISK FACTORS

The risk factors comprise pelvic tumors, radiation treatment, diabetes, complicated childbirth, heparin therapy, and trauma.

Pregnancy Considerations

Delivery can result in a lumbar plexopathy. The incidence of obstetrics-related nerve injuries is estimated to be 1/2,600 and 1/6,400 of all deliveries.

ETIOLOGY

- Idiopathic lumbosacral plexopathy or painful lumbosacral plexus neuritis was described in 1981 as the acute onset of pain in one or both legs followed by weakness, loss of stretch reflexes, and variable atrophy of affected muscles. An autoimmune basis is the presumed etiopathogenesis of this disorder which slowly improves over time.
- Preceding infection, usually an upper respiratory infection, exposure to *Borrelia burgdorferi* the agent of Lyme disease, Epstein–Barr viral infection, and preceding immunization can predate the onset of lumbosacral plexopathy leading to a presumed relation to its onset.
- One particular type of proximal diabetic neuropathy is lumbosacral radiculoplexus neuropathy (DLSRPN) with a characteristic syndrome of pelvi-femoral pain followed by weakness, beginning focally in the upper leg or thigh with spread to the contralateral limb, and variable weight loss, due to multifocal involvement of lumbosacral roots, plexus, and peripheral nerves. Such cases have been reported under a variety of eponymic terms including diabetic myelopathy, diabetic amyotrophy, femoral-sciatic neuropathy in diabetes mellitus, femoral neuropathy, ischemic mononeuropathy multiplex associated with diabetes mellitus, diabetic neuropathic cachexia, subacute proximal diabetic neuropathy, Bruns–Garland syndrome, diabetic polyradiculopathy, painful lumbosacral plexopathy with elevated erythrocyte sedimentation rate, subacute diabetic proximal neuropathy, progressive polyradiculoneuropathy in diabetes.
- Relapsing lumbosacral plexopathy can present as painless recurrent episodes of acute demyelinating nerve palsy often in the second decade of life associated with a deletion or abnormal structure of the PMP22 gene on chromosome 17p11.2-12 of hereditary neuropathy with pressure palsy (HNPP).
- Direct injury to the lumbosacral plexus located deep in the pelvis along the posterior abdominal wall close to the bony and soft tissue and other organs, can lead to focal compression of the constituent nerves as they exit the bony pelvis.
- Intragluteal injection is rarely if ever due to direct needle injury rather, results from the inadvertent injection of angiotoxic medications into the inferior gluteal, ipsilateral iliac, or aortic bifurcation vessels, leading to thrombosis and arteritis of the internal and external iliac artery and to ischemic neuropathy.
- Abdominal aortic aneurysms can lead to lumbosacral plexopathy particularly as they expand. Compression of the iliohypogastric and ilioinguinal nerves leads to referred pain in the lower abdomen and inguinal area.
- Pelvic surgery, notably kidney transplantation and abdominal hysterectomy, may be associated with lumbosacral plexopathy. The former has been attributed to aneurysm of the internal iliac artery. Those undergoing abdominal hysterectomy are more prone to traction injury of the intrapelvic portions of the iliohypogastric, ilioinguinal, and genitofemoral nerves during surgery.
- Systemic and local cancer presents certain challenges to the etiopathogenesis, diagnosis, and management of lumbosacral plexopathy because of the frequent association with external radiation, implants, adverse reactions to intra-arterial chemotherapy, metastasis, and contiguous spread.
- Apart from accidental and postoperative bleeding, and aneurysmal leaks and rupture, lumbosacral plexopathy may also follow retroperitoneal bleeding in association with hemophilia, anticoagulation, or acquired coagulopathy.
- Trauma probably accounts for only 5% of all lumbosacral plexopathies and are often associated with a pelvic fracture.

COMMONLY ASSOCIATED CONDITIONS

Cancer, whether local in the pelvis (colorectal, uterine, cervical, ovarian, prostate, and testicular cancers) or from distant sites (breast and thyroid carcinoma, sarcoma, and lymphoma), and diabetes are the major associated diseases.

DIAGNOSIS

- In general, lumbosacral plexopathy presents with weakness, sensory loss, paresthesias, pain, loss of reflexes, and atrophy in the affected lower extremity. Many of the etiologies mentioned above may result in bilateral lumbosacral plexopathies resulting in signs and symptoms in both legs. Preferential involvement of the sacral plexus results in more prominent weakness below the knee, and involvement of the gluteus medius and maximus, with a diminished Achilles reflex. Preferential involvement of the lumbar plexus results primarily in weakness of proximal muscles, such as the quadriceps and thigh adductors and patellar reflex loss.
- Patients with cancer infiltration present with back and leg pain in at least 75% of cases. Leg edema and a rectal mass are found in some patients. Bowel and bladder involvement can be seen uncommonly.
- As opposed to neoplastic infiltration, radiation plexopathy presents with paresthesias and indolent leg weakness. Pain may eventually occur, but is less common and not as severe as in cancer infiltration.

- Patients with retroperitoneal hemorrhage due to heparin therapy present with acute-onset low back and leg pain, leg weakness, and paresthesias. The lumbar plexus is involved to a greater degree in retroperitoneal hemorrhage.
- In diabetic amyotrophy, intense pain begins in the anterior thigh, and inguinal region. Over the following weeks, the patient has progressive weakness, primarily in the distribution of the lumbar plexus, although the more distal sacral plexus innervated muscles may also be involved. The opposite leg may be involved to a milder degree. Some patients have a significant degree of weight loss.
- Neuralgic amyotrophy of the lumbosacral plexus presents similarly to diabetic amyotrophy with severe pain and preferential involvement of the lumbar plexus.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

The laboratory evaluation of a patient with suspected lumbosacral plexopathy should be directed first toward confirming the diagnosis and then toward uncovering the most likely etiopathogenesis. Routine blood studies should be obtained for the commonest endocrinologic, autoimmune, and inflammatory indices including ESR, serologically specific connective tissue autoantibodies; Lyme, viral, parasitic, bacterial, mycobacterial studies, and other postulated sources of infection; HgA1c, fasting glucose, and molecular genetic studies as may deemed appropriate.

Imaging

Contrast abdomen and pelvis CT and MRI should be performed in all patients even those with seemingly innocuous trauma and suspected cases of retropelvic tumor, hematoma, aneurysm, or abscess. MRI of the lumbar plexus and MRI of the lumbar spine should be performed to discern infiltrative disease of the plexus and incidental or contributory spine disease.

Diagnostic Procedures/Other

Electrodiagnostic studies should be performed in all patients, including motor and sensory nerve conduction studies and concentric needle EMG to localize the disorder to the lumbosacral plexus or its constituent nerves in symptomatic cases regardless of the duration of the illness. Typical findings include asymmetrically reduced sensory nerve action potential amplitudes and conduction velocity that reflect the number of functioning axons, variably prolonged F responses, and patchy active and chronic denervation potentials sparing paraspinal muscles with neurogenic recruitment pattern of high amplitude motor unit potentials on maximal effort reflective of the degree of muscle weakness.

DIFFERENTIAL DIAGNOSIS

Lumbosacral radiculopathy, cauda equina syndrome, and sciatic neuropathy can be effectively excluded by detailed neuroimaging and electrodiagnostic studies.

TREATMENT

MEDICATION

Although an immune-mediated pathogenesis has been suggested for diabetic and non-diabetic LSRPN, the benefit of immunotherapy has been controversial. The only placebo-controlled clinical trial noted equally significant objective improvement in primary outcome measures of 49 patients with DLSRPN randomized to 1 g three times weekly of intravenous methylprednisolone for 12 weeks, compared to 26 patients with DLSRPN who received placebo when analyzed at 52 and 104 weeks. However, the methyl-prednisolone-treated patients reported a greater degree of symptom improvement as judged by changes in a neuropathy symptom change subscore for pain. A randomized double-blind placebo-controlled trial of IVIg on recovery time is still ongoing but no longer recruiting study participants, and has yet to publish its findings.

Notwithstanding, conventional pain management includes nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and narcotic medications.

ADDITIONAL TREATMENT

General Measures

If a tumor is identified, radiation treatment may be indicated depending on the tumor type. If the patient is on heparin, this should be discontinued immediately.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Pain management is an important concern in most causes of lumbosacral plexopathy. Physical therapy may be beneficial.
- Adjunctive treatment
  - If a neoplasm is identified, chemotherapy, radiation therapy, and other treatments are indicated. Patients with retroperitoneal hemorrhage may require blood transfusion and correction of the bleeding disorder.

SURGERY/OTHER PROCEDURES

A pelvic tumor may in some cases benefit from surgical resection. Surgical evacuation for retroperitoneal hemorrhage is controversial and most patients are treated conservatively.

ONGOING CARE

PATIENT EDUCATION

Due to the wide variety of disorders that can cause lumbosacral plexopathy, the patient can be referred to support groups for the underlying disease (e.g., cancer and diabetes).

PROGNOSIS

Prognosis varies widely depending on the etiology.

ADDITIONAL READING

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CODES

ICD9

- 353.1 Lumbosacral plexus lesions
- 953.2 Injury to lumbar nerve root

POLIOMYELITIS

Ersin Tan, MD

BASICS

DESCRIPTION

Polio is a generalized viral infection of humans that can involve the anterior horn cells of spinal cord and motor nuclei of cranial nerves with resultant paralysis.

EPIDEMIOLOGY

- Incidence/Prevalence
  - Today the disease has already been eradicated from large parts of the world except Asia and West and Central Africa. In the US and other countries where the wild virus has been eradicated, paralytic polio is still seen due to live attenuated virus vaccine. In Western Pacific region, in 2010, there were total 317 acute flaccid paralysis cases without specimens that were classified as confirmed polio based on temporal and geographical association with the outbreak of wild poliovirus type 1. Recently, an outbreak was also reported in Congo with a total of 560 acute flaccid paralysis cases between September 2010 and February 2011.
- Age
  - Any age can be affected; however, in 50% of cases children under the age of 3 are affected.
- Sex
  - No sex difference is present.
- Season
  - The disease is most frequent in summer and fall (July through September). However, the important parameter is believed to be the humidity rather than the temperature.

RISK FACTORS

- Several factors increase the likelihood of paralytic form of the disease:
  - Tonsillectomy
  - Intramuscular injections
  - Immune deficiency
  - Hypogammaglobulinemia
  - Pregnancy
  - Exercise
  - Adult age (>18 years)

Pregnancy Considerations

Pregnancy is associated with increased risk of paralytic disease.

ETIOLOGY

Poliovirus is a single-stranded RNA enterovirus belonging to the Picornaviridae family. It has three serologically distinct types (polio 1, 2, and 3). Polio spreads through food or drink contaminated by feces. Also flies can passively transfer the virus from feces to food.

COMMONLY ASSOCIATED CONDITIONS

- Vaccine-associated paralytic polio
- Postpolio syndrome
  - In a group of patients, 2–3 decades after the paralysis, deterioration in muscle function with slowly progressive weakness and atrophy of previously affected or unaffected muscles may develop. This condition is called "postpolio syndrome." Fatigue and pain accompany the picture. The precise cause of postpolio syndrome or the rate of progression in comparison with normal ageing is not known.

DIAGNOSIS

- The incubation period varies between 5 and 35 days, and oral and fecal shedding of the virus starts within 24 hours of the exposure.
- About 90% polio infections are asymptomatic.
- Minor illness (abortive polio): 5–10% of infected people develop nonspecific influenza-like syndrome characterized by fever, malaise, anorexia, headache, sore throat, and myalgia. Symptoms last for 2–3 days.
- Nonparalytic poliomyelitis (aseptic meningitis): In about 1% of patients 7–10 days after the minor illness, aseptic meningitis characterized by fever, headache, neck stiffness, and back pain develops. Symptoms resolve completely in most patients.
- Paralytic poliomyelitis: 1% of people infected develop the paralytic form of the disease. Paralysis develops 2–5 days after abortive polio when patient starts to recover. Symptoms start with fever, headache, and muscle pain. Asymmetrical weakness develops over several hours to days, affects legs more than arms. Neurologic examination reveals neck stiffness, decreased or absent deep tendon reflexes, and flaccid paralysis. A single muscle or groups of muscles of one or more extremities can be involved. While monoparesis is common in children, quadriparesis is more frequent in adults. Sensory examination is normal. Dysautonomia (cardiac arrhythmias, blood pressure instability, bladder and bowel dysfunction) can be seen. Involvement of the cervical or thoracic cord may lead to intercostal and diaphragmatic weakness. Bulbar involvement is seen in 10–15% of cases. Symptoms include dysphagia, dysphonia, facial paralysis, diplopia, stridor, and respiratory weakness. Death may result from respiratory insufficiency and autonomic disturbances. Long-term sequelae include weakness, atrophy of limbs, and growth failure especially in young children.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Routine blood tests are normal except for lymphocytic pleocytosis.
- CSF examination: Typically pleocytosis with increased protein is seen. Cell count does not usually exceed 500 cells/mm^3, initially polymorphonuclear leukocytes shifting to lymphocytic predominance after 72 hours. Protein content increases up to 200 mg/dL in the first few weeks. Virus isolation from CSF is rare.
- Virus can be isolated from feces and throat swabs 2 weeks before paralysis and several weeks after the onset of symptoms.
- A fourfold or greater increase in neutralizing antibody titers between acute phase and convalescent (3–6 weeks later) serology is diagnostic.

Imaging

Hyperintense signal of the ventral horns of the spinal cord has been demonstrated on spinal MRI in patients with poliomyelitis. These findings are nonspecific but may be helpful to differentiate acute lower motor neuron syndromes from Guillain–Barré syndrome.

Diagnostic Procedures/Other

- Electrodiagnostic studies
  - Nerve conduction velocities are usually normal; compound muscle action potentials may have low amplitudes. Needle EMG shows a reduced number of voluntary motor unit potentials; and fibrillation potentials appear at about 3 weeks. As improvement occurs, giant motor units indicating reinnervation appear.

DIFFERENTIAL DIAGNOSIS

- Acute causes of peripheral neuropathy
- Guillain–Barré syndrome
- Acute intermittent porphyria
- Lyme disease
- Diphtheria
- Transverse myelitis
- Heavy metal poisoning
- Acute spinal cord compressive lesions
- Other viral infections (Coxsackie virus, echovirus, enterovirus 71)

TREATMENT

MEDICATION

There is no specific antiviral agent proven effective against polio infection. Vaccination is the most effective measure for prevention.

- *Prophylaxis*—there are two kinds of polio vaccine, both providing immunity against three types of poliovirus.
- Inactivated polio vaccine (IPV) (Salk)
  - Administered subcutaneously.
  - The simplest way is to revaccinate persons aged <18 years with IPV according to the schedule.
  - Provides only serum humoral immunity; therefore, cannot prevent the multiplication of virus in gastrointestinal system and shedding in stool.
  - Safe for immunizing people with immune system problems.
  - Advisory Committee on Immunization Practices recommends IPV to be administered at ages 2, 4, and 15 months and 4–6 years. Minimum age is 6 weeks. If 4 or more doses are administered prior to age 4 years an additional dose should be administered at age 4–6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months following the previous dose.
  - Does not cause vaccine-associated polio.
  - Contraindications: In children allergic to neomycin, streptomycin, or polymyxin B.
- Oral polio vaccine (OPV) (Sabin)
  - Live attenuated vaccine.
  - Easy to administer.
  - In addition to serum humoral immunity, provides secretory immunity in mucous membranes; therefore, limits the multiplication of virus in gastrointestinal system and prevents person-to-person transmission. Therefore, preferred in areas where the wild virus is still present.
  - Carries vaccine-associated polio paralysis risk 1 in 2.4 million doses, more common with the first dose.
  - Contraindications: Contraindicated in children with immunodeficiency, hypogammaglobulinemia, leukemia, lymphoma, malignancy, and lowered resistance due to corticosteroid treatment, chemotherapy, or radiation and close contacts of such patients.
- Precautions
  - Four doses of polio vaccine are enough to protect from polio. Committee on Infectious Diseases of the American Academy of Pediatrics recommends OPV for routine immunization. OPV is administered at ages 2, 4, and 15 months and 4–6 years. An additional dose can be administered at 6 months of age in areas with high risk of disease.
  - Immunization programs in countries where polio has been eradicated may employ combined immunization schedules with both OPV and IPV. The Centers for Disease Control and Prevention recommends first and second doses as IVP in the US. This decreases the risk of vaccine-associated poliomyelitis by 50–75% and provides the advantages of both vaccines.
  - For people traveling to areas where polio is common: If vaccinated previously, they should receive an additional dose of the vaccine they previously had. If they have not been previously vaccinated, they should be immunized with IPV.
  - People younger than 18 years of age who have not been vaccinated in infancy can get two doses of OPV separated by 2 months and a third dose 6–12 months later.
  - People >18 years of age should not be given OPV as the risk of paralysis with OPV is higher in adults.

ADDITIONAL TREATMENT

General Measures

Intensive care with respiratory support may be lifesaving. When forced vital capacity decreases <12 mL/kg (<1–1.5 L for adults) or significant subjective dyspnea appears, intubation and mechanical ventilation should be considered. Cardiac function should be monitored. Bulbar functions should be followed and aspiration precautions observed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Bed rest, analgesics, and hot wet packs relieve the muscle pain during acute illness.
- Adjunctive treatment
  - In the acute phase, respiratory exercises, hot packs to relieve pain, and passive exercises to prevent contractures should be performed. Active exercises and occupational therapy can be started at the subacute phase.

SURGERY/OTHER PROCEDURES

There are no surgical procedures for the acute illness. For chronic phase correction of scoliosis, tendon lengthening and transfers are examples of rehabilitative surgeries. As improvement may continue up to 2 years, surgical procedures should be postponed until this time.

IN-PATIENT CONSIDERATIONS

Admission Criteria

For acute paralytic disease, hospitalization and bed rest are mandatory.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients in the convalescent phase of poliomyelitis may require physical therapy, bracing, and other orthoses.

PATIENT EDUCATION

Polio is a rare disease now and is already eradicated from a large part of the world. However, there is a risk of spread of polio by travelers in areas where polio still exists. Improvement of hygiene and sanitation, and immunization are important to prevent and eradicate polio infections. Immunization programs should be continued until the disease is eradicated all over the world even in areas free of polio.

- Centers for Disease Control and Prevention: http://www.cdc.gov/nip
- World Health Organization: http://www.who.int/gpv-polio

PROGNOSIS

- Recovery from polio infection is complete except paralytic disease.
- CNS involvement determines the outcome of paralytic poliomyelitis. Ten percent of paralytic cases die due to respiratory and bulbar involvement. In bulbar poliomyelitis cases mortality goes up to 60%. Fifty percent of cases recover completely. The rest are left with neurologic sequelae.
- Paralysis is evident by 2–3 days of onset of symptoms. Improvement begins in weeks and plateaus by 6 months.
- Postpolio syndrome is an extremely slowly progressive condition and the patients should be reassured about this. Treatment may include intravenous immunoglobulin, lamotrigine, muscle strengthening exercises, and physical therapy but the effectiveness of these interventions is not clear.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Heine–Medin disease

CODES

ICD9

- 045.10 Acute poliomyelitis with other paralysis, unspecified type of poliovirus
- 045.20 Acute nonparalytic poliomyelitis, unspecified type poliovirus
- 045.90 Unspecified acute poliomyelitis, unspecified type poliovirus

POLYMYOSITIS

Boyd M. Koffman, MD, PhD

BASICS

DESCRIPTION

Polymyositis (PM) is an idiopathic inflammatory myopathy. The syndrome is characterized by primary inflammation of skeletal muscle with myofiber necrosis; other organs may be involved. The history, pattern of weakness, and muscle pathology distinguish polymyositis from the other idiopathic inflammatory myopathies (inclusion body myositis and dermatomyositis [DM]).

EPIDEMIOLOGY

Incidence

- Most studies group PM and DM together. The annual incidence ranges from 0.1 to 0.93 per 100,000 population.
- Sex
  - – Females have PM more frequently in all age groups.

Prevalence

- Rochester, MN: 0.6/100,000 (among all ages); 0.925/100,000 (≥18 years old)
- Race
  - – 0.32/100,000 (white Americans)
  - – 0.77/100,000 (black Americans)

RISK FACTORS

None identified.

Pregnancy Considerations

PM is a rare event in pregnancy. Perinatal mortality approaches 60% in the few cases (<2 dozen) reported.

Genetics

- PM is associated with human leukocyte antigen (HLA) DR3 in 48% of white patients and also with HLA-B7 and HLA-DRw6 in black patients.
- Genetic associations are also noted based on autoantibody production: Anti-PM-Scl antibodies are associated with DR3 and DQw2; antisynthetase antibodies are associated with B8, DR3, DRw52, DQA1*0501; anti-Mi-2 antibodies are associated with DR7, DRw53, and DQA1*0201; signal recognition particle (SRP) antibodies are associated with DR5, DRw52, DAQ1*0301.

PATHOPHYSIOLOGY

The cause is unclear. PM involves cell-mediated myofiber damage, often including invasion of nonnecrotic fibers by CD8+ lymphocytes, activated through the major histocompatability-I (MHC-I) complex, and suggesting recognition of an (unspecified and unknown) muscle fiber antigen.

ETIOLOGY

The cause of PM is unknown. A viral etiology has been speculated but not demonstrated. Speculation has included viral infection triggering an altered immune response directed against self-antigens, possibly from cross-reactivity with specific muscle antigens. PM may occur alone or in association with a number of connective tissue diseases, autoimmune, or infectious conditions (see commonly associated conditions). PM is sporadic, without family history of weakness.

COMMONLY ASSOCIATED CONDITIONS

- Polyarthritis (25–50%).
- Cardiac: Secondary congestive heart failure, cardiac conduction defects (up to one third of PM); anti-SRP associated with myocarditis.
- Pulmonary: Interstitial lung disease in 10% of PM (often with anti-Jo-1 antibodies).
- Overlap syndromes: PM may be associated with connective tissue diseases, and overlap syndromes are diagnosed when criteria for two diseases are present. PM may occur with scleroderma myositis, Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, antisynthetase syndrome, and mixed connective tissue disease.
- Malignancy: Many authors report an increased association (0–28%) between PM and malignancy, though the evidence is less strong than that between DM and malignancy.

DIAGNOSIS

HISTORY

- Polymyositis primarily affects adults.
- Insidious onset of weakness of proximal greater than distal muscles
- Dysphagia may affect up to one third
- Muscle pain/tenderness may occur
- Arthritis in 25–65% of PM patients

PHYSICAL EXAM

- Proximal and distal muscles may both be affected, proximal muscles are weaker than distal muscles
- Usually symmetric, occasionally asymmetric or focal on presentation
- Neck flexor weakness
- Cardiac abnormalities: Bundle branch block, atrioventricular conduction defects, atrial dysrhythmias
- Dyspnea, suggesting diaphragm involvement, interstitial lung disease, or aspiration

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Initial lab tests comprise elevated CPK and aldolase.

Follow-up & special considerations

CPK should decrease with treatment.

Imaging

Initial approach

Short TI inversion recovery MRI may serve to visualize muscle and subcutaneous edema and inflammation. While this is rarely helpful in making the diagnosis, it may serve to guide muscle biopsy.

Diagnostic Procedures/Other

EMG/NCS—sensory action potentials, late responses (F-waves and H-reflexes), conduction velocities, and repetitive nerve stimulation, are normal. The compound muscle action potential (CMAP) is normal in latency and amplitude early in disease; the CMAP amplitude may decrease with disease progression, reflecting loss of myofibers. Needle EMG studies demonstrate increased insertional activity (>500 msec), increased spontaneous activity (fibrillations, occasional complex repetitive discharges, and, rarely, myotonic discharges), and reduced amplitude and duration of voluntary motor unit action potentials (MUAPs). Voluntary MUAPs are often polyphasic with increased recruitment patterns. Chronic PM may demonstrate long duration motor unit action potentials.

Pathological Findings

Muscle biopsy is the preferred diagnostic test for PM, and demonstrates CD8+ lymphocytes surrounding nonnecrotic myocytes, and there is deposition of MHC-I on nonnecrotic cells.

DIFFERENTIAL DIAGNOSIS

- The primary differential diagnosis is inclusion body myositis.
- Also consider: DM without rash, myositis with underling connective tissue disease (overlap syndrome), necrotizing myopathy (associated with cancer or connective tissue disease), myositis-associated antibodies (Jo-1, SRP), inflammatory myopathy associated with infection (HIV, HTLV I), muscular dystrophies (facioscapulohumeral, dysferlinopathies), metabolic myopathy, drug-induced myopathies (statins, colchicine), polymyalgia rheumatica.

TREATMENT

MEDICATION

First Line

- Prednisone (at least 1 mg/kg/day, typically 60–80 mg) administered once daily for 3–4 weeks, followed by a slow taper over 10 weeks to 1 mg/kg on alternate days. In severe cases, intravenous methylprednisolone 1 g daily or on alternate days for 5–6 doses can be used initially. If prednisone demonstrates efficacy, reduce the dose by 5 or 10 mg every 3–4 weeks until the least necessary dose is determined. If prednisone is ineffective, another immunosuppressive medication may be initiated and prednisone more rapidly tapered.
- Contraindications
  - – Hypersensitivity to any of the corticosteroids.
  - – Peptic ulcer (except life-threatening situations).
  - – An apparent association of corticosteroids and left ventricular free-wall rupture after recent myocardial infarction (MI) has been suggested, and corticosteroids should be used with extreme caution in patients with recent MI.

- Precautions
  - Corticosteroids may reduce resistance to bacterial, viral, or fungal infections and mask signs of infection. Corticosteroids can reactivate tuberculosis, and chemoprophylaxis is used in patients with a history of active tuberculosis undergoing prolonged steroid treatment.
  - Anaphylactoid reactions are seen in some patients given parenteral glucocorticoids, and may represent hypersensitivity to paraben preservatives.
  - Corticosteroids should be used with caution in persons with diverticulitis, nonspecific ulcerative colitis, cirrhosis, hypothyroidism (who may demonstrate an exaggerated response to the drugs), hypertension, psychosis, and congestive heart failure.

Second Line

- Considered if prednisone is ineffective or if relief for steroid complications is sought.
- Azathioprine 2–3 mg/kg daily orally for approximately 4–6 months.
- If azathioprine ineffective, consider methotrexate 15–25 mg/week orally.
- Alternative treatment options
  - Cyclophosphamide 0.5–1.0 mg/m^2 IV monthly; cyclosporine 150 mg orally, twice a day.
  - IVIG (intravenous immunoglobulin)
  - Anecdotal early reports (investigational): Tacrolimus, daclizumab, etaneracept, infliximab, rituximab.

ADDITIONAL TREATMENT

General Measures

Once PM is suspected, the main focus should be exclusion of alternative causes of myopathic weakness and treatment of the disease; respiratory function should be monitored with vital capacity and negative inspiratory force if presentation includes respiratory distress.

Issues for Referral

- Speech pathology evaluation and swallow study should be considered for dysphagia.
- Physical therapy and occupational therapy should be considered to preserve range of motion.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Several small controlled trials with PM (1–19 subjects over 2–12 weeks) examined the effects of isometric, low intensity or progressive resistance training, or submaximal resistance strength training and demonstrated at least maintenance of strength, and usually an increase in strength.
- Creatinine improves functional performance when combined with home exercise therapy.

SURGERY/OTHER PROCEDURES

Cricopharyngeal myotomy may rarely be considered for dysphagia refractory to medical treatment.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Evaluation and treatment of weakness affecting speech, respiration, or ambulation.

Admission Criteria

Admission criteria comprise severe weakness, dysphagia, and dyspnea.

IV Fluids

Hydration necessary if rhabdomyolysis detected in order to prevent renal failure.

Nursing

Nursing comprises potential fall risk.

Discharge Criteria

- Improved muscle strength
- Improvement in muscle-associated enzymes (e.g., CPK, LDH, AST, ALT, aldolase)

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Transfer or admission to a rehabilitation facility should be considered when there is significant weakness.

Patient Monitoring

- Recommendations about following creatine kinase vary, depending on the author. Clinical examination is the best measure of progress and treatment efficacy.
- Patients on steroids should have weight, blood pressure, serum glucose, potassium, and eyes (for cataract formation) monitored.
- For patients on azathioprine or methotrexate, blood count and liver function tests should be monitored every 1–2 months.
- Consider supplementing patients on methotrexate (a folic acid analog inhibiting dihydrofolate reductase) with folic acid 5 mg once weekly after the methotrexate dose.

DIET

No added salt diet while on corticosteroids.

PATIENT EDUCATION

- Advise patients on long-term corticosteroids of potential complications (electrolyte disturbances, osteoporosis, peptic ulcer, weight gain, bruising, insomnia, hyperglycemia, and cataracts). Additional sources of information and research:
  - The Myositis Association (TMA), 1737 King Street, Suite 600, Alexandria, VA 22314. Telephone: 703-299-4850 (DC Area); 800-821-7356 (Toll-free); Fax: 703-535-6752; email: TMA@myositis.org. Website: http://www.myositis.org/template/page.cfm?id=24
  - Muscular Dystrophy Association. 3300 E. Sunrise Drive, Tucson, AZ 85718. Telephone: 1-800-572-1717. email: mda@mdausa.org. Website: http://www.mda.org/
- Patients should be instructed to notify any surgeon, anesthesiologist, or dentist if a surgical procedure is required and they have been on glucocorticoids within 12 months.

PROGNOSIS

The prognosis in PM without malignancy is relatively favorable, but may require lifelong treatment. Five-year survival rates range from 70% to 93%. Poor prognostic features include older age, malignancy, interstitial lung disease, cardiac disease, respiratory muscle weakness, dysphagia, acute onset, fever, presence of Jo-1 or SRP antibodies, and a delay in, or inadequate, treatment.

COMPLICATIONS

- Chronic corticosteroid use:
  - Steroid myopathy a risk during chronic corticosteroids administration
  - Cataracts
  - Hyperglycemia
  - Hypokalemia
  - Weight gain/fat redistribution
  - Adrenocortical insufficiency

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Dermatomyositis
- Inclusion body myositis

CODES

ICD9

710.4 Polymyositis

CLINICAL PEARLS

If a patient with presumed PM fails treatment, reassess for inclusion body myositis, including repeat biopsy, if necessary.

PORPHYRIA

J. Ned Pruitt II, MD

BASICS

DESCRIPTION

Porphyria is an autosomal dominant condition with highly variable expression. It results from a relative deficiency of enzymes in the heme biosynthesis pathway. Acute intermittent porphyria is the most common porphyria associated with neurologic manifestations due to deficiencies in porphobilinogen deaminase (also known as uroporphyrinogen-1). Acute intermittent porphyria is classified as a hepatic porphyria due to the overproduction and accumulation of porphyrin precursors in the liver.

EPIDEMIOLOGY

Incidence

Porphyria has an incidence of approximately 1 in 50,000. It is much more common in Sweden with an incidence of approximately 1 in 1,000.

Prevalence

Age/Sex: Manifestations usually occur in adult women. Attacks of acute intermittent porphyria are rare before puberty.

RISK FACTORS

Many drugs and hormones may precipitate attacks. Drugs that are contraindicated are typically inducers of the P450 system and include barbiturates, carbamazepine, ergots, synthetic estrogens and progesterones, carisoprodol, grisefulvin, valproate, rifampin, and sulfonamide antibiotics. Attacks in women are often in the luteal phase of their menstrual cycle. Marked reductions in caloric intake (especially reduced carbohydrate intake) are frequently the cause of acute attacks.

Genetics

Many deletions and point mutation in the porphobiliogen-deaminase gene on chromosome 11 have been described.

PATHOPHYSIOLOGY

See below.

ETIOLOGY

The deficiency of porphobiliogen deaminase results in higher levels of aminolevulinic acid and porphobiliogen in both the blood and urine during attacks. How accumulation of these porphyrin precursors contributes to the clinical neurologic symptoms is not well understood.

Pregnancy Considerations

As many as 75% of patients experience an exacerbation of porphyria during pregnancy with some series showing up to 20% mortality. Sometimes these exacerbations are related to medications given during pregnancy (metoclopramide) or poor nutrition. During an attack there is a high risk for spontaneous abortions. There are no known effects on the fetus, although there is passive transfer of porphyrins through the placenta.

DIAGNOSIS

HISTORY

Attacks of acute intermittent porphyria manifest themselves as acute attacks of abdominal pain. This pain is often poorly localized and may be associated with abdominal cramping, nausea with vomiting, and abdominal distention. Neuropsychiatric manifestations also can occur ranging from restlessness and agitation to delirium with psychosis. Rarely seizures may occur. Long-term complications may include chronic arterial hypertension, chronic renal failure, hepatic damage, and hepatocellular carcinoma.

PHYSICAL EXAM

About 2–3 days after the onset of abdominal pain the patients often develop a predominantly motor axonal neuropathy. Weakness develops rapidly and is primarily proximal although the extensors of the fingers and wrists seem to be usually affected. Cranial nerve and phrenic nerve involvement may lead to bulbar symptoms and respiratory failure. Reflexes are diminished but are not usually lost in the early course of the illness, unlike acute demyelinating neuropathies such as Guillain–Barre syndrome. An autonomic neuropathy is frequently encountered and may result in unexplained arrhythmias and wide fluctuations in blood pressure.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Porphyria is easily diagnosed once the disease is suspected. During an acute attack, high levels of porphobilinogen and aminolevulinic acid are present in the blood. Definitive diagnosis depends on measurement of erythrocyte porphobilinogen deaminase activity in erythrocytes. Nerve conduction studies and electromyography confirm the axonal nature of the neuropathy and help distinguish it from an acute demyelinating neuropathy or rhabdomyolysis.

DIFFERENTIAL DIAGNOSIS

- Acute abdominal pain associated with common conditions such as appendicitis, ectopic pregnancy, or subacute bacterial peritonitis
- Paralytic ileus
- Guillian–Barre syndrome
- Arsenic poisoning
- Thallium poisoning

TREATMENT

MEDICATION

First Line

- No medications are available to prevent acute attacks. Avoidance of contraindicated drugs is recommended.
- Contraindications:
  - Barbiturates, carbamazepine, carisoprodol, ergots, danazol, estrogens and progesterones, rifampin, grisefulvin, valproate, sulfonamide antibiotics, meprobamate, phenytoin

ADDITIONAL TREATMENT

General Measures

Long-term management focuses on avoiding precipitating factors and recognizing the possibility of acute intermittent porphyria in the setting of an acute attack of abdominal pain.

Additional Therapies

- Symptomatic management:
  - Specific treatment of an acute porphyric attack involves intravenous administration of glucose or heme. Both agents inhibit the heme biosynthetic pathway by inhibiting aminolevulinic acid synthase activity. Glucose is given as a 10% solution with doses of at least 300 g/day for milder attacks. Heme in the form of hematin, heme albulmin, or heme arginate at doses of 3–4 mg/kg/day for 4 days should be used in more severe cases and especially in cases with neurologic involvement. Narcotics can be used safely to treat the abdominal pain and phenothiazines are safe for the treatment of nausea and vomiting. Seizures may be difficult to treat since many of the typical anticonvulsants are contraindicated. Benzodiazepines can be used safely.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Initial stabilization might be necessary for evaluation of persistent abdominal pain and/or extremity weakness.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

No reports available.

Patient Monitoring

The acute axonal neuropathy may also affect cranial nerves causing bulbar weakness and increasing the risk for aspiration. Respiratory weakness can also occur due to involvement of the phrenic and intercostal nerves. Seizures may also result from hyponatremia.

DIET

Not related to attacks of the disease.

PATIENT EDUCATION

Patients should be aware of potential precipitating medications and wear a medical identification bracelet. Family members of patients identified as having porphyria should also be screened for the genetic defect.

PROGNOSIS

The recoveries from the attacks of acute abdominal pain are often quite rapid. Recovery of strength is dependent on the degree of axonal injury. Recurrent attacks with prolonged and incomplete recovery from severe axonal injury are common and may lead to depression and increased risk of suicide.

COMPLICATIONS

Possible persistent weakness of the extremities.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Acute intermittent porphyria

CODES

ICD9

277.1 Disorders of porphyrin metabolism

CLINICAL PEARLS

- Often presents as persistent intermittent episodes of abdominal pain.
- Extremity weakness from peripheral neuropathy is common early on in many patients.

PRIMARY LATERAL SCLEROSIS

David S. Younger, MD

BASICS

DESCRIPTION
Primary lateral sclerosis (PLS) is a clinical term applied to a disorder that in life remains restricted to the corticospinal tracts (CSTs) and is proven only at autopsy. The definition of PLS mandates the exclusion of other likely causes of progressive spastic paraparesis such as demyelinating disease, hereditary conditions, structural disorders, malformations, and infection of the CNS.

EPIDEMIOLOGY
PLS is a rare disorder, and as a result the incidence and prevalence have not been established. There is no known predilection for race, age, or sex.

RISK FACTORS
There is a paraneoplastic association of PLS with cancer of the lung and breast and lymphoma; however, a discrete autoantibody has not been isolated.

Pregnancy Considerations
There is no association with pregnancy.

Genetics
There is no known genetic predisposition.

ETIOLOGY
PLS is a neurodegenerative disorder with predominant degeneration of the upper motor neurons. Autopsy studies demonstrate loss of large pyramidal Betz cells in layer V with secondary degeneration of the pyramidal tract. There is a mis-sense mutation associated with the juvenile PLS (JPLS) gene termed ALS2 that encodes the protein alsin that contains multiple guanine nucleotide exchange factor domains. First identified in a 34-year-old patient with typical signs of JPLS including generalized and severe spasticity of the limbs and bulbar region, dysphagia, limb atrophy, preserved cognition and sensation; mutant alsin also induces neuronal cell death and significantly enhances the apoptogenic effect of NMDA and staurosporine.

COMMONLY ASSOCIATED CONDITIONS
PSL may be a forme fruste of amyotrophic lateral sclerosis (ALS).

DIAGNOSIS

Spasticity in PLS results from the underlying upper motor neuron (UMN) lesion and the disinhibition of velocity-dependent increase in muscle tone during passive stretch. The associated positive clinical signs of this disinhibition are hyperreflexia, Babinski signs, and painful extensor and flexor spasms. The negative signs of spasticity are UMN weakness, fatigability, and incoordination.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
Electromyography and nerve conduction studies (EMG-NCS) should be performed in all patients for the possibility of ALS, because fibrillation, positive sharp waves, and widespread fasciculation should not be seen in PLS.

Imaging
MRI of the brain and cord excludes structural disorders of the CNS, and in conjunction with sensory evoked responses of the arms and legs, auditory evoked responses, and visual evoked responses, and lumbar CSF analysis excludes multiple sclerosis (MS) and chronic infection.

Diagnostic Procedures/Other
Transcranial magnetic stimulation complements EMG-NCS because it quantitates central conduction time, which should be reduced in isolated disease of the CST.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis includes primarily progressive spinal MS, hereditary spastic paraplegia, cervical spondylotic myelopathy, tumors of the foramen magnum and upper cervical spinal cord, syringomyelia, spinal arteriovenous malformations, human T-lymphotrophic virus and HIV infections, and bilateral strokes.

TREATMENT

MEDICATION
Oral antispasticity agents should be tried in all patients. Baclofen, a γ-aminobutyric acid analogue, is the drug of choice for the treatment of spasticity associated with PLS. It is given in doses of 10–40 mg PO t.i.d. to q.i.d. (and often higher doses, although the PDR recommended limit is 100 mg per day). It penetrates the blood–brain barrier poorly; thus to obtain significant therapeutic benefit, high doses need to be taken that may induce unacceptable weakness, lethargy, somnolence, and other side effects.

- Contraindications
  - Known hypersensitivity to baclofen.
- Precautions
  - Oral antispasticity agents may cause increased weakness, sedation, and nausea. These agents should be started at low doses and titrated up gradually.
- Alternative drugs
  - Alternative oral agents for spasticity include tizanidine, diazepam, clonidine, dantrolene, and cyproheptadine.
  - Botulinum toxin can be injected into affected muscles in selected individuals with focal sever spasticity, but there may be bruising, focal weakness, flu-like symptoms, and antibody development with chronic use.
  - Baclofen can be delivered intrathecally via a surgically implanted programmable pump with the advantage of easier penetration of the drug into the CNS and higher drug levels. However, the disadvantages include an operative procedure and potential malfunction of the pump system.

ADDITIONAL TREATMENT

General Measures

The goal of treatment is to prevent or reduce the undesirable consequences of spasticity that include decreased mobility, disabling pain, contractures, dependency for activities of daily living (ADL), sexual dysfunction, and sleep disturbances. Untreated, these consequences lead to low self-esteem and mood disorders. The management of spasticity should ideally be based on ongoing clinical assessment leading to an appropriate therapeutic plan.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - – Physiotherapy should be prescribed to prevent contractures, improve overall active function, and provide comfort, but it is rarely sufficient therapy alone. Occupational therapy is needed periodically to optimize ability to perform ADLs.
- Adjunctive treatment
  - – No reports available.

SURGERY/OTHER PROCEDURES

Selective dorsal rhizotomy (SDR) can be performed in selected patients who do not benefit from other measures to manage spasticity. Physiologically, this procedure reduces spasticity by removing the stimulating afferent input of muscle stretch receptors on motor neurons. However, SDR invariably leaves the patient with some undesirable sensory deficits.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission is not generally required except for management of complications such as aspiration pneumonia.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

A thorough clinical assessment is crucial in formulating a local management program that requires a multidisciplinary approach. The Ashworth Scale is an objective bedside rating system of spasticity that can be easily applied to patients with PLS, both in initial assessment and in determining treatment benefit.

PATIENT EDUCATION

National Institute of Neurologic Disorders and Stroke information page: http://www.ninds.nih.gov/health_and_medical/disorders/primary_lateral_sclerosis.htm

PROGNOSIS

The course is usually slowly progressive, leading to a bed-bound state over decades. Oropharyngeal involvement can predispose to aspiration pneumonia.

ADDITIONAL READING

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CODES

ICD9

335.24 Primary lateral sclerosis

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Mark D. Anderson, MD
Paul L. Moots, MD

BASICS

DESCRIPTION
- Progressive multifocal leukoencephalopathy (PML) is a subacute infectious disease primarily involving oligodendroglia. Classically this is attributed to the activation of JC virus.
- Those with PML are at risk if developing immune reconstitution inflammatory syndrome (IRIS).

EPIDEMIOLOGY
PML is a rare disease, mostly seen in immunocompromised individuals, although it has been described in immunocompetent individuals.

Incidence
- PML was a rare event prior to 1984, with an age-adjusted death rate of 0.2 per 1 million people per year, highest among those with an immune disorder or taking immune suppression related to cancer or organ transplantation (1).
- With the increase in HIV and immune modifying therapies, the age adjusted death rate peaked at 3.3 per 1 million people in 1994 (2.76 on average for 1992–1995) (1).
- Beginning in 1996, HAART anti-retroviral therapy became standard clinical care for HIV-infected patients and the age-adjusted death rate decreased to an average of 0.66 per 1 million people for 2002–2005 (1).

Prevalence
From 1979 to 2005, there have been 7,476 deaths attributed to PML. It is reported that PML affected up to 5% of patients with HIV or AIDS prior to anti-retroviral therapy (1).

RISK FACTORS
- Immune compromised state from:
  - HIV infection
  - Transplant recipient
  - The use of novel immunosuppressive monoclonal antibodies therapies such as natalizumab, efalizumab, and rituximab

Pregnancy Considerations
There is no evidence of an increase in incidence of PML in pregnancy, although there are case reports of pregnant women with PML and no other source of immune compromise.

Genetics
PML appears to be sporadic.

GENERAL PREVENTION
Individuals at risk can be screened for serum antibodies for JC virus for latent infection.

PATHOPHYSIOLOGY
- JC virus is neurotropic, binding to serotinergic receptors on oligodendrocytes and astrocytes, although it is also found in lymphoid tissues, kidney epithelium, and plasma (2)[C].
- Reactivation of the virus is felt to be mediated by compromise of the cellular immune response and mutations in the regulatory DNA of the virus.
- An intact humoral immune response is not associated in prevention of JC virus, as elevated JC virus antibodies do not predict outcome.

ETIOLOGY
- The cause of PML is believed to be reactivation of the JC virus, a polyomavirus named after the patient from whom it was initially isolated.
  - Most people have been or are currently infected with JC virus, as 58% of the population has antibodies.

COMMONLY ASSOCIATED CONDITIONS
- HIV, AIDS, lymphoproliferative disorders, neoplasms, TB, or sarcoid or being treated with immunosuppressive medications or monoclonal antibodies.
- Patients with PML are at risk for developing an IRIS (rare).
- JC virus is associated with JC virus granule cell neuronopathy in the cerebellar white matter, JC virus encephalopathy from grey matter involvement and JC virus meningitis, which can happen with or without PML (2)[C].

DIAGNOSIS

HISTORY
- The presenting symptoms can vary but usually involve a focal neurologic deficit that can include muscle weakness, sensory deficits, visual field deficits, cognitive dysfunction, aphasia, coordination difficulties, and ataxia.
  - Onset can be abrupt or gradual.
- Usually does not involve the optic nerves or the spinal cord and headaches, seizures, or extra-pyramidal symptoms are uncommon.

PHYSICAL EXAM
Exam findings vary depending on the presenting symptoms, usually confirming the presence of a focal neurologic deficit.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
Initial lab tests
- There is no serologic test to determine active JC virus infection, but one can test for antibodies to JC virus in the serum.
- Most blood work is to rule out other diseases of concern by checking sedimentation rate, CBC, coagulation profile, HIV, RPR, vitamin B12, basic metabolic panel, liver enzyme testing, ammonia, toxoplasmosis titer.
- Lumbar puncture for CSF analysis is essential to aid in the diagnosis of PML.
  - Cell counts, protein, and glucose are essentially normal in most cases.
  - PCR of the JC virus DNA should be sent, although the presence is not specific for PML, it can help in directing diagnosis.
  - In addition, cytology, gram stain, bacterial culture, fungal culture, viral culture, AFB, and VDRL should also be sent.

Follow-up & special considerations

The CD4 count has prognostic value (3)[B].

Imaging
Initial approach
- Lesions of PML on CT appear as patchy or hypodense areas, in any white matter distribution, but are predominately in bilateral parieto-occipital regions. MRI is the recommended imaging test.
- MRI is much more sensitive and shows areas of hyperintensity on T2-weighted and fluid attenuated inversion recovery images, and hypointensity on T1-weighted images in the areas of white matter involvement.
  - Contrast enhancement, edema, and mass effect are absent in classic PML. Contrast enhancement, edema, and mass effect are often seen in PML lesion with patients who have developed PML-associated IRIS. In patients being treated with monoclonal antibodies who develop PML, cavitating lesions can be seen and more commonly show contrast enhancement (2)[C].

Follow-up & special considerations
MR spectroscopy can further evaluate PML, and MR magnetization transfer can help distinguish PML from HIV encephalitis.

Diagnostic Procedures/Other
Brain biopsy: In cases with typical clinical and radiological presentation, JV virus detection by PCR in the CSF is sufficient if other causes of infection or tumors have been ruled out. With monoclonal antibody treatment, JC viral loads can often be negative, and brain biopsy may be necessary.

Pathological Findings
Brain biopsy can firmly establish the diagnosis of PML by immunohistochemistry. The histology of PML is characterized by lysis and inflammation of oligodendrocytes and astrocytes, which leads to the multifocal demyelination in the CNS. There is often reactive gliosis and multinucleated giant cells in affected areas (2)[C].

DIFFERENTIAL DIAGNOSIS
Differential diagnosis comprises HIV demyelination, HIV encephalopathy, multiple sclerosis, posterior reversible encephalopathy syndrome, vasculitis, primary CNS lymphoma, toxoplasmosis, glioma, central pontine myelinolysis, radiation-induced changes, stroke, acute disseminated encephalomyelitis, and CMV.

TREATMENT

MEDICATION

First Line

There are no antiviral treatments for JC virus.

Second Line

- Investigation therapies—JC virus-targeted T-cell transplantation, immunotherapy with dendritic cell vaccines, interferon, and mefloquine (4)[C], 5[C], 6[C].
- In vitro and observational data suggest cidofovir, cytarabine and cytosine arabinose would be effective against JC virus, but controlled studies and multi-cohort analyses have not shown a survival benefit or reduced disability in AIDS-associated PML (7)[B].

ADDITIONAL TREATMENT

General Measures

- Management hinges on modification of risk factors and symptom management.
  - – Evaluate for immunocompromised state
  - – Stop immune compromising medications if possible
  - – HAART therapy should be started if HIV+
- Monitor for worsening symptoms from IRIS, which occur in the setting of increased inflammation in PML lesions (3)[B].
  - – With recent HAART initiation, it is not clear whether HAART should be maintained, but most clinicians continue therapy (3)[B]
  - – In HIV– patients, corticosteroids are usually given to reduce the inflammatory response, but steroids are not for HIV+ patients or those with cancer and autoimmune disease
- Withdrawal of monoclonal antibody treatments in the setting of PML almost always results in the development of IRIS.
- In patient with monoclonal antibodies, plasmapheresis has been shown to be effective in clearing the antibody, however, there is only anecdotal evidence for clinical efficacy.
- Symptomatic treatment
  - – Seizures–start anti-epileptic medication
  - – Central or neuropathic pain—trial of TCA, SSRI, gabapentin, lyrica, or narcotics
  - – Spasticity—oral Baclofen and Zanaflex. Consider Botox injections if refractory
  - – Psychiatric symptoms—TCA and SSRI for mood changes, atypical antipsychotics for behavioral changes

Issues for Referral

Close follow-up with neurology.

Additional Therapies

- Physical, occupational, and speech therapy may be of benefit when weakness, aphasia, or swallow dysfunction occurs.
- Palliative care consultation should be considered if appropriate.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Mirtazapine has been shown to have a trend toward benefit when studied, thought to be related to the serotonin receptor blocker action of the drug.

SURGERY/OTHER PROCEDURES

There are no surgical treatments available.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

For progressive neurological deficits, infection, stroke or tumor should be evaluated. Altered mental status, fevers, or seizures should also prompt further diagnostic evaluation.

Admission Criteria

Workup of focal neurologic deficits.

IV Fluids

If NPO, patient should be on IV fluids.

Nursing

Neurochecks and vital signs every 4 hours.

Discharge Criteria

- No evidence of other causes of disease, stable or improving neurologic deficit, controlled symptoms.
- Depending on the symptoms at discharge, patient may need placement at a skilled nursing facility, inpatient rehabilitation, or in hospice care if treatment options are exhausted.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients can be followed frequently by neurology to observe progression.

DIET

As tolerated.

PATIENT EDUCATION

Patients and family should be counseled on the prognosis and the expectation of an adverse outcome.

PROGNOSIS

- PML is a fatal disease for most patients and has no direct treatment, though survival has improved since 1996. Estimates for survival
  - – At 1 year is near 52% for all HIV+ patients and 58% for HIV– patients with PML (8)[B]
  - – At 1 year in HIV+ patients with HAART therapy is near 62% (9)[B]
- Decreased JC viral load in CSF and increased JC virus specific cytotoxic T cells were correlated with improved survival. JC viral load in the serum or urine did not impact survival. Median survival is now nearly 2 years (from 6 to 9 months) (8)[B].
- Long-term survival (>5 years) is now not uncommon.
- Development of PML-IRIS does not affect overall survival (3)[B].

COMPLICATIONS

Morbidity is common among survivors, with 2/3 of patients having mild, moderate or severe disability and 1/5 of patients having symptomatic seizures (3)[B].

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CODES

ICD9

- 042 Human immunodeficiency virus (HIV) disease
- ICD-9-CM: 046.3 Progressive multifocal leukoencephalopathy

CLINICAL PEARLS

- Affects immune compromised individuals.
- Poor, but improving prognosis with limited treatment options.

PROGRESSIVE SUPRANUCLEAR PALSY

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BASICS

DESCRIPTION

- Progressive supranuclear palsy (PSP) is one of the Parkinson plus syndromes. Despite clinical similarities, however, the basic neuropathological processes are significantly different from idiopathic Parkinson's disease (IPD). Clinically, PSP is regarded as one of the akinetic-rigid syndromes. Pathologically, however, it falls more in the class of tauopathies, which include, but are not limited to, Alzheimer's disease, frontotemporal dementias including Pick's disease, corticobasal degeneration (CBD), and others.
- Characterized by early gait disturbance, bradykinesia, rigidity, and occasionally tremor, it is most commonly misdiagnosed as IPD early in its onset. Relentlessly progressive, PSP usually leads to significant motor and cognitive decline in 5–8 years, resulting in institutionalization and death.
- Like many of the Parkinson plus syndromes, PSP shares the clinical characteristic of being poorly responsive or totally unresponsive to dopaminergic stimulation.
- Synonym: Steele–Richardson–Olszewski syndrome

EPIDEMIOLOGY

Incidence

- PSP represents approximately 1% of all cases of parkinsonism, while IPD represents at least 85%.
- Incidence rates of PSP increase with age and have been estimated at <2 new cases per year in the 6th decade up to nearly 15 per year in the 9th and later decades per 100,000 individuals.

Prevalence

Prevalence rates in the UK may approach 6–7 cases per 100,000 population.

RISK FACTORS

- Race: No known ethnic predilection.
- Age: The median age of diagnosis is mid-to-late 50s to early 60s, slightly earlier than IPD.
- Sex: Some authors suggest a male predominance, while other studies have found no gender differences.

Genetics

- PSP is one of the 4R tauopathies, characterized by accumulation of this specific isoform of tau with 4 repeats in the microtubule-binding domain.
- Rare cases of autosomal dominant, familial clusterings have been reported but the gene has not been identified yet. Recent evidence suggests that homozygous carriers of mutations affecting the tau gene may be at increased risk of developing PSP.

PATHOPHYSIOLOGY

- Prominent neurofibrillary tangles, neuronal loss along with astrocytic tufts and oligodendroglial inclusion bodies that stain immunocytochemically for tau proteins in pallidum, subthalamic nucleus, red nucleus, substantia nigra, pontine tegmentum, striatum, oculomotor nucleus, medulla, and dentate nucleus. In addition, there is frequently neuronal and glial pathology in the precentral gyrus (primary motor cortex).

ETIOLOGY

The cause of PSP is unknown. The possibility of infection has been raised due to similarities between PSP and post-encephalitic parkinsonism.

DIAGNOSIS

HISTORY

The earliest symptoms of PSP include frequent falling with profound postural instability (usually affecting >95% of patients at time of diagnosis), frequently accompanied by bilateral bradykinesia, i.e., masked facies, paucity of spontaneous limb movement, slowness, and shuffling of the gait.

PHYSICAL EXAM

- Patients occasionally have a resting tremor and may have complicating postural and intention tremors. The distribution of increased resistance to passive manipulation is predominantly axial, affecting neck and trunk more than the limbs. This pattern is typically opposite of that seen in IPD. Bradykinesia and rigidity are also typically more symmetric at onset in PSP, differentiating it from the largely asymmetric onset of signs and symptoms in IPD.
- The classic neuro-ophthalmologic features of PSP, while sometimes delayed relative to the gait disturbance, include loss of voluntary vertical gaze followed by loss of voluntary horizontal gaze. This "supranuclear" ophthalmoplegia can be overcome by doll's eyes maneuvers, confirming intact brainstem nuclei and their connections. Patients may have a neck dystonia with retrocollis, eyelid retraction, and wrinkling of the forehead, resulting in a prominent "staring/startled" appearance or the Procerus sign. Other neuro-ophthalmologic hallmarks include gaze impersistence, loss of optokinetic nystagmus (first in vertical, then in horizontal planes), and square wave jerks with ocular fixation.
- Other frequent symptoms include dysarthria, dysphagia, disinhibition, and frontal lobe symptoms such as perseveration, impulsivity, grasping, apathy, and/or depression.
- Three general clinical phenotypes of brainstem PSP have been described:
  - *PSP-Richardson (PSP-R)* presents with classic symptoms as outlined in the NINDS criteria, axial greater than limb rigidity, usually with little or no responsiveness to levodopa, and have the poorest prognosis.
  - *PSP-parkinsonism (PSP-P)* may mimic IPD more closely than other forms of PSP with asymmetric limb greater than axial rigidity and early, partial responsiveness to levodopa therapy. Prognosis is typically better than PSP-R, but response to levodopa therapy is usually less than that seen in IPD and wanes over 1–2 years.
  - *PSP-pure akinetic gait freezing (PSP-PAGF)* presents with axial greater than limb rigidity, isolated freezing of gait, and little or no response to levodopa. Prognosis for PSP-PAGF is typically better than PSP-R.
- There are cortical variants of PSP, but these are discussed in the chapter on CBD.

Diagnostic Criteria (NINDS)/Society for PSP

- Criteria for possible PSP are as follows:
  - Gradually progressive disorder with onset when the individual is aged 40 years or older.
  - Either vertical supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset.
  - No evidence of other diseases that can explain the clinical features.
- *Probable PSP* modifies the "possible" criteria by requiring *both* a supranuclear vertical gaze palsy *and* prominent postural instability with falls in the first year of onset.
- *Definite PSP* can only be diagnosed histopathologically at autopsy. Not having the above-mentioned features does not exclude the diagnosis.
- There are numerous *mandatory exclusionary criteria* and *supportive criteria*.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Bloodwork: There are no specific blood tests to diagnose PSP, but the following tests should be considered to identify potential underlying secondary causes of parkinsonism: Serum vitamin B12 level, thyroid function tests, serum ceruloplasmin, 24-hour urine copper excretion.

Imaging

- Functional neuroimaging using PET and SPECT scanning using markers for neuronal activity (fluorodeoxyglucose), dopaminergic terminals (beta-CIT, DTBZ, and others), and dopamine receptors (IBZD) may distinguish PSP from IPD, but does not distinguish from other Parkinson plus syndromes. These methods are not being widely implemented.
- There is no evidence to suggest that structural imaging studies (CT, MRI) can assist in the diagnosis of PSP. MRI imaging may reveal evidence of other causes of parkinsonism, such as vascular insults, mass lesions, calcium or iron deposition in the striatum, atrophy in the posterior fossa suggestive of multiple system atrophies, and cortical atrophy patterns suggestive of other dementing illnesses.

Diagnostic Procedures/Other

Studies of cardiac innervations utilizing ^{131}I-labelled meta-iodobenzylguanidine are normal in PSP versus abnormal in IPD although this study is rarely performed.

Pathological Findings

See "Pathophysiology"

DIFFERENTIAL DIAGNOSIS
- Corticobasal degeneration
- Dementia with Lewy bodies
- Drug-induced parkinsonism (e.g., anti-psychotics, anti-emetics, and other dopamine-blocking agents)
- Multiple system atrophy (MSA)
- Vascular parkinsonism
- Parkinsonism dementia complex of Guam
- Progressive non-fluent aphasia
- Post-encephalitic parkinsonism
- Post-traumatic parkinsonism
- Wilson's disease
- Frontotemporal dementia with parkinsonism

TREATMENT

MEDICATION
- Rarely, patients with PSP will transiently respond to carbidopa/levodopa therapy at the beginning of the disease process. This response is usually minimal and short-lived. Antidepressants, especially amitriptyline and trazodone, have helped ameliorate some of the symptoms of rigidity, bradykinesia, and gait disturbance. Botulinum toxin injections have been useful for severe dystonias.
- Contraindications: Individuals with a history of cardiac arrhythmias or orthostatic hypotension may have adverse effects when prescribed tricyclic antidepressants.
- Precautions: The use of high doses of carbidopa/levodopa and other dopaminergic therapies may be associated with confusion, hallucinations, and agitation, especially in individuals with advanced symptoms of PSP.

ADDITIONAL TREATMENT
General Measures
There is no effective treatment for PSP. Management is aimed at alleviating consequences of the motor changes including dysphagia and cognitive impairment.

Issues for Referral
PSP is rarely seen in general neurology practices and even more rarely in primary care. Once a patient demonstrates atypical parkinsonism, referral to a dedicated movement disorders specialist is indicated.

Additional Therapies
The primary symptom of gait instability may be overcome by the use of 4-wheeled walkers, although the predominant tendency of patients with PSP to fall backwards usually limits the effective duration of this intervention. Dysarthria and dysphagia may benefit from speech pathology intervention. Exposure keratitis may be prevented by frequent administration of artificial tears.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Co-enzyme Q10 is frequently prescribed by specialists for people with PSP at a dose of 100–400 mg 3 times daily. No controlled clinical trials in PSP have been completed with CoQ10.

SURGERY/OTHER PROCEDURES
Percutaneous endoscopic gastrostomy (PEG) may be performed to provide life-sustaining nutrition.

IN-PATIENT CONSIDERATIONS
Admission Criteria
PSP is usually managed in an outpatient setting. Rarely, concomitant illnesses, especially aspiration pneumonia, can lead to an acute exacerbation of PSP symptoms, requiring hospitalization for dysphagia, airway management, and issues of decreased mobility. Psychosis symptoms may precipitate hospitalization and/or institutionalization.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
PSP is a relentlessly progressive illness, typically leading to death within 6–10 years. Patients are monitored in the outpatient setting, usually at 4–6 month intervals. Judicious use of antidepressant medications and timely discussion of PEG tube placement are recommended to assist patients and their families prepare for future decline.

DIET
As dysphagia develops, use of pureed foods may be indicated to avoid aspiration pneumonia. As mentioned previously, patients may require PEG tube placement in order to maintain nutritional status.

PATIENT EDUCATION
The severe gait instability in PSP prevents the use of ambulatory exercise, although stretching and strengthening exercises in a sitting position may be useful. Aqua therapy with close supervision may help forestall some of the immobility issues associated with this illness. Speech therapy is useful for speech and swallowing disturbances. National organizations provide information to patients and their families.

PROGNOSIS
Due to its progressive nature, the symptoms of PSP always worsen with time. Death usually occurs as a consequence of pulmonary embolism or aspiration pneumonia.

COMPLICATIONS
PSP frequently leads to aspiration pneumonia and/or complications of falling. Due to impulsivity, patients with PSP will frequently force food into their mouth incessantly.

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See Also (Topic, Algorithm, Electronic Media Element)
- Parkinson's disease
- Dementia with Lewy bodies
- Multiple system atrophy
- Corticobasal degeneration

CODES

ICD9
333.0 Other and unspecified extrapyramidal diseases and abnormal movement disorders

CLINICAL PEARLS
The clinical characteristic of patient falling in PSP is almost always *backward* in contrast to IPD, which is usually reported as falling *forward*.

PSEUDOTUMOR CEREBRI

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BASICS

DESCRIPTION

Pseudotumor cerebri (PTC) is a condition that mainly affects obese women and is associated with significant morbidity due to increased intracranial pressure (ICP). Headaches, transient visual obscurations (TVOs), and progressive visual loss are the most common presenting symptoms. The elevated ICP is transmitted through the optic nerve sheaths to the optic discs, causing papilledema, which is generally considered a medical emergency. CT scan demonstrates no evidence of a mass lesion, while lumbar puncture reveals an elevated opening cerebrospinal fluid (CSF) pressure. This unchecked process can lead to irreversible blindness.

EPIDEMIOLOGY

Incidence/Prevalence

- Obese women of childbearing age are most commonly affected (1)[B].
- Female/male ratio of 8:1 in the adult population.
  - Incidence in general population 0.9:100,000
  - In women age 20–44, >20% over ideal body weight 19.3:100,000
- No known association with race.
- Peak incidence is in the third decade, but can occur from infancy to old age.

RISK FACTORS

- Female
- Obesity

Pregnancy Considerations

No evidence of an increased risk of PTC onset or exacerbation during pregnancy.

Genetics

No known genetic syndrome.

GENERAL PREVENTION

Maintain ideal body weight.

PATHOPHYSIOLOGY

- Increased resistance to CSF egress at the arachnoid villi or through extracerebral lymphatics
- Brain edema and increased brain water content
- Increased venous pressure and cerebral blood volume

ETIOLOGY

The majority of cases are *idiopathic*; but resistance to CSF egress may be *secondary* to venous occlusive disease, sarcoidosis, meningeal carcinomatosis, systemic lupus, Behcet's disease, meningitis, and acromegaly. A variety of medications, including nalidixic acid, fluoroquinolones, tetracycline, doxycycline, minocycline, Accutane, growth hormone and hypervitaminosis A are well known secondary causes. An association with strep throat is common in the pediatric population.

COMMONLY ASSOCIATED CONDITIONS

- Polycystic ovarian syndrome
- Sleep apnea

DIAGNOSIS

HISTORY

- Headache (most frequent symptom)
  - Generally holocranial or retrobulbar
  - Relatively constant, "aching" or "throbbing" quality, variable intensity
  - May be associated with nausea or light-headedness
- TVOs
  - Unilateral or bilateral blurring, dimming, or loss of vision lasting for 2–3 seconds
  - Secondary to optic disc swelling
- Visual loss (optic disc related)
  - May be due to compressive optic nerve damage, optic disc infarction, choroidal folds, and subretinal hemorrhage
- Visual field loss
- Diplopia
- Pulsatile tinnitus

PHYSICAL EXAM

- Relative afferent pupillary defect with asymmetric optic nerve involvement.
- Bilateral optic disc swelling secondary to increased ICP (i.e., papilledema) is generally noted; however, asymmetric, unilateral or no optic disc edema may occur.
- Cranial nerve VI palsy, which may be unilateral or bilateral.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Blood work is generally unnecessary in the typical idiopathic PTC patient. In an atypical patient (e.g., thin male) or in a patient with uncharacteristic symptoms or signs (e.g., arthralgias, malar rash, tetanic muscle spasms, cranial nerve III palsy), other laboratory tests may prove diagnostic for secondary forms of PTC: VDRL, antinuclear antibody, anti-dsDNA, serum Ca^{2+}, ACE, lysozyme, growth hormone or IgF-1.

Follow-up & special considerations

Basic metabolic panel to follow electrolytes and kidney function after initiating treatment with diuretics.

Imaging

Initial approach

CT and MRI are the main imaging techniques used in PTC. Normal- to small-sized ventricles are seen with no evidence of mass lesion. Up to 70% of PTC patients have evidence of an empty sella. Clear differentiation between the optic nerve and sheath, with an enlarged, elongated subarachnoid space, and flattening of the posterior aspect of the globe may also be seen. MRI is better than CT to rule out infiltrative diseases and venous sinus thrombosis. Stenosis of the venous sinuses, often noted on MRI, generally resolves with lowering of the ICP; it appears to be secondary to raised ICP rather than causative (2)[C].

Follow-up & special considerations

Shunt series for patients with recurrent symptoms and signs of raised ICP to evaluate shunt placement and integrity.

Diagnostic Procedures/Other

- Lumbar puncture (LP) is necessary to obtain the opening pressure (OP) and to rule out infection or inflammation. OP >20 cm H_2O are considered elevated. Falsely low OP may occur when the LP requires multiple attempts with reinsertion and redirection of the needle. Falsely high OP may occur with patient positioning or Valsalva. LP under radiologic guidance should be considered in obese patients, especially when normal landmarks cannot be palpated. CSF analysis should include cell counts, differential, cytology, protein and glucose levels, Gram stain, and routine cultures and sensitivities. These are all within normal limits in idiopathic PTC.
- Visual acuity testing, pupillary responses, slit lamp and dilated funduscopic evaluation, and visual fields are necessary to assess baseline visual function. Stereoscopic optic disc photographs taken on initial evaluation can be used to monitor disease progression. Fluorescein angiography of the fundus may help to differentiate optic disc drusen (i.e., pseudopapilledema) from true papilledema. Disc drusen may autofluoresce on initial red-free photographs along with late staining, but no true leakage.
- Visual field loss
  - Enlarged blind spot and generalized constriction are most common.
  - Nasal step, arcuate defects, and cecocentral scotomas may also be encountered.

Pathological Findings

Unknown.

DIFFERENTIAL DIAGNOSIS

The diagnosis of idiopathic PTC is largely one of exclusion. Therefore, it is necessary to rule out other causes of papilledema and increased ICP as well as secondary PTC. Focal neurologic signs other than cranial nerve VI palsy should suggest a diagnosis other than PTC.

- Intracranial mass lesion with obstructive hydrocephalus
- Pseudopapilledema (i.e., optic disc drusen)
- Meningitis (i.e., bacterial, viral, neurosyphilis)
- Venous sinus thrombosis
- Medication related (e.g., tetracycline, growth hormone therapy)
- Systemic disease (e.g., systemic lupus erythematosus, Behcet's disease, acromegaly)

TREATMENT

MEDICATION

First Line

Carbonic anhydrase inhibitors (CAIs): Neptazane 50 mg b.i.d. to q.i.d. and acetazolamide 250 mg b.i.d. to 500 mg q.i.d. are generally well tolerated.

- Contraindications
  - CAIs are not contraindicated in patients reporting a sulfa allergy to antibiotics as they have a different sulfa moiety. There is a relative contraindication during the first trimester of pregnancy (class C).
- Precautions
  - Common adverse effects: Tingling and numbness in the fingers and toes, fatigue, nausea, metallic taste, and K+ wasting. Aplastic anemia is a rare idiosyncratic reaction.

Second Line

- Furosemide: 20 mg b.i.d. to 40 mg q.i.d. is also effective; however, it is important to monitor serum potassium.
- Corticosteroids may be useful in patients with an underlying inflammatory condition such as systemic lupus.
- Octreotide, a somatostatin analog has been found in a small case series to lower ICP, relieve headache, reduce papilledema, and improve vision in PTC patients, although the mechanism of action is unknown (3)[B].

ADDITIONAL TREATMENT

General Measures

Suspect exogenous agents should be discontinued.

Issues for Referral

- Intractable headache, blurred vision, TVOs
- Papilledema, visual field loss, CN VI palsy

Additional Therapies

Analgesics may be used for symptomatic relief of headache.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Weight loss may reduce the need for medications or surgery, and may require consultation with a dietician.

SURGERY/OTHER PROCEDURES

Surgery may be necessary to control intractable headaches and to preserve visual function. The main options for PTC are neurosurgical shunting and optic nerve sheath fenestration (ONSF). Lumboperitoneal shunting may be preferable in patients with small ventricles, whereas ventriculoperitoneal shunting is a better option in patients with Chiari malformation. In a retrospective study of 30 PTC patients who underwent LP shunting, headache improved in 82%, papilledema resolved in 96%, and visual acuity or field improved in 68% (4)[B]. The mean follow-up duration was 34.9 months and the mean shunt revision rate was 4.2 per patient. In ONSF, a window is made in the anterior dural covering of the optic nerve. ONSF is useful to decompress the optic nerve in cases with papilledema. It is less likely to relieve high ICP in the long run; however, it does reduce the risk of visual loss with recurrent elevation of ICP. Gastric bypass surgery may be indicated to improve weight loss in morbidly obese patients.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Intravenous acetazolamide or furosemide for rapid decompression of optic disc
- Potential use of high dose methylprednisolone to reduce optic disc edema
- Papilledema should be reduced with restoration of blood flow in the optic nerve head prior to consideration of ONSF; performing ONSF on an ischemic optic disc was associated with an increased risk of visual loss (5)[A]
- Electrolytes, BUN, creatinine monitored daily

Admission Criteria

Hospital admission may be indicated for (a) expedited brain MRI, fluoroscopically-guided lumbar puncture and initiation of medical therapy, or (b) urgent surgical intervention to preserve vision.

IV Fluids

May be indicated with or without intravenous caffeine for low tension headache after lumbar puncture.

Discharge Criteria

Stabilization with definitive outpatient plan.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Papilledema may not resolve completely with appropriate treatment and may not recur significantly with elevated ICP once it becomes chronic in nature. Optic disc appearance alone is not adequate to assess for recurrent elevation in ICP; subjective symptoms and visual field progression may be more reliable.

DIET

Low sodium diet with a goal toward maintaining ideal body weight.

PATIENT EDUCATION

Patients should be educated about the signs and symptoms of PTC as well as the importance of weight loss and regular follow-up.

PROGNOSIS

Once the condition is controlled on medication for 6 months, attempts to wean off the medication should be made periodically, especially when weight loss has been achieved. Systemic hypertension is a risk factor for greater visual loss.

COMPLICATIONS

- Permanent, irreversible vision loss
- Intractable headache with lost productivity

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See Also (Topic, Algorithm, Electronic Media Element)

- Idiopathic intracranial hypertension

CODES

ICD9

- 348.2 Benign intracranial hypertension
- 377.00 Papilledema, unspecified

CLINICAL PEARLS

Obese females of childbearing age with chronic headache (with or without papilledema) should receive a thorough eye exam, an MRI brain with gadolinium, and a lumbar puncture.

P

RABIES

Sevim Erdem Ozdamar, MD

BASICS

DESCRIPTION

Rabies ("rage" or "madness" in Latin) is a viral infection that causes rapidly progressive and almost always fatal encephalomyelitis. It is transmitted to humans primarily through close contact with saliva (bites, scratches, licks on broken skin, and mucous membranes) of infected animals (dog, bat, raccoon, fox, and skunk), rarely through laboratory exposure, inhalation (caves that harbor bats), and iatrogenic (rarely via corneal or solid organ transplants) tissue exposure.

EPIDEMIOLOGY

- Incidence/Prevalence
  - Rabies causes about 50,000–55,000 deaths each year worldwide, primarily in Asia and Africa. About 15 million people receive postexposure prophylaxis each year. In 2009, 6,690 cases of animal rabies and 4 human cases were reported to CDC in the US.
- Race
  - No race difference has been reported.
- Age
  - Although rabies can occur at any age, about half of the cases reported occur in children.
- Sex
  - No sex difference has been reported.

RISK FACTORS

The risk of an unimmunized person to develop rabies after a bite of a rabid animal is 5–15%. Modifying factors include the site and the severity of bite and the virus concentration of saliva. Bites on the head and face result in the highest incidence of disease with the shortest incubation period.

Genetics

No definite genetic factors are identified.

Pregnancy Considerations

Transplacental transmission of rabies has rarely been reported, and the possibility of transmission through lactation has not been excluded. Postexposure prophylaxis of pregnant women has been reported as safe in several case reports.

GENERAL PREVENTION

The most important source of rabies for human is rabies in dogs. Therefore adequate animal vaccination, controlling the exposure of domestic animals to wild life, informing animal control about any ill animals in the neighborhood, preexposure prophylaxis for risk groups and postexposure prophylaxis after exposure will prevent disease development.

PATHOPHYSIOLOGY

Rabies virus is a highly neurotrophic virus and enters the central nervous system by ascending along the peripheral nerved from the wound site.

ETIOLOGY

Rabies virus is a single-stranded RNA virus which belongs to the *Rhabdoviridae* family. The infection is transmitted to humans usually through an infected animal bite. The principal reservoir is the domestic dog in Africa, Asia, and Latin America, while wild carnivores and bats are the main hosts in developed countries. Other than transdermal inoculation, inhalation of aerosolized rabies virus is a potential non-bite route. However, a significant proportion of human rabies cases lack an identified route of transmission.

DIAGNOSIS

HISTORY

- In a patient with symptoms of encephalitis the history of a bite by an animal that can carry the virus, history of exposure to bats, or a recent travel to a country where rabies is endemic should alert the physician for rabies.
- The incubation period for human rabies is usually 1–3 months after contact with a rabid animal, although varies extremely up to a year.

PHYSICAL EXAM

- The evolution of rabies encephalitis starts with a prodromal phase followed by excitatory or paralytic phase and ends with coma and death. The clinical features vary according to the phase if the infection.
- Prodromal phase: Lasts 2–10 days, consisting of fever, malaise, headache, nausea, and sore throat. Abnormal sensations like pain, itching, tingling, and paresthesias at the site of inoculation are important symptoms seen in up to 80% of patients.
- Excitatory (encephalitic, furious) phase: Seen in 80% of cases and may last up to a week. There is anxiety, agitation, confusion, and hallucinations. Increased sensitivity to bright light and loud noise and autonomic dysfunction (increased salivation, lacrimation, perspiration, mydriasis, tachycardia, bradycardia, cyclic respiration, urinary retention, and constipation) are seen. Hydrophobia resulting from intense spasms of pharyngeal and laryngeal muscles when patients attempt to swallow liquids is the classic manifestation. Aerophobia also induces spasms. Once coma develops, inspiratory spasms replace them. Muscle tone is increased. Cranial nerve dysfunctions (ocular palsies, facial weakness, hoarseness, hippus, nystagmus) are seen. Seizures, although rare, can be seen. Death can result in this phase due to respiratory arrest. If not, patients lapse into coma.
- Paralytic phase: About 20% of patients experience paralytic or dumb rabies which lasts 1–4 weeks before coma develops. A progressive, flaccid paralysis develops simulating Guillain–Barré syndrome (GBS). Consciousness is spared and there is no agitation. Phobic spasms, inspiratory spasms, and autonomic signs are present.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Routine blood work is nonspecific except leukocytosis. Routine CSF examination is normal until late in the disease.

Imaging

Neuroimaging may show nonspecific signs of encephalitis and is not particularly helpful for diagnosis.

Diagnostic Procedures/Other

- Antibody detection in the serum and CSF: Serum antibodies may not be present until several days after the onset of symptoms. Rapid fluorescent focus inhibition test is currently the gold standard serology test, it measures the neutralizing antibodies, while indirect immunofluorescence assay detects antibody reactive to rabies antigen in infected cell cultures
- Virus isolation from saliva, nuchal skin, CSF, oral or nasal mucosa, and brain
- Antigen detection by direct fluorescent antibody testing from nuchal skin biopsy, corneal, and salivary impressions
- Detection of viral RNA in saliva
- Histological examination of brain tissue (see pathological findings)
- Molecular techniques for detection of viral RNA are becoming widely accepted for the diagnosis of rabies (1)[C]

Pathological Findings

Histological examination will show Negri bodies—cytoplasmic eosinophilic inclusions throughout the central nervous system, most commonly in the pyramidal cells of the hippocampus and the Purkinje cells of cerebellum. Perivascular cuffing of lymphocytes and mononuclear cells and focal collections of microglia called Babes nodules are other histopathological findings of rabies encephalomyelitis. Also immunohistochemistry can be applied to detect viral inclusions.

DIFFERENTIAL DIAGNOSIS

- Other causes of viral encephalitis
  - Herpes simplex virus encephalitis
  - Arbovirus encephalitis
- Nonviral causes of encephalitis
  - Mycoplasma pneumonia
  - Legionnaire disease
  - Central nervous system toxoplasmosis
  - GBS (paralytic or dumb rabies cases)
  - Poliomyelitis
  - Tetanus
- Allergic encephalitis due to nerve tissue-derived rabies vaccine
- Acute hepatic porphyria with neuropsychiatric disturbances
- Alcohol withdrawal (delirium tremens)

TREATMENT

- As rabies is almost always fatal after the onset of symptoms, wound cleaning and immunization are extremely important to prevent the onset of rabies.
  - Bites and scratches should immediately be washed for a minimum of 15 minutes with soap and water. If available, povidine–iodine solution should be used to irrigate the wound. Deep wounds should be irrigated by syringe and these solutions should be applied by cotton-tipped applicators.
  - Do not suture the wound. If suturing is unavoidable, do it after immune globulin infiltration.

PROPHYLAXIS

- Preexposure prophylaxis:
  - It should be applied to high-risk individuals (veterinarians, certain laboratory workers, animal control workers, travelers to countries where rabies is endemic). Cell culture vaccines [human diploid cell vaccine (HDCV), purified chick embryo cell vaccine] should be used if possible. Vaccine should be administered IM (1.0 mL) or ID (0.1 mL) in the deltoid area on Days 0, 7, and 21 or 28 (according to package instructions). About 2–3 weeks after the last injection, the antibody titer should be checked and if inadequate, a booster dose should be given. Follow-up of the antibody titer every 6 months for persons who work with live rabies virus and every year for those under continuous risk (veterinarians, travelers to endemic areas) is recommended.
- Indications for postexposure prophylaxis:
  - For touching or feeding a suspected rabid animal and licks on intact skin there is no need of postexposure measures.
  - For nibbling of uncovered skin, minor scratches, or abrasions without bleeding immediate vaccination is necessary.
  - For transdermal bites or scratches, licks on broken skin, contamination of mucous membranes with the saliva of the suspected animal and exposure to bats both vaccination and rabies immune globulin administration are necessary.
- Postexposure prophylaxis:
  - Human rabies immune globulin (HRIG): Infiltrate 20 IU/kg HRIG in the tissues around the wound. As much HRIG as anatomically possible should be given to the wound and the rest intramuscularly to the anterior thigh. HRIG should be given as early as possible, but can be given up to 8 days after the first dose of the vaccine. Doses given in and after the 8th day will compromise the patient's response to vaccine.
  - Vaccination:
    - Five doses of cell culture vaccine, 1 mL each is enough. First dose should be given as soon as possible, subsequent doses on Days 3, 7, 14, and 28 after the first dose. The new recommendations of Advisory Committee on Immunization Practices has recently reduced the number of vaccine doses to 4 on Days 0, 3, 7, and 14 for immunocompetent people (2)[A]. For immunocompromized the recommendation is still 5 doses.
    - Vaccine should be given IM in the deltoid muscle in adults and older children. For infants anterolateral thigh may be used. Gluteal area should not be used.
- Postexposure prophylaxis for those previously immunized: Two doses of vaccine on Days 0 and 3 IM in the deltoid area should be given. HRIG should not be administered.
- If suspected animal is available, it should be kept under observation. Vaccination can be stopped if the animal remains healthy for 10 days. If ill it should be euthanized and the brain should be examined for rabies virus antigen. If antigen negative vaccination can be stopped.

MEDICATION

No specific treatment of rabies after the onset of symptoms is present. Only a single case of 15-year-old female has been reported to survive after therapeutic induction of coma by midazolam and ketamine along with IV ribavirine and amantadine (Milwaukee Protocol) (3)[C].

- Contraindications
  - No reports available.
- Precautions
  - Never draw HRIG with the same syringe with the vaccine and do not administer in the same site.

ADDITIONAL TREATMENT

General Measures

Rabies is almost always fatal after the onset of symptoms. Pulmonary and cardiac functions should be monitored. Dysautonomia, seizures, and increased intracranial pressure should be managed aggressively. Sedation with barbiturates, benzodiazepines, and phenothiazines may be necessary.

Issues for Referral

All patients should be followed in the intensive care unit (ICU).

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Patients with wounds that have broken the skin should also receive tetanus prophylaxis.
- An antibacterial agent can be applied to prevent secondary infections.

SURGERY/OTHER PROCEDURES

There is no surgical procedure for rabies. Brain biopsy for diagnosis is debatable because of the risks of the procedure and the inaccessibility of tissues with greatest involvement. If done, eosinophilic viral inclusions (Negri bodies) will be seen.

IN-PATIENT CONSIDERATIONS

Admission Criteria

All suspected cases should be followed in the ICU.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

For rare cases of survival, follow-up focuses on the neurological complications.

DIET

No specific diet is available.

PATIENT EDUCATION

- Unfortunately, many people die from rabies although efficacious preventive measures are available. Websites:
  - World Health Organization: http://www.who.int/emc/diseases/zoo
  - Centers for Disease Control and Prevention: http://www.cdc.gov/ncidod/dvrd/rabies

PROGNOSIS

Once clinical signs of encephalitis have begun, rabies is almost always fatal. However, both complete recovery of rabies and survival with severe sequelae have been reported.

REFERENCES

1. Fooks AR, Johnson N, Freuling CM, et al. Emerging technologies for the detection of rabies virus: challenges and hopes in the 21st century. *Plos Negl Trop Dis* 2009;29;3:e530.
2. Centers for Disease Control and Prevention. Use of a Reduced (4-Dose) Vaccine Schedule for Postexposure Prophylaxis to Prevent Human Rabies. Recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2010; 59(No. RR-2):1–8.
3. Willoughby RE Jr, Tieves KS, Hoffman GM, et al. Survival after treatment of rabies with induction of coma. *N Engl J Med* 2005;352:2508–2514.

CODES

ICD9
071 Rabies

CLINICAL PEARLS

- Rabies is a preventable infection.
- Preexposure prophylaxis for risk groups and wound cleaning and postexposure prophylaxis is extremely important.

RADICULOPATHY, CERVICAL

Jennifer Werely, MD
David S. Younger, MD

BASICS

DESCRIPTION
Cervical radiculopathy refers to dysfunction of a cervical nerve root, usually due to compression and usually caused by degenerative spine disease or acute disc herniation. Typical clinical picture includes neck and arm pain with or without alterations in strength, sensation, and reflexes.

EPIDEMIOLOGY
- Incidence
  - Annual incidence rate 83.2/100,000 population.
- Age
  - Incidence of herniation of the nucleus pulposus (HNP) is highest at ages 50–54, mean age 47 and most often due to cervical spondylosis and spinal stenosis with root compression due to osteophytes rather than disc material, or both. Approximately 50% of compressive radiculopathy affects the C7 root, 30% C6, 10% C5, and 10% C8. Isolated T1 radiculopathy is rare.
- Sex
  - Male predominance.

RISK FACTORS
The only major risk factor is trauma.

ETIOLOGY
Degenerative spine disease (spondylosis) has two elements: Degenerative disc and joint disease (DJD). Primarily due to aging; superimposed macro- or microtrauma may aggravate the process. Degenerative disc disease predisposes to HNP ("soft disc") whereas DJD causes osteophytic narrowing of the neural foramina ("hard disc"). Either process may cause compressive radiculopathy. More advanced spondylosis may also lead to spinal stenosis and cord compression.

COMMONLY ASSOCIATED CONDITIONS
The commonly associated conditions comprise osteoarthritis.

DIAGNOSIS

- Features favoring radiculopathy as opposed to other etiologies of neck and/or arm pain are as follows:
  - Age 35–60
  - Acute/subacute onset
  - Past history of cervical or lumbosacral radiculopathy
  - Cervicobrachial pain radiating to shoulder, periscapular region, pectoral region, or arm
  - Paresthesias in arm or hand
  - Pain on neck movement—especially extension or ipsilateral bending
  - Positive root compression signs
  - Radiating pain with cough, sneeze, or bowel movement
  - Myotomal weakness
  - Decreased reflexes
  - Dermatomal sensory loss
  - Pain relief with hand on top of head
  - Pain relief with manual upward traction
- Onset acute in half, subacute in a quarter, insidious in a quarter; many patients awake with pain in neck and rhomboid region. Majority of patients symptomatic for about 2 weeks prior to diagnosis. Pain in pectoral region occurs in about 20%. Neck, periscapular, and pectoral region pain may be referred from disc itself; arm pain more likely due to nerve root compression. Only 56% of the patients have neck or shoulder pain, but 99% have pain in the upper arm, often poorly localized. Pain in forearm in 88%, usually poorly localized.
- Cervical range-of-motion maneuvers affect size of intervertebral foramen. Pains produced by movements that close the foramen suggest radiculopathy. Pain on symptomatic side on putting ipsilateral ear to shoulder suggests radiculopathy; increased pain on leaning or turning away from the symptomatic side suggests myofascial pain. Radiating pain with neck extended and tilted slightly to the symptomatic side suggests radiculopathy; brief breath holding in this position sometimes elicits radicular pain. Axial compression (Spurling maneuver) adds little. Light digital compression of the external jugular veins until the face is flushed sometimes elicits radicular symptoms: Unilateral shoulder, arm, pectoral or periscapular pain, or radiating paresthesias into the arm or hand (Naffziger's sign), a highly specific but insensitive finding.
- Findings that suggest a lesion at a given level are as follows:
  - C5—pain only in neck and shoulder, no pain below elbow, depressed biceps and brachioradialis reflexes, weakness of spinati or deltoid
  - C6—weakness of deltoid or biceps, paresthesias limited to the thumb, sensory loss over thumb only, depressed biceps and brachioradialis reflexes
  - C7—presence of scapular/interscapular pain, pain involving the posterior upper arm, pain involving the medial upper arm, paresthesias limited to index and middle fingers, whole hand paresthesias, depressed triceps reflex, weakness of triceps, sensory loss involving middle finger
  - C8—presence of scapular/interscapular pain, pain involving the medial upper arm, depressed triceps reflex, paresthesias limited to ring and small fingers, weakness of hand intrinsics, sensory loss involving small finger
  - T1—disproportionate weakness of abductor pollicis brevis

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
C-reactive protein, ESR, ANA, and rheumatoid factor support an acquired inflammatory process, whereas HLA B27 seropositivity suggests genetically mediated spondyloarthropathy.

Imaging
Plain cervical spine films with oblique views assess for osteoarthritis changes and osteophytes. Non-contrast MRI assesses disc herniation and evidence of root compression. Abnormalities on MRI are common in asymptomatic individuals.

Diagnostic Procedures/Other
EMG and nerve conduction studies including F-responses are essential in the diagnosis of cervical radiculopathy, but may be normal for up to 3 weeks after the acute insult while the root lesion matures. "Double crush injury" often seen in the setting of cervical radiculopathy refers to concomitant peripheral lesions noted on electrodiagnostic studies, such as carpal tunnel syndrome and ulnar entrapment that overlaps clinically with lower cervical root compression.

DIFFERENTIAL DIAGNOSIS

- Brachial plexopathy
- Entrapment neuropathy
- Nerve root tumors (neurofibroma, schwannoma)
- Infection [herpes zoster, Lyme disease, cytomegalovirus, epidural abscess]
- Meningeal carcinomatosis/lymphomatosis
- Multiple sclerosis (causing radiculopathy)
- Giant cell arteritis
- Non-neuropathic mimickers
  - – Cervical myofascial pain
  - – Shoulder pathology (bursitis, tendinitis, impingement syndrome)
  - – Lateral epicondylitis
  - – De Quervain tenosynovitis
  - – Facet arthropathy
  - – Referred pain from heart, lungs, esophagus, or upper abdomen

TREATMENT

MEDICATION

Empiric non-steroidal anti-inflammatory medications may be taken to avert abdominal upset decreases radicular inflammatory component and relieves pain; and should be combined with a muscle relaxant such as cyclobenzaprine 5–10 mg PO at bed time. Baclofen 10 mg PO t.i.d. can be substituted for cyclobenzaprine if muscle spasm is severe.

- Contraindications
  - – Known hypersensitivity for mediations.
- Precautions
  - – Standard precautions for the drug employed.
- Alternative drugs
  - – When there is radiographic and electrodiagnostic evidence of acute disc herniation and root compression, a course of oral methylprednisolone taken as a "6 day pack" affords effective anti-inflammatory benefit but should be taken with meals to avoid abdominal upset, and may be repeated if necessary. In selected circumstances of severe pain or focal deficit, consideration may be given to epidural injection of a depot corticosteroid mixed with a long-acting anesthetic under fluoroscopic guidance, typically in a hospital setting by a physician experienced in this procedure.

ADDITIONAL TREATMENT

General Measures

Treatment relies on three approaches: Mechanical, medical, and surgical. Nerve roots lying in the foramen normally enjoy freedom of movement through a small range. The size of the intervertebral foramen and the lateral recess changes dynamically with neck movement. When neck is extended or tilted or turned ipsilaterally, foramen is narrowest; with flexion or contraversive movement, foramen is wider. When caliber of foramen or lateral recess is narrowed because of osteophyte or disc herniation, neck movement may cause microtrauma, which induces inflammation and edema. With HNP, intradiscal inflammatory mediators may spill onto the root, exacerbating the process. Mainstay of treatment is to reduce neck movement and increase the size of the foramen.

- Soft cervical collar is usually helpful. For compressive cervical radiculopathy, the collar should be worn "backward," with high side posterior, to maintain neck in slight flexion and open foramina. Hard collars cannot be turned around in this fashion and are not as useful for a radiculopathy syndrome. Soft collar should be worn at night if tolerated; if not, use cervical pillow. Prolonged use of collar may weaken neck muscles.
- Gentle manual cervical traction administered by a licensed physical therapist or chiropractor may be helpful.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - – Modality physical therapy, or local heat or ice, may provide some relief of axial pain component, but the effects seldom persist much beyond the individual treatment session. Cervical range of motion exercises are of no benefit and possibly harmful.
- Adjunctive treatment
  - – Acupuncture may be helpful in reducing pain but does not change the natural course of the disorder.

SURGERY/OTHER PROCEDURES

Cervical root decompression should be considered when conservative medical treatments fail to diminish severe pain and ameliorate focal muscle weakness, and neuroimaging and electrodiagnostic concur in the causative underlying root or roots involved.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Hospital admission not required for medically treated patients.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Follow especially strength and reflexes of involved segment; worsening strength or loss of reflex may prompt more aggressive treatment.

PROGNOSIS

The typical patient is significantly improved by 2–3 months. Generally favorable long-term prognosis; 90% have minimal to no symptoms on prolonged follow-up. When due to HNP, cervical radiculopathy has a tendency to recur: 31% have previous history of CR, 32% have recurrence during follow-up.

ADDITIONAL READING

- Younger DS. Rupture of an intervertebral disc and related spinal disorders. In: Younger DS, ed. *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

CODES

ICD9

- 353.2 Cervical root lesions, not elsewhere classified
- 721.0 Cervical spondylosis without myelopathy
- 722.0 Displacement of cervical intervertebral disc without myelopathy

RADICULOPATHY, LUMBOSACRAL

Jennifer Werely, MD
David S. Younger, MD

BASICS

DESCRIPTION

Lumbosacral radiculopathy refers to irritation of a lumbar or sacral nerve root that most often presents as low back and referred leg pain, with associated dermatomal (sensory) and myotomal (motor) deficits, and altered segmental reflexes. Affliction of more than one root is termed polyradiculopathy.

EPIDEMIOLOGY

Studies show that the lifetime prevalence for low back pain is up to 80% distributed equally in men and women.

- Majority of herniated discs occur at L4-L5 and L5-S1 (>90%), less frequently at L3-L4, and rarely at L1-L2 and L2-L3.
- The incidence of degenerative disc disease is highest in the fourth and fifth decades, whereas compression from degenerative joint disease occurs at older ages.

RISK FACTORS

Trauma is a major risk factor. Other possible risk factors include cigarette smoking, greater number of hours spent in a motor vehicle, and occupations requiring lifting while twisting the body. Advancing age is a risk factor for degenerative joint disease.

ETIOLOGY

The majority of lesions causing lumbosacral radiculopathy are compressive in nature resulting from disk herniation or spondylosis, with nerve root entrapment. Infrequently, intrinsic processes such as infiltration from neoplastic, infectious or inflammatory disease can be the cause.

COMMONLY ASSOCIATED CONDITIONS

The commonly associated conditions comprise osteoarthritis.

DIAGNOSIS

Features favoring lumbosacral radiculopathy over other etiologies of back pain include:

- Age over 30
- Acute/subacute recurrent back pain with radiating symptoms down one or both legs
- Past history of cervical or lumbosacral radiculopathy
- Pain or paresthesias in the distribution of the posterior leg, lateral and sole of foot or lateral leg and top of foot
- Radiating pain with cough, sneeze, or bowel movement
- Positive root compression signs:
  - Straight leg raise (Lasègue's sign): With the patient supine, the affected leg is raised at the ankle. Reproducing pain or paresthesias on the symptomatic side between 30 and 70 degrees of passive flexion has a sensitivity of 90% for lumbosacral radiculopathy.
  - Crossed straight leg raise: With the patient supine, the asymptomatic leg is lifted at the ankle. Reproducing pain or parasthesias in the affected leg with passive flexion is a positive test. More specific but less sensitive than the straight leg raise.
  - Femoral stretch test (reverse straight leg raise): With the patient prone, the hip of the symptomatic leg is maximally extended. Reproducing symptoms on the affected side is a positive test, mostly useful in upper level herniated discs (L2, L3, L4).
  - Myotomal weakness.
  - Dermatomal sensory loss.
  - Decreased reflexes.
  - Bowel or bladder dysfunction (polyradiculopathy/cauda equina syndrome from canal stenosis).
- Findings suggesting a lesion at a given level are as follows:
  - L1-L3— altered sensation in the inguinal region, anterior thigh, and medial aspect of knee. May have weakness in iliopsoas (hip flexion), quadriceps (knee extension), and thigh adductors. Cremasteric reflex (L1-L2) and patellar reflex (L3-L4) may be depressed. Positive femoral stretch test.
  - L4—altered sensation over the knee and medial leg, may have weakness in the quadriceps and tibialis anterior (foot dorsiflexion and inversion). Patellar reflex may be depressed (L3-L4).
  - L5—altered sensation over the lateral leg, dorsomedial foot, and great toe. May have weakness in gluteal muscles (hip extension, hip abduction), tensor fascia latae (thigh abduction and internal rotation), hamstring muscles (knee flexion), tibialis posterior (foot plantar flexion and inversion), tibialis anterior, peronei (foot plantar flexion and eversion), extensor hallucis longus (great toe extension and foot dorsiflexion).
  - S1—altered sensation over the little toe, lateral foot, and sole of foot. May have weakness in the gluteus maximus (hip extension), hamstring muscles, gastrocnemius (foot plantar flexion), flexor hallucis longus (foot plantar and great toe flexion), and flexor digitorum longus (foot and toe plantar flexion except for large toe). Achilles reflex (S1-S2) may be depressed.
  - S2-S5—altered sensation involving the perianal region, buttocks, posterior thigh, and calf. May have bowel or bladder disturbance. Anal reflex may be absent.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

- MRI is the imaging procedure of choice in suspected lumbosacral radiculopathy. It has the benefits of imaging in the sagittal view, providing excellent soft tissue resolution without radiation exposure. Contraindicated for patients with implanted magnetic sensitive devices, difficult to perform on patients with claustrophobia or obesity.
- CT has lower sensitivity but is an acceptable alternative in patients unable to undergo MRI and has superior visualization of bone structures.

- Plain lumbosacral spine films are appropriate in the setting of suspected spinal fracture (AP and lateral views).
- There is a high incidence of lumbosacral abnormalities on neuroimaging in asymptomatic individuals. CT and MRI potentially demonstrate abnormalities in 36% and 30%, respectively, of asymptomatic individuals. Therefore, imaging should be done only when clinically indicated.

Diagnostic Procedures/Other

Electrodiagnostic studies

- Electromyography and nerve conduction studies are indispensable in the localization and prognosis of radiculopathy
- Highest yield if conducted between 3 weeks and 6 months
- Electromyography will show evidence of denervation involving paraspinal muscles and denervation involving limb muscles of the same root innervation (myotome)
- Weakness in conjunction with lumbosacral radiculopathy is classically recognized by demyelinative conduction block, axonal degeneration, or both

DIFFERENTIAL DIAGNOSIS

- Diabetic lumbosacral radiculoplexus neuropathy
- Traumatic sacral plexopathy
- Common peroneal neuropathy (may be confused with a solitary L5 root disorder)
- Paraneoplastic polyradiculopathy
- Lumbar stenosis (hallmark is neurogenic intermittent claudication, often associated with back pain and stiffness in legs with ambulation relieved by rest or flexion of lumbar spine)
- Compression fractures
- Inflammatory arthritis (suggested with young age, morning stiffness, improvement with exercise and gradual onset)
- Facet arthropathy
- Primary or metastatic neoplasm (lung, breast and prostate)
- Osteomyelitis (*S. aureus*, TB)
- Discitis
- Epidural abscess (*S. aureus*)
- Epidural hematoma
- Retroperitoneal hematoma
- Referred pain from abdominal and pelvic organs, aorta

TREATMENT

MEDICATION

- Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, or the newer class of nonsteroidals, the cyclooxygenase-2 (COX-2) inhibitors (celecoxib).
  - – Contraindications: Previous hypersensitivity reaction to NSAIDs, history of asthma, and nasal polyps. Also, celecoxib should not be given to patients who have a history of allergic reactions to sulfonamides.
  - – Precautions: Use with caution if there is a history of renal, hepatic, or hematologic disease. May cause gastrointestinal distress (much less common with the COX-2 inhibitors; however, these are currently more expensive).
- Acetaminophen
- Muscle relaxants: Up to 2-week course (i.e., cyclobenzaprine). Common side effects include nausea, dizziness, and lethargy.
- Oral corticosteroids: Although there is clear scientific rationale, the evidence is circumstantial and anecdotal. A 6-day tapering dose pack may be considered in the acute phase of symptoms.
- Narcotics: Rarely indicated, especially in chronic pain, may be helpful in the acute phase of symptoms.

ADDITIONAL TREATMENT

General Measures

- Although bed rest is a common recommendation, more proactive approaches have emerged including low-stress aerobic activity. Physical therapy may be of benefit. There is no evidence to support the use of lumbar braces, corsets, spinal traction, acupuncture, or transcutaneous electrical nerve stimulation.
- Epidural injections and selective nerve root blocks may provide short-term relief of pain symptoms.

SURGERY/OTHER PROCEDURES

Refer to surgeon if pain is refractory to conservative management or if there is a neurologic deficit. Emergent referral if suspicion for cauda equina syndrome, trauma, epidural abscess, epidural hematoma, or osteomyelitis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Not required unless rapidly progressing neurologic deficits, as might be seen in cauda equina syndrome or if pain limits ambulation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Follow neurologic exam, especially strength and reflexes of involved segment. Worsening or persistent signs and symptoms should prompt more aggressive evaluation.

PATIENT EDUCATION

Weight loss if obese, smoking cessation, avoiding prolonged hours in a motor vehicle and avoiding excess lifting especially with a twisting motion can help prevent low back pain.

PROGNOSIS

Prognosis is favorable, with 80–90% of patients recovering from back pain in about 6 weeks with conservative treatment measures.

ADDITIONAL READING

- Younger DS. Rupture of an intervertebral disc and related spinal disorders. In: *Motor disorders*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

See Also (Topic, Algorithm, Electronic Media Element)

- Sciatica; herniated nucleus pulposus

CODES

ICD9

- 722.10 Displacement of lumbar intervertebral disc without myelopathy
- 724.4 Thoracic or lumbosacral neuritis or radiculitis, unspecified
- 953.2 Injury to lumbar nerve root

REFSUM'S DISEASE

Adrian J. Wills, MD

BASICS

DESCRIPTION
Sigvald Refsum described Refsum's disease in 1945. It is caused by defective metabolism of phytanic acid with subsequent accumulation. This can lead to impairment of function of a wide variety of bodily systems.

EPIDEMIOLOGY
Refsum's disease is very rare. There may be a number of patients, particularly with retinitis pigmentosa, who are undiagnosed.

- Race
  - The disease may be slightly more common in Scandinavian races and other racial groups with Nordic or Viking ancestry.
- Age
  - The onset of symptoms is usually in late childhood.
- Sex
  - Males and females are equally affected.

Incidence
Incidence: $1/10^6$.

Prevalence
Prevalence is unknown.

RISK FACTORS
- Pregnancy considerations
- Pregnancy may be associated with acute and subacute presentations.

Genetics
Inheritance is autosomal recessive. In 90% of cases the cause is defective gene (*PHYH*) on chromosome 10. PEX7, which encodes the PTS2 receptor is mutated in the remaining 10%. The resulting enzymatic deficiencies in Refsum's disease affect phytanoyl CoA hydroxylase, which normally catalyzes the second step in the breakdown of phytanic to pristanic acid or the peroxisome-targeting signal type-2 receptor. This results in accumulation of phytanic acid with elevated levels in blood and other tissues including fat and neurons. The mechanism of phytanic acid toxicity is unclear.

GENERAL PREVENTION
Avoidance of high phytanic acid containing foods.

PATHOPHYSIOLOGY
The mechanism of phytanic acid toxicity is unclear.

ETIOLOGY
Accumulation of phytanic acid.

COMMONLY ASSOCIATED CONDITIONS
No reports available.

DIAGNOSIS

HISTORY
The cardinal neurologic manifestations include a demyelinating neuropathy (causing distal weakness and sensory disturbance), sensorineural deafness, cerebellar ataxia, anosmia, and cranial nerve involvement. Night blindness secondary to retinitis pigmentosa (RP) is common.

PHYSICAL EXAM
There may be marked nerve hypertrophy and pes cavus. RP and anosmia occur most frequently. Cataracts, photophobia, and miosis occur less frequently. Cardiac involvement may cause premature death usually secondary to arrhythmias. The skin is thickened and dry, and epiphyseal dysplasia and syndactyly may lead to a characteristic shortening of the fourth toe, which can be diagnostically useful. However, this latter feature is present in only 30% of patients.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
Initial lab tests
Plasma phytanic acid levels markedly elevated (>200 μmol/L, normal range <19 μmol/L).

Follow-up & special considerations
Monitor phytanic acid levels following dietary modification.

Imaging
Initial approach
Not indicated.

Diagnostic Procedures/Other
CSF protein levels are often elevated.

Pathological Findings
Nerve biopsy is no longer particularly useful, but onion bulb formation and targetoid inclusions have been described.

DIFFERENTIAL DIAGNOSIS
Phytanic acid accumulates in other conditions including Zellweger's disease, neonatal adrenoleukodystrophy, infantile Refsum's disease, and rhizomelic chondrodysplasia punctata. However, these conditions have a different phenotype. Other enzymatic defects in the metabolic pathway of phytanic acid have also been described. Patients with a deficiency of α-methylacyl-CoA racemase have a Refsum's phenotype, but in that condition pristanate levels are also elevated, whereas in classical Refsum's disease the pristanate to phytanate ratio is <0.0007. Friedreich's ataxia, mitochondrial disease, other hereditary neuropathies, and vitamin E deficiency can usually be differentiated on clinical grounds.

TREATMENT

MEDICATION

First Line

No reports available.

Second Line

No reports available.

ADDITIONAL TREATMENT

General Measures

Phytanic acid is almost exclusively of exogenous origin, and dietary restriction reduces plasma and tissue levels. Fish, beef, lamb, and dairy products should be avoided. Poultry, pork, fruit, and vegetables are freely allowed. The diet should contain enough calories to prevent weight loss and consequent mobilization of phytanic acid from fat. Dietary treatment needs to be lifelong.

Issues for Referral

Refer to dietician; aim to reduce phytanic acid levels to 100–300 μmol/L.

Additional Therapies

Emolient creams for dry skin.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

No reports available.

SURGERY/OTHER PROCEDURES

Cataract surgery and orthopedic correction of foot deformities may be necessary in some patients.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Occasionally, where phytanic acid levels are extremely high or where the presentation is acute Refsum's disease may mimic Guillain–Barré syndrome or cause cardiac arrhythmia. This can be precipitated by rapid weight loss, intercurrent illness or pregnancy. Resuscitate patient and ensure adequate hydration. Perform ECG. Consider lipapharesis or plasmapharesis but not dialysis.

Admission Criteria

Rapidly increasing phytanic acid levels. Cardiac arrhythmia.

IV Fluids

About 3 L/day minimum. Ensure glucose levels normal.

Nursing

High calorie diet.

Discharge Criteria

Reduction in phytanic acid levels. Resolution of weakness and/or arrhythmia.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Annual measurement of phytanic acid levels. Annual ECG.

Patient Monitoring

Annual review by neurologist, cardiologist, ophthalmologist, and dietician.

DIET

High calorie diet.

PATIENT EDUCATION

- http://www.refsumdisease.org/patients/supportnetwork.shtml
- There is a Refsum's clinic at the Chelsea and Westminster Hospital, London, UK (phone: 0044-2082372730).

PROGNOSIS

The neurologic, cardiac, and dermatologic sequelae usually can be reversed to some extent by lowering plasma phytanic acid levels. The visual and hearing deficits and anosmia are less responsive to treatment. Pregnancy, rapid weight loss, and fever may be associated with rapid deterioration. Life expectancy is not significantly reduced.

COMPLICATIONS

As above.

ADDITIONAL READING

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CODES

ICD9

356.3 Refsum's disease

CLINICAL PEARLS

- Consider Refsum's disease in any patient with RP or unexplained anosmia.
- Refsum's disease can mimic Guillain Barre syndrome if phytanic acid levels rapidly increase due to intercurrent illness, pregnancy or extreme weight loss (phytanic acid is stored in fat).
- Syndactyly can be diagnostically useful.

RESTLESS LEG SYNDROME

Jeffrey Weiland, MD

BASICS

DESCRIPTION

Restless leg syndrome (RLS) is a disorder characterized by uncomfortable sensations in the calves or feet and, rarely, the upper extremities. The sensations are variously described as painful, tingling, crawling, or "pins and needles." Typically, the sensations begin late in the evening around bedtime and may present as insomnia. However, patients may be awakened by the sensations or they may occur earlier in the day and may interfere with sedentary work or driving. The uncomfortable sensation is immediately quenched by movement of the extremity but frequently returns when movement ceases.

EPIDEMIOLOGY

RLS is thought to affect 2–5% of the population.

- Race
  - There appears to be no racial preference.
- Age
  - Although the syndrome tends to appear in middle age, symptoms are frequently present for many years prior to presentation.
- Sex
  - Men and women are affected equally.

RISK FACTORS

Pregnancy Considerations

Symptoms of RLS have been reported in 10–20% of pregnant women and usually resolve after delivery.

Genetics

Approximately 50% of patients with RLS describe relatives with similar symptoms, suggesting a genetic factor, although the high prevalence of this condition in the general population may make this simply a chance happening. In contrast, families have been described with multiple members clearly affected in a pattern suggestive of autosomal-dominant inheritance. A French-Canadian family was reported with apparent autosomal-recessive mode of inheritance and several candidate locations on chromosome 12.

ETIOLOGY

Etiology is unknown. RLS occurs as an idiopathic form without evidence of any other disease process and as secondary or symptomatic disease in association with several other medical conditions. Some researchers theorize that some of the manifestations of RLS result from disinhibition of descending inhibitory spinal pathways. In addition, the response of many patients to dopaminergic medications suggests that there may be a dysregulation of dopaminergic pathways in the brainstem or spinal cord.

COMMONLY ASSOCIATED CONDITIONS

In addition to pregnancy, RLS has also been shown to be associated with iron deficiency with or without anemia and chronic renal failure (especially patients on dialysis). There also appears to be a higher frequency in patients with Parkinson's disease, peripheral neuropathy, and radiculopathy. Tricyclic antidepressants as well as fluoxetine, caffeine, and verapamil have all been demonstrated to increase symptoms of RLS. Other conditions with less well-established associations include:

- Magnesium deficiency
- Folate deficiency
- Rheumatoid arthritis
- Diabetes

DIAGNOSIS

Diagnostic criteria put forth by the International Restless Legs Syndrome Study Group in 1995 include:

- Desire to move the extremities in association with unpleasant sensations in the calves or feet (and occasionally the upper extremities). These unpleasant sensations are variable and described as a deep burning, tingling, cramping, aching, crawling, or itching.
- Motor restlessness: People with RLS feel a compelling urge to move a limb but do have some choice of which type of movement to perform. The spectrum of movements includes walking, pacing, rocking, shaking, stretching, etc.
- Symptoms are worse at rest with partial and temporary relief with movement, but recur as soon as the patient stops moving and rests.
- Symptoms are worse in the evening or at night, worsening to a peak around midnight and then improving in the morning. These movements may prevent or fragment sleep.
- Although the syndrome is chronic, there is tremendous fluctuation in the intensity of symptoms. Patients may go weeks or months without symptoms followed by nightly occurrences. There is some evidence that stress may play a role as symptoms tend to be more severe at the end of the work week.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

CBC, electrolytes, BUN and creatinine, vitamin B_{12}, folate, iron, and ferritin.

Diagnostic Procedures/Other

- Although 80–90% of patients with RLS have frequent periodic limb movements (PLMs) during sleep, polysomnography is of little diagnostic value because of the frequency of PLMs in patients without RLS. Thus the diagnosis of RLS is clinical, based on the presence of dysesthesias of the limbs with the desire to move the extremity, motor restlessness, and worsening of the symptoms at rest or at night.
- NCV/EMG should be considered if there is any evidence of distal sensory loss or diminution of reflexes.

DIFFERENTIAL DIAGNOSIS

Nocturnal leg cramps tend to have an abrupt onset at night and may awaken the patient from sleep. They are painful, tend to be located in the calf or foot, and are accompanied by visible and palpable muscle cramps.

- Fibromyalgia: Symptoms tend to occur throughout the day, are not improved by movement, and usually involve more widespread areas of the body (neck, shoulders, and hips).
- Radiculopathy.
- Neurogenic claudication.
- Akathisia (neuroleptic induced): This syndrome of restlessness with a compulsion to move is seen most commonly with phenothiazine use or in association with Parkinson's disease. In contrast to RLS, the sensory features are less and are more likely to affect the entire body as opposed to the extremities. Symptoms are less prominent at night, and consequently there is less sleep disturbance.
- Small-fiber polyneuropathies: In contrast to RLS, small-fiber polyneuropathies are usually associated with distal sensory loss or abnormal reflexes.
- Painful legs and moving toes syndrome: Usually described as aching pain in the feet or toes associated with involuntary writhing movements. The movements are not increased during the evening and night and therefore are not associated with a sleep disturbance.
- Vesper's curse: This is the sudden awakening from sleep with painful calf cramps and fasciculations, frequently with the urge to move. An increase in right atrial filling pressures with subsequent increase in paraspinal venous volume associated with lumbar stenosis has been cited as the cause.

TREATMENT

MEDICATION

- Dopamine agonists: This class of drugs has become the treatment of choice for RLS. Pramipexole Dihydrochloride (Mirapex) or Ropinirole Hydrochloride (Requip) is considered the mainstay of treatment for RLS. Pramipexole is given as an initial dose of 0.125 mg orally, 2–3 hours before bedtime and the dose can be doubled every 4–7 days to a maximum of 0.5 mg/day. The main side effect is postural hypotension which tends to occur with each initial change in dose. Dosages may need adjustment with renal insufficiency. The drug also may cause some sedation if taken during the day. Likewise, Ropinirole is given 1–3 hours before bedtime with an initial dose of 0.25 mg that can be doubled every 2–3 days to a maximum of 4 mg daily. Side effect profiles are similar. Both drugs may have an interaction with Kava. It appears that the daytime occurrence of RLS symptoms is less with the dopamine agonists.
- Levodopa/carbidopa: Historically, levodopa/carbidopa has been the treatment of choice for RLS. However, due to the limitations described below, their use has largely been supplanted by the dopamine agonists. The starting dose is 100 mg levodopa and 25 mg carbidopa. Most patients can be controlled with doses of 200 mg of levodopa. Unfortunately, two major problems can occur with this drug. First, many patients will suffer a recurrence of symptoms during the night. In this setting, a second dose can be taken or consideration given to using a sustained release form of L-dopa. However, this preparation tends to be less efficacious. A second problem that may occur with L-dopa, particularly when a second dose is taken, is the onset of paresthesias and restlessness during the day. In this setting, a prolonged trial of a benzodiazepine (clonazepam) may be beneficial. Tardive dyskinesia, a possible long-term side effect of L-dopa, does not usually appear in patients with RLS. However, tolerance to the beneficial effects of the drug also may develop.
- Other agents that have proven to be effective in the treatment of RLS include the anticonvulsants gabapentin and carbamazepine. Of these, gabapentin has probably been most effective in doses of 300–1,000 mg at bedtime.
- Contraindications
  - Hypersensitivity to levodopa/carbidopa products
  - History of melanoma, undiagnosed skin lesions
  - Narrow-angle glaucoma
  - Nonselective MAO inhibitors
- Precautions
  - There is a 10% incidence of orthostatic hypotension with use of the dopamine agonists.
- Alternative drugs
  - Benzodiazepines, and specifically clonazepam (0.5–2 mg at bedtime), have been shown to be effective at reducing the symptoms of RLS and improving subjective sleep quality, but the major drawback to these drugs is daytime sedation, particularly in the elderly. Finally, opioids (propoxyphene 65 mg, hydrocodone 5 mg, codeine 30 mg) have long been recognized to reduce the symptoms of RLS and improve sleep quality, but the risks of these medications need to be considered.

ADDITIONAL TREATMENT

General Measures

The mainstay of treatment is the use of various medications that reduce the uncomfortable symptoms of RLS (see below). There is some evidence that daily vigorous exercise may improve the symptoms of RLS. Also, reduction or the elimination of caffeine may be of benefit.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Avoid tobacco products, alcohol, antinausea medications, neuroleptics.
  - Avoid sleep deprivation.
  - Some patients find a massage or stretching helpful before sleep.
  - Hot baths or cold or hot compresses to the limbs.
- Adjunctive treatment
  - No reports available.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Polysomnography is of little use in RLS. Therefore, clinical assessment with questioning both the patient and bed partner about the quality of sleep as well as the presence of daytime sleepiness is indicated on a regular basis.

PATIENT EDUCATION

Because of the relatively high prevalence of this disorder, numerous support groups are available, such as WEMOVE, website: www.wemove.org.

PROGNOSIS

In general the prognosis is good. However, RLS is a lifelong condition, although the intensity of symptoms tends to fluctuate greatly.

ADDITIONAL READING

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CODES

ICD9

333.94 Restless legs syndrome (RLS)

RHABDOMYOLYSIS

J. Ned Pruitt II, MD

BASICS

DESCRIPTION

Rhabdomyolysis is a term used to indicate the acute lysis of skeletal muscle. This often causes the release of myoglobin into the circulation and then into the urine resulting in myoglobinuria.

EPIDEMIOLOGY

Incidence

Because of the many causes of rhabdomyolysis, the exact incidence is unknown.

RISK FACTORS

- Hereditary causes of rhabdomyolysis are often precipitated by brief, intense exercise and/or fasting. Malignant hyperthermia is precipitated by the inhaled anesthetic halothane.
- Traumatic crush injury may damage the muscle directly but may also cause ischemia to the muscle resulting in muscle infarctions.
- Rhabdomyolysis may be a complication of prolonged status epilepticus.
- Extreme muscle exertion, even in well-conditioned individuals may cause rhabdomyolysis.
- Drugs associated with rhabdomyolysis include alcohol, cocaine, heroin, phencyclidine, amphetamines, phenylpropanolamine, and toluene. Lipid lowering agents, especially in combination with fibrates or cyclosporine may cause rhabdomyolysis. Snake and insect venoms often cause rhabdomyolysis. Rapid withdrawal of dopaminergic agents may induce a neuroleptic malignant syndrome with rhabdomyolysis.
- Prolonged immobilization may be a risk factor.

Genetics

Many different hereditary disorders may predispose to rhabdomyolysis; see under etiology section.

GENERAL PREVENTION

Avoidance of precipitating factors such as overexertion and medications associated with rhabdomyolysis.

PATHOPHYSIOLOGY

Breakdown of muscle fibers is associated with leakage of myocyte contents into the circulation including myoglobin, potassium, phosphate, and sulfate. Plasma fluid may be sequestered within injured myocytes.

ETIOLOGY

- Many hereditary and acquired diseases may cause rhabdomyolysis but the most frequent cause is crush injuries. The main hereditary disorders that cause rhabdomyolysis are due to inborn errors of metabolism affecting carbohydrate and lipid metabolism within the muscle. The glycolytic defects include deficiencies in muscle phosphorylase (McArdle's disease), phosphorylase b kinase, phosphofructokinase, phosphoglycerate mutase, phosphoglycerate kinase, and lactate dehydrogenase. Lipid metabolism defects may also cause recurrent rhabdomyolysis with the most common being carnitine palmitoyltransferase deficiency. Defects in long, medium, and short chain fatty acid oxidation may also cause recurrent rhabdomyolysis. More recently, rhabdomyolysis with mitochondrial and respiratory chain disorders have been described. Other biochemical defects can cause recurrent episodes including deficiencies of glucose-6-phosphate dehydrogenase and myoadenylate deaminase. Dystrophinopathies such as Duchenne's muscular dystrophy and Becker muscular dystrophy are sometimes associated with rhabdomyolysis. Malignant hyperthermia is a rare cause of rhabdomyolysis associated with certain types of inhaled anesthetics.
- Although traumatic injury is the most frequent cause of a single episode of rhabdomyolysis many toxins, drugs, infections, and metabolic derangements may induce the syndrome.

COMMONLY ASSOCIATED CONDITIONS

- Acute renal failure
- Renal tubular acidosis
- Hyperkalemia
- Hypocalcemia
- Compartment syndromes

Pregnancy Considerations

Pregnant women with carnitine palmitoyltransferase deficiency or myophosphorylase deficiency may benefit from intravenous glucose at the time of delivery.

DIAGNOSIS

HISTORY

A history of trauma or extreme physical exertion is often present. The initial complaint is of muscle pain; a minority of patients report darkened or abnormally colored urine. Patients should be asked if there is a past history of episodes of rhabdomyolysis or pigmenturia.

PHYSICAL EXAM

Rhabdomyolysis that causes myoglobinuria often causes severe myalgias and muscle swelling. Often the patient is unable or unwilling to move due to the severe myalgias. Nausea and vomiting are often present. If an injury has occurred to a well-localized area a compartment syndrome may develop causing further damage to the muscle secondary to ischemic injury as the internal pressures within the muscle compartment rise. Compartment syndromes may lead to arterial and nerve compression with near irreversible damage to the limb. A drop in urine output is a warning of impending renal failure. With rhabdomyolysis, large releases of potassium from the muscle may cause cardiac arrhythmias. Disseminated intravascular coagulation is a rare complication.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Pigmenturia is present when concentrations of urine myoglobin are >100 μg/mL. Serum levels of creatine kinase peak within the first 2 days after the onset of the illness.
- Urine dipstick for blood, urinalysis.
- Hyperkalemia and hyperphosphatemia with hypocalcemia are often present and electrolyte, BUN, and creatinine levels should be monitored.
- Prothrombin time, activated partial thromboplastin time, and platelet count should be assessed.

Follow-up & special considerations
If the history suggests recurrent episodes of rhabdomyolysis, a muscle biopsy with routine histochemistry and quantitation of enzymes associated with rhabdomyolysis should be done. This should be done after the acute episode has resolved.

Diagnostic Procedures/Other
Muscle biopsy should be considered when there is a history of recurrent episodes as above.

Pathological Findings
Pathological findings comprise necrosis of muscle fibers.

DIFFERENTIAL DIAGNOSIS
- Other causes of pigmenturia such as hematuria, hemoglobinuria, and porphyria.
- A history of recurrent pigmenturia suggests a potential inborn error in metabolism.

TREATMENT

ADDITIONAL TREATMENT
General Measures
The major complications of rhabdomyolysis include renal failure, hyperkalemia, and hypocalcemia. Renal failure can often be prevented with fluid replacement to avoid hypotension and intravenous mannitol or furosemide to maintain urine output. Alkalinization of the urine with intravenous sodium bicarbonate promotes the excretion of myoglobin. Hemodialysis is needed if urine output falls despite these efforts. Hyperkalemia needs to be managed with electrocardiogram monitoring and intravenous glucose and insulin.

Issues for Referral
- Orthopedic consultation should be obtained for suspected compartment syndrome.
- Nephrology consultation is needed for renal failure, severe hyperkalemia, or acid–base imbalance.
- Consider referral to a neuromuscular specialist if there is a history of recurrent episodes.

Additional Therapies
- Symptomatic treatment
- Myalgias often respond to intravenous fluid replacement but narcotics may be helpful

COMPLEMENTARY AND ALTERNATIVE THERAPIES
No reports available.

SURGERY/OTHER PROCEDURES
Compartment syndromes require emergent fasciotomy to prevent further ischemia to the muscle and nerve injury.

IN-PATIENT CONSIDERATIONS
IV Fluids
IV fluid replacement with isotonic crystalloid fluids and close attention to electrolyte levels.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Maintenance of urine output and management of hyperkalemia are key features for the first several days after the onset of the illness.

PATIENT EDUCATION
Precipitating factors need to be avoided.

PROGNOSIS
Most patients recover fully with no lasting effects on their muscle strength if renal failure is avoided. Patients with inborn errors of metabolism or a dystrophinopathy may develop muscle weakness late in life due to recurrent muscle injury.

COMPLICATIONS
Potential for acute or chronic renal failure.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)
- Myoglobinuria

CODES

ICD9
728.88 Rhabdomyolysis

CLINICAL PEARLS
- Rhabdomyolysis may be caused by a wide spectrum of etiologies.
- Recurrent episodes suggest a potential underlying myopathic or metabolic disorder.
- Patients should be monitored closely for the development of electrolyte derangements, renal failure, and compartment syndromes in the acute period.

RHEUMATOID ARTHRITIS, NEUROLOGICAL COMPLICATIONS

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Rheumatoid arthritis (RA) is a chronic multisystem immune complex disease. Extra-articular manifestations occur in 10–20% of patients. Neurologic complications usually occur in patients with moderate to severe RA and can involve the central and peripheral nervous systems (CNS, PNS), including the spine. Chronic synovitis of the spine typically occurs in the cervical region, with damage to the atlantoaxial complex. Complications affecting the PNS are frequent, with carpal tunnel syndrome (CTS; compression neuropathy of the median nerve) being most common.

EPIDEMIOLOGY

Incidence/Prevalence

- RA affects 1–2% of the population. Cervical spine involvement occurs in 30–50% of all RA patients. CTS occurs in 20–65% of RA patients. Vasculitis is noted in 5–15% of all patients. Central nervous system vasculitis and RA nodules are uncommon.
- All races and ethnic groups are affected. Onset is usually between 35 and 50 years of age, but can occur at any age. There is a female predilection, accounting for 75% of cases of RA.

RISK FACTORS

Atlantoaxial subluxation (AAS) is more likely in patients with RA of 10 years or more duration, seropositivity, erosive and deforming peripheral joint disease, and male gender. Compression neuropathies correlate with the severity of local synovitis. Vasculitis is more likely to occur in patients with long-standing RA; the incidence is higher in males.

Pregnancy Considerations

A hormonal role is suspected in disease expression, because there is an increased risk of RA in nulliparous women and a possible protective effect in women that use oral contraceptives.

Genetics

There can be a genetic predisposition for RA; first-degree relatives of seropositive patients are four times more likely to develop RA than controls.

GENERAL PREVENTION

There are no preventive measures available.

PATHOPHYSIOLOGY/ETIOLOGY

RA is mediated by interaction of autoantibodies, such as rheumatoid factor (IgM or IgG class), with circulating immunoglobulins. The immune complexes are composed of IgG combined with IgM or IgG anti-IgG antibodies. Deposition of the immune complexes into the joints and soft tissues induces activation of complement and other inflammatory pathways. AAS results from rheumatoid synovial tissue-induced laxity or destruction of the transverse ligament in combination with odontoid erosion. Subaxial subluxation can occur with rheumatoid involvement of the longitudinal ligaments, vertebral endplates, apophyseal joints, and intervertebral discs. Peripheral neuropathy results from entrapment, segmental demyelination, or rheumatoid vasculitis of the small-to-medium size vessels. Nerve entrapment syndromes arise from inflamed synovial sacs and can affect the median, ulnar, and posterior tibial nerves.

COMMONLY ASSOCIATED CONDITIONS

There is a higher incidence of vasculitic complications in RA patients with Felty's syndrome (i.e., RA, splenomegaly, neutropenia, anemia, and thrombocytopenia).

DIAGNOSIS

HISTORY

- *Spine involvement*: In most cases AAS is asymptomatic, despite the radiologic appearance. Cord and nerve compression is more likely to occur if there is an atlanto-dens interval of >9 mm. Compression of the second spinal nerve roots often causes localized neck pain with radiation to the occiput and scalp. Early signs of cervical radiculopathy are numbness and paresthesias in the glove-stocking distribution. Later signs of progression to cord compromise include myelopathy, lower motor neuron injury at the level of compression, and gait difficulty. Lhermitte's sign (sudden tingling parasthesias that radiate down the spine after cervical flexion) can occur at any stage. Intradural spinal nodules can cause nerve root compression, spinal stenosis, and cord compression.
- *CNS involvement*: Intraparenchymal rheumatoid nodules can cause encephalopathy, seizures, and obtundation. Cerebral vasculitis can present with seizures, stroke syndromes, encephalopathy, cranial neuropathies, ataxia, and hemorrhage (intracerebral or subarachnoid).
- *PNS involvement*: CTS typically presents with night numbness, paresthesias, and pain in the thumb, index, and middle fingers of the affected hand. In severe cases, atrophy of the thenar muscles may be present, along with thumb weakness, and retrograde pain up the forearm. Tinel's sign is often positive—reproduction of symptoms elicited by percussion of the median nerve on the volar aspect of the wrist. Phalen's sign may also be present—flexion of the wrist for at least 1 minute, eliciting numbness, tingling, or pain in the median nerve distribution. Tarsal tunnel syndrome presents as parasthesias, pain, and burning in the toes and soles of the feet. Weakness and atrophy of the intrinsic toe muscles may occur.
- Other PNS manifestations of RA include mild and severe forms of sensorimotor polyneuropathy, as well as a mononeuritis multiplex.

PHYSICAL EXAM

Variable depending on the specific region on involvement, as noted above.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Serological testing for rheumatoid factor and other autoantibodies is necessary.

Imaging

Initial approach

- To evaluate spinal involvement, lateral radiographs of the cervical spine (flexion and extension views) are required to demonstrate subluxation. Lateral AAS can be demonstrated on open-mouthed, anteroposterior views. MRI can further evaluate bony spinal degeneration and screen for spinal cord compression. MRI is also indicated for patients with suspected basilar invagination for whom standard radiographs are inconclusive. A dynamic flexion–extension MRI may be able to reveal subtle instability patterns (e.g., atlantoaxial instability) of the spinal column.
- MRI (with or without MR angiography) can be helpful for the diagnosis of CNS vasculitis.

Diagnostic Procedures/Other
Somatosensory evoked potentials can evaluate the functional integrity of central sensory pathways. Disease processes affecting the cervical spinal cord may produce prolongation of wave and interwave latencies recorded along these pathways. Electromyography and sensory nerve conduction studies are the most accurate method to diagnose compression neuropathies and peripheral neuropathies. Sural nerve biopsies can be helpful if the diagnosis of vasculitis is unclear.

Pathological Findings
Pathological findings include synovial inflammation, formation of invasive rheumatoid synovial tissue or pannus, and vasculitis.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis is broad and includes other causes of myelopathy, cervical subluxation disorders, CNS and PNS vasculitis, entrapment neuropathies, and peripheral neuropathy. RA must be distinguished from degenerative osteoarthritis and from deforming inflammatory arthritis associated with other connective tissue disorders.

TREATMENT

MEDICATION
First Line
Pharmacotherapy of neurological manifestations of RA consists of a combination of corticosteroids and a cytotoxic agent, such as oral cyclophosphamide or methotrexate. The corticosteroid is started at 60–100 mg/day and then tapered over several weeks. Monotherapy with one of the cytotoxic agents is then continued for long-term maintenance therapy. The efficacy of other immunosuppressive therapies such as plasmapheresis and IVIG is unknown.

ADDITIONAL TREATMENT
General Measures
- For patients with cervical spine disease, neck pain without neurologic features tends to be self-limited and usually improves. In the absence of cord compression, conservative management is appropriate with anti-inflammatory or disease modifying anti-rheumatic medications, physical therapy, and soft cervical collars.
- Rheumatoid vasculitis is a potentially life-threatening problem that requires high-dose corticosteroids in combination with a cytotoxic drug such as oral cyclophosphamide or methotrexate.

Additional Therapies
Soft cervical collars can stabilize the spine and reduce neck pain in patients with severe AAS. Local corticosteroid injections and splints may be of benefit for compression neuropathies.

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Simple neck traction may be helpful in patients with severe AAS or subaxial subluxation. Physical and occupational therapy should be considered for patients with myelopathy, peripheral neuropathy, and other forms of weakness.

SURGERY/OTHER PROCEDURES
- For patients with AAS, surgical intervention with C1–2 arthrodesis stabilizes the atlantoaxial complex and usually eliminates occipital pain. The indications for surgery include basilar invagination, neurologic abnormality with spinal instability, intractable neck and head pain, vertebral artery compromise, and asymptomatic spinal cord compression on MRI.
- Surgical release of compression neuropathy may be indicated when there is a significant motor or sensory abnormality and evidence of denervation on neurophysiologic testing.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Admission is uncommon except in cases of acute neurological deterioration where the diagnosis is indeterminate or therapeutic intervention is necessary. Patients with CNS or PNS vasculitis are the most likely subgroup to require admission, usually for weakness, seizures, encephalopathy, gait dysfunction, or other acute complications.

Discharge Criteria
Variable depending on specific complication.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Variables will be depending on the specific syndrome involved.

Patient Monitoring
Rheumatoid arthritis patients that should be screened for AAS with radiographic evaluation include those with posterior skull and/or neck pain and stiffness, and patients with long-standing erosive RA in whom radiographs have not been done within the previous 2 or 3 years. Serial neurological examinations and appropriate follow-up testing (e.g., MRI of the brain or spine, electromyography and nerve conduction testing) will be necessary.

PATIENT EDUCATION
- National Institute of Arthritis and Musculoskeletal Disorders: www.niams.nih.gov
- Arthritis Foundation Home Page: www.arthritis.org

PROGNOSIS
The best course of management is to prevent significant morbidity in RA. Aggressive immunosuppressant therapy will reduce the neurological complications of RA. The overall 5-year mortality rate of RA patients with radiographic evidence of cervical subluxations (with or without neurologic symptoms) is similar to severe RA patients without cervical involvement. The risk of developing upper cervical spinal cord compression secondary to anterior AAS is increased by male sex, anterior subluxation >9 mm, and coexistent atlantoaxial impaction. There is a higher incidence of fatality with basilar invagination. The prognosis of rheumatoid vasculitis is poor. Independent variables that best predict mortality include cutaneous vasculitis, multifocal neuropathy, and depressed C4 level.

COMPLICATIONS
Variables as noted above.

ADDITIONAL READING

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- Nadeau SE. Neurologic manifestations of connective tissue disease. *Neurol Clin* 2002;20:151–178.

See Also (Topic, Algorithm, Electronic Media Element)
- Vasculitis, myelopathy, entrapment neuropathy, peripheral neuropathy

CODES

ICD9
- 714.0 Rheumatoid arthritis
- 714.89 Other specified inflammatory polyarthropathies
- 727.01 Synovitis and tenosynovitis in diseases classified elsewhere

CLINICAL PEARLS
- Patients with longstanding RA and progressive neck pain should be screened for AAS.
- A screening neurological exam should pick up myelopathy and/or CTS.

SARCOIDOSIS, NEUROLOGICAL COMPLICATIONS

Melissa R. Ortega, MD
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BASICS

DESCRIPTION

Sarcoidosis is a chronic disorder of unknown etiology characterized by multisystem dissemination of noncaseating granulomas. It most often involves the lungs, skin, and eyes, but virtually any organ can be involved. Neurosarcoidosis (NS) affects 5 to 10% of patients. Of these, 10 to 17% of patients have isolated neurological involvement. Sarcoidosis can affect all parts of the nervous system including the brain, spinal cord, optic nerves, peripheral nerves, and muscle.

EPIDEMIOLOGY

Incidence

- Worldwide incidence ranges from 1 to 64 per 100,000 with the highest incidence in northern European countries. In the USA, the disorder is thought to occur more frequently in the southeastern states.
- Race
  - There appears to be significantly more involvement of African-Americans with a tenfold increase compared to Caucasians in the southeastern part of the USA.
- Age
  - Occurs in all ages
- Sex
  - A slight preponderance is reported in females.

RISK FACTORS

There are no known risk factors for this disorder. However, for reasons that are unclear, the disorder favors the nonsmoker.

Pregnancy Considerations

Specific information regarding pregnancy is lacking. Anecdotal reports of remission as well as flare-ups during pregnancy have been reported.

Genetics

- A genetic basis for this disease is speculated, but no specific gene has been identified.
- Having a first-degree relative with sarcoidosis increases the risk for disease fivefold.

PATHOPHYSIOLOGY

- The pathological hallmark of sarcoidosis is a granuloma that consists of a central follicle made up of epithelioid and CD4 lymphocytes surrounded by a ring of CD8 lymphocytes, B cells, and fibroblasts.
- Neurologic dysfunction is due to granulomas that may vary from small white matter lesions to large space-occupying lesions with mass effect.

ETIOLOGY

- The cause of this disorder is unknown. The prevailing hypothesis is that in the genetically susceptible individual, there are abnormalities of cell-mediated immune responses to an as-of-yet unidentified environmental agent or agents.

COMMONLY ASSOCIATED CONDITIONS

- None. However, patients with sarcoidosis can have increased susceptibility to mycobacterial infections.
- Patients may also exhibit cutaneous anergy and have false negative purified protein derivative skin test for tuberculosis.

DIAGNOSIS

HISTORY

- Symptoms will vary depending on what part of the nervous system is involved.
- In the CNS, sarcoidosis affects the basal meninges and the area around the third ventricle, including the thalamus, hypothalamus, and pituitary gland.
  - Patients may present with features of meningitis such as headache or neck stiffness.
  - Hypothalamic and pituitary gland can manifest as the syndrome of inappropriate secretion of vasopressin (SIADH) or diabetes insipidus (DI). Almost half of the patients with CNS sarcoidosis develop hyperprolactinemia with secondary glactorrhea in either sex.
- Optic neuritis occurs, especially in the form of papillitis.
- Seizures of any type may occur.
- Multiple cranial nerve palsies are common, especially unilateral or bilateral Bell's palsy. Recurrent seventh nerve palsy of the lower motor neuron type, especially when bilateral, should suggest sarcoidosis.
- The spinal cord can be involved and may be enlarged with evidence of an intramedullary mass and resultant compressive myelopathy and its clinical manifestations.
- Sarcoidosis can affect the peripheral nervous system in conjunction with other nervous system involvement or in isolation. The symptoms of peripheral nerve involvement are due to the space-occupying nature of the granulomas that result in expansion of the nerves and sometime compression.
- Muscle involvement in systemic sarcoidosis is common. The patient may have muscle pain or present with weakness from myopathy. It can be a useful site for biopsy for demonstration of the sarcoid granuloma.
- It is important to obtain a thorough review of systems to help detect other organ involvement.

Pediatric Considerations

- Children with NS are more likely to have seizures and space-occupying lesions, and less likely to have cranial nerve palsies.

PHYSICAL EXAM

- A thorough neurological exam to localize the site of nervous system involvement is important.
- A thorough general physical exam must be done to evaluate for signs of extraneurologic involvement.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- CSF
  - Since meningeal involvement is common, CSF evaluation is particularly helpful.
  - CSF pressure is usually normal.
  - Fluid is colorless unless associated with elevated spinal fluid protein, which causes xanthochromia.
  - Moderate to severe pleocytosis is common, causing concern of an infectious process. White blood cells counts can be around 100/mm^3. Most cells are mononuclear, predominantly CD4 T-cells. Some B cells are evident as well.
  - Increased production of intrathecal IgG is common with abnormally elevated IgG index and the presence of oligoclonal bands.
  - ACE levels in the CSF may be elevated in NS, but the test has many limitations. It can be seen in systemic sarcoidosis and in patients with liver disease of other etiologies. It can be transported from serum into CSF across an intact blood-brain barrier, thus CSF levels may be elevated without any evidence of CNS involvement. Conversely, CSF ACE levels can be normal in patients with true NS and isolated spinal cord or brain granulomas.
- In every patient with suspected sarcoidosis of the CNS, evaluation should be done to identify multisystem involvement. This may include measurement of serum ACE levels, liver enzyme levels, and calcium level which may increase from granuloma formation. Certain imaging findings are highly suggestive of sarcoidosis and can provide guidance for a biopsy site, including chest radiography for hilar adenopathy or CT of the chest to evaluate for adenopathy or granulomas. Gallium and positron emission tomography scanning can also reveal occult disease. Bronchoalveolar lavage with phenotyping of the washed cells; biopsy of skin, conjunctiva, liver, lung, or lymph node; or rarely a CNS biopsy may be necessary to make a diagnosis.

Imaging

- MRI can detect granulomatous involvement of the meninges, cerebral parenchyma, and spinal cord. CT of the brain does not have any role because of low sensitivity to detect sarcoid lesions.
- MRI with gadolinium shows enhancement of the meninges affected by the sarcoid granulomata as well as parenchymal lesions with disruption of the blood–brain barrier.

Diagnostic Procedures/Other
There are no specific tests for the diagnosis of isolated sarcoidosis of the CNS. In the absence of systemic sarcoidosis, biopsy is the only method of diagnosis. In a third of patients with CNS sarcoidosis, such methods may be necessary.

Pathological Findings
Noncaseating Granulomas

DIFFERENTIAL DIAGNOSIS
Entities to be considered include infectious disorders such as cryptococcosis, histoplasmosis, coccidioidomycosis, tuberculosis, syphilis, and Lyme disease; inflammatory disorders including vasculitis, Behcet's disease, multiple sclerosis, acute disseminated encephalomyelitis; and malignancies such as meningeal carcinomatosis, primary lymphoma of the CNS, metastatic disease, and gliomatosis cerebri.

TREATMENT

MEDICATION
First Line
- Corticosteroids are the mainstay treatment of sarcoidosis, and NS is no exception.
  - – Acutely, patients may be treated with intravenous steroids for disorders that require immediate resolution. Methylprednisolone is administered in doses of 500 to 1,000 mg in D5/0.45% NaCl daily for 3 to 5 days.
  - – Oral prednisone may be necessary in severe cases and is used in doses of 1 mg/kg daily or every other day to prevent side effects. There are no good controlled studies that have examined the dose, route of administration, or duration of treatment necessary for NS. The duration of treatment can vary depending on patient's response during treatment and during steroid withdrawal.
- Contraindications
  - – Corticosteroids are contraindicated in cases of known hypersensitivity or allergy. Steroids should be used with caution in patients with hypertension, diabetes, or known history of gastroduodenal ulcer.
- Precautions
  - – Corticosteroid treatment can be associated with gastrointestinal ulcers, glucose intolerance, and elevated blood pressure. In rare individuals, aseptic necrosis of bone/joint, more commonly the femur or shoulder, can occur and require surgical replacement. Daily treatment for prolonged periods can result in adrenal insufficiency, which can be minimized with an alternate-day regimen. Chronic treatment can also lead to osteoporosis and increased susceptibility to opportunistic infections.

Second Line
Drugs that have been used as adjunctive therapy with steroids to reduce the granuloma load and to reduce the steroid doses required include methotrexate, cyclosporine, cyclophosphamide and, less often, indomethacin, allopurinol, hydroxychloroquine, and levamisole. Their use has been reported in small case reports and series but there are no good controlled trials of any medication in NS. Most recently, tumor necrosis factor -alpha inhibitors and mycophenolate have been tried with mixed results. For pulmonary sarcoidosis, a trial of an anti-CD20 monoclonal antibody (NCT00855205) and a trial of atorvastatin (NCT00279708) are currently underway.

ADDITIONAL TREATMENT
- In addition to steroids and immunosuppressants, supportive measures may be required depending on the mode of presentation. Antiepileptic drugs may be needed for seizures. With SIADH or DI electrolyte imbalances may need correcting. Patients with myelopathy may require attention to bowel and bladder function.
- Adjunctive therapy to reduce steroid complications is necessary. H2 blockers or proton pump inhibitors should be given for prevention of peptic ulcer disease. Bisphosphonate therapy should be considered in patients with osteoporosis. When appropriate, use of trimethoprim with sulfa for chemoprophylaxis against *Pneumocystis carinii* shold be considered.

SURGERY/OTHER PROCEDURES
- Sugery is rarely indicated for treatment as granulomas usually resolve with steroids and/or immunosuppressants.
- If disease is confined to the CNS, biopsy of a lesion or meninges may be necessary for diagnosis.

IN-PATIENT CONSIDERATIONS
Admission Criteria
Admission may be dictated by the nature of CNS involvement, such as altered mental status from meningitis and hydrocephalus, spinal cord involvement with paresis, etc.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Patients should be monitored for corticosteroid-induced complications as well as response to treatment. Cushingoid side effects can be minimized by reduction of oral salt intake. Patients should be instructed on a low-carbohydrate diet to minimize weight gain and glucose intolerance. Patients on chronic steroids should have yearly bone density scans monitoring for osteoporosis. ACE levels are often not elevated, and therefore seldom helpful in monitoring tretment. Imaging with gadolinum-enhanced MRI can be helpful. The best guide to effective treatment, however, is the clinical reponse of the individual patient.

PATIENT EDUCATION
Instruct patients on chronic steroid therapy to maintain a 1-g sodium and 1,500–2,000-calorie low-carbohydrate diet to minimize weight gain and cushingoid side effects. To minimize bone mass loss, patients should do regular weight-bearing exercise and refrain from smoking.

PROGNOSIS
Excellent resolution of the symptoms can be expected in the short term with corticosteroid therapy. Patients with extensive basal meningeal disease, endocrinoapthy, or spinal cord granulomas often require more chronic therapy. With long-term therapy, prognosis for complete resolution is often excellent.

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See Also (Topic, Algorithm, Electronic Media Element)
- Hutchinson's disease
- Boeck's disease
- Uveoparotid fever
- Heerfordt's disease
- Blau's syndrome

CODES

ICD9
135 Sarcoidosis

CLINICAL PEARLS
- Recurrent or bilateral facial palsy (simultaneous or sequential) is a red flag that merits evaluatiion for sarcoidosis.
- Consider sarcoidosis if the CSF shows an elevated IgG index or oligoclonal bands, but there is a white cell count >50 mm^3 or an elevated protein >100 mg/dL or a high CD4/CD8 ratio.

SLEEP APNEA

Jeffrey Weiland, MD

BASICS

DESCRIPTION

Obstructive sleep apnea (OSA) is a severely underdiagnosed disorder characterized by intermittent nocturnal upper airway occlusion. This occlusion causes loud, irregular snoring, hemoglobin desaturation, and recurrent arousals from sleep. In addition to its impact on patient well-being, there is a growing body of evidence that untreated OSA has serious long-term cardiovascular effects. OSA also has public health ramifications, largely due to its effects on driving and workplace performance.

EPIDEMIOLOGY

- Incidence/prevalence
  - OSA is estimated to affect 2% of women and 4% of men over the age of 50. The prevalence is somewhat lower in younger populations, though it has been reported to affect even very young children, largely due to congenital upper airway abnormalities. At least, one series suggests that a significant minority of OSA occurs in patients without the "typical" body habitus.
- Race
  - OSA has no well-established racial predilection.

RISK FACTORS

Risk factors include obesity, increased neck circumference (>16 in. in females, >17 in. in males), retrognathia, macroglossia, other craniofacial abnormalities, acromegaly, hypothyroidism, neuromuscular disorders, and use of alcohol or sedative medications. While some authors believe that chronic nasal obstruction is a risk factor, this subject remains controversial.

Pregnancy Considerations

Several case reports have suggested an association between untreated OSA and preeclampsia.

Genetics

Although familial clustering of OSA has been widely noted, a definitive genetic basis for the disease has not yet been identified.

ETIOLOGY

- Partial or complete upper airway obstruction during sleep is the crucial event in the genesis of OSA. The physiologic decrease in pharyngeal muscle tone seen in all sleeping persons is a major contributor, though this effect alone is generally inadequate to cause symptomatic obstruction. Sedative drugs and alcohol accentuate the decrease in muscle tone and can worsen the occlusion. Most patients also have anatomic upper airway narrowing, usually related to the peripharyngeal infiltration of fat seen in obesity. Retrognathia, macroglossia, and abnormally large tonsils, soft palate or uvula are other abnormalities that are sometimes seen. Additionally, posterior movement of the tongue in the supine sleeper narrows the airway further.
- Obstruction of the airway causes apnea or hypopnea in the face of repeated respiratory efforts, oxyhemoglobin desaturation, and ultimately, arousal. Arousal then increases muscle tone in the upper airway, relieving the obstruction. Arousal is usually partial, and may occur more than a hundred times per hour, leading to fragmented sleep.

COMMONLY ASSOCIATED CONDITIONS

- Multiple large series have demonstrated a relationship between OSA and systemic hypertension; the relative risk of hypertension is greater with more severe degrees of OSA. Whether treatment of OSA improves hypertension is less clear, although this effect has been seen anecdotally.
- There is no definitive evidence that OSA causes pulmonary hypertension or congestive heart failure, though numerous series suggest that these conditions can improve if coexisting OSA is treated.
- Untreated OSA has a well-documented correlation with automobile accidents; one series from Canada demonstrated an accident rate in untreated OSA three times that of non-OSA controls. In another study, patient-reported near-miss rates decreased almost eightfold after treatment with continuous positive airway pressure (CPAP).

DIAGNOSIS

Loud, irregular snoring and daytime hypersomnolence are the hallmarks of OSA. Patients commonly awake in the morning unrefreshed, and often describe falling asleep during quiet activities, such as reading, watching TV, or driving. A history from the patient's bed partner is crucial, and often reveals witnessed episodes of apnea during sleep. Other symptoms include nocturnal choking, sore throat, morning headache, difficulty concentrating, memory impairment, irritability, and depression.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

A thyroid-stimulating hormone level should be measured to assess for hypothyroidism; CBC may reveal polycythemia if nocturnal desaturations are significant.

Imaging

Radiologic studies are generally not useful in OSA.

Diagnostic Procedures/Other

- Polysomnography (PSG) performed in a sleep lab is the test of choice for diagnosing OSA. PSG consists of EEG, electrooculography, electromyogram, electrocardiography, pulse oximetry, nasal and oral airflow measurements, and measurement of chest and abdominal wall movement, all done during a night of sleep. PSG in a patient with OSA typically demonstrates repeated apneas and hypopneas with EEG-documented arousal and varying degrees of oxyhemoglobin desaturation.
- The number of apneas and hypopneas per hour of sleep is referred to as the respiratory disturbance index (RDI); an RDI of greater than 5 is usually considered abnormal.
- The high cost of PSG has given rise to various portable monitors (PM) for home diagnosis of OSA; PM may be used as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA but is not appropriate for the diagnosis of OSA in patients with significant comorbid sleep disorders or the general screening of asymptomatic populations. PM may also be indicated in the monitoring of response to non-CPAP treatments for OSA.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of OSA includes simple snoring, central sleep apnea, narcolepsy, insufficient sleep, idiopathic CNS hypersomnia, periodic limb movement disorder, psychiatric disorders, and alcohol or sedative drug use.

TREATMENT

MEDICATION

Although a number of medications have been used to treat OSA in the past, none are effective, and pharmacotherapy is not currently indicated for this disorder.

ADDITIONAL TREATMENT

General Measures

- CPAP is the primary nonsurgical treatment for OSA. CPAP acts as a pneumatic splint for the upper airway, preventing obstruction during sleep, and is quite effective in most cases. It can be delivered either via nasal mask or full-face mask, and is titrated to a normal RDI during PSG. Compliance data are mixed, although adherence to therapy tends to be greater in those with more severe OSA.
- Mandibular advancement devices are oral appliances custom fit to the patient's mouth, and designed to direct the mandible anteriorly, preventing obstruction at the level of the hypopharynx. Though well tolerated, these devices are not as effective as CPAP, and are only useful in those with mild-moderate OSA.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - There is no symptomatic treatment for OSA other than those listed above.
- Adjunctive treatment
  - Weight loss can decrease the severity of OSA, and can occasionally be curative, but is usually difficult to maintain. Avoidance of the supine sleeping position can also be helpful, and the use of alcohol and sedative medications should be limited if possible.

SURGERY/OTHER PROCEDURES

- Uvulopalatopharyngoplasty (UPPP) is the most commonly performed surgical procedure for OSA. It consists of removal of the uvula, posterior soft palate, and redundant peripharyngeal tissue. Long-term cure rates with this procedure are less than 50%, and many patients ultimately require CPAP or repeat surgery. UPPP is probably most effective in those with mild OSA.
- More invasive base-of-tongue and mandibular advancement procedures can be effective in carefully selected patients; these procedures require an experienced ENT surgeon and carry a higher risk of complications.
- Tracheostomy is curative for OSA, but is reserved for patients with very severe OSA who are noncompliant or unresponsive to maximal CPAP.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Periodic reassessment of the patient's sleep quality by interview is important to assure sustained response to therapy. Current CPAP devices allow downloadable documentation of both compliance and efficacy. If symptoms such as daytime hypersomnolence or snoring recur, repeated PSG is sometimes needed to titrate CPAP or evaluate the need for further therapy. However, auto-titrating devices have largely eliminated the need for repeat CPAP titration.

PATIENT EDUCATION

- Patients should be advised that weight gain could decrease the effectiveness of most therapies for OSA
- For those patients using CPAP, an experienced respiratory therapist is an invaluable educational resource, and can often provide advice regarding the technical aspects of CPAP use that the physician cannot.
- There is an extensive body of information on OSA available via the internet, including professional societies, nonprofit organizations, and support groups. Links to many of these groups can be found at www.sleepapnea.org.

PROGNOSIS

The prognosis for treated OSA is generally good. While surgery or significant weight loss can sometimes lead to a permanent cure, OSA usually requires lifelong therapy.

ADDITIONAL READING

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CODES

ICD9

- 327.23 Obstructive sleep apnea (adult) (pediatric)
- 780.57 Unspecified sleep apnea

SPHINGOLIPIDOSES

Eveline C. Traeger, MD

BASICS

DESCRIPTION

- Inherited degenerative storage disorders caused by deficiency of an enzyme that is required for the catabolism of lipids that contain ceramide. The lipids that accumulate in tissues and organs of affected individuals are from the normal turnover of cells and cell components. Differences in properties of the accumulating substances as well as the type of tissue in which a particular lipid component is rapidly turning over account for the diverse clinical manifestation of the disorders.
- There are nine diseases, most of which have variable phenotypes that correlate with the level of residual enzyme activity. Central and/or peripheral nervous system involvement is true of all except type 1 Gaucher and Niemann-Pick type B. The clinical features described in this chapter are for the most common phenotype with neurologic manifestations. Phenotypes that may be characterized by delayed onset during adolescence or adulthood and usually associated with variable neurologic and systemic manifestations are described in more extensive reviews.

EPIDEMIOLOGY

Incidence/Prevalence

- Tay Sachs (GM2-Gangliosidosis, Type I): Incidence is highest among people of Ashkenazi Jewish descent with a carrier rate of 1 in 27 people. Incidence is also increased in the Pennsylvania Dutch group, French-Canadians in Quebec, and Cajun community of Louisiana. In the general population, 1 in 250 people are carriers.
- Sandhoff (GM2-Gangliosidosis, Type II): Incidence of 1/384,000 live births. Creole population in Argentina, Métis Indians in Saskatchewan, and individuals of Lebanese heritage have a higher incidence.
- GM1-gangliosidosis: Estimated incidence is 1:100,000-200,000. A high incidence of 1/3,700 is reported in the population of Malta.
- Fabry: Prevalence estimated between 1/40,000 and 1/117,000.
- Niemann-Pick type A: Panethnic but with an increased incidence in Ashkenazi Jews of 1/40,000.
- Gaucher: Panethnic. Type I is most commonly diagnosed in Ashkenazi Jews. Type 3 is more common in the Norrbottnian region of Sweden.
- Farber Lipogranulomatosis: Very rare. Incidence is not known.
- Krabbe: Panethnic with an incidence estimated at 1/100,000 births. Incidence of 6/1,000 births in some Arab communities in Israel. Incidence also increased in the Scandinavian countries, reported as 1/50,000.
- Metachromatic Leukodystrophy: Panethnic with an incidence estimated at 1/40,000 to 160,000 births. A particularly high incidence of 1/75 in the Habbanite Jewish community in Israel. Incidence of 1/2,500 in the western portion of the Navajo Nation and 1/8,000 among Arab groups in Israel.

Sex

Because of X-linked inheritance, patients with Fabry are male. Female heterozygotes may manifest symptoms of the disease but symptoms are less severe and of later onset.

RISK FACTORS

Genetics

The sphingolipidoses are inherited in an autosomal-recessive manner except for Fabry, which is X-linked. Carrier identification and prenatal testing are available.

PATHOPHYSIOLOGY

Deficiency of a lysosomal hydrolase required to degrade glycosphingolipids, an essential component of cell membranes. Lysosomal accumulation of the enzyme's substrate results in physiologic and morphologic alterations of specific tissues and organs with clinical manifestations that may include neurodegeneration, organomegaly, skeletal abnormalities, bone marrow dysfunction and pulmonary infiltration.

DIAGNOSIS

HISTORY

- Tay-Sachs and Sandhoff: Onset at 3 to 5 months with exaggerated startle response to sound and decreased visual attentiveness. By 6 to 10 months of age, there is progressive weakness and loss of previously attained milestones. Thereafter, progression is rapid. A cherry-red spot is present in almost all patients. Seizures usually develop by the end of the first year. Macrocephaly from reactive cerebral gliosis is common. Organomegaly is a feature of Sandhoff disease, but not Tay Sachs disease.
- GM1- gangliosidosis: Onset of developmental arrest before 6 months of age followed by progressive CNS deterioration. Of patients, 50% have a cherry-red spot. Hepatosplenomegaly is almost always present. Skeletal dysplasia seen. Patients become vegetative with generalized spasticity, contractures, and generalized seizures.
- Fabry disease: Onset in preteen and adolescent boys. Early signs of characteristic corneal and lenticular opacities, small punctuate reddish-blue angiokeratoma on the umbilicus, flank, thighs, penis and scrotum, pain in the extremities (acroparesthesia), and hypohidrosis. Progressive CNS damage from prothrombotic and occlusive abnormalities, and large vessel ectasias with transient ischemic attacks, vascular thromboses, seizures, hemorrhagic or ischemic strokes. Progressive cardiac and renal disease.
- Niemann-Pick type A: Onset prior to 6 months of age with psychomotor retardation. A cherry-red spot is present in 50% of patients. Progressive spasticity, rigidity, and vegetative state. Hepatosplenomegaly.
- Gaucher disease type 2: Onset from infancy to 6 months of age with progressive CNS damage including marked mental retardation, seizures, hypertonicity with hyperactive reflexes, cranial nerve involvement with strabismus, facial weakness, and dysphagia. Hepatosplenomegaly.
- Farber lipogranulomatosis: Onset from infancy to 4 months of age. Swollen, painful joints with subcutaneous nodules over affected joints and pressure points. Progressive aphonia, swallowing, and feeding difficulties due to laryngeal involvement. Lower motor neuron involvement, which manifests as hypotonia and muscular atrophy. Psychomotor development variable from severe involvement to normal intelligence. Cherry-red spot macula.
- Krabbe: Onset 3 to 6 months of age with psychomotor delay, tonic seizures, progressive motor impairment with hypertonicity. Deafness and blindness are common. Peripheral neuropathy detected. CSF protein increased. Clinical symptoms restricted to nervous system.
- Metachromatic leukodystrophy: Late infantile form with onset at age 1 to 2 years, with progressive ataxia, hypotonia, and diminished deep tendon reflexes. Progressive optic atrophy and spastic quadriparesis. Slowing of conduction velocities of peripheral nerve. CSF protein increased.

PHYSICAL EXAM

- Progressive neurodegeneration with loss of previously attained milestones.
- Macrocephaly in GM2-Gangliosidosis
- Organomegaly in Sandhoff, GM1 gangliosidosis, Niemann-Pick type A, Gaucher type 2.
- A cherry-red spot macula on ophthalmologic exam in GM2 and GM1-Gangliosidosis, Niemann-Pick type A and Farber disease.
- Skeletal abnormalities in GM1 gangliosidosis.
- Angiokeratoma in Fabry disease.

Imaging

Initial approach

- Neuroimaging studies may reveal nonspecific changes such as atrophy.
- Skeletal radiographs for patients with GM1 gangliosidosis may reveal anterior beaking of vertebrae, enlargement of sella turcica, and thickening of calvaria.

Diagnostic Procedures/Other

- Diagnosis is made by enzymatic assay of the specific enzyme in leukocytes, or skin fibroblasts.
  - Tay Sachs: Hexosaminidase A deficiency
  - Sandhoff: Hexosaminidase A and B deficiency
  - GM1: β-galactosidase deficiency
  - Fabry: α-galactosidase A (ceramide trihexosidase) deficiency
  - Niemann-Pick type A: Sphingomyelinase deficiency
  - Gaucher: Glucocerebrosidase deficiency
  - Farber: Ceramidase deficiency
  - Krabbe: Galactocerebrosidase deficiency
  - Metachromatic Leukodystrophy: Arylsulfatase A deficiency

DIFFERENTIAL DIAGNOSIS

The sphingolipidoses must be differentiated from other inherited neurodegenerative diseases.

TREATMENT

MEDICATION

First Line

- Enzyme replacement therapy (ERT) with recombinant glucocerebrosidase for patients with Gaucher type 2 and type 3 disease as a palliative measure to treat severe visceral involvement. Treatment does not alter the neurologic progression.
- ERT with recombinant alpha-galactosidase A for patients with Fabry disease.
- There are no specific treatments for the other disorders.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - Carbamazepine or phenytoin, occasionally in combination with amitriptyline, is used to treat the painful neuropathy in patients with Fabry disease.
  - Kidney transplant and long-term hemodialysis in patients with Fabry disease with renal failure.
  - Bone marrow transplant for treatment of Gaucher type 3 may decrease visceral storage.
- Adjunctive Treatment
  - The indication for physical therapy should be assessed on an individual basis.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are usually admitted for evaluation and treatment of the neurologic and systemic complications of their disorder.

ONGOING CARE

PATIENT MONITORING

Patient follow-up is guided by the predicted course and potential complications of the disease.

PATIENT EDUCATION

- United Leukodystrophy Foundation, 2304 Highland Dr., Sycamore, IL 60178. Phone: 800-728-5483.
- National Tay-Sachs and Allied Diseases Association, 2001 Beacon St., Ste. 204, Brighton, MA 02135. Phone: 800-90-NTSAD.
- National Gaucher Foundation, 11140 Rockville Pike, Ste. 350, Rockville, MD 20852-3106. Phone: 800-925-8885.

PROGNOSIS

- Tay Sachs and Sandhoff: Vegetative state rapidly ensues with death by 2 to 4 years of age.
- GM1: Death ensues a few years after onset of the disease.
- Fabry: Death usually occurs from renal failure, cardiovascular involvement, or cerebrovascular disease. Average age at death is 41 years.
- Niemann-Pick type A: Death occurs by 2 to 3 years of age.
- Gaucher type 2: Death in infancy.
- Farber: Death in late infancy or early childhood.
- Krabbe: Death in infancy or early childhood.
- Metachromatic leukodystrophy: Death 1 to 7 years after onset.

ADDITIONAL READING

- Ierardi-Curto L. Genetics of Niemann-Pick Disease. http://emedicine.medscape.com/article/951564.
- Ierardi-Curto L. Lipid Storage Disorders. http://emedicine.medscape.com/article/945966.
- Sidransky E. Gaucher Disease. http://edmedicine.medscape.com/article/944157.
- Tegay DH. GM1 Gangliosidosis. http://emedicine.medscape.com/article/951637.

CODES

ICD9

- 272.7 Fabry, Niemann-Pick type A, Gaucher
- 272.8 Farber
- 330.0 Krabbe, Metachromatic Leukodystrophy

CLINICAL PEARLS

- Inherited neurodegenerative disorders caused by deficiency of an enzyme that results in lysosomal accumulation of the enzyme's specific sphingolipid substrate in the central nervous system and/or visceral organs.
- Diagnosis is confirmed by demonstration of a specific enzyme deficiency in blood leukocytes or fibroblasts.
- Carrier detection and prenatal testing are available.
- ERT is available for treatment of Fabry disease and palliative treatment of visceral involvement in Gaucher type 2 and 3.

SPINAL CORD SYNDROMES, ACUTE

David S. Younger, MD

BASICS

DESCRIPTION

Acute spinal cord syndromes are neurologic emergencies that have the propensity for permanent loss of function. Examples include complete or incomplete transection of the spinal cord from trauma, vascular occlusion resulting in tissue infarction, vascular hemorrhage, abscesses, disc herniation, extreme flexion and extension of the spine, and compression by primary and metastatic tumors. Such syndromes are important to recognize early because long-term prognosis is related to the speed and accuracy of diagnosis and subsequent successful treatment.

EPIDEMIOLOGY

- According to the National Institute of Neurological Disorders and Stroke (NINDS):
  - The precise incidence of acute spinal cord injury is not well known. There are estimated 10,000–12,000 spinal cord injuries every year in the USA.
  - A quarter of a million Americans are currently living with spinal cord injuries.
  - The cost of managing the care of spinal cord injury patients approaches $4 billion each year.
  - Of all spinal cord injuries, 38.5% happen during car accidents. Almost a quarter, 24.5%, are the result of injuries relating to violent encounters, often involving guns and knifes. The rest are due to sporting accidents, falls, and work-related accidents.
  - Of spinal cord injury victims, 55% are between 16 and 30 years old.
  - More than 80% of patients with spinal cord injury are men.

RISK FACTORS

Recent trauma, underlying cancer, coagulopathies, drug abuse, cervical spondylosis, and infection.

ETIOLOGY

- Compression due to various mass lesions.
- Ischemia due to atherosclerosis, embolic disease, hypercoagulable states or vasculitis.

COMMONLY ASSOCIATED CONDITIONS

Include cancer and cervical spondylosis.

DIAGNOSIS

- The clinical symptoms and signs of spinal cord lesions relate to four essential characteristics of the offending lesion: (a) The level, because the higher the lesion the greater the loss of motor, sensory and autonomic function; (b) the extent of damage in the transverse plane leading to expected incomplete or complete transverse cord syndrome; (c) the extent of the lesion in the longitudinal plane and therefore the number of spinal segments involved; and (d) the duration of lesion.
  - Patients may give "red flags" in the history that raise the suspicion of acute spinal cord dysfunction such as, numbness that corresponds to a spinal cord dermatome, back pain in a belt-like distribution around the trunk, spastic or overflow urinary incontinence, bowel incontinence, and new leg weakness.
  - Physical exam findings that should raise suspicion of an acute spinal cord syndrome include segmental weakness or a sensory level to pin and light tough with loss of vibration and proprioceptive sensation below the level, reflex changes, limited range of motion of the spine, and gait imbalance.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Parainfectious, metabolic, autoimmune, and markers of cancer should be determined in all patients with suspected acute spinal cord syndrome.

Imaging

The most helpful imaging study is enhanced MRI, which non-invasively images spinal cord tumors, disc protrusions, epidural abscess and hematoma, and intrinsic cord lesions. In patients with epidural metastases contrast CT and plain x-ray films show bony abnormalities in the majority of patients. Myelography is usually reserved for cases where more precise imaging of nerve root elements is needed, or where MRI cannot be used (e.g., patients with pacemakers, etc.).

Diagnostic Procedures/Other

Special studies include whole body positron emission tomography fused with CT to image cancer and inflammatory foci throughout the body including the nervous system, including solid tumors and lymph nodes which may direct further evaluation and therapy, and provide suitable tissue for biopsy. Lumbar CSF analysis may be helpful in those with a parainfectious, an autoimmune, a cancerous, and a hemorrhagic etiopathogenesis but should be deferred in the setting of frank cord compression.

DIFFERENTIAL DIAGNOSIS

- Diagnosis must be made early through a combination of accurate history, directed physical and neurologic exam, and imaging studies. The differential diagnosis to consider when collecting the history and physical exam data can be lengthy, but the mnemonic Vibrated Spasms is helpful for both acute (A) and chronic (C) spinal cord syndromes:
  - **V**ascular (A/C)
  - **I**nfectious, idiopathic (A/C)
  - **B_{12}** deficiency (C)
  - **R**adiation (C)
  - **A**myotrophic lateral sclerosis (C)
  - **T**umor (A/C), trauma (A), toxic-metabolic (A)
  - **E**pidural abscess, electricity (A)
  - **D**evelopmental, hereditary (C)
  - **S**pondylosis (A/C)
  - **P**araneoplastic (C)
  - **A**rachnoiditis (A/C)
  - **S**yringomyelia (C)
  - **M**yelitis (A), multiple sclerosis (A/C)
  - **S**ystemic disorders (A/C)

TREATMENT

MEDICATION

- Methylprednisolone, a steroid drug, became standard treatment for acute spinal cord injury in 1990 when a large-scale clinical trial supported by the NINDS showed significantly better recovery in patients who were given the drug within the first 8 hours of injury. It appears to reduce the damage to nerve cells and decreases inflammation at the site of injury by suppressing immune activation. Notwithstanding, some authorities argue that its use in the acute phase of spinal cord is controversial. Dexamethasone is the high-potency steroid of choice for patients with neoplastic spinal cord compression.
  - Contraindications
    - Known acute hypersensitivity to medications
  - Precautions
    - Glucose monitoring if corticosteroids are used in spinal cord injury especially for diabetics.

ADDITIONAL TREATMENT

General Measures

- Adjunctive measures including antibiotics for aspiration pneumonia, anticoagulation to prevent deep vein thrombosis and pulmonary embolism, attenuation of pressure sores, assurance of adequate ventilation, blood pressure, and detection of heart rhythm disturbances; adequate treatment of neurogenic pain, and bowel and bladder function, should be managed acutely.
- Surgery/other procedures
  - The need for other measures should be guided by the nature of the injury and the response to conservative management. Surgical intervention may be indicated in those with incomplete recovery as for example from spinal injury and instability, vascular malformations, incomplete resolution of an epidural abscess, lack of tumor pathology especially in those with compressive lesions that fail to respond or regress with specific medication interventions or radiotherapy.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Suspicion of spinal cord dysfunction is reason for the acute evaluation and management. After the acute phase of treatment, transfer to a dedicated rehabilitation medicine unit should be contemplated to assure coordinated care.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Careful follow-up of these patients is indicated and depends on the diagnosis. For example, a patient whose tumor was the cause of spinal cord compression is at risk for metastases at other locations.

PATIENT EDUCATION

Patients should understand the nature of spinal cord injury, the relationship between their clinical symptoms and the cord injury, the nature of treatments and the rehabilitation, and the options for care. In rehabilitation, they should become acquainted with assistive devices, bowel and bladder regimens, vocational opportunities, etc.

PROGNOSIS

This depends on the etiology and severity of neurologic injury. In general, patients with milder deficits, shorter time to decompression of cord compression, younger age, and better general medical status have a better prognosis.

ADDITIONAL READING

- http://www.ninds.nih.gov/disorders/sci/detail_sci.htm

CODES

ICD9

- 336.1 Vascular myelopathies
- 336.9 Unspecified disease of spinal cord
- 952.9 Unspecified site of spinal cord injury without spinal bone injury

SPINAL CORD SYNDROMES, CHRONIC

David S. Younger, MD

BASICS

DESCRIPTION

Spinal cord syndromes are clinically, pathologically, and genetically heterogeneous. Clues to the offending disease process can be obtained by a careful neurological history and examination followed by selective laboratory investigations. The goal is to establish the neurological symptoms and signs, their temporal progression, associated findings, the formulation of a categorical diagnosis and localization in the nervous system. Establishing the specific etiopathogenesis of chronic spinal cord involvement further requires the application of selective laboratory testing from among available electrophysiological, neuroimaging, serological, and genetic studies.

EPIDEMIOLOGY

Precise incidence and prevalence is not known.

RISK FACTORS

Include cervical spinal degeneration or preceding surgery (cervical spondylotic myelopathy), retroviral infection (HIV myelopathy), malnutrition (B12 deficiency and tropical spastic paraparesis), trauma (causing syringomyelia), systemic infection (epidural abscess), radiation (myelopathy), and dysimmunity (MS). There are various familial syndromes of chronic spinal cord disease (hereditary spastic paraplegia, spinocerebellar degeneration, and adrenomyeloneuropathy).

COMMONLY ASSOCIATED CONDITIONS

Include underlying cancer, cervical spondylosis, vasculitis, systemic infections, and known toxin exposure as for example nitrous oxide, which may precipitate a syndrome related to subacute combined degeneration).

DIAGNOSIS

Paresthesias (numbness, tingling) in limbs and trunk; limb weakness; change in urine or bowel function (either more or less frequent); incontinence; back pain; and root distribution pain, which may encircle the trunk. Patients may complain most of a progressive gait disorder urgency of urination and constipation. Those with cervical spine disease, weakness, dysesthetic sensation, and stiffness may notice predominant symptoms in the hands and neck pain. Double-crush injury from a tandem carpal tunnel may be the first clue to an exacerbating cervical spine condition.

- Loss of pin sensation below a certain spinal segment with corresponding weakness in arm or leg muscles, sparing the face; increased muscle tone; paraparesis, overactive reflexes, Babinski signs, ankle clonus, loss of anal sphincter tone; and distended bladder are clues to a probable intramedullary lesion or transverse myelitis.

DIAGNOSTIC TESTS AND INTERPRETATION

The choice of laboratory studies in a patient with chronic spinal cord syndrome depends upon the suspected or the presumed etiologic or the differential diagnosis and may including one or more of the following: blood tests, neuroimaging, electrophysiological studies, lumbar CSF analysis, genetic analysis.

Lab

Blood and CSF can be processed for a variety of studies depending upon the presumptive diagnosis. Tests for B12, thyroid, HIV, and parathyroid should be performed in all high risk patients and are relatively inexpensive and may reveal important information at the outset of the evaluation. Autoimmune and parainfectious serology and CSF analysis play pivotal roles in the diagnosis of poliomyelitis, HIV myelopathy, and MS, as well as the etiological causes of transverse myelitis and carcinomatous meningitis. While more expensive, genetic analysis should be carefully chosen for the likeliest associated clinical diagnoses rather than indiscriminant screening.

Imaging

Clues to the etiopathogenesis of chronic spinal cord disease may be obtained by contrast MRI of the brain and spinal cord employing thin sections.

Diagnostic Procedures/Other

Rarely, spinal cord angiography may be necessary for dural arteriovenous (AV) fistulas or spinal cord arteriovenous malformation (AVM). Such studies should then be performed in specialized centers due to risk of permanent spinal cord injury and interpreted by experienced neuroradiologists.

DIFFERENTIAL DIAGNOSIS

Selective anterior horn cell involvement due to poliomyelitis, postpolio syndrome, and spinal muscular atrophy leads to chronic flaccid paralysis of the involved segments in the corresponding arms or legs, whereas, combined anterior horn cell and anterolateral tract involvement leads to stepwise or progressive segmental paralysis and spasticity, further separable by electrophysiological, serological, and genetic analysis. Alteration of bladder, bowel, and sexual function most often results from anterior spinal artery thrombosis, compression by an extramedullary tumor or multiple sclerosis further definable by neuroimaging. The most frequent etiologies of combined posterior column and lateral corticospinal tract involvement resulting in spastic ataxia are B12 deficiency, hereditary ataxia, posterior spinal artery insufficiency, compressive cervical spondylotic myelopathy, foramen magnum tumor, and vascular malformation also further separable by serological, neuroimaging, and genetic studies. Syringomyelia is the classic example of a central spinal cord syndrome with resulting pathology along a transverse and longitudinal plane. The presenting findings are weakness, wasting of small hand muscles due to anterior horn cell involvement and dissociated sensory loss due to damage of decussating pain, and temperate fibers by the enlarging cavity with preservation of dorsal tracts.

TREATMENT

MEDICATION

Medical management of chronic spinal cord syndromes depends on the cause. Parenteral corticosteroids are indicated in patients with MS to treat an acute attack, and adjuvant immunotherapy is warranted to prevent relapses. Combined oral corticosteroids (i.e., dexamethasone) and radiotherapy are useful in the management of chronic spinal cord compression due to epidural metastases. Once a diagnosis of chronic B12 deficiency is ascertained, B12 is administered parenterally by injection or sublingually checking levels to assure therapeutic responsiveness.

General Measures

Measures that are applicable to all patients with chronic spinal cord conditions include provision of therapy aimed at stretching and strengthening the affected muscles; avoiding decubitus ulcers in severely affected patients; provision of adequate bowel and bladder care; and attention to issues of rehabilitation including assistive devices, wheelchairs, transfer aids, and other appropriate support.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - The anti-spasicity medications baclofen (Lioresal) or tizanidine (Zanaflex) are commonly prescribed. Side effects of Lioresal include fatigue and leg weakness, particularly at higher doses. Those of tizanidine include fatigue, hypotension, and occasionally altered liver function tests. Occasionally, very spastic muscles may require treatment with botulinum toxin or implantation of an intrathecal pump for Lioresal infusion near the spinal cord.
- Adjunctive Treatment
  - Consider deep vein thrombosis prophylaxis as necessary.

SURGERY/OTHER PROCEDURES

Surgical drainage of an epidural abscess can be attempted after a therapeutic course of antibiotics. Surgical decompression should be considered in those with compressive cervical spondylotic myelopathy to avert progression, although there is no assurance of improvement.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Depends on the diagnosis. For example, patients with MS often require routine or frequent follow-up visits.

PATIENT EDUCATION

Patients should be educated generally about the effect of chronic spinal cord injury on sensory and motor function, bowel and bladder activity, and gait. The specific cause and its prognosis should be discussed with the patients. If there are specific societies with information for the etiology, the patient should be made aware of these (for example, the amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) societies).

PROGNOSIS

Depends on the etiology of the spinal cord syndrome.

ADDITIONAL READING

- Younger DS. Overview of motor disorders. Chapter 1. In: DS Younger (Ed.) Motor Disorders, 2nd ed. Lippincott Williams and Wilkins, Philadelphia, 2005.
- Younger DS. The diagnosis of progressive flaccid weakness. *Semin Neurol* 1993;13:241–246.
- Younger DS. The diagnosis of progressive spastic paraparesis. *Semin Neurol* 1993;13:319–321.

See Also (Topic, Algorithm, Electronic Media Element)

- Chronic myelopathy
- Chronic spastic paraparesis
- Spinal Cord Syndromes, Acute; Multiple Sclerosis; Vitamin B12 Deficiency; Spinal Cord, Neoplastic Cord Compression

CODES

ICD9

- 334.1 Hereditary spastic paraplegia
- 336.8 Other myelopathy
- 952.9 Unspecified site of spinal cord injury without spinal bone injury

SPINAL CORD TUMOR: ASTROCYTOMA

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Spinal astrocytomas (SCA) are intradural, intramedullary tumors that arise from the gray or the white matter of the spinal cord and can affect patients of all ages. They occur most commonly in the cervical and the upper thoracic region, but can develop anywhere in the cord. Although most SCA are low grade, they are all very infiltrative and typically span 4 to 6 spinal cord segments at diagnosis.

EPIDEMIOLOGY

Incidence/Prevalence

- Spinal cord tumors (SCT) are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. Spinal cord astrocytomas comprise 6 to 8% of all primary SCT, approximately 30% of all intramedullary SCT, and only 3 to 4% of all CNS astrocytomas. They are more common in children, comprising 35 to 60% of all pediatric SCT, and represent the most common type of intramedullary SCT.
- All races and ethnic groups affected. Caucasians are affected more commonly than blacks, Latinos, and Asians. Typical presentation is between 25 and 40 years, but can occur at any age; a secondary peak occurs in the pediatric years. Males have a higher incidence than females: 4:1.

RISK FACTORS

Risk factors for SCA remain unclear, but may be similar to astrocytomas of the intracranial cavity; these include spinal radiation (≥10 Gy), and genetic diseases with a predilection for gliomas, such as Turcot's syndrome, Neurofibromatosis (NF) types I and II, and Li-Fraumeni syndrome.

Genetics

Astrocytomas of the spinal cord are usually sporadic tumors, but can occur in association with NF1.

GENERAL PREVENTION

No preventive measures are available.

PATHOPHYSIOLOGY/ETIOLOGY

- The World Health Organization (WHO) classifies astrocytomas of the spinal cord similar to those of the brain; pilocytic astrocytoma as grade I (50%), fibrillary astrocytoma as grade II (22%), anaplastic astroctyoma (20%) as grade III, and glioblastoma multiforme (GBM; 8%) as grade IV.
- Spinal cord astrocytomas are mainly low grade (i.e. grades I and II; LGA). High-grade tumors are less common. The tumors are derived from transformed astrocytes. Pathological evaluation of LGA reveals mild to moderate cellularity without anaplasia or severe nuclear atypia, minimal mitotic activity and endothelial proliferation, no necrosis, and frequent staining for glial fibrillary acidic protein. High-grade tumors have high cellularity, cellular, and nuclear atypia, moderate to high mitotic rate, endothelial proliferation, and necrosis (in GBM).
- Molecular genetic studies of LGA reveal frequent allelic deletions of chromosome 17p, often with loss or mutation of the tumor suppressor gene, p53. Amplification of oncogenes (e.g., MDM2, CDK2, gli) and deletion of tumor suppressor genes (e.g., p16, retinoblastoma) may be present in some tumors.

DIAGNOSIS

HISTORY

Spinal cord astrocytomas are often slow-growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 6 to 10 months in high-grade SCA, 5 to 7 years in low-grade SCA). The presentation will vary with tumor location, rate of growth, amount of edema, and compression of regional spinal cord. The most common early symptom (70 to 80%) is slowly progressive localized back and/or radicular pain. Weakness of the lower extremities and gait dysfunction are the next most common symptoms. Sensory symptoms occur next and consist of paresthesias and dysesthesias. Central cord pain syndromes of the legs can develop in some patients. Scoliosis may be noted in children; dysfunction of bowel and bladder is a symptom that occurs later.

PHYSICAL EXAM

Common neurological signs include evidence for myelopathy, with weakness and spasticity of the legs and/or arms, reflex asymmetry, loss of abdominal reflexes, Babinski signs, sensory loss, and sphincter dysfunction. Patients with cervical SCA may demonstrate lower motor neuron signs and atrophy of the upper extremities, due to destruction of anterior horn cells.

DIAGNOSTIC TESTS AND INTERPRETATION

Imaging

Initial approach

MRI, with and without gadolinium contrast, is the most critical diagnostic test; axial, coronal, and midsagittal enhanced images should be obtained. MRI is more sensitive than CT for intramedullary SCT. On T1 images, the tumor is usually hypointense or isointense compared to normal spinal cord and causes diffuse multi-segmental enlargement. On T2 images, the tumor is hyperintense. SCA have mild to moderate enhancement after administration of gadolinium. Regions of cyst, peritumoral edema, and areas of hemorrhage may be noted. CT demonstrates a hypodense enlargement of the spinal cord with variable enhancement and edema. Hydrocephalus can be noted in a small percentage of patients.

Diagnostic Procedures/Other

Intraoperative neurophysiological monitoring with evoked potentials may be helpful during surgical resection to maximize tumor removal and minimize neurological morbidity. Ultrasound may be helpful for the surgeon to accurately localize the tumor before myelotomy and removal.

Pathological Findings

Pathology is similar to astrocytomas in the brain, but often with more low-grade features, such as mild to moderate cellularity with neoplastic astrocytes, infrequent mitoses, mild vascularity, and lack of necrosis.

DIFFERENTIAL DIAGNOSIS

Includes other intramedullary enhancing spinal masses such as ependymoma, metastasis, and abscess; other disorders which can have a similar neurological presentation are syringomyelia, multiple sclerosis, transverse myelitis, herniated disk, amyotrophic lateral sclerosis, and vitamin B12 deficiency.

TREATMENT

MEDICATION

First Line

Dexamethasone (2 to 8 mg/day) may be of benefit to reduce spinal cord edema and often improves pain; it may also relieve transient symptoms of pressure and swelling after radiation therapy (RT). Narcotic analgesics may be necessary to control severe pain prior to surgery and/or RT.

Second Line

All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

ADDITIONAL TREATMENT

General Measures

Consists of corticosteroids to control symptoms of spinal cord edema and pain control caused by compression of the spinal meninges and other neurovascular structures.

Additional Therapies

- RT should be considered for all adult patients with a SCA, even those of low grade that have undergone an apparently complete resection. All patients with residual tumor or high-grade histology will require involved field RT. The recommended doses are 50 to 55 Gy over 6 weeks using 180 to 200 cGy/day fractions. Children with completely resected pilocytic SCA (WHO grade I) can be followed without RT. Patients with high-grade SCA that disseminate to the neuraxis may benefit from palliative RT.
- Chemotherapy has a limited role in the treatment of SCA. It should be considered for patients who cannot undergo surgical resection and for tumors that recur despite surgery and/or RT. Drugs to consider only have modest activity and are the same as those used for astrocytic tumors of the brain; they include temozolomide, nitrosoureas BCNU (carmustine) and CCNU (lomustine), PCV (procarbazine, CCNU, vincristine), etoposide, cyclophosphamide, and carboplatin. Intra-thecal chemotherapy with methotrexate or cytarabine should be considered for patients with high-grade SCA that develop leptomeningeal metastases.

SURGERY/OTHER PROCEDURES

Surgical resection is required for biopsy of diagnostic tissue and maximal tumor removal, while minimizing surgical neurological morbidity. Many low-grade SCA can be completely resected with modern microneurosurgical techniques if a cleavage plane is discerned. Infiltrative low-grade tumors and most high-grade SCA will only allow a sub-total resection. Ideal surgical candidates have intact or almost normal gait and neurological function.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Will be variable depending on the acute presentation of the SCA.

Admission Criteria

Admission is generally reserved for pre-surgical evaluation and biopsy/resection. Patients can be admitted with progressive spinal neurological dysfunction from tumor growth or leptomeningeal dissemination. Intravenous dexamethasone may be helpful to reduce spinal cord edema and control pain; new treatment may be necessary (e.g., RT, chemotherapy).

Discharge Criteria

Discharge is appropriate after stabilization of acute neurological issues and recovery from surgery, often to a rehabilitation facility.

ONGOING CARE

PATIENT MONITORING

Patients are followed with serial MRI scans and assessment of neurological function every 3 to 6 months.

PATIENT EDUCATION

- SCT – Astrocytoma, benign: www.medhelp.org/forums/neuro/archive/2276.html
- Spine and Nerve Center at MGH/Harvard: www.neurosurgery.mgh.harvard.edu/Inkspine.htm

PROGNOSIS

- The 5-year survival rate for patients with low-grade SCA after complete resection, with or without RT, is 70 to 80%. After incomplete removal plus RT, the survival is lower, with a 5-year rate of 50 to 65%. The prognosis for patients with high-grade SCA is poor, with typical overall survival ranging from 6 to 12 months.
- Factors that improve the prognosis for survival are young age, low-grade histology, relatively intact neurological function before and after surgery, and complete resection; factors that worsen the prognosis include high-grade histology, older age, significant neurological dysfunction with poor performance status, and incomplete removal of tumor.

COMPLICATIONS

Complications can arise from surgical biopsy or resection of the tumor, or from progressive growth of the tumor within the spinal cord, resulting in progressive spasticity, leg weakness, and gait dysfunction.

ADDITIONAL READING

- Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: A review. *Curr Neurol Neurosci Rep* 2011;Feb:[Epub ahead of print].
- Parsa AT, Lee J, Parney IF, et al. Spinal cord and intradural-extraparenchymal spinal cord tumors: Current best care practices and strategies. *J Neuro-Oncol* 2004;69:291–318.
- Roonprapunt C, Houten JK. Spinal cord astrocytomas: Presentation, management, and outcome. *Neurosurg Clin N Am* 2006;17:29–36.

CODES

ICD9

- 191.9 Malignant neoplasm of brain, unspecified
- 192.2 Malignant neoplasm of spinal cord

CLINICAL PEARLS

- SCA typically present with slowly progressive leg weakness and gait difficulty, often with localized back pain.
- Early work-up and diagnosis with MRI scan of the spine is important to maximize neurological function after treatment.

SPINAL CORD TUMOR: EPENDYMOMA

Herbert B. Newton, MD, FAAN
Jacob J. Mandel, MD

BASICS

DESCRIPTION

Spinal ependymomas (EPN) are intradural tumors that arise from the ependymal lining cells of the central canal of the spinal cord, affecting patients of all ages. They occur most often in the extramedullary portions of the lumbar spine (60%; cauda equina and filum terminale). In 40% of patients, the tumor is intramedullary and develops within the spinal cord parenchyma. The cervical and upper thoracic cord are the most common (65 to 70%) locations for intramedullary EPN. Most EPN are low grade, with less infiltrative capacity than astrocytic tumors. At diagnosis, most EPN span 1 to 2 spinal cord segments.

EPIDEMIOLOGY

Incidence/Prevalence

Spinal cord tumors (SCT) are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. Spinal EPN comprise 12 to 15% of all primary SCT, approximately 50 to 60% of all intramedullary SCT, and 30 to 35% of all CNS EPN. They are less common in children, comprising 12 to 15% of all pediatric SCT.

RISK FACTORS

Risk factors for spinal EPN remain unclear, but may be similar to EPN of the intracranial cavity; these include spinal radiation (≥10 Gy), and Neurofibromatosis type 2 (NF2).

Genetics

EPN of the spinal cord are usually sporadic tumors, but can occur in association with NF2.

PATHOPHYSIOLOGY/ETIOLOGY

- Spinal cord EPN are mainly low-grade and although they are not encapsulated, they are typically well demarcated from surrounding neural tissues. Infiltration of spinal cord or nerve roots is uncommon. Histological features include moderate cellularity, monotonous nuclear morphology, ependymal rosettes, perivascular pseudorosettes, rare or absent mitoses, and very infrequent areas of necrosis. Foci of calcification, hemorrhage, and myxoid degeneration may be noted. High-grade tumors are more cellular and have frequent nuclear atypia, mitoses, and regions of necrosis.
- Cytogenetic studies reveal frequent abnormalities of chromosome 22 (30%), including monosomy, deletions, and translocations. Mutations in the MEN1 gene (located at 11q13) are found most often in tumors that do not demonstrate chromosome 22 abnormalities. Less common abnormalities affect chromosomes 9q, 10, 17p, and 13; molecular studies suggest that amplification of oncogenes (e.g., MDM2) and mutation of tumor suppressor genes (e.g., NF-2) are involved in transformation of EPN.

Pregnancy Considerations

Pregnancy does not affect the clinical behavior of spinal EPN.

DIAGNOSIS

HISTORY

Spinal cord EPN are usually slow growing tumors, with an insidious onset of symptoms. The time to diagnosis is typically prolonged (i.e., 3 to 5 years). The presentation will vary with tumor location, rate of growth, and amount of edema and compression of regional neural structures. Tumors that arise in the lumbar region typically present with low-back pain, with or without sciatica, lower extremity sensory dysfunction (e.g., numbness, paresthesias), bowel and bladder incontinence, and lower extremity weakness. Intramedullary EPN have a different presentation, with milder, more diffuse back pain, sensory complaints that usually manifest as dysesthesias, and less severe lower extremity weakness and bowel and bladder dysfunction.

PHYSICAL EXAM

The most common neurological sign is mild lower extremity weakness. Intramedullary tumors develop weakness as a late sign and have an upper motor neuron pattern (i.e., spasticity, hyperactive reflexes, Babinski sign); extramedullary tumors develop weakness earlier and have a lower motor neuron pattern (i.e., flaccidity, hypoactive or absent reflexes, flexor plantar responses). Other frequent signs include sensory loss, sphincter dysfunction, gait disturbance, and loss of abdominal reflexes.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Cerebrospinal fluid analysis and evaluation of cytology are diagnostic (in addition to cranial and/or spinal MRI) for those rare spinal EPN (high-grade, myxopapillary) that disseminate to the leptomeninges.

Imaging

Initial approach

MRI, with and without gadolinium contrast, is the most critical diagnostic test. Axial, coronal, and midsagittal enhanced images should be obtained; MRI is more sensitive than CT for intramedullary and extramedullary SCT. On T1 images, the tumor is usually hypointense or isointense compared to normal spinal cord and causes a well-demarcated, multi-segmental enlargement of the cord or a mass in the cauda equine. On T2 images the mass is hyperintense; spinal EPN have mild to moderate enhancement after administration of gadolinium. Regions of cyst occur frequently in intramedullary EPN (50 to 55%; even cranial–caudal distribution). Peritumoral edema may be noted. CT demonstrates a hypodense enlargement of the spinal cord or a mass in the lumbar region with mild enhancement and edema.

Diagnostic Procedures/Other

Intraoperative neurophysiological monitoring with evoked potentials may be helpful during surgical resection to maximize tumor removal and minimize neurological morbidity. Ultrasound may be helpful for the surgeon to accurately localize the tumor before myelotomy and resection.

Pathological Findings

The World Health Organization (WHO) classifies EPN of the spinal cord similar to those of the brain. Sub-EPN and myxopapillary tumors are classified as WHO grade I and myxopapillary are the most common type of EPN to arise in the cauda equina and filum terminale, typical EPN are classified as WHO grade II, anaplastic or malignant EPN correspond to WHO grade III.

DIFFERENTIAL DIAGNOSIS

Includes other intramedullary and extramedullary enhancing spinal masses such as astrocytoma, metastasis, and abscess; other disorders which can have a similar neurological presentation are syringomyelia, multiple sclerosis, transverse myelitis, herniated disk, and vitamin B12 deficiency.

TREATMENT

MEDICATION

First Line

- Dexamethasone (2 to 8 mg/day) may be of benefit to reduce spinal cord edema and often improves pain. It may also relieve transient symptoms of pressure and swelling after surgery or radiation therapy (RT). All patients should be on an H2 blocking drug while receiving chronic dexamethasone.
- Narcotic analgesics may be necessary to control severe pain prior to surgery and/or RT.

Second Line

Chemotherapy has a limited role in the treatment of spinal EPN. It should be considered for patients with incompletely resected tumors and tumors that progress despite RT. Drugs to consider only have modest activity and are the same as those used for EPN of the brain. They include temozolomide, procarbazine, lomustine (CCNU), vincristine, etoposide, cyclophosphamide, cisplatin, and carboplatin. Imatinib has also been reported to have a minor response in a spinal EPN that expressed the platelet-derived growth factor receptors.

ADDITIONAL TREATMENT

General Measures

RT should not be considered for spinal EPN of low-grade that have undergone a complete resection. Similarly, RT should be held in patients with extensive sub-total resection until evidence of tumor progression. All patients with high-grade histology will require involved field RT; the recommended doses are 45 to 50 Gy over 6 weeks using 180 to 200 cGy/day fractions. Patients with high-grade tumors that disseminate to the neuraxis may benefit from palliative RT.

Issues for Referral

May require physical and/or occupational therapy depending on location of tumor and patients amount of weakness.

SURGERY/OTHER PROCEDURES

Surgical resection with gross-total removal is the treatment of choice for all spinal EPN. Even intramedullary tumors can be totally removed in most cases, since a clear cleavage plane is often present. Infiltrative low-grade and all high-grade intramedullary tumors will only allow a sub-total resection. Some myxopapillary EPN of the lumbar region cannot be totally excised due to adherence to, or envelopment of, surrounding nerve roots and vascular structures. Ideal surgical candidates have intact or almost normal gait and neurological function.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Consists of corticosteroids to control symptoms of spinal cord edema and pain control caused by compression of nerve roots, spinal meninges and other neurovascular structures.

Admission Criteria

Admission is generally reserved for pre-surgical evaluation and resection. Patients can be admitted with progressive spinal neurological dysfunction from tumor growth. Intravenous dexamethasone may be helpful to reduce spinal cord edema and control pain. New treatments may be necessary (e.g., RT, chemotherapy).

Discharge Criteria

Stabilization of the patient and sufficient pain control following surgery will be required before discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients are followed with serial MRI scans and assessment of neurological function every 6 to 12 months.

Patient Monitoring

Patients on chemotherapy may require more frequent assessments as well as monitoring of complete blood counts, liver function, and metabolic panel.

PROGNOSIS

- The 5- and 10-year survival rates for patients with low-grade spinal EPN after complete resection (without RT) are 75 to 90% and 65 to 70%, respectively. After incomplete removal plus RT, the survival is lower. The prognosis for patients with high-grade EPN is poor, with typical overall survival ranging from 12 to 18 months.
- The most important prognostic factor is degree of surgical resection. Factors that improve the prognosis for survival and quality of life are complete surgical resection, relatively intact neurological function before and after surgery, and typical low-grade histology. Factors that worsen the prognosis include incomplete removal of tumor, high-grade histology, significant neurological dysfunction with poor performance status, and tumor location within the conus medullaris.

COMPLICATIONS

Pain and neurological deficits, including sensory loss and/or weakness, are possible complications following surgery.

ADDITIONAL READING

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CODES

ICD9

- 192.2 Malignant neoplasm of spinal cord
- 225.3 Benign neoplasm of spinal cord

CLINICAL PEARLS

- Spinal cord EPN are generally low-grade tumors with clear cleavage planes.
- After complete surgical resection, further therapy is often not required.

SPINAL CORD TUMOR: MENINGIOMA

Herbert B. Newton, MD, FAAN
Jacob J. Mandel, MD

BASICS

DESCRIPTION

Spinal meningiomas are intradural, extra-medullary tumors that arise from the meninges of the spinal neuraxis; they are slow-growing, encapsulated masses which can develop in any location that has continuity with the meninges; the distribution within the spine is as follows: thoracic (75 to 85%), cervical (15 to 20%), and lumbar (2 to 4%); 10% of spinal meningiomas can extend outside of the dura into the paraspinal soft tissues and bone.

EPIDEMIOLOGY

Incidence/Prevalence

Spinal cord tumors are relatively uncommon, representing only 0.5% of newly diagnosed tumors in adults. The estimated incidence of spinal meningiomas is less than 0.18 to 0.23 cases/100,000 people/year. Meningiomas comprise 20 to 25% of all primary spinal cord tumors in patients over 20 years of age.

RISK FACTORS

Risk factors for spinal meningiomas remain unclear, but may be similar to meningiomas of the intracranial cavity; these include spinal radiation ($\geq$10 Gy), breast cancer, regional trauma, and rare familial clusters.

Genetics

Meningiomas of the spine are usually sporadic tumors; in rare cases, they can be familial. The incidence of meningiomas is significantly increased in patients with both type I and type II neurofibromatosis.

GENERAL PREVENTION

There are no preventive measures for the development of meningiomas.

PATHOPHYSIOLOGY/ETIOLOGY

- The cells of origin of meningiomas are transformed arachnoidal cap cells from the outer layer of the spinal arachnoid membrane. Typical meningiomas of the spine are low-grade and demonstrate uniform sheets of spindle-shaped cells, minimal cellular and nuclear atypia, whorl formation, psammoma bodies, and no evidence for mitotic activity or brain infiltration; higher-grade tumors reveal higher cellularity, more prominent nucleoli, high mitotic activity, necrosis, and tissue invasion.
- Meningiomas are believed to be the result of a multistep progression of genetic changes. These transformations may involve activation of oncogenes or inactivation of tumor suppressor genes. Molecular genetic studies reveal frequent deletions of chromosomes 22q and 1p; the NF2 gene (located at 22q12.3) is mutated in up to 60% of meningiomas, with dysfunction of the merlin protein; the majority of meningiomas are positive for estrogen and progesterone receptors; other receptors of importance include the epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptors, both of which stimulate secretion of vascular endothelial growth factor; the RAS signaling pathway is activated via stimulation by EGF and PDGF.

Pregnancy Considerations

In some women, pregnancy can accelerate the growth and increase the clinical symptoms of spinal meningiomas; this is rare compared to cranial meningiomas.

DIAGNOSIS

HISTORY

Typical presentation is between 45 and 65 years of age. Meningiomas are slow-growing tumors, with an insidious onset of symptoms; the time to diagnosis is typically prolonged (i.e., 12 to 24 months); the presentation will vary with tumor location, rate of growth, and amount of compression of nearby nerve roots and spinal cord; the most common early symptom is pain, which occurs in 42 to 50% of patients; with tumor enlargement pain becomes more prominent, effecting 65 to 85% of patients by the time of initial admission; the pain can be localized and/or radicular (i.e., down an extremity, around the thorax); the pain is often depicted as burning or aching in quality and frequently is constant in nature; leg weakness occurs in 35 to 50% of patients, and is also progressive; sensory abnormalities develop in 22 to 25% of patients and include parasthesias, numbness, or hot and cold sensations; disturbances of bowel and bladder function can arise in later stages.

PHYSICAL EXAM

Common neurological signs include motor weakness (usually of the legs) in 90 to 95% of patients, reflex asymmetry and spasticity of the lower extremities, sensory loss of the extremities (65 to 70%), and sphincter abnormalities (25%); frank myelopathy can be noted in more advanced patients with spinal cord compression; up to one-third of patients will be non-ambulatory due to leg weakness and/or pain.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Although typically unnecessary with MRI, cerebrospinal fluid evaluation usually demonstrates an elevated protein; the WBC is frequently normal; a mild pleocytosis may occur in some cases.

Imaging

Initial approach

MRI, with and without gadolinium contrast, is the most critical diagnostic test; axial, coronal, and midsagittal enhanced images should be obtained; MRI is more sensitive than CT for tumors of the spinal column; on T1 images, the tumor is usually isointense to spinal cord while on T2 images it is hyperintense; spinal meningiomas enhance densely after administration of gadolinium; MRI usually demonstrates a site of dural attachment or a dural tail; the displacement of nerve roots and/or the spinal cord is well delineated by MRI; meningiomas can cause hyperostotic changes in bones of the spinal column, but less commonly than in the intracranial cavity.

Follow-up & special considerations

Angiography is performed in selected patients to assess vascular anatomy and collateral blood supply prior to surgery; it may also be useful as a prelude to pre-surgical embolization (to minimize intra-operative bleeding).

Pathological Findings

The World Health Organization (WHO) grades typical low-grade meningiomas (e.g., syncytial, transitional) as WHO grade I; intermediate tumors (e.g., atypical, clear cell) are WHO grade II; malignant tumors (e.g., anaplastic) are WHO grade III; the vast majority of spinal meningiomas are WHO grade I.

DIFFERENTIAL DIAGNOSIS

Includes other extra-axial enhancing spinal masses such as schwannoma, metastasis, and abscess; other disorders which can have a similar neurological presentation are syringomyelia, multiple sclerosis, transverse myelitis, a herniated disk, and vitamin B12 deficiency.

TREATMENT

MEDICATION

First Line

- Dexamethasone (2–8 mg/day) may be of benefit to reduce edema and swelling for patients with spinal cord compression; it may also improve transient symptoms of pressure and swelling after radiotherapy (RT); analgesics may be necessary prior to surgery and/or RT. All patients should be on an H2 blocking drug while receiving chronic dexamethasone.
- Chemotherapy has a very limited role in the treatment of spinal meningiomas; it should be considered for patients that cannot undergo surgical resection and for tumors that recur despite surgery and/or RT; drugs with modest activity in phase II trials against intracranial meningioma could be considered and include intravenous cyclophosphamide (500 mg/m^2/day for 3 days), adriamycin (15 mg/m^2/day for 3 days), and vincristine (1.4 mg/m^2 for 1 day) and hydroxyurea (induces apoptosis in meningioma cells); chemotherapy usually induces tumor stabilization—shrinkage is uncommon. Modest success has also been reported with interferon-α-2B treatment (4 mU/m^2/day, 5 days/week) in a small study of patients with unresectable and malignant meningiomas. Molecular approaches to chemotherapy, using drugs such as imatinib and erlotinib that inhibit the growth factor receptors involved in the oncogenesis of meningiomas are also under study.

ADDITIONAL TREATMENT

General Measures

- In certain patient cohorts, spinal meningiomas are followed conservatively after diagnosis, including those with poor health, elderly patients with small lesions or who are reluctant to proceed to surgery, and patients with small tumors that do not correlate with symptoms; observation should include an enhanced MRI every 4 to 6 months to monitor for growth; tumors may remain quiescent if they are stable during the initial observation period; conservative approaches are unjustified in symptomatic patients and most young patients, especially if growth potential is demonstrated.
- Patients do not require irradiation after complete surgical resection. However, conventional external beam RT may be of benefit for those infrequent patients with large symptomatic tumors after subtotal removal, for recurrent or progressive tumors that cannot be approached surgically, and for those rare patients with malignant pathology (WHO grade III); it remains unclear whether or not RT provides a survival advantage for patients with spinal meningiomas after subtotal removal or at recurrence, since no clinical trial data have been published; recommended RT doses are 50 to 55 Gy over 6 weeks, with 180 to 200 cGy/day fractions.
- The use of radiosurgery for spinal meningioma is controversial, considering these tumors follow an indolent clinical course; radiation exposure may be unwarranted when microsurgical resection is highly successful. Although the possibility of radiation-induced myelopathy in these patients is exceedingly worrisome, radiosurgery as an adjuvant therapy may be indicated in cases of en plaque and relapsing meningiomas, subtotal resections, inaccessible tumors, proximity to vital structures, and preexisting comorbidities.

SURGERY/OTHER PROCEDURES

Surgical resection is the treatment of choice for most symptomatic patients; the surgical approach will vary depending on the location of the tumor; complete surgical extirpation is the goal whenever possible; subtotal removal is recommended for tumors intimately associated with spinal nerves and/or vessels; after removal of the tumor, involved bone and dural attachments should also be resected with a wide margin; dural defects should be repaired with grafts.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Consists of corticosteroids to control symptoms of spinal cord compression and pain control due to irritation or compression of nerve roots and other neurovascular structures.

Admission Criteria

Admission is generally reserved for pre-surgical evaluation (including angiography in some patients) and surgical resection; patients with severe spinal cord compression might benefit from admission for intravenous dexamethasone.

Discharge Criteria

Stabilization of the patient and sufficient pain control following surgery will be required before discharge.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Rehabilitation and outpatient physical therapy and occupational therapy as needed.

Patient Monitoring

Patients are followed with serial MRI scans and assessment of neurological function every 6 to 12 months.

PATIENT EDUCATION

- Spine and Nerve Center at MGH/Harvard: http://neurosurgery.mgh.harvard.edu/spine/lnkspine.htm
- University Southern California Neurosurgery: www.uscneurosurgery.com/glossary/m/meningioma/htm

PROGNOSIS/COMPLICATIONS

- The complete resection rate in most series is 85 to 95%, using preoperative MRI planning and modern microsurgical techniques; approximately 90% of patients will have functional improvement after surgery; symptomatic patients with neurological deficits can often improve dramatically after surgery releases pressure on nerve roots and the spinal cord; factors shown to impact surgical efficacy and complete recovery include patient age, severity of preexisting neurological impairment and disposition and location of the tumor. Tumor recurrence or progression occurs in 3.5 to 7% of patients after complete surgical resection.
- Factors that increase the probability for recurrence include incomplete removal of tumor and all dural attachments, invasion of bone, soft tumor consistency, extradural extension, and malignant histology.
- Pain and neurological deficits including sensory loss and/or weakness are possible complications following surgery.

ADDITIONAL READING

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CODES

ICD9

225.4. Benign neoplasm of spinal meninges

CLINICAL PEARLS

Spinal meningiomas are typically slow-growing tumors that respond well to surgical resection.

SPINAL CORD—NEOPLASTIC CORD COMPRESSION

Herbert B. Newton, MD, FAAN

BASICS

DESCRIPTION

Neoplastic epidural spinal cord compression (ESCC) is a common neurological complication of systemic cancer that is associated with severe neurological morbidity; ESCC develops after growth of metastatic deposits to the vertebral column (85%; usually vertebral bodies), paravertebral space (10 to 12%), or epidural space (1 to 3%); the most common primary tumors include cancers of the prostate, breast, kidney, and lung, as well as melanoma, myeloma, and lymphoma. In children, ESCC can arise from sarcoma, neuroblastoma, and lymphoma. ESCC develops most often in the thoracic spine (70%), but is also noted in the lumbar spine (20%) and cervical spine (10%). Approximately, 90% of ESCC occurs in patients with an established diagnosis of cancer. In 10% of cases, ESCC is the first manifestation of the malignancy; after the onset of back pain, neurological deterioration can occur quickly in patients with ESCC.

EPIDEMIOLOGY

Incidence/Prevalence

- The estimated incidence of ESCC is 5 to 14% of all cancer patients in the USA; this corresponds to more than 25,000 patients each year that are at risk. ESCC occurs most often in adults, with a secondary peak in children.
- All races and ethnic groups equally affected. Typical presentation is between 45 and 65 years of age. The incidence of ESCC is equal between males and females.

RISK FACTORS

The only risk factor for ESCC is widespread aggressive disease from a systemic malignancy; especially from primaries of the lung, breast, and prostate.

Genetics

ESCC is a sporadic process without any specific genetic influence.

PATHOPHYSIOLOGY/ETIOLOGY

- Systemic tumor cells gain access to the vertebral column and spinal bones through hematogenous spread in the majority of cases. The concentration of growth factors found in bone marrow stroma and the wide distribution of drainage of the vertebral venous plexus predispose the thoracic spine to ESCC. Other routes of access include tumors located in paravertebral and epidural sites (e.g., lymph nodes) and the Batson's vertebral venous plexus.
- Neurological function is disrupted by ESCC through several mechanisms, including an increase in the regional venous pressure, micro-hemorrhages within the spinal cord parenchyma, elevation of serotonin and prostaglandin E2 levels, increased vascular permeability and secondary edema formation, elevated concentrations of glutamate and calcium, spinal cord ischemia and infarction, and regional demyelination of long tracts.
- Tumor cells most likely to metastasize to the vertebral column have a more aggressive and motile phenotype; these changes are mediated by scatter factor, autocrine motility factor, amplification of oncogenes, and mutation of metastasis-suppressor genes (e.g., nm23).

COMMONLY ASSOCIATED CONDITIONS

Include other common general and neurological complications of patients with cancer such as infection and sepsis, metabolic encephalopathy, carcinomatous meningitis and brain metastasis.

DIAGNOSIS

HISTORY

Back pain is a common symptom with an annual incidence of 5% and a lifetime prevalence of 60 to 90% in the general population; most back pain is benign and self-limited. In patients with cancer, the presenting symptoms of ESCC are mild at first, then progressively worse. The initial symptom is always pain (95%), which can develop anywhere, but usually in the thoracic spine; the pain is regional and often associated with a radicular component (e.g., down an arm, around the ribs). Several weeks after the onset of pain, other symptoms will develop, including extremity weakness (75%; usually the legs), autonomic dysfunction (60%; urinary retention, urinary and/or bowel incontinence), sensory alterations (50%) of the lower extremities such as ascending numbness and paresthesias, and gait disturbance.

PHYSICAL EXAM

The general physical examination often reveals localized pain to percussion over the involved vertebral bodies (usually thoracic); the neurological examination usually demonstrates leg weakness; early on, the weakness is mild and may only involve the iliopsoas and hamstring muscle groups. Later in the course, a myelopathy develops, with upper motor neuron pattern weakness, spasticity, Babinski's sign, and exaggerated reflexes; ESCC of the lumbar region will affect the cauda equina and produce a lower motor neuron syndrome (hypotonia, areflexia, muscle atrophy, fasciculations); sensory loss is mild initially, with distal decrement to vibration and proprioception. With advanced disease, a level develops below the ESCC, characterized by loss of light touch and pinprick sensation.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Patients with a history of fever require a white blood cell count, blood cultures, and sedimentation rate to rule out epidural abscess, discitis, and osteomyelitis.

Imaging

Initial approach

Spine x-rays can identify an abnormality of the involved region in 85 to 90% of cases; the most common lesions are vertebral body erosion and collapse, subluxation, and pedicle erosion. MRI of the spine, with and without gadolinium contrast, is the most sensitive imaging test (≥90%); axial, coronal, and midsagittal enhanced images should be obtained. MRI can easily demonstrate epidural or paravertebral masses and any associated ESCC; the degree of cord displacement is clearly revealed, along with cord damage, as shown by high signal within the parenchyma; non-malignant lesions are clearly delineated (e.g., herniated disk, degenerative spine disease).

Diagnostic Procedures/Other

CT and myelography are not as sensitive as MRI and are not required if MRI is available.

Pathological Findings

In regions of ESCC, vasogenic edema, hemorrhage, demyelination, ischemia, and infarction are noted within the spinal cord parenchyma.

DIFFERENTIAL DIAGNOSIS

Includes other diseases that can involve the vertebral column and spinal cord, such as herniated disk, degenerative joint disease, epidural abscess, spinal osteomyelitis, primary spinal cord tumor, intramedullary metastasis, leptomeningeal tumor, spondylolisthesis, spinal stenosis, and facet syndrome.

TREATMENT

MEDICATION

First Line

Intravenous dexamethasone is always necessary as initial treatment of ESCC, to reduce edema and swelling of the spinal cord. Recommended initial dosing consists of a load of 20 to 100 mg, followed by maintenance doses of 2 to 24 mg q6h. Dexamethasone often improves pain and neurological function.

Second Line

- Narcotic analgesics are usually necessary for adequate amelioration of pain.
- All patients should be on an H2 blocking drug while receiving chronic dexamethasone.

ADDITIONAL TREATMENT

General Measures

- Consists of high-dose intravenous dexamethasone and pain control; pain is often severe and may need treatment before imaging can be performed. Definitive treatment (surgery and/or radiotherapy (RT)) should begin within 24 hours after the initiation of dexamethasone.
- Conventional RT is the mainstay of treatment of ESCC in most patients. The recommended dose is 30 Gy in 10 daily fractions over two weeks; the radiation port should include two vertebral bodies above and below the region of compression. RT is also usually necessary after surgical decompression of ESCC; many patients improve during RT (30 to 50% with increase in leg strength and/or ambulation).
- Chemotherapy has a limited role in most patients with ESCC; in some cases, it can be used as adjunctive therapy in addition to surgical resection or RT. Chemotherapy should only be considered first-line treatment for ESCC from Hodgkin's lymphoma, germ cell tumors, or neuroblastoma, which are very chemosensitive tumors and respond rapidly.

Issues for Referral

Referrals should be made to physical therapy, occupational therapy, and rehabilitation.

SURGERY/OTHER PROCEDURES

Surgical intervention is appropriate for carefully selected patients with ESCC; it should be considered for patients with acute deterioration of neurological function at presentation, if there is progressive neurological dysfunction during RT, an unknown primary tumor, evidence for spinal instability, bone involvement with ESCC, and if the involved tumor is known to be radioresistant (e.g., renal). The anterior surgical approach is preferred (i.e., vertebral body resection) in most patients, since it removes the bulk of the tumor and directly decompresses the spinal cord. Spinal stability is better following the anterior approach than the posterior approach (i.e., laminectomy).

IN-PATIENT CONSIDERATIONS

Initial Stabilization

As above.

Admission Criteria

Admission is for initial diagnosis and treatment of ESCC; re-admission may occur for patients with recurrent or progressive spinal disease.

Nursing

Follow neurological status closely, ability to urinate, etc.

Discharge Criteria

Discharge to rehabilitation, once neurologically stable after surgery and/or RT has begun.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients are followed with assessment of neurological function and spinal MRI every 3 to 6 months.

Patient Monitoring

As above.

PATIENT EDUCATION

- University of Washington—ESCC—www.stat.washington.edu/TALARIA/LS2.3.2.html
- ESCC Patient/Family Resources—uasomdl.slis.ua.edu/patientinfo/orthopedics/back/spinal-cord-compression

PROGNOSIS

- ESCC is a severe complication of cancer that requires emergent treatment. In ESCC, patients who are ambulatory at the start of treatment, 80% will remain so after therapy; only 45% of patients with paraparesis and 5 to 10% of patients with paraplegia will be ambulatory after treatment. Patients with non-ambulation have reduced survival due to medical complications such as pneumonia, decubitus ulcers, urinary infections, and septic episodes.
- The most important factor for improved prognosis is preservation of gait and neurological function at the onset of treatment; factors related to poor prognosis include very rapid onset of compression and neurological deficit, duration of paraplegia of greater than 24 hours, and presence of autonomic dysfunction at the time of diagnosis.

COMPLICATIONS

Risk of persistent weakness and gait dysfunction as noted above.

ADDITIONAL READING

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CODES

ICD9

- 198.5 Secondary malignant neoplasm of bone and bone marrow
- 336.9 Unspecified disease of spinal cord

CLINICAL PEARLS

- If ESCC is suspected, work-up and imaging should be performed immediately, along with dexamethasone and necessary analgesia.
- Treatment with surgical resection and/or RT as quickly as feasible.

SPINAL MUSCULAR ATROPHY

David S. Younger, MD

BASICS

DESCRIPTION

- The spinal muscular atrophies (SMA) are a group of inherited disorders characterized by lower motor neuron (LMN) weakness and wasting that is usually symmetrical and slowly progressive. This distinguishes SMA from progressive muscular atrophy variants of amyotrophic lateral sclerosis (ALS), which is more rapidly progressive and usually fatal. SMA may show a proximal distribution of muscle weakness as in the childhood recessive SMA due to mutations in the *SMN* gene, or distally accentuated, as can be seen in dominantly inherited, later-onset forms of SMA.
- The childhood recessive forms of SMA due to mutations in the *SMN* gene are classified according to severity. Type I (previously known as Werdnig–Hoffmann disease) presents with severe neonatal hypotonia, due to *in utero* motor neuron loss. Infants may require resuscitation and artificial ventilation. Affected children show signs before 6 months of age but fail to achieve the ability to sit unaided and generally succumb to respiratory failure before the age of 2, though patients can survive longer with modern assisted ventilation. Type II SMA (intermediate SMA) is defined by onset in infancy, but affected children achieve the ability to sit but cannot stand unaided. Long-term outcome is dictated by the degree of respiratory muscle involvement and associated kyphoscoliosis. Approximately, 60% of children survive to age 20 years. Type III SMA (previously known as Kugelberg–Welander syndrome) is the mildest form, and children in this group achieve the ability to walk unaided. Onset for the majority is in infancy but rare cases of adult onset, even into the 40's and 50's, have been described. Life expectancy is usually normal and the probability of remaining ambulant in the long term is related to the age of onset. If this occurs before the age of 3 years, only 20% of patients are still ambulant 40 years later compared with 60% of those with an age of onset after 3 years.

EPIDEMIOLOGY

- Childhood-onset autosomal-recessive SMA is one of the commonest causes of neurologic disability in childhood and has an incidence of 1 in 10,000 live births. Epidemiologic data on other forms of SMA are lacking but taken together they are probably just as common.
- Sex
  - Males and females are affected equally except for Kennedy's disease (spinobulbar muscular atrophy), which is an X-linked form of SMA.

RISK FACTORS

SMA are single-gene disorders with no known environmental influence on incidence or progression.

Pregnancy Considerations

There have been occasional reports of women with mild proximal recessive SMA (type III) undergoing significant deterioration during pregnancy. Careful monitoring of respiratory function is advisable.

ETIOLOGY

Sporadic cases of SMA in adulthood are not uncommon but most clinically well-characterized forms of the disease are single-gene disorders. Inactivating mutations in the survival motor neuron *(SMN1)* gene causes recessive proximal SMA of childhood. Disease severity correlates with the level of residual SMN protein derived from a neighboring gene *(SMN2)*, which varies in copy number. SMN appears to function as a cofactor in ribonucleoprotein metabolism and mRNA splicing. It may have a hitherto unknown function in motor neurons. Another, much rarer, form of infantile SMA with diaphragmatic involvement is due to mutations in another putative RNA interacting protein called IGHMBP2. The X-linked form of bulbar SMA is due to polyglutamine expansion in the first exon of the androgen receptor gene. This leads to partial androgen insensitivity as well as SMA. None of the genes for dominantly inherited forms of SMA has yet been identified. However, scapuloperoneal SMA and distal lower limb SMA have both been linked to different regions of chromosome 12q, while upper limb predominant SMA has been linked to chromosome 7p.

DIAGNOSIS

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Creatine kinase levels can be normal or slightly elevated in different forms of SMA. Levels greater than 10 fold normal should raise suspicion of primary myopathy. Neurophysiology is mandatory in cases of suspected SMA at any age as (a) this provides the primary diagnostic confirmation of an anterior horn cell disease, (b) differentiates SMA from a myopathy or peripheral neuropathy, and (c) excludes treatable conduction block neuropathy. Muscle biopsy is often performed in difficult cases where electrophysiology cannot distinguish between a myopathy and denervating disorder.

Imaging

While MRI scanning of muscle is under investigation as a tool for distinguishing neurogenic muscle atrophy from primary myopathies, it is unlikely to replace neurophysiology as the primary diagnostic test.

Diagnostic Procedures/Other

Direct genetic analysis is routinely available for mutations in the *SMN* gene and the trinucleotide expansion associated with Kennedy's disease. For other rarer forms of SMA for which genes have not yet been identified, contact should be made directly with research laboratories undertaking linkage studies.

DIFFERENTIAL DIAGNOSIS

- Childhood recessive SMA: A large number of genetic syndromes lead to neonatal hypotonia, which may be confused with infantile SMA. Rare "SMA-mimic" syndromes occur including cerebellar hypoplasia with anterior horn cell involvement, SMA with congenital contractures, and metabolic disorders due to mitochondrial dysfunction. The key features that distinguish SMA are the normal intellect, sparing of the diaphragm and facial muscles, and the proximal distribution of weakness. The legs are weaker than the arms and are typically held in a "frog-like" posture. SMA with respiratory distress, due to mutations in IGHMBP2, presents with distal muscle weakness and prominent diaphragmatic involvement leading to eventration of abdominal contents into the thorax.

- Pure LMN forms of ALS account for about 10% of cases and are generally rapidly progressive with most patients ultimately developing upper motor neuron signs. Those with ALS generally show asymmetrical onset compared with SMA, which is almost always symmetrical. There is a degree of confusion among specialists about whether distal SMA should be classified as a pure form of motor neuropathy (the so-called spinal form of Charcot–Marie–Tooth disease) or as an anterior horn cell disease.
- One other consideration in the differential diagnosis of SMA is multifocal motor neuropathy with motor nerve conduction block that typically shows slowly progressive asymmetrical weakness and wasting of the upper limbs. This condition responds to treatment with intravenous immunoglobulin.

TREATMENT

ADDITIONAL TREATMENT

General Measures

The prognosis for infantile SMA presenting with respiratory compromise in the first few months of life is very poor and early and sensitive discussion with the parents is required in deciding when to withdraw ventilation. All children with childhood forms of SMA should be assessed for respiratory compromise on a regular basis. Physiotherapy can limit recurrent infections. A careful assessment for the development of scoliosis is important, as this leads to preventable disability.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Noninvasive ventilation is increasingly being used in type II SMA and prolongs life. A multidisciplinary team in a specialist center is required to support patients on home ventilation.
- Adjunctive treatment

SURGERY/OTHER PROCEDURES

Patients who develop painful muscle contractures may benefit from orthopedic intervention. Patients with types II and III SMA may require spinal surgery for scoliosis.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

As with other chronic neurologic disorders, SMA is best managed by a dedicated multidisciplinary team (with physiotherapy, occupational therapy, dietetics, and respiratory care specialists) in a specialist setting. The clinical course of the different forms of SMA dictates the pattern of follow-up, but the childhood recessive forms generally require more medical supervision. The role of the neurologist in milder adult-onset forms is primarily diagnostic.

PATIENT EDUCATION

A major issue is that patients are appropriately informed about the pattern of inheritance (dominant versus recessive) of their disorder so that they can make choices about family planning. Referral to a clinical geneticist is usually advisable. For recessive SMA due to mutations in the *SMN* gene, preimplantation genetic diagnosis is available in selected centers.

PROGNOSIS

Described above and dependent on the exact type of SMA.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Kennedy's disease (spinobulbar muscular atrophy)
- Werdnig–Hoffmann disease
- Kugelberg–Welander syndrome

CODES

ICD9

- 335.0 Werdnig-Hoffmann disease
- 335.10 Spinal muscular atrophy, unspecified
- 335.19 Other spinal muscular atrophy

SPINOCEREBELLAR ATAXIAS

Hongyan Li, MD, PhD

BASICS

DESCRIPTION

- Cerebellar ataxia is the leading manifestation of many progressive neurodegenerative diseases. In general, these diseases can be grouped into hereditary and non-hereditary ataxias. Hereditary cerebellar ataxias include autosomal dominant, autosomal recessive, X chromosome-linked, and mitochondrial types. Non-hereditary (or sporadic) cerebellar ataxias include acquired and idiopathic types (1,2,3).
- Spinocerebellar ataxias (SCAs) compose of the majority of the autosomal dominant cerebellar ataxias (ADCAs). Besides SCAs, dentatorubropallidoluysian atrophy (DRPLA) and episodic ataxias (EAs) are also included in the ADCA category. Researchers have also showed that a few SCA subtypes inherit in an X-linked recessive pattern (SCAX). EAs and other types of cerebellar ataxias are the topics of other chapters and therefore are not discussed here.
- At present, more than 30 different SCA subtypes have been reported.

EPIDEMIOLOGY

Incidence

1–5/100,000

Prevalence

- 0.9–3/100,000 (2)
- SCA1, 2, 3, 6 and 7 account for ~75% of SCAs (2). SCA3 (Machado-Joseph disease) is the most common subtype worldwide (20–50% of all SCAs).
- Geographical distribution of SCA subtypes varies significantly. For example, SCA3 accounts for 80% of SCAs in Brazil and Portugal. SCA3, 6, 16, 31 are common in Japan. SCA2 is seen in Cuba, SCA8 in Finland, SCA32 in China, and SCA10 in Mexico (4).

RISK FACTORS

Family history of typical symptoms. However, a familial history may be absent.

Genetics

- Genetic mutations (4):
  - Include translated or untranslated repeat expansions and point mutations
  - Trinucleotide CAG repeats: SCA1, 2, 3, 6, 7, 12, 17, and DRPLA
  - Other repeats: SCA8 (CTG), 10 (ATTCT), and SCA31 (TGGAA)
  - Other mutations: SCA5, 11, 12, 13, 14, 15, 16, 23, and 27
- Hereditary patterns: Autosomal dominant for all subtypes except SCAX1-5
- Characteristics of inheritance
  - Some SCAs demonstrate anticipation (most prominent in SCA1, 7, DRPLA).
  - Preference to paternal transmission
- Affected genes, gene products, and chromosomal loci (partial listing) (3,4,5):
  - SCA1: ATXN1, ataxin-1, 6p23
  - SCA2: ATXN2, ataxin-2, 12q24
  - SCA3: ATXN3, ataxin-3, 14q24.3-q31
  - SCA4: Q9H7K4, puratrophin-1, 16q22.1
  - SCA5: SPTBN2, spectrin β chain, 11q13
  - SCA6: CACNA1A, voltage-gated calcium channel α-1A subunit, 19p13
  - SCA7: ATXN7, ataxin-7, 3p21.1-p12
  - SCA8: KLHL1AS, 13q21
  - SCA10: ATXN10, ataxin-10/E46L, 22q13
  - SCA11: 15q14-q21.3
  - SCA12: PPP2R2B, protein phosphatase 2A brain specific regulatory subunit, 5q31-q33
  - SCA13: 19q13.3-q13.4
  - SCA14: PRKCG, protein kinase C γ subunit, 19q13.4
  - SCA27: FGF14, fibroblast growth factor 14, 13q34
  - SCA28: AFG3L2, ATPase family gene 3-like 2, 18p11.22
  - SCA30: ODZ3 (candidate gene), 4q34.3-q35.1
  - SCA31: TGGAA repeat insertion, 16q22.1
  - SCA32: 7q32-q33
  - SCA35: TGM6, transglutaminase 6, 20p13
  - SCA Unlinked: No chromosomal linkage
  - DRPLA: DRPLA, atrophin-1, 12p13.31
  - SCAX1: Xp11.21-q21.3
  - SCAX5: Xq25-q27.1

PATHOPHYSIOLOGY

- Genes with mutations may become unstable, miscode, or lose their functions. These genetic errors may eventually result in gene products in reduced or excessive amounts, as well as defected products. Consequently, the specifically coded phenotypes by these genes may be expressed incorrectly or even missing. Genetically defected cells therefore may be functionally or structural abnormal. Patients with SCA6, 13, and 27 have defective ion channels. Those with SCA5 and DRPLA have defective neurotransmitter receptors. SCA1, 2, and 3 are associated with defected cytoplasmic or nuclear proteins.
- Many mutations interrupt degradation of the gene products. Intracytoplasmic or intranuclear accumulations of these products in excessive amounts lead to progressive degeneration and eventual cell death. SCAs with repeat mutations (such as CAG with SCA1, 2, 3, 6, 7, 12, 17, and DRPLA) share this phenomenon.

ETIOLOGY

All SCAs are hereditary diseases. However, family history may not always be identified (SCA6 is an example of this).

COMMONLY ASSOCIATED CONDITIONS

Cerebellar ataxia, pyramidal and extrapyramidal signs, peripheral neuropathy, cortical symptoms (mental retardation, dementia, epileptic seizures, and psychosis), and ocular signs (ophthalmoplegia, pigmentary retinopathy, nystagmus, impaired gaze control, etc.).

DIAGNOSIS

HISTORY

- Common symptoms (4):
  - Progressive cerebellar ataxia (gait ataxia and dysarthria) is the hallmark symptom for all SCAs.
  - Pyramidal signs (upper motor neuron signs, hyperreflexia, and spasticity): SCA1, 3, 7, 8, 11, 12, 23, 35
  - Extrapyramidal symptoms (tremor, dystonia, choreoathetosis, dyskinesia, etc.): SCA2, 3, 9, 12, 16, 17, 21, 27, SCAX2, DRPLA
  - Axonal peripheral neuropathy: SCA1, 2, 3, 4, 8, 12, 14, 18, 25, 27
  - Oculomotor abnormalities: Hypermetric saccades (SCA1), hypometric saccades (SCA2, 7, 17), slow saccades (SCA2, 7, 35), nystagmus (SCA3, 6, unlinked), and ophthalmoplegia (SCA1, 2, 3, 9, 28).
  - Impaired cognition: SCA1, 2, 3, 12, 13, 14, 17, 19, 21, 17, 32, SCAXs, DRPLA
- Other symptoms: Pigmentary retinal degeneration (SCA7), seizures (SCA7, 10, 17, DRPLA), myoclonus (SCA2, 14, 19, DRPLA), hearing loss (SCA7, SCAX3), muscular atrophy (SCA18), hyporeflexia (SCA22), palatal tremor (SCA20), psychiatric disorders (SCA27, DRPLA), spasmodic torticollis (SCA35), azospermia (SCA32), etc.
- Symptomatic classification:
  - ADCA I: Cerebellar ataxia plus other central neurological symptoms (SCA1, 2, 3, 4, 8, 9, 12, 17, 27, 28, and 35)
  - ADCA II: Cerebellar ataxia plus pigmentary retinopathy (SCA7)
  - ADCA III: Pure cerebellar ataxia (SCA5, 6, 10, 11, 15, 22, 26, 30, 31, and SCA unlinked)
  - Other: SCA13
- The onset ages are usually during adulthood with the majority in their 30–50s. SCA2, 5, 7, 13, SCAXs, and DRPLA start during childhood. SCA6 may become symptomatic after age 60.
- Progression: The disease durations vary significantly from less than a decade (SCA10, SCAXs) to normal lifespan (SCA6, 8, 11, 30). Slow progression occurs in SCA5, 15, 22, and 23.

PHYSICAL EXAM

Neurological examination shows significant cerebellar ataxia with or without the other physical abnormalities as aforementioned.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Tests to rule out other causes of cerebellar ataxias, especially acquired conditions.
- Samples of blood and cerebrospinal fluid are usually tested.

Follow-up & special considerations
- Results from the initial laboratory testing may lead to considerations of further investigations.
- Genetic tests, which use DNA samples from blood cells, are available for many hereditary ataxias. Selection is based on clinical and initial laboratory evaluations.

Imaging
Initial approach
- Brain MRI with contrast is the initial imaging of choice. Significant findings include cerebellar and brainstem atrophies. Brain MRI also helps to rule out other causes of cerebellar ataxia.
- Functional studies, such as functional MRI, MRS, diffusion tensor MRI, and positron emission tomography, may also be used as indicated.

Follow-up & special considerations
- Brain MRI may be repeated once every 6–12 months.

Diagnostic Procedures/Other
- Family history and pattern of inheritance
- Genetic tests: Commercially available for many SCA subtypes (SCA1, 2, 3, 6, 7, 8, 10, 12, 13, 14, 17, and 18) (Athena Diagnostics, Inc., Website: www.athenadiagnostics.com).
- Pathology from autopsy when possible.

Pathological Findings
- Cerebellar atrophy is the hallmark pathological feature for all SCAs although its severity varies significantly among different subtypes.
  – Diffuse degeneration is essential. Meanwhile, some subtypes may preferentially affect certain regions. For example, SCA15 mainly affects dorsal vermis and SCA19 prefers hemispheres (4).
  – Degeneration and loss of Purkinje cells are the consistent findings. However, Purkinje cells are spared in SCA3. Granular cells may also been affected.
  – SCA1, 2, 3, 7, 23 affect dentate nucleus.

DIFFERENTIAL DIAGNOSIS
- Other hereditary cerebellar ataxias
  – Other ADCAs (EAs)
  – Autosomal recessive cerebellar ataxias (Friedreich's ataxia, ataxia with primary vitamin E deficiency, ataxia telangiectasia, abetalipoprotinemia, autosomal cerebellar ataxias, etc.)
  – X chromosome-linked ataxias: Fragile X-associated tremor/ataxia syndrome, adrenoleukodystrophy
  – Mitochondrial cerebellar ataxias
- Non-hereditary cerebellar ataxias: Thiamin deficiency-related cerebellar degeneration, paraneoplastic cerebellar lesions (presence of anti-Hu, Yo, Ri, Tr, mGlu-R antibodies), autoimmune-mediated cerebellar injuries (presence of anti-glutamic acid decarboxylase and antigliadin antibodies).
- Infections: Post-infection cerebellitis (varicella and Epstein-Barr viruses) and prion diseases
- Cerebellar lesions resulting from alcoholism or exposures to neurotoxic agents (lithium, toluene, phenytoin, amiodarone, 5-fluorouracil, and cytosine arabinoside) or heavy metals (mercury and thallium).
- Sporadic degenerative ataxias such as multiple system atrophy

TREATMENT

MEDICATION
First Line
Specific treatment is unavailable.

Second Line
- Symptomatic treatments of complications.
- Treatments for some symptoms: Nystagmus (benzodiazepams, gabapentin), tremor and myoclonus (benzodiazepams, topiramate, valproic acid), seizures (antiepileptic drugs), spasticity (baclofen), cognitive deficits (antidepressants, memantine, amphetamines), etc.

ADDITIONAL TREATMENT
General Measures
- Family and social supports
- Environmental modifications to ensure safety

Issues for Referral
- Genetic counseling
- Physical therapy and physiatric evaluation

Additional Therapies
Equipments: Special supporting devices, canes, walkers, wheelchair, automatic scooters

COMPLEMENTARY AND ALTERNATIVE THERAPIES
Investigational therapies include 3,4-diaminopyridine, memantine, amantadine, antioxidant cocktail (Co-Q10, vitamin E, and vitamin C), L-carnitine, acetazolamide, idebenone, 5-hydroxytryptophan, physostigmine, N-acetylcysteine, phosphatidylcholine, vigabatrin, and trimethoprim–sulfamethoxazole.

SURGERY/OTHER PROCEDURES
- Injections (baclofen and botulinum toxin) and implanted delivery pumps (balofen) for spasticity.
- Alleviative surgeries for contracture release, tracheostomy, and feeding tube placements.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Regular office follow-ups once every 3–12 months to monitor disease progression and complications. Frequency and intervals may be individually adjusted.

PATIENT EDUCATION
National Ataxia Foundation, 2600 Fernbrook Lane Suite 119, Minneapolis, MN 55447-4752 Tel: 763 553-0020 Fax: 763 553-0167 E-mail: naf@ataxia.org Website: www.ataxia.org

PROGNOSIS
All SCA subtypes are progressive and eventually debilitating. However, the disease progression and severity of debilitation vary significantly. These with SCA6, 8, 11, and 30 may expect normal lifespan.

COMPLICATIONS
- Injuries from falls, seizures, and aspiration
- See other complications as listed in **HISTORY** and **PHYSICAL EXAM**.

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ADDITIONAL READING

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CODES
ICD9
- 334.8 Other spinocerebellar diseases
- 334.9 Spinocerebellar disease, unspecified
- 781.3 Lack of coordination

CLINICAL PEARLS
- SCA includes many subtypes of which all are featured by progressive ataxia from cerebellar degeneration.
- SCAs account for the majority of ADCAs. SCA3 is the most common subtype worldwide. Variations among the subtypes are significant.
- There is no available specific treatment.

STIFF PERSON SYNDROME

David S. Younger, MD

BASICS

DESCRIPTION

Stiff person syndrome (SPS) is characterized by muscle rigidity and spasms of axial and limb muscles that lead to continuous contraction of agonist and antagonist muscles.

EPIDEMIOLOGY

- The prevalence has not been reported, but it is clear that SPS is rare.
  - Race:
    - There is no clear racial or ethnic predisposition.
  - Age:
    - The age of onset of symptoms is usually in the fifth decade of life but ranges from the third through the seventh decade. Cases in children are rarely reported.
  - Sex:
    - The disease may be more common in women than in men.

ETIOLOGY

The etiology of SPS is unknown; however, it is believed to be CNS mediated as suggested by the following. Approximately, 10% of patients with SPS have seizures. Drugs that enhance CNS levels of γ-aminobutyric acid (GABA), such as diazepam and valproic acid improve muscle symptoms. One theory proposes that patients with SPS have impaired cortical and spinal inhibitory GABA-nergic intraneurons. The proposed loss of GABA input produces tonic firing of motor neurons at rest and leads to hyperactive excitation. In support of this theory is that up to 65% of patients with SPS have antibodies against glutamic acid decarboxylase (GAD), which is the rate-limiting enzyme for the synthesis of GABA at their respective nerve terminals. Anti-GAD antibodies cause a functional impairment in the synthesis of GABA and therefore may play a pathogenic role in the disease. Such antibodies have been isolated in both the serum and CSF of patients with SPS.

- In a subgroup of patients, SPS is a paraneoplastic disease. In these patients, the stiffness is mostly in the proximal muscles and may predate the detection of the tumor. The most commonly associated tumor is breast cancer.

COMMONLY ASSOCIATED CONDITIONS

- Type 1 diabetes mellitus, pernicious anemia, autoimmune thyroiditis, epilepsy, and tumors not infrequently associated conditions. The autoimmune pathogenesis of SPS is further strengthened by the:
  - presence of anti-GAD antibodies and anti-islet cell antibodies (anti-ICA) in some affected patients
  - presence of other autoimmune diseases or autoantibodies in patients with SPS and first-degree relatives
  - response to immunosuppressive and immune modulating therapy.
- The tumors most commonly associated with SPS are small cell lung cancer, thymomas, and breast cancer. Patients with paraneoplastic SPS harbor antibodies that react with amphiphysin, a 128-kD synaptic protein. Such antibodies have also been identified with SPS associated with lung cancer, colon carcinoma, and Hodgkin lymphoma. Paraneoplastic rigidity and spinal myoclonus may occur as part of the syndrome termed progressive encephalomyelitis with rigidity. This disorder is similar to SPS and causes muscle rigidity and spasms of the trunk and limb muscles, with additional brainstem involvement and sometimes peripheral neuropathy. Pathological studies show perivascular inflammatory infiltrates and neuronal degeneration, mainly involving the cervical portion of the spinal cord and brainstem with preservation of corticospinal tracts. One reported patient with breast cancer, paraneoplastic opsoclonus-myoclonus, ataxia, muscle rigidity, and spasms-harbored anti-Ri antibodies in serum and CSF.

DIAGNOSIS

Stiffness and spasms begin insidiously and progresses over months to years with a sensation of stiffness that involves the paraspinal musculature and manifests over time as paraspinal hypertrophy and lumbar hyperlordosis. The muscles may feel firm. Rigidity extends to the limbs in a symmetrical or asymmetrical fashion, and may even involve facial muscles. Painful muscle spasms can be triggered by emotional duress, unexpected noise, and tactile stimulation. Collectively, these symptoms impair a patient's ability to ambulate effectively. Muscle spasms superimposed on this rigid unsteady gait cause the patient to freeze and fall. The spasms vary in intensity but have been known to be as severe as to cause fractures and to bend the pins used in their repair.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

The presence of anti-GAD, anti-ICA, and other autoantibodies in the serum and CSF of suspected patients support the diagnosis of SPS.

Imaging

Although neuroimaging of the brain and spinal cord are typically normal, these studies are recommended to exclude another CNS process. Whole body positron emission tomography with CT can facilitate early detection and treatment of occult cancer in those eventually found to have paraneoplastic SPS.

Diagnostic Procedures/Other

Eelectrodiagnostic studies show continuous motor unit discharges that fail to relax.

DIFFERENTIAL DIAGNOSIS

Diseases that should be differentiated from SPS include chronic tetanus, neuromyotonia, and degenerative diseases of the extrapyramidal system.

TREATMENT

MEDICATION

- *Diazepam* is the most widely and historically first used agent in the treatment of SPS at a dose of 40 to 60 mg/day with few taking more than 100 mg/day. Mood changes and sedation are common. Although there are no double-blind placebo-controlled trials of the use of diazepam, most patients with SPS empirically show benefit and favorably respond for an extended period of time.
- *Vigabatrin* that decreases GABA catabolism, and *tiagabine* that interferes with GABA uptake, may also be helpful agents.
- *Baclofen* that increases GABA activity reduce rigidity and spasms when administered orally and intrathecally, the latter of which had the additional benefit of less sedating side effect.
- *Corticosteroids* and *azathioprine* immunosuppressants have also been associated with long-term benefit but carry the risk of potentially serious systemic side effects.
- Alternative Drugs
  - *Intravenous immunoglobulin* and *plasma exchange* should be considered in those patients who are intolerant of immune suppressant medication.

ADDITIONAL TREATMENT

General Measures

Patients require a significant amount of counseling to educate them on the condition. Attention should be given to how the disorder affects their quality of life. If appropriate, psychological and social services should be offered to support patients as they cope with their disability.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment:
  - There is no cure for SPS, but a variety of medications are available to alleviate symptoms. On the basis of the proposed pathogenesis of the disorder, two types of therapy are rationally applied: (a) drugs that enhance CNS GABA activity, and (b) immunomodulators.
- Adjunctive treatment:
  - Behavioral medicine and biofeedback may be helpful in managing the psychological factors that can aggravate symptoms.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Hospitalization may be indicated for management of severe spasms, spasticity, and pain.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Regular visits to screen for patient comfort and quality of life are important to the patient, as is routine laboratory work to screen for toxic effects of therapies such as steroids and azathioprine.

PATIENT EDUCATION

- Patients can learn more about this disorder through the National Institute of Neurological Disorders and Stroke. Website: www.ninds.nih.gov

PROGNOSIS

Patients with SPS generally have a progressive course with variable response to treatment.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Stiff man syndrome
- Woltman–Moersch syndrome

CODES

ICD9

333.91 Stiff-man syndrome

STURGE–WEBER SYNDROME

Hongyan Li, MD, PhD

BASICS

DESCRIPTION

- Sturge–Weber syndrome (SWS), or encephalotrigeminal angiomatosis, is a rare sporadic neurocutaneous disease resulting from congenital malformations of cephalic venous microvasculature.
- SWS is named after British physicians William A. Sturge, who first described the condition in 1879, and Frederick P. Weber, who reported the intracranial vascular lesions in 1922.
- The characteristic intracranial vascular anomaly is leptomeningeal angiomatosis that most often affects the posterior parietal and occipital brain regions. The typical cutaneous vascular malformation is congenital facial capillary dilatation in the territories of trigeminal nerves, especially the ophthalmic nerve ipsilateral to the intracranial involvement.
- SWS is clinically characterized by early onset epileptic seizures, congenital facial stains (*port-wine stains* or *nevus flammeus*), ocular lesions, headaches, recurrent hypoxic or ischemic events, focal neurological deficits, developmental delay, and mental retardation.
- Subtypes:
  - Type I: Leptomenigeal angiomatosis with facial angioma (and possibly glaucoma)—the most common type
  - Type II: Facial angioma (and possibly glaucoma) without leptomeningeal angioma
  - Type III: Leptomenigeal angiomatosis without facial or ocular involvement

EPIDEMIOLOGY

Incidence

About 1/50,000

Prevalence

Rare (less than 1/200,000)

RISK FACTORS

Unknown

Genetics

Sporadic—unlikely genetic

PATHOPHYSIOLOGY

- Vascular malformation causes interruption of venous drainage. Consequently, the vascular structures become dilated and tortuous. In the cortical areas with leptomeningeal angiomatosis, the pia matter becomes thickened and the superficial venous drainage is poor. Without sufficient alternative deep pathways, oxygenation of the cells in the affected cortical and subcortical brain areas becomes jeopardized by microcirculatory stasis and obstructions. The cells are damaged from recurrent thrombosis, hypoxia, and ischemia, leading to necrosis. The affected cortex eventually becomes atrophic, discolored, and appears like cobblestones from gliosis and calcification.
- Recurrent hypoxia may contribute to clinical transient ischemic events, migraine-like headaches, and focal neurological deficits.
- Hypoxic and ischemic events are made worse with dehydration and during recurrent seizures that, when refractory, often indicate a likelihood of progression and poor prognosis.

ETIOLOGY

- Congenital
  - SWS may result from failed regression of primitive venous plexus within the cephalic mesenchyme during early pregnancy.

COMMONLY ASSOCIATED CONDITIONS

Seizures, ischemic events, glaucoma, headaches, and cognitive impairments

DIAGNOSIS

HISTORY

- Epilepsy
  - Recurrent seizures are the most common neurological symptoms with SWS and affects 72–90% of patients by age 3.
  - Typical seizure onset is in early infancy. However, it varies between birth and adolescence.
  - Initial seizures are predominantly focal and involve the contralateral body side to the brain lesion. However, seizures can be of any type, including infantile spasm, generalized tonic–clonic, and status epilepticus. The first seizure is often febrile.
  - Recurrent seizures are common and result from microvascular stasis, hypoxia, and cell damage in the affected cortical regions by angiomatosis. Increased regional demand for oxygen may precipitate brain injury. Thus, early onset and intractable seizures often indicate poor prognosis.
- Headaches
  - Recurrent migraine-like vascular headaches affect 30–60% patients with SWS (1,2). The mechanism is the same as for transient ischemic attacks (TIA).
- TIA episodes
  - These episodes reflect exacerbation of hypoxia and ischemia within the affected parenchyma by the vascular lesions. They often occur when acute illnesses, such as seizures and dehydration, precipitate microcirculatory thrombosis and hypoxia.

PHYSICAL EXAM

- Cutaneous vascular malformation
  - Port-wine stains are well-demarcated macular birthmarks in fresh red or purple color. They typically affect the facial skin areas innervated by the trigeminal nerve branches, predominantly V1 (ophthalmic nerve) and less often V2 and V3. The majority are exclusively unilateral and rarely extend beyond the midline.
  - Port-wine stains affect 3:1,000 live births (3). Only about 8–15% patients with SWS demonstrate this cutaneous lesion (2). Exclusive unilateral or bilateral involvement of V1 territory (forehead and upper eyelid) suggests higher risk of SWS with ipsilateral intracranial vascular malformations.
- Ocular and visual abnormalities
  - These abnormalities result from the vascular malformations that affect conjunctiva, episclera, retina, and choroids.
  - Glaucoma is the most common ocular abnormality in 30–70% patients with SWS (1,2) and affects the ipsilateral eye to port-wine stain. When both signs are present, the risk of developing SWS is very high.
  - Choroidal hemangioma is common and affects the eye ipsilateral to port-wine stains.
  - Other ocular findings include buphthalmos, conjunctiva and episcleral hemingioma, iris heterochromia, retinal pigment degeneration, retinal detachment, optic disc coloboma, nevus of Ota, and cataracts.
- Focal deficits
  - Neurological deficits related to cortical lesions are common in the contralateral face and body. Common focal deficits are hemiparesis (25–56%) and hemianopia (40%) (1,2).
- Developmental delay and mental retardation
  - Cognitive impairments affect 50–75% patients with SWS (2). Those with early onset and chronic refractory seizures and significant focal neurological deficits, including recurrent TIA's, are more severely affected then the others.
  - Attention deficit and hyperactivity disorder (ADHD) is also common in patients with SWS (1).

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

No specific diagnostic test is available.

Imaging

Initial approach

- Brain MRI with contrast is the preferred imaging technique for the diagnosis of SWS. The demonstration of pial enhancement from angioma is essentially diagnostic. Other intracranial pathological changes that are well demonstrated by MRI are regional brain lesions, cerebral atrophy, gliosis, calcification, accelerated myelination, and enlarged ipsilateral choroid plexus. MRI of orbits with contrast is useful in detecting choroidal hemangioma.
  - Head CT can be better than MRI in demonstrating intracranial calcification underneath the leptomeningeal angiomatosis, which is typically more striking in the posterior region ipsilateral to facial and ocular vascular lesions.
  - Skull x-ray was used in the past for diagnosing SWS. The classic *tram-track* (or *tram-line*) sign suggests calcification in leptomeningeal hemangioma.
  - Cerebral angiography is less commonly used in diagnosing SWS. Cerebral venogram may demonstrate defective superficial cortical veins and deep venous anomalies.

– Functional imaging techniques may be useful in some cases. Single-photon emission computed tomography may show hypoperfusion underlying leptomeningeal angiomatosis. Positron emission tomography may identify regional low glucose metabolism at early stages of brain lesions and therefore can be particularly useful in evaluation for seizures, ischemic events, and cognitive functions.

Follow-up & special considerations
Follow-up neuroimaging studies may be required to monitor disease progression and to diagnose neurological complications.

Diagnostic Procedures/Other
- EEG recording usually shows abnormalities, such as asymmetry, regional slowing, and epileptiform discharges, in the region with brain regions. It is particularly helpful in diagnosing and treating seizures.
- Ophthalmic evaluation
- Dermatological evaluation
- Neuropsychological tests

Pathological Findings
- Leptomeningeal angiomatosis is the hallmark intracranial finding with SWS.
  – The affected pia matter is thick and discolored from venous dilatation. Engorged superficial and transmedullary veins with stasis and thrombosis and enlargement of the ipsilateral choroid plexus are seen.
  – Laminar necrosis, neuronal loss, and reactive gliosis develop in the affected brain regions. Hemorrhage is rare.

DIFFERENTIAL DIAGNOSIS
- Other causes of focal or regional intracranial vascular malformations (arteriovenous malformation, venous angioma, congential or secondary cerebral vascular events)
- Other congenital or secondary focal brain lesions (neuronal migrational disorders)
- Other capillary vascular malformations in face (port-wine stain without ocular or intracranial involvement)
- Other causes of brain atrophy and intracranial calcification (gestational infection, primary and secondary neurodegeneration of early childhood)
- Other causes of early onset and recurrent focal or generalized seizures with developmental delay and progressive cognitive impairment.
- Other causes of infantile or early childhood ocular diseases (orbit tumors)

TREATMENT

MEDICATION
First-Line (1,4)
- Epilepsy: Carbamazepine or other antiepileptic drugs (AEDs)
- Glaucoma: Beta blocker eye drops
- Transient ischemia: Aspirin
- Headaches: Ibuprofen
- Hyperactivity and attention deficit: Stimulants such as methylphenidate

Second Line
- Epilepsy: Alternative AEDs
- Glaucoma: Carbonic anhydrase inhibitor, adrenergic eye drops
- Headaches: Propanolol, nortriptyline
- Behavioral disorders: Clonidine, risperidone

ADDITIONAL TREATMENT
General Measures
- Early diagnosis and treatments for seizures, hypoxia, and cognitive deficits may minimize severe complications and lead to better prognosis.
- Better education of parents, family members, and caregivers favors higher quality of cares.
- Modification of living environment helps the control of complications and reduces risks of developing secondary injuries.

Issues for Referral
- Evaluation by epileptologist for possible epilepsy surgeries for selected patients with refractory focal epileptic seizures
- Ophthalmological evaluation for diagnosis and treatment of ocular complications
- Evaluation for rehabilitation and physical therapies when neurological deficits are identified.
- Neuropsychological/psychiatric evaluations for developmental and behavioral disorders.
- Dermatological evaluation for skin lesions

Additional Therapies
- Physical therapy and rehabilitation for neurological deficits. Special education programs for cognitive and behavioral abnormalities.
- Cosmetic measures for cutaneous lesions may facilitate managements of psychological and behavioral problems.

SURGERY/OTHER PROCEDURES
- For refractory epileptic seizures, surgical options include focal cortical resection, lobectomy, hemispherectomy, callosotomy, and vagal nerve stimulation.
- Surgeries for glaucoma include cyclocryotherapy, laser goniotomy, and trabeculotomy or trabeculectomy.
- Laser and other cosmetic surgical procedures have been used to treat facial vascular stains.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patients with SWS should follow regularly with pediatric neurologists, epileptologists, and other specialists (ophthalmologists, dermatologists, psychologists, and physiatrists). The frequency of following up and the intensity of attention must be determined on an individual basis.

PATIENT MONITORING
Clinical symptoms (seizures, transient hypoxia, headaches, vision, and cognition) and neurological deficits are followed for any progression or changes.

PATIENT EDUCATION
- Many sources of educational information and instructions are available online.
  – The Sturge–Weber Foundation (address: PO Box 418, Mt. Freedom, NJ 07970-0418 USA; Tel: 973-895-4445 or 800-627-5482; Fax: 973-895-4846; Email: swf@sturge-weber.org; website: www.sturge-weber.org

PROGNOSIS
- SWS is not a fatal disease. Morbidity and mortality vary significantly among the affected patients, of whom many have normal life expectancy.
- The quality of life depends upon the severity of disease and the effectiveness in controlling complications. Those with early onset and intractable seizures, recurrent hypoxic and ischemic attacks, extensive brain lesions, and progressive deteriorations are less favored.

COMPLICATIONS
Seizures, visual loss, hemiplegia, hemianopia, developmental delay and mental retardation, behavioral problems (ADHD), and headaches

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CODES

ICD9
759.6 Other hamartoses, not elsewhere classified

CLINICAL PEARLS
- The hallmark pathological change with SWS is the intracranial leptomeningeal angiomatosis.
- Infants with port-wine stains in the ophthalmic nerve territory should undergo brain MRI with contrast study for SWS.
- The disease can result in progressive and severe complications. Early diagnosis and symptomatic treatments may reduce the severity of these complications.

SUBCLAVIAN STEAL SYNDROME

Alan B. Sanderson, MD

BASICS

DESCRIPTION

- Subclavian steal syndrome (SSS) refers to the condition where stenosis of the subclavian artery proximal to the origin of the vertebral artery causes diminished blood flow to the distal subclavian artery, and blood flow in the vertebral artery flows in a retrograde fashion in order to supply the distal subclavian artery. Thus, the blood supply to the ipsilateral arm is "stolen" from the posterior cerebrovascular circulation, which then relies on the contralateral vertebral artery. The development is usually chronic.
- SSS was first recognized by conventional angiography in the 1960s. Noninvasive imaging has shown that SSS is much more common than was initially thought, and is usually asymptomatic.
- Most symptoms can be ascribed to ischemia of the posterior cerebrovascular territory. Arm claudication is less common. A related phenomenon, called "coronary-subclavian steal," involves myocardial ischemia after using the internal mammary artery in coronary artery bypass surgery.
- Systems affected: Central nervous system, Cardiovascular system
- Synonyms: The term "subclavian steal phenomenon" refers to asymptomatic SSS. Some authors reserve the term "subclavian steal syndrome" for symptomatic cases only.

EPIDEMIOLOGY

Incidence

No specific data are available.

Prevalence

- Estimates range from 0.4–6.4%.
- A 2010 study found subclavian steal in 5.4% (429/7,881) of patients referred for carotid duplex ultrasound to investigate cerebrovascular disease. Only 8.9% (38/429) of these were symptomatic (0.5% of total subjects) (1).
- Age/gender: Most patients are male, aged >50 years old.

RISK FACTORS

- Smoking, hypertension, dyslipidemia, and diabetes

Genetics

No genetic syndrome is identified.

GENERAL PREVENTION

Smoking cessation, medical management of hypertension, dyslipidemia, and diabetes

PATHOPHYSIOLOGY

- When the blood pressure in the basilar artery is greater than the blood pressure in the distal subclavian artery, then blood flow along the vertebral artery will be in a retrograde direction.
- The left side is involved about 80% of the time. Bilateral SSS is uncommon.
- Subtypes:
  - Complete: Flow in the vertebral artery is retrograde throughout the cardiac cycle.
  - Partial: Flow in the vertebral artery is anterograde during diastole, retrograde during systole.

ETIOLOGY

- Atherosclerosis is by far the most common cause.
- Takayasu arteritis is a rare cause, classically occurring in females of Asian descent younger than 30 years old. Takayasu arteritis involves proximal subclavian stenosis in up to 85% of patients, and is more likely than atherosclerosis to cause bilateral disease.

COMMONLY ASSOCIATED CONDITIONS

Vascular disease at other sites, including coronary artery disease, carotid stenosis, and peripheral vascular disease.

DIAGNOSIS

HISTORY

- Symptoms of vertebrobasilar insufficiency can include dizziness, vertigo, visual changes, loss of consciousness.
- A minority of patients complain of arm claudication.
- Patients with coronary-subclavian steal may complain of cardiac chest pain.
- Symptoms are usually transient, and may accelerate in severity or frequency over months. Exercise of the ipsilateral arm may provoke symptoms.

PHYSICAL EXAM

- Vital signs: A blood pressure differential (PD) between the two arms >20 mm Hg is strongly associated with SSS. SSS was found in 77% of patients with PD of 20–30 mm Hg, 90% of patients with PD of 30–40 mm Hg, and 100% of patients with PD >40 mm Hg. As PD increases, complete SSS becomes more likely. The proportion of symptomatic patients also increases with increasing PD. Bilateral SSS is less likely to have PD >20 mm Hg, but the systolic blood pressure in both arms is usually <100 mm Hg in these patients (1)[C].
- Cardiovascular: Listen for bruits over the heart and great vessels, including the neck vessels. Palpate the radial and/or brachial pulses bilaterally, noting any differences in timing or amplitude between sides.
- Neurologic: Perform a complete screening neurologic examination, paying careful attention to the cranial nerves and visual system. Between episodes the neurologic examination is usually normal.
- Symptoms can sometimes be elicited during examination by having the patient exercise the ipsilateral arm.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

There are no specific laboratory tests.

Follow-up & special considerations

Consider checking serum inflammatory markers in patients suspected of having Takayasu arteritis.

Imaging

Initial approach

Duplex ultrasound is the initial test of choice because it is noninvasive, relatively inexpensive, has few contraindications, and readily visualizes the direction of flow in vessels (1)[C].

Follow-up & special considerations

CT, MRI, or conventional angiography may also be useful in certain cases, especially if intervention is planned (1)[C].

Pathological Findings

Biopsy is not usually performed. Histology usually shows atherosclerosis. Histology of Takayasu arteritis shows inflammation of the vasa vasorum during the acute phase, and fibrosis with destruction of elastic tissue during the chronic phase (4)[C].

DIFFERENTIAL DIAGNOSIS

- Other causes of neurologic symptoms: Vertebral or basilar artery stenosis, thromboembolic disease, basilar migraine, infectious, inflammatory, or neoplastic disease involving the brainstem, toxic or metabolic conditions such as hypo- or hyperglycemia, syncope, seizure, trauma
- Other causes of arm symptoms: More distal arterial stenosis or occlusion, peripheral neuropathies, including mononeuritis multiplex, entrapment neuropathies, and brachial plexopathies, other causes of thoracic outlet syndrome, asymmetric myopathy
- Other causes of cardiac symptoms: Coronary artery disease, coronary vasospasm, non-cardiac chest pain

TREATMENT

MEDICATION

First Line

- Because SSS is rare, there are no randomized trials to guide management.
- Antiplatelet agents, such as aspirin 81 mg daily (1,2)[C].
- Medical management of underlying risk factors for vascular disease, including blood pressure, diabetes, and dyslipidemia (1,2)[C].
- Treatment of Takayasu arteritis where applicable, usually with corticosteroids (4)[C].

Second Line

Other antiplatelet agents, such as clopidogrel 75 mg daily.

ADDITIONAL TREATMENT

General Measures

- Smoking cessation
- Patients may be counseled to avoid exercise of the affected arm, and to avoid other inciting factors such as neck positions, etc.

Issues for Referral

Patients should be followed by a vascular surgeon. There are no data to guide the timing or interval of visits (1,2)[C].

SURGERY/OTHER PROCEDURES

Endovascular approaches have been used since the 1990s. A 2009 paper reported 104 consecutive patients treated with either balloon angioplasty alone or angioplasty with stenting, with an overall technical success rate of 96% and sustained 1-year primary patency of 88%. Complication rates are low, and the procedure is less invasive, so many recommend this approach as first-line therapy (2)[B].

- Traditional vascular surgery approaches such as carotid-subclavian bypass show superior 5-year patency rates in the range of 95%, but complication rates between 12 and 29% (2)[B].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- There are no specific data to guide management.
- Assure adequate blood pressure
- Control blood glucose
- Prompt diagnosis to rule out other conditions

Admission Criteria

There are no specific data to guide management. It is prudent to admit patients who may be candidates for intervention due to severity of symptoms, or who need a number of diagnostic tests to rule out other potential conditions.

IV Fluids

If indicated for hypotension in the setting of active symptoms. There is no preference for one type of IV hydration.

Nursing

- Assure glucose control in patients with diabetes.
- Manage accurate administration of medications.
- Provide patient education on SSS and comorbid conditions.

Discharge Criteria

There are no specific data to guide management. Clinicians should use their best judgment to discharge patients safely after an appropriately thorough workup, and after watching for and managing any complications of therapy.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients should be followed by a vascular surgeon.
- Primary care doctors or medical specialists should provide treatment for underlying medical risk factors.
- Neurologists may be involved to follow the course of neurologic symptoms.

PATIENT MONITORING

- Most patients can be managed in the outpatient setting, but may be admitted for initial diagnosis or for procedures.
- There is no consensus on surveillance imaging after diagnosis or after procedural interventions.
- Patients who undergo endovascular procedures may require additional procedures to repeat angioplasty or stenting in the case of restenosis (1,2,3)[C].

DIET

- Diets shown to be helpful in other atherosclerotic vascular diseases are likely to be helpful in vertebrobasilar insufficiency, but there are no research studies addressing this topic.
- Diabetic diet if applicable.

PATIENT EDUCATION

- Patients should be educated regarding the cause of their symptoms and treatment options.
- Patients should be informed of underlying risk factors for SSS and counseled regarding smoking cessation and compliance with medical therapies for hypertension, dyslipidemia, and diabetes.
- Patients should know what symptoms should prompt them to seek medical care.

PROGNOSIS

The overall prognosis is not known. Whether symptomatic patients improve with medical therapy alone or whether they eventually require procedural intervention is not known.

COMPLICATIONS

Coronary-subclavian steal can occur in patients who have coronary artery bypass surgery using the internal mammary artery.

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See Also (Topic, Algorithm, Electronic Media Element)

- Vertebrobasilar Insufficiency
- Syncope

CODES

ICD9

435.2 Subclavian steal syndrome

CLINICAL PEARLS

- SSS is usually caused by atherosclerosis, and is usually asymptomatic.
- Check the blood pressure in both arms of patients with symptoms of posterior circulation ischemia. A difference in blood pressure between the two arms of >20 mm Hg correlates strongly with SSS.
- Both endoscopic techniques and open vascular surgeries are used with success in SSS.

SYDENHAM'S CHOREA

S. Anne Joseph, MD

BASICS

DESCRIPTION

First described by Thomas Sydenham in 1686, Sydenham's chorea is an immune-mediated acquired chorea that occurs after streptococcal pharyngitis. It may be associated with other features of rheumatic fever (Jones criteria). Chorea refers to involuntary, forceful, random jerks that involve any part of the body. They can include abnormal movements of the respiratory muscles, producing grunts and other sounds. Chorea is present at rest and increases with voluntary movements. Chorea at rest and with posture gives rise to the appearance of a restless child who is unable to sit still. "Piano-playing" movements of fingers, when the hand is held outstretched, and the "milkmaid's grip," when grasping an object, are features of chorea. Volitional movements are often jerky, and the gait often has a lurching quality. Chorea may be accompanied by athetosis, which consists of involuntary movements that have a more writhing, sinusoidal quality.

EPIDEMIOLOGY

- Incidence/Prevalence
  - Most prevalent acquired chorea in childhood.
  - There had been a previous decline in the incidence. However, more recently, there has been a resurgence of cases.
  - Occurs in 10–20% of patients with rheumatic fever.
- Age
  - Seen mostly between the ages of 5–15 years. Can be seen as young as 2 years.
- Sex
  - Female preponderance occurring at a ratio of approximately 2:1 that becomes more evident after age 10 years.

RISK FACTORS

Family history of rheumatic fever, Sydenham's chorea, or post-streptococcal carditis appears to increase the risk of an individual developing Sydenham's chorea.

Pregnancy Considerations

Women who had Sydenham's chorea in childhood may rarely have a recurrence of symptoms during pregnancy.

ETIOLOGY

It is thought that group A β-hemolytic streptococci (GABHS) trigger antistreptococcal antibodies that, by molecular mimicry, cross-react with epitopes on the basal ganglia of susceptible hosts. These anti-basal ganglia antibodies are hypothesized to alter the corticostriatal circuits, leading to motor dysfunction via the putamen, and behavior changes via the caudate and cortex. Genetic susceptibility is suggested by the higher than expected familial incidence of this condition and the more frequent presence of the D8/17 alloantigen in the B lymphocytes of patients.

COMMONLY ASSOCIATED CONDITIONS REPORTED WITH SYDENHAM'S CHOREA

- Rheumatic fever
- Cardiac involvement in 33.7%
- Other neurologic symptoms: Approximately 38.7% had dysarthria. Encephalopathy, with personality changes, emotional lability, disorientation, confusion and, more rarely, delirium occurred in 10%.
- Other psychiatric symptoms: Obsessive-compulsive symptoms were seen in 82%. Other symptoms included emotional lability, irritability, distractibility, motoric hyperactivity, age-regressed behavior, nightmares, and anxiety. These symptoms may start 2–4 weeks prior to onset of chorea, peak as the motor severity does, and remit shortly after the chorea disappears.

DIAGNOSIS

- Chorea and emotional lability appear abruptly several months after streptococcal pharyngitis. Although usually fairly abrupt in onset, symptoms may progress in severity over a few weeks and persist for months. In a retrospective study of 240 patients between 1951 and 1976 at the University of Chicago, 81% had generalized chorea and 19% had hemichorea. Duration of chorea ranged from 1 to 22 weeks (median 12 weeks). 80% had no recurrences.
- Diagnosis is made by establishing a preceding exposure to GABHS, either by history or by elevated antistreptococcal antibody titers (ASO [antistreptolysin-O] or anti-DNase B). However, in about 20% of cases, no clinical or serologic evidence of a preceding GABHS can be established, because the chorea can lag behind the etiologic infection by 6 months. Without documentation of an antecedent streptococcal infection, the diagnosis of Sydenham's chorea is made by excluding other causes of childhood chorea.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Search for evidence of a previous streptococcal infection with ASO titers, anti-DNase B titers, and a throat swab to determine whether the patient still has streptococcal colonization of the throat. Other tests should include a rheumatological screen with ESR, ANA, RF, and antiphospholipid antibodies. If there is evidence suggesting an acute primary CNS infection, CSF analysis should be performed. When Sydenham's chorea is a consideration, a search should be undertaken for cardiac involvement with ECG and ECHO.

Imaging

MRI: Analysis of cerebral MRIs of subjects with Sydenham's chorea and controls in one study demonstrated increased size of the basal ganglia in the Sydenham's chorea group. However, as a diagnostic tool in Sydenham's chorea, cerebral MRI appears to be more helpful in eliminating certain other mimickers than in confirming the diagnosis, as it may often look fairly normal in Sydenham's chorea.

Diagnostic Procedures/Other

SPECT scan of the brain may show hyperperfusion in the basal ganglia.

DIFFERENTIAL DIAGNOSIS

- Primary CNS vasculitis
- Systemic lupus erythematosus
- Acute encephalitis
- Toxins/drugs
- Wilson's disease
- PANDAS (pediatric autoimmune neuropsychiatric disorders after streptococcal infections)
- G_{M1} and G_{M2} gangliosidoses
- Glutaric aciduria
- Methylmalonic and propionic acidemia
- Antiphospholipid antibody syndrome
- Thyrotoxicosis

TREATMENT

MEDICATION

- Prednisone: In one retrospective study, children treated with prednisone appeared to have a shorter course of chorea than those treated with haloperidol, valproate, or diazepam. Prednisone can cause weight gain, cushingoid appearance, mood lability, psychosis, hypertension, hyperglycemia, electrolyte imbalances, and gastritis. It can suppress the immune system, thereby decreasing the individual's ability to fight off intercurrent infections.
- Valproate: In a study of 18 children with Sydenham's chorea, valproate appeared to have a better efficacy than carbamazepine and haloperidol. Side effects can include an allergic skin rash, weight gain, thrombocytopenia, pancytopenia, pancreatitis, hepatic failure, and gastritis.
- Carbamazepine: Side effects can include liver dysfunction, an allergic skin rash, leukopenia, pancytopenia, drowsiness, ataxia, and hyponatremia.
- Haloperidol: Potential side effects include an acute dystonic reaction, weight gain, hyperthermia, and drug-induced dyskinesias.
- Pimozide: Potential side effects include those of haloperidol, with the potential for cardiac dysrhythmias.
- Benzodiazepines: Sedation appears to be the main side effect.
- Intravenous immunoglobulins: Anecdotal case reports in the literature suggest that this may be a treatment option.

Prophylaxis to prevent recurrent streptococcal infections is recommended.

ADDITIONAL TREATMENT

General Measures

- Eradication of *Streptococcus* if still present in the pharynx with antibiotics, and prevention of further infection with antibiotic prophylaxis
- Treatment of cardiac dysfunction if present
- Treatment of chorea
- Treatment of behavior/psychiatric symptoms

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Treatment of chorea (see later). Psychiatric manifestations warrant evaluation and appropriate therapy depending on severity. Cardiac manifestations should be treated and monitored closely.
- Adjunctive treatment
  - Measures for physical safety in patients with significant difficulties in ambulation. Difficulties in the realms of behavior, fine motor skills, and cognition should be addressed by a team consisting of the medical provider, psychology/psychiatry, educators, and physical and occupational therapists.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission for rapid evaluation and monitoring if symptoms suggest a primary CNS infection or if there are symptoms of cardiac dysfunction. Patients with severe chorea who are unable to ambulate may benefit from initial inpatient rehabilitation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Monitor response to treatment and for potential side effects of the drug used. Gradually wean medications as symptoms resolve.

PATIENT EDUCATION

- Compliance to antibiotic prophylaxis against further streptococcal infection should be stressed.
- Good source for patient information is the website: www.wemove.org

PROGNOSIS

Sydenham's chorea is considered self-limiting. However, on occasions, chorea can be so severe as to cause significant impairment in motor function and ambulation. Psychological manifestations may range from minimal to extremely severe. Without treatment the symptoms tend to gradually remit, but may take weeks to a year. Recurrent attacks can occur in up to 20% of cases. Usually there is only one recurrence, on average 1.8 years after the first attack. Recurrences many years after the initial attack are uncommon and suggest that late chorea may be due to reactivation by another mechanism, such as pregnancy or drugs. Patients with Sydenham's chorea may have chorea during pregnancy (chorea gravidarum) and are at higher risk for chorea induced by phenytoin or oral contraceptives.

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See Also (Topic, Algorithm, Electronic Media Element)

- Rheumatic chorea
- Chorea minor
- St. Vitus dance
- Encephalitis rheumatica

CODES

ICD9

- 392.9 Rheumatic chorea NOS
- 781.0 Abnormal involuntary movements

SYPHILIS, NEUROLOGICAL COMPLICATIONS

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BASICS

DESCRIPTION

Syphilis is a systemic infection that can involve the CNS at any stage. Early on, neurosyphilis (NS) can involve meninges, CSF or cerebral and spinal cord vessels. Later, NS affects the brain and spinal cord parenchyma.

- Syndromes or forms of NS:
  - Meningeal:
    - Early and late asymptomatic NS: CSF abnormalities without clinical neurologic disease. Treatment prevents development of symptomatic NS.
    - Acute syphilitic meningitis: Occurs at any time but mainly within first year of infection.
  - Meningovascular: Vascular NS is an infectious endarteritis leading to ischemia in any vessel territory; most commonly, the middle cerebral artery distribution. Occurs 5–12 years after initial infection. Involvement often occurs with or progresses to parenchymal disease.
  - Parenchymatous:
    - General paresis: Parenchymal invasion of the cerebrum by Treponema pallidum. Develops 15–20 years after initial infection; progresses subacutely over years. Terminal if untreated.
    - Tabes dorsalis: Parenchymal invasion of dorsal nerve roots and spinal cord posterior columns. It is now rare; occurs in untreated patients after 20–25 years of latency. The damage is often irreversible despite therapy.
    - Optic NS: Takes many forms, including uveitis, retinitis, optic atrophy, and papillitis.
    - Otosyphilis: Sensorineural hearing loss.
  - Gummatous NS: Gummas are space occupying lesions due to focal meningeal inflammation. They may remain asymptomatic or cause symptoms through compression of CNS meninges and/or parenchyma (extremely rare).

EPIDEMIOLOGY

Incidence

- According to the CDC, 14.7 cases/100,000 population for any stage of syphilis in 2009 (US).
- NS: True incidence/prevalence is unknown; can occur in 1/3 of those untreated with syphilis.

Prevalence

The number of reported new cases of syphilis (any stage) in the USA in 2009 was 44,828 cases.

RISK FACTORS

- Untreated syphilis at any stage increases the risk of progression to NS.
- HIV infection can pose an increased risk for progression to NS.

Genetics

No specific genetic or familial conditions are associated with an increased risk of transmission.

GENERAL PREVENTION

- Safe sexual practices are crucial. Early recognition/treatment prevents progression to NS.
- No vaccines are available.

PATHOPHYSIOLOGY

- Direct invasion of CSF occurs early in syphilis.
- Cell-mediated immunity has a role in clearing the organisms from the CSF.

ETIOLOGY

Treponema pallidum subspecies pallidum, a spirochete, is the causative agent of syphilis.

COMMONLY ASSOCIATED CONDITIONS

Other sexually transmitted diseases such as chlamydia, gonorrhea, or HIV can coexist with syphilis in the same patient.

DIAGNOSIS

HISTORY

- Clinical presentation depends on the particular syndrome. Overlap occurs.
- Acute syphilitic meningitis: Symptoms include headache, nausea, vomiting, stiff neck, confusion, or delirium; fever is typically absent or low grade.
- Meningovascular syphilis: Presentation depends on the vessel territory involved and can include hemiparesis, aphasia, or seizures. Symptoms are often preceded by premonitory headache, memory loss, or psychiatric changes lasting for weeks to months. Cord involvement may present with paraplegia, sensory abnormalities, and urinary/fecal incontinence.
- *General paresis:* Manifestations are variable and can mimic any neuropsychiatric disorder. Onset is insidious; early manifestations include forgetfulness and personality changes. Psychiatric symptoms i.e. mania or depression can develop. Early neurologic features include facial tremors, intention tremors, and impaired speech. Untreated disease may progress to dementia.
- Tabes dorsalis: Classic presentation includes lancinating pains/paresthesias. These are sudden paroxysms of severe stabbing pain lasting minutes that may occur anywhere, including viscera (e.g., gastric crisis may mimic appendicitis); most commonly affects the lower extremities. Loss of vibration sense occurs early and leads to ataxia.
- Ocular syphilis: Presentation depends on the area involved and includes eye pain, redness and loss of vision. Can be asymptomatic as well.
- Otosyphilis: Can present with hearing loss, tinnitus, or vertigo.
- Gummatous NS: Gumma location determines presentation; mimics a mass lesion.
- Congenital NS: Presentation is highly variable, but includes optic complications, aseptic meningitis, and cranial nerve palsies.

PHYSICAL EXAM

- Physical exam findings will depend on the clinical syndrome and may be seen in other conditions (e.g. stroke or aseptic meningitis).
- Pupillary abnormalities are common and may progress to Argyll Robertson pupils (small, fixed pupils that do not react to light but accommodate normally) especially in tabes dorsalis or general paresis.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- All patients with suspected NS should receive a serum non-treponemal antibody test [i.e., Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests] (1)[C].
- A confirmatory treponemal antibody test [i.e., fluorescent treponemal antibody adsorbed (FTA-ABS), the treponema pallidum passive particle assay or syphilis enzyme immunoassays] should be obtained (1)[C]. Treponemal tests remain positive even with treatment.
- An HIV test is advisable.
- In NS, the treponemal antibody tests will always be positive, and screening non-treponemal antibody test is positive in most cases.
- The PK TP is a serum treponemal antibody automated test now being used to screen blood donations for syphilis. Use of this as a screening test is leading to many more evaluations for NS.
- The CDC recommends a lumbar puncture (LP) for patients with syphilis and neurologic or ophthalmic signs or symptoms, evidence of active tertiary syphilis or treatment failure during any stage of syphilis (1)[C].
- An LP is suggested in all patients with HIV who have syphilis and a serum RPR titer $\geq$1:32 and/or CD4 count $<$350 cells/mL (2)[C].
- In NS, CSF changes include elevated intra-cranial pressure and protein, mononuclear pleocytosis (up to 2,000 cells per μL), and reduced glucose.
- VDRL-CSF is the standard test for NS and is diagnostic when reactive; however, a negative CSF VDRL does not exclude NS (1)[C].
- The CSF FTA-ABS is less specific but more sensitive than VDRL-CSF; a negative test excludes the diagnosis in most patients (1)[C].
- Non-reactive CSF VDRL in a non-HIV patient suggests an alternative diagnosis but does not definitively rule it out. CSF WBCs of $>$5 per μL or protein $>$45 mg/dl, supports the diagnosis of NS.

Follow-up & special considerations

- HIV infection alone can cause CSF pleocytosis and/or mildly elevated protein. Results of a CSF profile should be interpreted carefully.

Imaging

Initial approach

- CNS imaging is nonspecific; its role is in managing complications of syphilitic disease (e.g., hydrocephalus) or ruling out other neurologic syndromes with similar presentation (e.g., stroke).
- Typical findings of vascular NS are seen on cerebral angiography.

Follow-up & special considerations

Repeat imaging may be indicated in some cases, especially if new symptoms develop.

Diagnostic Procedures/Other

Consider biopsy of suspected gummas.

Pathological Findings

- Obliterative endarteritis
- Granulomatous lesions in gummas

DIFFERENTIAL DIAGNOSIS

- Acute syphilitic meningitis:
  - – Causes of lymphocytic and aseptic meningitis, including viruses
  - – Other spirochetes (e.g., *Borrelia burgdorferi*)
  - – Mycobacteria
  - – Fungi
  - – Autoimmune diseases
- Meningovascular syphilis:
  - – Other causes of stroke syndromes, including hypertension, cerebral emboli, CNS vasculitis, or vascular disease.
- Parenchymal disease/general paresis:
  - – Tumors, subdural hematoma, dementia, chronic alcoholism, multiple sclerosis, and psychiatric disease.
- Tabes dorsalis:
  - – Diabetic and/or peripheral neuropathy.
- Optic (neuro)syphilis:
  - – Uveitis, retinitis, perineuritis, and papillitis.
- CNS Gummas: Any CNS mass lesion.

TREATMENT

MEDICATION

First Line

- Current recommended treatment is aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or by continuous infusion for 10–14 days (1)[C].
- Alternative regimen: Procaine penicillin 2.4 million units IM daily, plus probenecid 500 mg PO four times daily; both for 10–14 days (1)[C].

Pediatric Considerations

For infants/children (>1 month of age), the recommended regimen is aqueous crystalline penicillin G 200,000–300,000 units/kg/day IV, administered as 50,000 units/kg every 4–6 hours for 10 days (1)[C].

Pregnancy Considerations

Pregnant patients with NS who are penicillin allergic should be desensitized (1)[C].

Second Line

- Limited studies suggest that ceftriaxone 2 g daily IM or IV can be used as alternative treatment for patients with a penicillin allergy; however, cross-reactivity can occur between penicillin and ceftriaxone (1)[C].
- Other alternative regimens have not been well studied and their use is not recommended.

ADDITIONAL TREATMENT

General Measures

The main focus of treatment is administration of appropriate antibiotics.

Issues for Referral

- Patients who are allergic to penicillin should ideally undergo desensitization.
- Ophthalmology for ocular syphilis.

Additional Therapies

- Physical therapy is useful for gait disorders.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Antiepileptics: Gabapentin may be tried for lancinating pains or if associated with seizures.

SURGERY/OTHER PROCEDURES

Biopsy of a suspected CNS gumma or management of syphilitic complications (e.g., shunt placement for hydrocephalus).

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Lumbar puncture, initiation of IV antibiotics in those with meningitis syndrome until the diagnosis of NS is established.

Admission Criteria

Most patients require admission for diagnosis, and treatment. Those with asymptomatic NS may be managed as outpatients with close follow-up.

IV Fluids

Unnecessary unless the patient is dehydrated.

Nursing

Penicillin infusion can be associated with allergic reactions and requires close monitoring.

- A Jarisch–Herxheimer reaction is due to the release of heat stable proteins from the spirochetes and may occur with initial treatment. It resembles the sepsis syndrome and is a medical emergency. Treatment is supportive with IV fluids, steroids and anti-inflammatory agents.

Discharge Criteria

When neurologic symptoms are stable, discharge with antibiotics administered through a long-term venous catheter (i.e. peripherally inserted central catheter) is fine.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

- Patient follow-up is critical to document clinical and serologic improvement/failure, observe for a Jarisch–Herxheimer reaction, and ensure compliance with therapy.
- The CDC recommends that serial CSF examinations should be repeated every 6 months after treatment until the CSF cell count and protein is normal and CSF VDRL is negative.
- Failure criteria: Persistence or development of clinical symptoms and failure of the CSF cell count to normalize by 6 months. VDRL–CSF test and protein may take up to 2 years to normalize.
- Failure warrants retreatment with penicillin.

DIET

No specific dietary recommendations

PATIENT EDUCATION

- Safe sexual practices at all times.
- Sexual contacts should be serologically/clinically evaluated and treated based on the epidemiologic association and findings.

PROGNOSIS

- Penicillin is effective in clearing CSF abnormalities and preventing progressive clinical disease in all types of NS.
- Antibiotic therapy cannot reverse structural damage that has already occurred.

COMPLICATIONS

NS, if untreated, can result in progressive neurological dysfunction and death.

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ADDITIONAL READING

- Golden MR, Marra CM, Holmes KK. Update on syphilis: Resurgence of an old problem. *JAMA* 2003;290(11):1510–1514.
- Marra CM. Update on neurosyphilis. *Current Infect Dis Rep* 2009;11(2):127–134.
- 2009 Sexually Transmitted Diseases Surveillance. http://www.cdc.gov/std/stats09/

CODES

ICD9

- 094.0 Tabes dorsalis
- 094.81 Syphilitic encephalitis
- 094.9 Neurosyphilis, unspecified

CLINICAL PEARLS

- NS should be considered in the differential diagnosis of patients presenting with neurological signs and symptoms.
- IV penicillin is the treatment of choice for all forms of NS.

SYRINGOMYELIA

R. Shane Tubbs, MS, PA-C, PhD
W. Jerry Oakes, MD

BASICS

DESCRIPTION

Syringomyelia refers to an abnormal fluid collection (syrinx) within the spinal cord (myelia). Terminology describing a syrinx (pl. syringes) is often confusing. Expansion of the ependymal lined central canal is termed *hydromyelia*. Expansion of the cavity into the cord and the resultant nonependymal lined cavity is termed *syringohydromyelia*. Often, syringomyelia is used as a generic term before an etiology is determined. The accumulation of fluid within the spinal cord is not thought to be the primary manifestation of any disease process (1)[C]. Syringohydromyelia is a secondary process with many etiologies. A useful classification is to divide these accumulations into communicating and noncommunicating varieties. Cavities with CSF-like fluid are communicating and are usually associated with altered CSF flow at the craniocervical junction (e.g., Chiari malformation) or occult spinal dysraphism (OSD; e.g., split cord malformation). Highly proteinaceous fluid containing cavities are generally found in noncommunicating forms caused by arachnoiditis, vascular anomalies, neoplasm, or trauma to the spinal cord.

EPIDEMIOLOGY

Incidence

Less than 1% of the population

Prevalence

- Seen in ~50–75% of patients with Chiari I malformation (2)[C] and 20–95% of patients with Chiari II malformation. Reported in approximately 1% of patients following spinal cord injury. Intramedullary spinal cord tumors have a reported incidence of syrinx in 25–57% of cases.
  - – Age
  - – Commonly seen in children with the advent of MRI

RISK FACTORS

Hindbrain herniation, spinal cord tumors, spinal cord trauma

Genetics

N/A, although up to 2% of syringes have been found in siblings and twins both monozygotic and dizygotic

PATHOPHYSIOLOGY

The precise cause of syrinx formation is still unknown; however, inappropriate CSF flow at the craniocervical junction (Chiari malformation) is associated with syrinx production (3)[C].

ETIOLOGY

- Chiari malformation (Types 0, I and II)
- Arachnoiditis (Tuberculosis, fungus, syphilis, following subarachnoid hemorrhage, etc.)
- Neoplasm of the spinal cord (usually glial in origin)
- Vascular malformation of the spinal cord
- Trauma to the spinal cord
- Following iatrogenic penetration of the subarachnoid space, e.g., lumbar puncture
- Idiopathic

COMMONLY ASSOCIATED CONDITIONS

- Myelomeningocele
- OSD
- Chiari malformation
- Disseminated tumor
- Systemic infection

DIAGNOSIS

HISTORY

- Syringomyelia symptoms tend to be chronic and often are subtle compared to the clinical signs because the patient has years to become accustomed to them. Symptoms include balance disorders, loss of pain/temperature appreciation in the hands and arms, sphincter disturbance, weakness in the hands, and dysphagia.

PHYSICAL EXAM

- Decreased pain/temperature appreciation, often in a "cape like" distribution
- Diminished deep tendon reflexes in the arms
- Spasticity in the legs
- Dysesthesia
- Scoliosis
- Muscle atrophy, primarily in the upper extremities
- Motor weakness
- Abdominal reflexes are often diminished or absent in the presence of syrinx, especially in patients with scoliosis

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Follow-up & special considerations

Yearly

Imaging

Initial approach

- MRI
  - – MRI is the test of choice in evaluation of a syrinx. A syrinx will have a CSF signal (black) on T1-weighted images. Contrast may be helpful in discerning tumor or inflammation as a cause of the syrinx. Flow studies (cine mode) of the craniocervical junction are often not useful, yielding many false-negative and false-positive results.
  - – Always evaluate the craniocervical junction in the presence of syrinx (i.e., is a Chiari malformation present?).
  - – Syringes produced by a Chiari malformation often involve the cervicothoracic region, whereas syringes from OSD are found in the distal cord (terminal syrinx).
  - – If a Chiari I malformation is the cause of the syrinx, hydrocephalus and cervical spine instability should be ruled out first (2)[C].
- Spine radiographs. Often a syrinx is first appreciated when uncommon curvatures (produced by the underlying syrinx) are found on x-ray films (e.g., a single-curve scoliosis with convexity to the left).

Follow-up & special considerations

Yearly for symptoms

Diagnostic Procedures/Other

MRI if symptoms persist

Pathological Findings

- Syrinx formation
  - – Hydrocephalus

DIFFERENTIAL DIAGNOSIS

- Chronic demyelinating lesions
- Intramedullary tumors
- Extrinsic compressive lesions of the cord

TREATMENT

MEDICATION

First Line

There is no medical treatment for syringomyelia.

ADDITIONAL TREATMENT

General Measures

- General Measures
- No specific measures; attention to issues such as bladder function, bowel regimen, decubiti in severely disabled patients, and deep vein thrombosis prophylaxis in hospitalized patients.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic Treatment
  - As per general measures, consider therapy for spasticity and pain management if applicable.
- Adjunctive Treatment
  - N/A

SURGERY/OTHER PROCEDURES

- Communicating syrinx: Consider surgical decompression at hydrostatic sites such as the posterior fossa. Insertion of a tube into the syrinx may provide for chronic decompression. Patients with severe scoliosis may require surgical correction with Harrington rod implantation.
  - Posttraumatic: Reestablish an open subarachnoid space, usually at the site of a spine fracture. If unsuccessful, then a syringopleural shunt should be placed.
  - Secondary to Chiari malformation: Craniocervical decompression with or without removal of a cerebellar tonsil (2)[C]
  - Secondary to neoplasm/vascular malformation: Resection of primary lesion
  - Secondary to arachnoiditis: Syringopleural shunt
  - Secondary to OSD: Syringo-subarachnoid stent
  - Idiopathic: Verify CSF egress from the fourth ventricle. If physiologic result: Syringopleural/peritoneal shunt. If no egress and no other cause of syrinx is found: Cranio-cervical decompression.
  - Asymptomatic: If the syrinx is small, consider observation and serial MRI. If the syrinx is large and expanding the spinal cord and no other cause is found, consider craniocervical decompression.

IN-PATIENT CONSIDERATIONS

Admission Criteria

If surgery is chosen, patients are brought in electively and observed carefully postoperatively.

IV Fluids

Standard surgical/postsurgical IV fluids

Nursing

ensure patient comfort, adhere to medical orders

Discharge Criteria

For both shunt procedures and decompressive procedures, patients are normally discharged in 1–2 days.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patients are seen 1 week postoperatively, then in 2 months. At the next follow-up in 6 months, a repeat MRI is obtained to assess the size of the syrinx. If the syrinx is shunted, observe for neurologic deterioration from either shunt malfunction or migration. Shunt infection may occur. Examples of complications of craniocervical decompression are cerebellar ptosis, continued presence of the syrinx, further neurologic compromise, acute hydrocephalus, and ventral compression from a retroflexed dens.

PATIENT MONITORING

Yearly

DIET

Normal

PATIENT EDUCATION

If operative intervention is necessary, patients may resume normal activities once the wound is healed and they have physically returned to baseline, usually in a period of weeks. Patients should be educated about the risk of burning their hands due to insensitivity, gait disorders, and bowel and bladder function, if appropriate. Patients should become acquainted with the nature of the illness and the mechanism of neurologic dysfunction.

PROGNOSIS

- Approximately, 90% of patients in whom hindbrain herniation is the cause of the syrinx have resolution on follow-up imaging.
- Syringopleural shunts and syringo-arachnoid stents do well in combating syringes but require close follow-up and maintenance.
- Syringes of tumor/vascular anomaly origin require that the mass be dealt with efficiently.

COMPLICATIONS

Bleeding, infection, increased neurological deficits

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2. Tubbs RS, Beckman J, Naftel RP, et al. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation Type I. *J Neurosurg Pediatr* 2011;7:248–256.
3. Tubbs RS, Shoja MM, Ardalan MR, et al. Hindbrain herniation: A review of embryological theories. *Ital J Anat Embryol* 2008;113:37–46.

ADDITIONAL READING

- http://www.ninds.nih.gov/disorders/syringomyelia/detail_syringomyelia.htm

See Also (Topic, Algorithm, Electronic Media Element)

- Spinal Cord Syndromes, Chronic
- Chiari Malformation

CODES

ICD9

336.0 Syringomyelia and syringobulbia

CLINICAL PEARLS

- Syringomyelia is most commonly seen in patients with hindbrain herniation. Therefore, if a syrinx is found on imaging, the craniocervical junction must be investigated.
- If a tumor is suspected as the cause of a syrinx, a contrasted MRI of the spine must be performed.
- Syringes due to Chiari I malformation respond the best to surgery. Syringes due to tumor, trauma, or infection do not respond as well to surgery.

SYSTEMIC LUPUS ERYTHEMATOSUS, NEUROLOGICAL COMPLICATIONS

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BASICS

DESCRIPTION

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disorder, affecting multiple systems, and marked by symptom flares alternating with remissions.

EPIDEMIOLOGY

Incidence

- SLE: 5.6 per 100,000[1]
  - Neurologic involvement: 60–75% of all patients with SLE at some point in disease.
- Race
  - More common in those of non-European descent including blacks, Asians and North American Indian groups.
- Sex
  - Nine times more common in women.
- Age
  - Most cases of SLE are diagnosed between 15 and 40 years, although all ages may develop SLE. Neuropsychiatric SLE (NPSLE) may develop at any time.

Prevalence

SLE: 130 per 100,000 in the US[1]

RISK FACTORS

- Risk factors for NPSLE include antiphospholipid antibody syndrome (APS), cutaneous vasculitis lesions, thrombocytopenia, positive anti–SS-B/La, and depressed C3 or C4.
- Arthralgias/arthritis and discoid rash are protective.

Genetics

Several genes predispose to SLE: HLA classes I and II, including DR2, DR3, and several C4 genes. Of patients, 10% have affected family members.

Pregnancy Considerations

SLE does not interfere with conception, and there is no increase in flares during pregnancy. However, there are increased rates of spontaneous abortion, prematurity, and intrauterine death. Prednisone does not cross the placenta and is given safely during pregnancy.

PATHOPHYSIOLOGY

- Auto-antibody production
  - Anti-phospholipid antibodies (aPLs) are correlated with thrombosis and cognitive dysfunction in SLE patients.
  - Anti-glutamate receptor antibodies are found in 25–30% of patients with SLE and correlate with cognitive and psychiatric dysfunction
  - Anti- ribonucleoprotein (RNP) antibodies are associated with psychosis.
- Microangiopathy: Associated with complement activation.
- Intrathecal production of pro-inflammatory cytokines
- Premature atherosclerosis
- Histopathological changes
  - Multifocal micro-infarcts
  - Gross infarcts
  - Cortical atrophy
  - Hemorrhage
  - Ischemic demyelination
  - Multiple-sclerosis-like patchy demyelination

ETIOLOGY

The etiology of SLE is unknown. It is associated with aberrant regulation of autoreactive antibody production and clearance. Tissues are damaged by deposition of autoantibodies and immune complexes, which induce antigen-specific immunologic damage or non–antigen-specific complement fixation. The mechanisms of neurologic injury in SLE include direct antibody (antineuronal)-mediated effects, distant effects of systemic inflammation (e.g., cardiac emboli from valvular disease, hemorrhagic stroke from thrombocytopenia), or secondary effects, such as infection, toxicity of medications, or metabolic abnormalities.

COMMONLY ASSOCIATED CONDITIONS

- CNS autoimmune disorders: Multiple sclerosis; primary CNS vasculitis
- Systemic autoimmune disorders: Rheumatoid arthritis, polymyositis, scleroderma, dermatomyositis; Raynaud's syndrome
- Toxic: Drug-induced SLE: Procainamide; chlorpromazine, methyldopa, hydralazine, isoniazid, phenytoin, penicillamine. Drug-induced lupus is rarely associated with CNS involvement.
- APS [may be separate from (primary APS) or a part of (secondary APS) SLE]
- Premature atherosclerosis (late-stage SLE)
- Sneddon's syndrome: Generalized livedo reticularis and stroke
- Reversible posterior leukoencephalopathy syndrome: Associated with SLE nephritis and hypertension

DIAGNOSIS

- The diagnostic criteria for SLE include having at least 4 of the following 11 features 2[C]:
  - malar rash
  - discoid rash
  - photosensitivity,
  - oral or nasopharyngeal ulcers
  - non-erosive arthritis of at least 2 joints
  - serositis
  - renal disorder (proteinuria and casts)
  - neurological disorder (seizures or psychosis)
  - hematological disorder
  - positive antinuclear antibody (ANA)
  - anti-dsDNA or anti-Smith antibody (or positive aPL or false positive Venereal Disease Research Laboratory).
- In adults, up to 40% of NPSLE manifestations develop before or around the time of the diagnosis of SLE.
- NPSLE symptoms (% prevalence) 1[C]:
  - Aseptic meningitis
  - Cognitive disorders (75–80%)
  - Mood disorder (69–74%)
  - Headache (39–61%)
  - Seizures (8–18%)
  - Cerebrovascular disease (2–8%), including stroke and cerebral venous thrombosis
  - Psychosis (3–5%)
  - Anxiety disorders
  - Cranial neuropathy (1.5–2.1%)
  - Movement disorders (1–3%)
  - Transverse myelopathy (1.5%) or other demyelinating syndrome
  - Peripheral neuropathy
  - Autonomic neuropathy
  - Sensorineural hearing loss

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serological testing: If ANA is positive, further testing includes *anti-double stranded DNA, anti-Smith, anti-SSA and anti-SSB, and anti-RNP*. Anti-dsDNA and anti-Sm are nearly 100% specific for SLE, but sensitivity of anti-dsDNA ranges from 50 to 75%, and anti-Smith from 18 to 31%.
- If clinical suspicion of SLE is high but ANA is *negative, positive anti-SSA(Ro)* antibodies indicate ANA-negative SLE, although this is rare.
- aPL and lupus anticoagulant should be screened in patients with a history of thrombosis.
- Total serum hemolytic complement (CH50) and individual complement components (C3 and C4) may be low in patients with active SLE due to the deposition of immune complexes.
- CSF studies often show pleocytosis (usually mononuclear cells), elevated protein, elevated albumin ratio, oligoclonal bands, and elevated IgG index, although NPSLE did not differ from SLE without neuropsychiatric involvement. Protein and albumin ratio may increase during relapse but is nonspecific.

Imaging

Initial approach

- MRI
  - 40–80% of MRI abnormalities in NPSLE are small focal lesions in the periventricular and subcortical white matter.
  - Decreased cerebral and corpus callosum volume
  - Atrophy
  - Ventriculomegaly
  - Gross infarctions
  - Hippocampal atrophy is associated with SLE duration, steroid dose, and number of NPSLE symptoms.
  - MRI shows atrophy in 18% of newly diagnosed patients with SLE, and focal lesions in 8%, suggesting the brain is affected early.

Diagnostic Procedures/Other

- Positron emission tomography
  - 60–80% of patients with active NPSLE show bilateral parieto-occipital hypometabolism with normal conventional MRI.
- Magnetic resonance spectroscopy
  - Neurometabolic abnormalities are detected with active and quiescent NPSLE, even in areas of normal MRI appearance.

- Diffusion tensor imaging
  - White matter changes are noted in NPSLE patients, even with normal MRI appearance.
- EEG: Routine or video/EEG monitoring may be needed in the management of seizures and/or encephalopathy.

DIFFERENTIAL DIAGNOSIS

- Autoimmune: Multiple sclerosis, primary isolated CNS vasculitis, Behçet's disease, sarcoidosis, mixed connective tissue disease.
- Reversible posterior leukoencephalopathy
- CNS lymphoma
- Psychiatric: Depression, schizophrenia, steroid-induced psychosis
- Epilepsy: Partial or generalized epilepsy
- Drug abuse
- Stroke: Cardioembolic, hemorrhagic
- Infections: Fungal, viral or bacterial meningitis, herpes simplex virus, Lyme disease, cytomegalovirus, HIV, syphilis, tuberculous meningitis, progressive multifocal leukoencephalopathy
- Metabolic encephalopathy
- Severe hypertension: Usually with active nephritis

TREATMENT

MEDICATION

First Line

- High dose or pulsed corticosteroid treatments are the mainstay of treatment for acute disease.
- In severe disease, other immunosuppressants (e.g., cyclophosphamide) may be needed for maintenance therapy.
- One small, randomized controlled trial found treatment response in the cyclophosphamide group significantly better at 94.7% (18/19) compared to 46.2% (6/13) in the methylprednisolone group at 2 years 3[C].
- Encephalopathy: Plasmapheresis and cyclophosphamide either 500 mg IV biweekly or 75–100 mg/day PO.
- Seizures: Anticonvulsants are effective. Further immunosuppression usually is not needed.
- Mood and psychotic disorders are treated with antidepressants or antipsychotics, respectively.
- Movement disorders: Plasmapheresis with azathioprine or cyclophosphamide is better than corticosteroids.
- Stroke: Treatment is directed by etiology.
  - Thrombosis: Antiplatelet agents
  - Emboli: Antibiotics or anticoagulants
  - Coagulopathy: Plasmapheresis, antiplatelet agents, and/or anticoagulation
  - If part of APS: Warfarin with target international normalized ratio 3–4
- Transverse myelopathy: High-dose corticosteroids (methylprednisolone >500 mg/day)
- Neuropathy/plexopathy: Corticosteroids
- Necrotizing vasculitis: Corticosteroids, immunosuppressive agents, plasmapheresis

Second Line

- No randomized, controlled trial data are available regarding the following:
- Alternative treatments 4[C]:
  - Autologous stem cell transplant.
  - Plasmapheresis: Ineffective in some manifestations of SLE (nephritis).
  - IVIG
- Alternative Drugs:
  - Antimalarials (hydroxychloroquine, chloroquine, and quinacrine) are used for cutaneous SLE.
  - Methotrexate (MTX) is used for cutaneous and articular SLE; experience in NPSLE is minimal. Intrathecal MTX has been reported as a possible treatment for NPSLE.
  - Mycophenolate mofetil
  - Azathioprine: Steroid-sparing. Anecdotal and case study data in NPSLE suggest benefit.
  - Rituximab
  - Iloprost

ADDITIONAL TREATMENT

General Measures

Infections must be considered when new symptoms develop. Postmortem studies in patients with presumed active SLE frequently find active CNS infection (fungal, viral) and quiescent SLE.

Issues for Referral

- Psychiatry: To manage psychosis. Inpatient treatment may be necessary for some patients.
- Rheumatology: For those with arthritis
- Nephrology: For those with renal impairment

Additional Therapies

- Physical therapy for those with neuropathy and/or myelopathy.
- Psychology: Group therapy has been shown to be effective for those with mood and psychotic disorders.

SURGERY/OTHER PROCEDURES

- Brain biopsy is rarely needed.
- Sural nerve biopsy may confirm neuropathy.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Treat acute stroke or seizures promptly.
- Infections must be excluded.

Admission Criteria

Admission may be required for acute confusional state, stroke, infection, or other neurologic complications.

Nursing

Patient safety issues in the case of seizure, encephalopathy, or psychosis may require bedside monitoring.

Discharge Criteria

Discharge may be considered when the patient is able to care for his/herself with little assistance. Discharge to home, rehabilitation or to an extended care facility may be considered.

ONGOING CARE

PATIENT MONITORING

Clinical monitoring is the best method to follow patients over time. In some patients, serologic studies parallel clinical activity and can be useful for early detection of exacerbations.

PATIENT EDUCATION

Lupus Foundation of America, 2000 L Street, N.W., Suite 410 Washington, DC 20036 Phone: 202-349-1155, website: www.lupus.org

PROGNOSIS

Short-term outcomes for patients with a neurological event attributed to SLE were better than for those with an event not attributed to SLE.

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CODES

ICD9

- 323.81 Other causes of encephalitis and encephalomyelitis
- 333.5 Other choreas
- 710.0 Systemic lupus erythematosus

CLINICAL PEARLS

- Neuropsychiatric symptoms are common in SLE.
- Corticosteroids and immunosuppressants are first-line treatments for NPSLE.
- Infection may mimic a flare of SLE, and should be excluded prior to treatment.

TARDIVE DYSKINESIA

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BASICS

DESCRIPTION

- Tardive dyskinesia (TD) is a disorder of abnormal involuntary hyperkinetic movements most often affecting not only the orobuccolingual musculature but also the truncal and limb musculature.
- It is associated with dopamine receptor-blocking agents, including antipsychotic drug therapy and metoclopramide.
- TD usually develops after >1 year of treatment, but cases where symptoms of TD appeared within 3–6 months of antipsychotic use have been reported in the literature. Most cases are mild-to-moderate, but a small percentage can be severely disfiguring and disabling.

EPIDEMIOLOGY

Incidence

- The incidence of TD is estimated at 2–5% per year over the first 5–10 years of treatment with neuroleptic agents
  - This may be higher in older adults

Prevalence

Lifetime prevalence is estimated to be approximately 20%, but the range is extremely wide (1–80%) for those requiring chronic treatment with neuroleptics

RISK FACTORS

- Elderly patients are much more vulnerable
- Women are at higher risk, with a female-to-male ratio of 1.7:1
- Higher dose of administered antipsychotic medication
- Longer duration of antipsychotic exposure
- Older age
- Gender
- Psychiatric diagnosis: Patients with mood disorders and/or medical diagnoses receiving antipsychotic medications have a higher incidence than those with schizophrenia
- Patients who exhibit acute extrapyramidal side effects from neuroleptics may be at greater risk of developing TD.
- Drug holidays: Recent studies have shown that intermittent neuroleptic treatment is *not* helpful and may be detrimental
- Possibly exposure to anticholinergic use, but the data are controversial
- Negative symptoms of schizophrenia
- Organic brain damage
- All typical antipsychotics appear to cause TD at a similar rate. No significant difference has been observed among the following factors:
  - Antipsychotic type: High-potency agents such as haloperidol (Haldol) versus low-potency agents such as chlorpromazine (Thorazine)
  - Oral agents versus long-acting injectable antipsychotic agents
  - The newer, atypical antipsychotic agents (risperidone, olanzapine, quetiapine) seem to have a lower incidence of TD. Clozapine (Clozaril) has definitely been shown to have a very low incidence of TD

Genetics

Investigation of genetic polymorphisms conferring susceptibility to TD focused on the dopamine D_3 and 5-HT_{2A} receptor genes.

GENERAL PREVENTION

Avoid exposure to dopamine receptor-blocking agents when possible.

PATHOPHYSIOLOGY

There are data suggesting that prolonged receptor blockade by antipsychotic agents may cause hyperactivity of the CNS dopaminergic and noradrenergic systems coupled with reduced activity in the γ-aminobutyric acid (GABA) and cholinergic systems.

ETIOLOGY

- The onset of TD is linked to the use of dopamine receptor-blocking agents, but the exact mechanism is not known.
- Metoclopramide and other dopamine receptor-blocking agents such as the antiemetic agent prochlorperazine and the antidepressant amoxapine also can result in TD. While the onset of TD usually has been associated with exposure to antipsychotic agents, TD associated with metoclopramide is becoming a major cause of TD in adults.
- TD should be distinguished from spontaneous (idiopathic) movement disorders associated with schizophrenia (prevalence of 15%), old age, and brain damage.

COMMONLY ASSOCIATED CONDITIONS

Tardive dystonia and tardive akathisia

DIAGNOSIS

HISTORY

- Careful clinical assessment is the sole basis for the diagnosis of TD.
- Several quantitative assessment tools have been published, but the most widely used one is the Abnormal Involuntary Movements Scale (AIMS). The AIMS should be assessed for all patients when dopamine receptor-blocking agents are initiated and at least every 3 months while patients continue to be treated with these agents.
- Physicians should not rely solely on patient complaints to make a diagnosis of TD because the early signs and symptoms of this disorder can easily escape notice.
- TD often becomes evident upon antipsychotic dose reduction or discontinuation.

PHYSICAL EXAM

- TD is a complex syndrome of irregular, abnormal, repetitive, involuntary movements of the mouth, lips, tongue, limbs, or trunk.
- The buccolinguomasticatory triad of symptoms is most common and consists of
  - Smacking, puckering movements of the lips
  - Lateral movements of the jaws
  - Puffing of the cheeks with the tongue thrusting and rolling inside the mouth
- Chewing motions (patients frequently bite the inside of their mouths or tongues).
- Athetoid and choreiform movements of the extremities. These movements are involuntary and purposeless.
- Trunk movements: Either anterior–posterior or rhythmical side-to-side swaying may be present.
- All involuntary movements are exacerbated by stress or anxiety and dramatically subside during sleep.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

There are no laboratory procedures or special tests to diagnose TD.

Imaging

Initial approach

There are no imaging studies to diagnose TD.

DIFFERENTIAL DIAGNOSIS

- Tardive dystonia, which consists of
  - Irregular postures (e.g., Pisa syndrome)
  - Slow, involuntary twisting movements of face, trunk, or limbs (patients may present with torticollis, blepharospasm, retrocollis, grimacing)
  - It occurs in 2% of patients treated with antipsychotic agents
  - It may coexist with TD and may be even more distressing and disabling
  - Use of anticholinergic drugs may lessen symptoms of tardive dystonia
- Tardive akathisia, which consists of
  - Motor restlessness
  - Subjective discomfort
- Huntington's disease
- Other basal ganglia disorders

TREATMENT

MEDICATION

First Line

- Multiple agents have been studied as potential treatments for TD, although many have limited or inadequate evidence supporting their use.
- Tetrabenazine is thought to be an effective treatment for TD. Potential limitations are cost and problems with tolerability including exacerbations in depression, akathisia, and parkinsonism and require close monitoring. Average daily doses range from 50 to 75 mg. QTc interval prolongation is possible (1)[B].
- Other dopamine-depleting medications, such as reserpine in doses up to 5–8 mg/day, may alleviate up to 50% of symptoms (2)[B].

Second Line

- Clozapine (an atypical antipsychotic agent) has been found to decrease symptoms of TD in several large studies and may be the treatment of choice for patients who need medications for their psychiatric disorder. Severe TD and particularly tardive dystonia seem to respond best to doses ranging from 300 to 750 mg/day. The main disadvantages to using clozapine are the potential side effects of agranulocytosis, seizures, and the need for weekly blood monitoring. Quetiapine, compared to other antipsychotics, is also thought to possibly have lowered rates of TD (3)[B].
  - However, one needs to keep in mind that all neuroleptics have been associated with the occurrence of TD.
- Vitamin E (an antioxidant) in doses of 1,600 IU/day has not been consistently shown to be beneficial in all studies. Small trials suggest vitamin E may be most helpful in protection against deterioration of TD. Patients who have had TD for <5 years appear to have a better response than patients with long-standing TD (4)[A].
- Clonazepam in doses of 0.5–3 mg/day has been found to reduce movements of TD, but caution must be exercised in chronic use of benzodiazepines, and the current evidence supporting benzodiazepine use is limited (5)[A].

ADDITIONAL TREATMENT

General Measures

- Prevention is the most important aspect of TD management. There is no reliable treatment other than discontinuation of the offending drug.
- Patients taking metoclopramide should be monitored closely for the development of TD (6)[A].
- Long-term use of antipsychotic agents should be restricted to patients whose chronic illness clearly necessitates it (e.g., schizophrenia). It should be avoided in patients suffering from depression, mania, anxiety, or personality disorders, except in unusual clinical circumstances.
- Ongoing periodic evaluations of the patient's need for long-term antipsychotic agents must be done with an assessment of the risks and benefits of treatment. The dose of medication must be adjusted so that patients receive the lowest antipsychotic dose that is still effective.
  - There is no reliable treatment of TD other than discontinuation of the offending agent.
  - Many patients recover spontaneously when antipsychotic agents are discontinued.
  - Tapering off dopamine receptor-blocking agents at the first sign of TD may be more helpful than abrupt discontinuation, which can exacerbate TD.
  - TD may improve in some patients even when they continue treatment with antipsychotics.
  - Anticholinergic medications should be avoided because they may aggravate TD, and it is not known whether long-term use of these agents increases the risk of developing TD.
- If an antipsychotic agent is necessary, use clozapine, which appears to have a much lower incidence of TD.

Issues for Referral

Changes in the offending agent may need to be deferred to the prescribing physician (e.g., psychiatrist, gastroenterologist)

IN-PATIENT CONSIDERATIONS

Initial Stabilization

TD is a chronic condition without an acute onset

Admission Criteria

Admission is rarely required unless dyskinesias become so severe that they interfere with breathing or swallowing.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be given an AIMS test every 3 months while taking dopamine-blocking agents so that any symptoms of TD can be identified early and discussed at length with the patient.

PATIENT EDUCATION

- Each patient should be informed about the long-term risk of developing TD and that the involuntary movements may be irreversible and treatment resistant. At the same time, the patient should be assured that the clinician will make every attempt to minimize the risk of TD and to closely monitor early signs and symptoms.
- Every clinician should obtain informed medical consent from the patient and/or the patient's family. Ongoing education and open communication should occur and should be clearly documented in the patient's record.
- Tardive Dyskinesia/Tardive Dystonia National Association, P.O. Box 4573, Seattle, WA 98145-0732. Phone: 206-522-3166.

PROGNOSIS

- We used to believe that the course of TD was progressive and irreversible. More recent data show that in most patients, TD develops to a certain degree and then stabilizes and may even improve.
- Remission rates vary between 8 and 33% after withdrawal of the causative agent. The most frequent pattern is waxing and waning of mild-to-moderate symptoms over many years.

COMPLICATIONS

Progression to severe TD is not common.

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See Also (Topic, Algorithm, Electronic Media Element)

- N/A

CODES

ICD9
333.82 Orofacial dyskinesia

CLINICAL PEARLS

- TD is an abnormal hyperkinetic involuntary movement disorder caused by dopamine receptor-blocking agents.
- Minimizing exposure to antipsychotic agents and metoclopramide when possible reduces risk, and careful monitoring for TD symptoms is necessary when prescribing these agents.
- Prevention and discontinuation of the offending agent are the cornerstones of management.

TETANUS

Sevim Erdem Ozdamar, MD

BASICS

DESCRIPTION

Tetanus is a noncommunicable and potentially fatal infection caused by *Clostridium tetani*. Clinically it is characterized by the acute onset of generalized rigidity and reflex spasms.

EPIDEMIOLOGY

Tetanus is seen worldwide, more often in the summer season and in hot, damp climates with soil rich in organic matter. Organisms are found in soil and intestinal tractus of animals. Tetanus is a nationally notifiable disease in the US. In 2009, a total of 18 cases were reported (0.01 cases per 100,000) (1). The death ratio is variable. In the US it has declined to 10% in recent years.

- Tetanus is not contagious from person to person.
- Race
  - – No information available.
- Age
  - – Newborns, because of nonsterile birth conditions, and the elderly have the highest risk for the disease.
- Sex
  - – Male-to-female ratio of 2.5:1.

RISK FACTORS

- Nonsterile obstetric delivery and contamination of umbilical stump with the organism (nonhospital births)
- Wounds bearing necrotic tissue, foreign bodies, and associated infection
- Chronic lesions (decubitus ulcers, abscesses)
- Parenteral drug abuse
- Absent or incomplete immunization
- Lack of immunization of pregnant female

Genetics

No definite genetic factors are identified.

Pregnancy Considerations

Poor obstetric conditions and lack of maternal immunization are risk factors for neonatal tetanus.

- Nonimmunized females should receive 2 doses of tetanus toxoid (at least 4 weeks apart) during pregnancy, the last one at least 2 weeks before delivery.

PATHOPHYSIOLOGY

Tetanus is caused by *Clostridium tetani* spores. Spores enter the body either through contaminated wounds or mucous membranes. They germinate to vegetative bacilli under anaerobic conditions and produce 2 exotoxins: Tetanolysin and tetanospasmin. Tetanospasmin is a strong neurotoxin which inhibits neurotransmitter release presynaptically at the neuromuscular junction, autonomic terminals, and inhibitory neurons of the CNS. Toxins are disseminated via blood and lymphatics.

ETIOLOGY

Clostridium tetani is a Gram-positive anaerobic, spore-forming bacteria that is universally found in the environment. The spores may remain dormant for years.

DIAGNOSIS

Diagnosis is mainly by history and clinical findings along with exclusion of other possible causes.

HISTORY

- The incubation period usually is between 5 and 14 days, although it can be prolonged up to 3 weeks. The distance of injury from the CNS determines the length of incubation period.

PHYSICAL EXAM

More than 80% of cases show a generalized syndrome while the rest are localized or cephalic.

- Stiffness of jaw (trismus) usually is the first symptom. A characteristic facial appearance (risus sardonicus) results from sustained contractions of facial muscles. Generalized muscle rigidity involving neck, trunk, and extremity muscles follows. Rigidity of back muscles causes opisthotonus.
- Paroxysmal tonic spasms can occur spontaneously or be precipitated by external stimuli. Pharyngeal muscular spasms cause dysphagia, and spasms of the glottis may lead to death by asphyxiation. Spasms of diaphragmatic, intercostal, and laryngeal muscles are life threatening.
- Autonomic dysfunction (labile hypertension, tachycardia, arrhythmias, hyperhidrosis) can be seen in severe cases.
- Reflexes are increased and sensory examination is normal. Irritability and restlessness are seen, but consciousness is preserved.
- High fever up to 41°C can be seen and signifies poor prognosis.
- Rarely tetanus is localized to an area close to site of injury (local form). Muscles in the region of injury go into intermittent painful spasms. This form is benign and muscular spasms subside spontaneously within weeks. When localized to the head, it is called the cephalic form.
- Manifestations of tetanus increase in severity during the first 3 days after onset, remain stable for 5–7 days, and resolve within 1–2 weeks.
- Neonatal tetanus: Occurs 3–14 days after delivery. Disease is due to nonsterile birth conditions and contamination of the umbilical cord stump. Mothers are unimmunized women. Difficulty in sucking, excessive crying, trismus, opisthotonus, and spasms are clinical signs. Mortality rate is variable, survivors can have residual neurological injury like cerebral palsy or mental retardation.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

There is no single laboratory procedure that gives definite diagnosis in every patient.

Initial lab tests

- Routine blood work is nonspecific except mild leukocytosis.
- CS examination is normal.

Imaging

Imaging studies are not helpful.

Diagnostic Procedures/Other

- Specimens from the wound may reveal Gram-positive bacilli.
- Anaerobic cultures for *C. tetani* are usually unsuccessful.
- Neutralization of toxin in mice is the standard method for detection of antitoxin in the serum.
- Low or undetectable levels of serum antitoxin at the time of onset are compatible with the diagnosis, but high levels do not exclude it.
- Electromyography may be helpful in certain cases.

Pathological Findings

A single autopsy case reported in the literature revealed toxin fragment C binding in motor neurons and axons of spinal cord with immunohistochemical analysis (2).

DIFFERENTIAL DIAGNOSIS

- Other causes of bacterial and viral meningitis
- Rabies
- Hypocalcemic tetany
- Strychnine poisoning
- Tonsillitis
- Peritonsillar abscess
- Dystonic reactions due to phenothiazines
- Post-partum eclampsia

TREATMENT

All Wounds Should Be Cleaned And Necrotic Tissue Should Be Removed (See Surgery/Other Procedures).

MEDICATION

- Antiserum: Administration of human tetanus immune globulin depends on the immune status of the person as well as the status of the wound. If a patient has received at least 3 doses of toxoid, there is no need for human tetanus immune globulin (HTIG). Otherwise administer HTIG 3,000–6,000 units IM as soon as possible, because antiserum neutralizes only the toxin that has not entered the nervous system. Part of the dose can be infiltrated around the wound if it can be identified (1)[A].
- Antibiotics: The organism is susceptible to several antibiotics. Metronidazole or penicillin should be given to eradicate the organism. Metronidazole is given 20–30 mg/kg/day IV over 1 hour in 3 or 4 divided doses following a loading dose of 15 mg/kg. Metronidazole should be given for 7–14 days. If metronidazole is not available, penicillin G 100,000 U/kg/day IV in 6 divided doses can be given.
- Tetanus toxoid: Because tetanus infection does not provide immunity against further attacks, active immunization of patients is necessary at the time of diagnosis or during convalescence.
- Contraindications: Known drug allergies

- Immunization (1)[A]
  - Tetanus vaccine (toxoid) is administered with diphtheria and pertussis vaccines at ages 2, 4, 6 months, 12–18 months, and before school (4–6 years). Routine boosters of tetanus with diphtheria (Td) should be given every 10 years.
  - Adults who have not been immunized previously should receive 2 doses of Td 4–8 weeks apart and the third dose 6 months to 1 year after the second dose.
  - Nonimmunized female should receive 2 doses of tetanus toxoid (at least 4 weeks apart) during pregnancy, the last one at least 2 weeks before delivery.
  - If a patient has received at least 3 doses of toxoid, there is no need for HTIG. Toxoid booster is required if more than 5 years (10 years for minor clean wounds) has elapsed.
  - For patients who received fewer than 3 doses, primary immunization series should be started. HTIG 250 units IM should be given prophylactically, except for fresh, clean, minor wounds.
  - Toxoid and antiserum must be given with separate syringes to different sites.
- Alternative drugs
  - Pooled human intravenous immunoglobulin may be an alternative to HTIG.

ADDITIONAL TREATMENT

General Measures

- Be sure that the airway is open and ventilation is adequate. Respiratory insufficiency due to laryngospasm or spasms of respiratory muscles is a major problem. Tracheostomy not only facilitates mechanical assistance of ventilation but also reduces the risk of aspiration and protects against suffocation due to laryngospasm. Although some milder cases can be managed without it, every patient should be considered a candidate for tracheostomy.
- Avoid external stimuli and keep the patient in a dim and quiet room.
- All treatments and manipulations should be kept to a minimum to prevent provocation of reflex spasms.
- Stop oral intake to prevent aspiration and start intravenous hyperalimentation because these patients are in an intense catabolic state.
- Monitor fluid and electrolyte balance.
- Position to prevent bedsores, paying attention not to provoke reflex spasms.
- Apply intermittent catheterization if urinary retention develops.
- Prevent deep vein thrombosis with low-dose heparin.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Muscle relaxation is necessary and mild sedation is desirable.
  - Diazepam is very effective. It not only relieves rigidity but also provides sedation. Administer diazepam 0.5–5 mg/kg/day IV in divided doses every 2–8 hours or 5–10 mg whenever spasms occur.
  - Phenobarbital 50–100 mg every 3–6 hours or pentobarbital 50–200 mg IV, chlorpromazine 200–300 mg daily, dantrolene, or intrathecal baclofen can be used as muscle relaxants.
  - If spasms cannot be controlled by these measures, curarization may be necessary.
  - D-Tubocurarine 15 mg/hour IM can be given after ventilatory support. Propofol can be given as sedative.
  - Propranolol with phentolamine or labetalol 0.25–1.0 mg/min can be used to decrease sympathetic activity.
- Adjunctive treatment
  - Physical therapy can be started 2–6 weeks after the onset of infection, when the spasms disappear. Many patients will also require psychotherapy.

SURGERY/OTHER PROCEDURES

Surgical debridement of wounds and drainage of abscesses is mandatory because anaerobic conditions are necessary for spore germination. Wounds should be irrigated with 3% hydrogen peroxide 3 times daily after the procedure.

IN-PATIENT CONSIDERATIONS

Admission Criteria

All patients should be treated in an ICU.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

As the infection does not provide natural immunity, primary immunization should be completed.

PATIENT EDUCATION

- Centers for Disease Control and Prevention. Websites:
  - http://www.cdc.gov/ncidod/diseases/submenus/sub_tetanus.htm
  - http://www.cdc.gov/vaccines/vpd-vac/tetanus/default.htm
- World Health Organization. Website: www.who.int/gpv-dvacc/diseases/NeonatalTetanus.htm

PROGNOSIS

Tetanus is self-limited, and patients who recover from the disease have usually no residual defect. The disease usually subsides within 3–6 weeks. Mortality rate is variable, decreased to 10% in the US. For neonatal tetanus, mortality goes up to 60–80%. Death usually occurs 3–10 days after infection, mostly due to asphyxiation during spasms, cardiovascular insufficiency, or superimposed infections.

COMPLICATIONS

- Acute complications:
  - Laryngospasm
  - Fractures
  - Hypertension
  - Secondary infection due to hospitalization
  - Pulmonary embolism
  - Aspiration pneumonia
  - Death
- Chronic sequels are uncommon once the patient heals, although focal deficits such as exotropia and facial muscle paresis have rarely been reported.

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CODES

ICD9

- 037 Tetanus
- 670.80 Other major puerperal infection, unspecified as to episode of care or not applicable
- 771.3 Tetanus neonatorum

CLINICAL PEARLS

- Tetanus is a preventable infection.
- Vaccination program is important to prevent the development of infection.
- Early diagnosis and intensive care is necessary to prevent death from tetanus infection.

TICS

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BASICS

DESCRIPTION

Tics are relatively brief involuntary movements (motor tics) or sounds (vocal tics) that usually are intermittent but may be repetitive and stereotypic. They fluctuate or wax and wane in frequency, intensity, and distribution. Typically tics can be volitionally suppressed, although this may require intense mental effort. Motor tics may persist during all stages of sleep. Tics typically are exacerbated by dopaminergic drugs and by CNS stimulants, including methylphenidate and cocaine.

- Premonitory feelings or sensations precede motor and vocal tics in >80% of patients. These premonitory phenomena may be localizable sensations or discomfort, or nonlocalizable, less specific, and poorly described feeling such as an urge, anxiety, and anger.
- The "intentional" component of the movement may be a useful feature differentiating tics from other hyperkinetic movement disorders.

EPIDEMIOLOGY

- Incidence/prevalence
  - Reported prevalence rates have varied markedly. The frequency of tics depends on the definition of the phenotype. Transient tic disorders occur relatively commonly in children (3%–15% in different studies), and chronic motor tics occur in approximately 2%–5%, although "chronic" may extend only 2–3 years in many of these individuals.
  - Because about one third of patients do not even recognize the tics, it is difficult to derive an accurate prevalence figure.
- Age
  - Onset is usually in childhood.
- Sex
  - Boys are much more likely than girls to have chronic tics. The male-to-female ratio in chronic motor tic disorder is approximately 5:1 (between 2:1 and 10:1 in different studies).

RISK FACTORS

- Family history of obsessive-compulsive disorder

Genetics

- Probable mixed model of inheritance, rather than simple autosomal mode of transmission.
- Tourette's syndrome is the most common cause of tics, manifested by a broad spectrum of motor and behavioral disturbances.

ETIOLOGY

Most of the tic disorders are idiopathic. The pathogenetic mechanisms of tics and Tourette's syndrome are unknown, but evidence supports an organic rather than psychogenic origin.

COMMONLY ASSOCIATED CONDITIONS

- Obsessive-compulsive behavior
- Hyperactivity with attention deficit and impulsive behavior
- Static encephalopathy
- Autistic spectrum disorders
- Neuroacanthocytosis
- Huntington's disease
- Dopamine receptor antagonists
- Cocaine
- Antiepileptic drugs
- Copropraxia (obscene gestures)
- Mannerism
- Stereotypes
- Compulsion

DIAGNOSIS

Tics may be *simple* or *complex*.

SIMPLE TICS

- Simple tics involve only 1 group of muscles, causing a brief jerk-like movement or a single meaningless sound.
  - Simple vocal tics: Throat clearing, sniffing, animal sounds (e.g., barking), coughing, yelling, hiccuping, belching
  - Simple motor tics: Eye blinking, nose twitching, sticking tongue out, head turning or neck stretching, shoulder jerking, muscle tensing, flexing fingers, blepharospasm, bruxism

COMPLEX TICS

- Complex tics consist of coordinated sequenced movements resembling normal motor acts or gestures that are inappropriately intense and timed. They may be seemingly nonpurposeful or they may seem purposeful.
  - Complex vocal tics: Parts of words or phrases repeated, talking to oneself in multiple characters, assuming different intonations, *coprolalia* (use of profanity)
  - Complex motor tics: Flapping arms, facial grimaces, picking at clothing, complex touching movements, jumping, shaking feet, pinching, poking, spitting, hair brushing
  - Also classified as
    - Transient (duration <12 months)
    - Chronic (duration >12 consecutive months)
- Neurological examination in patients with tics is usually normal.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Diagnosis of a tic is generally made during physical examination. If there are no other neurological findings, tics require no additional diagnostic testing. If other neurological signs or symptoms are present, further evaluation is guided by that finding.

Imaging

- Imaging studies are not needed routinely in the evaluation of patients with typical history and examination findings and are indicated only to exclude specific illnesses suggested by abnormal historical or examination findings.
- At present, no clinical utility exists for functional imaging studies in the evaluation of tic disorders.

Diagnostic Procedures/Other

Neuropsychological testing: Patients with difficulties in the school or work setting may benefit from identification of an existing learning disorder so that adaptive strategies can be devised.

DIFFERENTIAL DIAGNOSIS

- Abnormal movements that may accompany general medical conditions
- Drugs: Stimulants, levodopa, neuroleptics, carbamazepine, phenytoin, phenobarbital, cocaine
- Complex partial seizures
- Neuroacanthocytosis
- Chorea in adults
- Postherpetic chorea in children
- Post stroke
- Frontal lobe syndromes
- Hallervorden–Spatz disease
- Hemifacial spasm
- Huntington's disease
- Inherited metabolic disorders
- Mental retardation
- Movement disorders in individuals with developmental disabilities
- Neurosyphilis
- Periodic limb movement disorder
- Restless legs syndrome
- Tardive dyskinesia
- Tuberous sclerosis
- Wilson's disease

TREATMENT

MEDICATION

- Dopamine D_2 receptor antagonists: Chlorpromazine was reported to dramatically improve tic severity. Since then, several placebo-controlled randomized allocation studies with various neuroleptics (e.g., haloperidol, fluphenazine, pimozide) have confirmed these initial reports. On average, tic severity declines by approximately 50–80% with neuroleptic treatment.
  - Haloperidol (Haldol): FDA indication for treatment of tics
  - Pimozide (Orap): FDA indication for treatment of tics

  - Fluphenazine (Prolixin): Effective anti-tic drug
  - If these 3 drugs fail to adequately control tics, then risperidone (Risperdal), thioridazine (Mellaril), trifluoperazine (Stelazine), molindone (Moban), or thiothixene (Navane) can be tried.
  - It is not clear whether some of the new atypical neuroleptics, such as clozapine and olanzapine, will be effective in the treatment of tics or other manifestations of Tourette's syndrome.
  - Clonidine: This drug has been used frequently to treat tics. However, no proof exists for anti-tic efficacy after several small trials. A meta-analysis concluded that clonidine has clear efficacy. It may be most appropriate as a first agent in patients with problematic attention deficit hyperactivity disorder (ADHD) and mild tics.
- Mild-to-moderate tic disorder medications
  - Pimozide is superior to Haldol in 1 double-blind study
  - Fluphenazine is another good choice
  - Clonidine (Catapres) 0.05 mg PO b.i.d. to 0.1 mg PO q.i.d.
- Severe tic disorder medications: Neuroleptic preparations
  - Haloperidol (Haldol) 0.5–4 mg PO q.h.s.
  - Pimozide (Orap) 1–8 mg PO q.h.s.
  - Risperidone (Risperdal)
- Precautions
  - Use the lowest dose of medication that achieves acceptable tic suppression.
  - Neuroleptics may be associated with various extrapyramidal side effects, including dystonia, akathisia, and tardive dyskinesia, in up to 20% of children.
  - Sedation, depression, weight gain, school phobia, tardive dyskinesia, hepatotoxicity, prolongation of QT interval with pimozide, akathisia, and acute dystonic reaction.
- Contraindications
  - None of these drugs should be used if there is a known hypersensitivity.
  - Pimozide is contraindicated in patients with the long QT syndrome because it may prolong the QT interval. There are a few reports of deaths when pimozide is used in conjunction with macrolide antibiotics, so this drug combination should be avoided.
- Alternative drugs
  - Benzodiazepines: Retrospective reports suggest that benzodiazepines, such as clonazepam, reduce tic severity in some patients. The effect is less than that of neuroleptics and is probably nonspecific. Clonazepam (Klonopin) 0.25 mg PO b.i.d. to 1 mg PO t.i.d.
  - Botulinum toxin injections in motor tics: Botulinum toxin injections may improve urges or sensory tics, as well as observable tics, and may be the treatment of choice for patients with a single, especially problematic, dystonic tic.
  - Tetrabenazine: This is a presynaptic dopamine-depleting agent. It has not been reported to cause tardive movement disorders. A retrospective report noted "marked" clinical improvement in 57% of 47 patients with tics. It is not available in the US.
  - Guanfacine: This agent was tested in a 2001 randomized controlled trial in children with both ADHD and chronic tic disorders. The drug showed clear superiority to placebo in reduction of both ADHD and tic symptoms, with few adverse effects. It also has been shown to be efficacious in adults with non-tic ADHD.
  - An open trial using nicotine patch indicates that nicotine may suppress tics in patients not treated with D_2 receptor-blocking drugs.

ADDITIONAL TREATMENT

General Measures

- The goal of treatment should not be to completely eliminate all tics but to achieve a tolerable suppression.
- First step is proper education of the patient, relatives, and teachers about the nature of the disorder.
- Counseling and behavioral modification may be sufficient for mild symptoms.
- Medication should be considered when symptoms begin to interfere with activities of daily living.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Symptomatic treatment

- Symptomatic treatment consists of behavioral management:
  - Positive reinforcement
  - Target behaviors
    - Skill deficiencies
    - Behavior excesses

SURGERY/OTHER PROCEDURES

There are a few reports of patients with severe motor and phonic tics controlled by high-frequency deep brain stimulation

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission for management of tics is rarely necessary.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Because a medication for tics may not have any impact on obsessions or compulsions, and medications for ADHD may worsen tics in some patients, the selection of medications and combination of medications can become quite complex in a situation with associated or comorbid conditions.

PATIENT EDUCATION

- WeMove. Website: www.wemove.org

PROGNOSIS

- The prognosis for children who develop this disorder between the ages of 6 and 8 is good.
- Symptoms may last 4–6 years and then disappear without treatment in early adolescence.
- When the disorder begins in older children and there is no remission or reduction of symptoms well into the 20s, a chronic, lifelong disorder may be anticipated.

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See Also (Topic, Algorithm, Electronic Media Element)

Tourette's syndrome

CODES

ICD9

- 307.20 Tic disorder, unspecified
- 307.23 Tourette's disorder
- 333.3 Tics of organic origin

TORTICOLLIS

Ariane Park, MD, MPH
Andrea G. Malone, DO

BASICS

DESCRIPTION
Torticollis is a term used to describe disorders characterized by abnormal postures of the head and neck. Cervical dystonia (CD) is the preferred term for the idiopathic movement disorder that causes involuntary contraction of the cervical muscles, resulting in clonic (spasmodic, tremor) head movements and/or tonic (sustained) head deviation. Head deviation can be described as follows: Torticollis, torsion or rotation of the head; anterocollis, flexion of the neck, head forward; retrocollis, extension of the neck, head backward; or laterocollis, tilt of the head to 1 side.

EPIDEMIOLOGY
Incidence
CD is the most common form of focal dystonia, onset most commonly occurs in early-to-mid life with a female predominance. Torticollis and laterocollis are the most common head deviations; retrocollis and anterocollis are more rare. Most patients have combinations of neck deviations depending on the cervical muscles involved. Tremor is common with the tonic head deviation. There may be other dystonias and tremor involving facial, buccal–lingual, mandibular, and other body parts. The clinical course of CD is variable; most patients report some progression of symptoms. Spontaneous remission is rare (10–20%). Torticollis is a disorder of middle and late life. Torticollis in childhood is more likely to be acquired and nondystonic. In infancy, congenital muscular torticollis is the most common cause of restricted range of motion of the head.

RISK FACTORS
Torticollis usually occurs spontaneously, and there are no specific risk factors for its development.

Pregnancy Considerations
Torticollis is not associated with pregnancy. In terms of treatment, botulinum toxin is not approved for use during pregnancy. Other medications should be avoided if possible during pregnancy.

Genetics
Genetic mechanisms may play a role.

ETIOLOGY
Torticollis may be dystonic (either idiopathic, cause unknown, or secondary, related to some other process) or nondystonic (due to a mechanical process). The pathologic localization and mechanism underlying idiopathic CD is not well understood. The basal ganglia and vestibular system are implicated. Torticollis has a broad differential diagnosis (see below).

COMMONLY ASSOCIATED CONDITIONS
Torticollis may be idiopathic or secondary to other conditions (listed below). Head tremor is commonly associated with torticollis and may confuse the examiner.

DIAGNOSIS

- Head deviation: Rotation, tilt, flexion, extension, or some combination
- Tremor: If present, may be essential type involving head (no direction), oscillatory, jerky, or spasmodic
- Cervical pain: Nonradicular, aching, or radicular
- Palpable spasm and hypertrophy of muscle may be present
- Head deviation can be controlled temporarily by counterpressure and sensory tricks, *geste antagoniste:* Touching chin, face, or back of head
- Exacerbation occurs during periods of fatigue and stress

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
- With onset in patient <50 years old, obtain serum ceruloplasmin and liver function tests to exclude Wilson's disease.
- Review drug exposure (especially dopamine-blocking agents, i.e., neuroleptics, metoclopramide).
- Consider MRI of neck to exclude structural etiologies.
- Consider genetic testing if there is a strong family history of dystonia.
- Consider other laboratory studies (antinuclear antibody, ESR, rapid plasma reagin, CBC, electrolytes, renal, and liver function tests) if history or physical examination suggests the condition.

Imaging
There is no specific imaging abnormality demonstrable in idiopathic CD. However, appropriate imaging studies may be indicated to identify nondystonic forms of torticollis.

DIFFERENTIAL DIAGNOSIS
- Dystonic conditions
  - Idiopathic:
    - Primary focal dystonia (CD)
    - Associated with more generalized dystonia
  - Secondary:
    - Associated with neurological degenerative illnesses, e.g., parkinsonism (multiple system atrophy, progressive supranuclear palsy, idiopathic Parkinson's disease), Huntington's disease, Wilson's disease
    - Associated with metabolic disorders, e.g., amino acid disorders (such as homocystinuria), lipid storage disorders (such as metachromatic leukodystrophy), Lehigh's disease
    - Associated with other causes, e.g., perinatal injury (cerebral palsy), infection (encephalitis, Jakob–Creutzfeldt disease, syphilis), head trauma/cervical trauma, multiple sclerosis, stroke
    - Associated with toxins, e.g., manganese, carbon monoxide, methane
    - Associated with drugs, e.g., levodopa, dopamine agonists, neuroleptics, dopamine-blocking agents
- Nondystonic head tilt
  - Structural (mechanical):
    - Cervical spine fracture
    - Dislocation
    - Disc herniation
    - Cervical region abscess
    - Congenital fibrous bands
  - Neurological:
    - Vestibulo-visual: Fourth nerve palsy, hemianopia
    - Posterior fossa tumor
    - Spinal cord tumor
    - Arnold–Chiari malformation
    - Focal seizures
    - Cervical myopathy
    - Myasthenia gravis
  - Psychogenic

TREATMENT

MEDICATION

- Chemodenervation, botulinum toxin treatment
  - Botulinum injections are the treatment of choice for torticollis (CD), both idiopathic and secondary forms. Botulinum toxin injections block acetylcholine release, causing focal neuromuscular junction blockade. By selectively injecting various doses into affected muscles, the symptoms of CD and other dystonias often are dramatically relieved. Repeated injections often are necessary every few weeks or months, depending on the response.
- Contraindications: Neuromuscular disorders such as Lambert–Eaton syndrome and myasthenia gravis are relative contraindications to botulinum toxin use. It also should be avoided in myopathies and in motor neuron disorders.
- Precautions: Botulinum injections should be administered only by a physician expert in the diagnosis and treatment of dystonias and in the administration of this medication. Side effects are rare when used appropriately. Subcutaneous hematomas and pneumothorax have been reported. Temporary muscle weakness is a predictable response to this therapy. Occasionally, temporary dysphagia occurs with higher doses. Secondary resistance to botulinum toxin is becoming an issue in clinical practice.
- Alternative drugs
  - Anticholinergic agents (trihexyphenidyl)
    - Often require high doses with significant side effects
    - Dry mouth, urine retention, psychosis
  - Tricyclic antidepressants (amitriptyline)
    - Often requires high doses with significant side effects
    - Dry mouth, urine retention, weight gain
  - Benzodiazepines (clonazepam, lorazepam)
    - Antispasticity agents (baclofen)
  - For tremor component of torticollis
    - Primidone
    - Benzodiazepine
    - β-Blocker

ADDITIONAL TREATMENT

General Measures

Physical measures such as stretching, heat, and physical therapy may be considered. The role of such measures is limited in idiopathic torticollis.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Nonpharmacological therapies such as biofeedback, hypnosis, relaxation techniques, acupuncture, and other modalities have been used in torticollis but are generally unhelpful. Botulinum therapy has become the standard of care.
- Adjunctive treatment
  - There may be occasionally a role for sensory feedback therapy or relaxation techniques in the relief of associative symptoms such as pain.

SURGERY/OTHER PROCEDURES

Rhizotomy, neurectomy, or myotomy has been advocated for patients who do not respond to chemodenervation and medical pharmacotherapy. Currently, the application of basal ganglia ablative surgery (i.e., thalamotomy) and deep brain stimulation is considered only for treatment of more generalized forms of dystonia.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients undergoing botulinum toxin injections should be monitored for response to medication and evaluated at regular appointments, usually every 3 months, for repeated injections. No routine laboratory or imaging studies are required.

PATIENT EDUCATION

Patients should be made aware of the risk of muscle weakness, dysphagia, bruising, and rarely pneumothorax with botulinum injections. They should know that treatment is temporary and needs close follow-up. They should understand that torticollis is a treatable condition that usually does not cause major disability.

PROGNOSIS

Approximately 60–80% of patients benefit from botulinum toxin injections, usually with reduced but not completely abolished symptoms.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- CD
- Spasmodic torticollis
- Wry neck
- Stiff neck
- Capitium obstipum
- Rhaebocrania
- Dystonia
- Dystonic reaction (botulinum toxin, acute CD)
- Parkinson's disease

CODES

ICD9

- 333.83 Spasmodic torticollis
- 723.5 Torticollis, unspecified; excludes: Torticollis, unspecified
- 754.1 Congenital musculoskeletal deformities of sternocleidomastoid muscle

TOURETTE'S SYNDROME

Sarah M. Roddy, MD

BASICS

DESCRIPTION

- Tics are a movement disorder characterized by brief, repetitive, stereotyped movements or sounds. Tic disorders are classified along a spectrum based on severity.
  - Transient tic disorder: Single or multiple motor and/or vocal tics, which have occurred for <1 year.
  - Chronic tic disorder: Single or multiple motor or vocal tics, but not both, which have persisted for >1 year.
  - Tourette's syndrome (TS): Multiple motor and 1 or more vocal tics, which have persisted for >1 year.

EPIDEMIOLOGY

Incidence

- The exact incidence of TS is unknown, but estimates suggest up to 1% of children.
- Tics begin most commonly by age 6–7 years and always before 18 years.
- Males are more commonly affected than females.
- Transient tics occur in up to 20% of children.

Prevalence

The prevalence is unknown, but it is estimated that 200,000 Americans have the most severe form of TS.

RISK FACTORS

- Risk factors include male sex and a family history of tics and obsessive–compulsive disorder (OCD).
- In patients with TS, stress, fatigue, and excitement may exacerbate tics.

Genetics

TS is a genetic disorder with an unclear mode of inheritance, but evidence suggests polygenic inheritance.

GENERAL PREVENTION

- There is no known prevention for TS.
- Tics may be reduced, though, by decreasing stress.

PATHOPHYSIOLOGY

There is faulty inhibition of the cortical–subcortical pathways resulting from a complicated interplay of mainly dopamine but also gamma-aminobutyric acid (GABA), glutamate, serotonergic, noradrenergic and cholinergic pathways.

ETIOLOGY

- There is no precise etiology known.
- Streptococcal infection or other environmental factors may play a triggering role in some genetically susceptible individuals.

COMMONLY ASSOCIATED CONDITIONS

- 50% of patients with TS have attention deficit hyperactivity disorder (ADHD).
- 20–90% of patients with TS have OCD.
- There is a higher incidence of learning disabilities in children with TS.
- Episodic outbursts and self-injurious behaviors such as hitting or biting oneself are relatively common.

DIAGNOSIS

HISTORY

- Tics develop abruptly, with initial tics usually being motor tics. Common motor tics include eye blinking, head jerking, and facial grimacing.
- Vocal tics include throat clearing, sniffing, grunting, and coughing. Coprolalia, which is involuntary swearing, develops in about 10% of patients and is not usually present until 4–7 years after initial symptoms.
- Tics vary in frequency, location, type, and severity. Although initial tics may involve the head, over time the tics often involve the limbs and trunk.
- Tics may spontaneously wax and wane, and there may be periods of days to months when all symptoms disappear. They also change over time, with 1 tic disappearing and another developing.
- Patients can voluntarily suppress tics for varying periods of time; however, the suppression creates an inner tension and eventually the tics must be released.
- Tics may occur during sleep whereas most other movement disorders disappear during sleep.
- History should also include symptoms of ADHD and OCD as well as any family history of tics, ADHD, and OCD.

PHYSICAL EXAM

There are no diagnostic findings on exam. The patient may suppress the tics during the exam, and none may be witnessed. The patient should be observed when leaving the visit since the suppressed tics may be released then.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- There is no laboratory test that is diagnostic for TS.
- The diagnosis is based on clinical criteria.
- If there is a preceding history of sore throat, tests for streptococcal infection including anti-streptolysin titer or streptozyme may be indicated.

Imaging

Initial approach

Neuroimaging studies do not show any structural abnormalities and are not helpful in making the diagnosis.

Follow-up & special considerations

An EEG may rarely be needed to make sure that a motor tic is not seizure activity.

Pathological Findings

- There are no diagnostic pathological findings.
  - There are limited neuropathological studies in postmortem brains, but a marked reduction in the number and density of GABAergic parvalbumin-positive cells in the basal ganglia has been found.

DIFFERENTIAL DIAGNOSIS

- Chorea
- Myoclonus
- Seizures
- Late onset of tics can be associated with Wilson's disease or Huntington's disease

TREATMENT

MEDICATION

First Line

- Clonidine reduces tics in some children and can also be helpful for treatment of ADHD (1)[B].
  - A dose of 0.05 mg per day is started and increased by 0.05 mg q 5–7 days to a maximum of 0.2–0.3 mg/day. Clonidine has a short half-life, so t.i.d. or q.i.d. dosing is often required. The patch form has the advantage of providing a constant level of medication.
  - Contraindications include documented hypersensitivity. Use with caution if renal or hepatic function is impaired.
  - Patients need to be monitored for sedation and hypotension and, in those treated with the transdermal form, skin reaction. It is advisable not to abruptly stop the medication because of the risk of hypertension.
- Guanfacine treats tics and comorbid ADHD and is less sedating than clonidine (1)[B].
  - The initial dose is 0.5 mg at h.s. with the dose increased by 0.5 mg q 5–7 days to a maximum of 4 mg/day given b.i.d.
  - Use with caution in patients with cerebrovascular disease or impaired hepatic and renal function.
  - Adverse effects include sedation, dizziness, and hypotension.

Second Line

- Pimozide is a typical neuroleptic and may be more effective for tics than the first-line drugs but may cause more side effects than the first-line drugs. It is less sedating than haloperidol (2)[A].
  - The initial dose is 0.5–1 mg q.h.s. with an increase by 0.5–1 mg q 5–7 days as needed. The usual dose is 2–4 mg divided b.i.d. with a maximum daily dose of 10 mg.
  - Contraindications include prolonged QT interval and history of cardiac arrhythmias.
  - Because pimozide can prolong the QT interval, patients need to have an EKG prior to starting treatment and regular EKG monitoring.

- Fluphenazine is a traditional neuroleptic that is effective in controlling tics (3)[B].
  - A dose of 0.5–1 mg q.h.s. is started with weekly increases as needed to a maximum dose of 5 mg divided b.i.d.
  - Severe cardiac disease and liver disease are contraindications.
  - Side effects include weight gain, drowsiness, extrapyramidal reactions, and restlessness.
- Haloperidol was the first neuroleptic shown to be effective for tic suppression and may be the most effective for severe cases (3)[A].
  - A dose of 0.5 mg q.h.s. is started, with an increase of 0.25–0.5 mg weekly until satisfactory tic control is achieved. Doses >4 mg per day are rarely required.
  - Contraindications in children are unusual but include cardiac and liver disease and history of acute dystonia.
  - Patients need to be monitored for lethargy, weight gain, personality changes, cognitive impairment, and school phobia. Tardive dyskinesia is a potential side effect from use of haloperidol, but this rarely occurs in children with tics.
- Risperidone is an atypical neuroleptic that may improve tics and can be helpful for impulsive and oppositional behavior (1)[A].
  - The initial dose is 0.25–0.5 mg q.h.s. The dose can be increased as needed every week to a maximum of 4 mg divided b.i.d.
  - Contraindications in children are unusual but include prolonged QT interval.
  - Side effects include weight gain, hyperglycemia, and dystonic reactions.

ADDITIONAL TREATMENT

General Measures

- Explaining the nature of TS to the child and family is the most important initial intervention.
- Parents need to know that tics are involuntary and that children should not be punished for symptoms they cannot control.
- They also need to understand that tics are not a sign of psychological disease but that stress can exacerbate the symptoms.
- Any events or conditions that exacerbate tics should be identified and eliminated if possible.
- Parents should be educated to ignore tics as much as possible, because focusing attention on them often increases the frequency of tics.
- Management should also focus on educational issues that may result from the tics or associated ADHD or OCD. A comprehensive neuropsychological assessment can help determine what interventions will be helpful to make the child successful in school.
- Pharmacotherapy is indicated for children whose symptoms impair their psychosocial or educational functioning.

Additional Therapies

- Behavioral therapy, including relaxation therapy, habit reversal training, and comprehensive behavioral intervention for tics, is helpful in some patients. Behavior therapy is not widely available, and not all patients have long-term benefits.
- Atomoxetine or stimulants such as methylphenidate or dextroamphetamine can improve the attention span and help with impulsive behavior. Stimulants can be used in children with tics with very little risk of worsening tics.
- Selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, fluvoxamine, or paroxetine, may help decrease OCD symptoms. These medications usually must be given for 4–6 weeks before improvement is seen.
- Local intramuscular injection of botulinum toxin (Botox) can reduce a single severe motor tic but the benefits last only 3–6 months.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Acupuncture has been reported to be effective in some small trials.
- There is no convincing evidence that vitamin or mineral preparations or special diets are helpful.

SURGERY/OTHER PROCEDURES

Deep brain stimulation has been helpful in some patients refractory to medical management. The criteria for identifying patients who will have the greatest benefit from this procedure have not been determined.

IN-PATIENT CONSIDERATIONS

Admission Criteria

It is very unusual for patients with TS to require admission for their symptoms.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients with mild symptoms who do not need medications can be followed on an as-needed basis. Patients with more severe symptoms will need follow-up every few weeks to months to monitor medication response, school progress, and psychosocial issues.

DIET

There is no special diet that helps the tics.

PATIENT EDUCATION

- The Tourette Syndrome Association provides many services for patients, families, physicians, and caregivers. Local chapters throughout the country provide additional services, including support groups. Tourette Syndrome Association, 42-40 Bell Boulevard, Bayside, NY 11361-2820. Phone: 718-224-2999, fax: 718-279-9596, website: http://tsa-usa.org
- "Tourette Syndrome Fact Sheet" NINDS.

PROGNOSIS

- Approximately one third of patients have complete remission of tics by late adolescence. An additional third of patients report that their tics significantly lessen in frequency and severity by late adolescence. The remaining third of patients continue to be symptomatic into adulthood, although in some there may be continuing gradual improvement throughout life.
- ADHD symptoms tend to improve during the adolescent years, although some patients continue to have symptoms that may affect their occupation.
- OCD symptoms, which tend to begin later than tics, may persist and have a negative impact on the patient's life.

COMPLICATIONS

Tics can lead to muscle soreness and strain and rarely dislocation of a bone.

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ADDITIONAL READING

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CODES

ICD9

- 307.20 Tic disorder, unspecified
- 307.23 Tourette's disorder

CLINICAL PEARLS

- Tic disorders are common and occur along a spectrum of severity.
- TS is often associated with ADHD and OCD, and these symptoms may be more significant that the tics.
- Pharmacotherapy is considered if tics are interfering academically, psychosocially, or causing musculoskeletal discomfort.
- Patients with TS usually improve and may have resolution of tics by late adolescence.

TRANSVERSE MYELITIS

D. Joanne Lynn, MD

BASICS

DESCRIPTION
Transverse myelitis (TM) is an acute syndrome of inflammation of the spinal cord, usually involving multiple segments and both gray and white matter, with resultant myelopathy or spinal cord dysfunction.

EPIDEMIOLOGY
Incidence
Estimated incidence ranges from 1.3 to 8 cases per million. There is a bimodal peak in incidence at 10–19 and 30–39 years of age. Incidence increases to approximately 25 cases per million if acquired demyelinating causes are included such as multiple sclerosis.

Prevalence
Not known.

RISK FACTORS
Systemic illness, especially respiratory

Genetics
None identified.

GENERAL PREVENTION
None.

PATHOPHYSIOLOGY
Inflammatory response in the spinal cord prompted by infection or as part of a systemic autoimmune process.

ETIOLOGY
The most common cause is an autoimmune disease precipitated by an infectious illness (such as mycoplasma, cytomegalovirus, Epstein–Barr virus, mumps, or varicella) or vaccination (in up to 60% of pediatric cases). Some cases occur as the result of a direct infection of the spinal cord while other cases are related to an acquired demyelinating disease such as multiple sclerosis (MS), neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), or other autoimmune disorders such as systemic lupus erythematosis (SLE), Sjogren's syndrome, and sarcoidosis. A small number of cases are due to a paraneoplastic etiology. In careful studies, 15–30% of cases appear to be idiopathic. Many cases of MS with TM tend to have a partial myelitis as opposed to a more complete cord syndrome.

COMMONLY ASSOCIATED CONDITIONS
- Multiple sclerosis
- NMO
- SLE

DIAGNOSIS

HISTORY
TM symptoms develop rapidly over several hours to several weeks. Approximately 45% of patients reach maximal deficit within 24 hours.

PHYSICAL EXAM
Most patients develop leg weakness of varying degrees of severity. The arms are involved in a minority of cases. Initial muscle tone is flaccid in cases of severe weakness, with spasticity developing over hours to days. Sensation is diminished below the level of spinal cord involvement. Some patients experience paresthesias or numbness. Bowel and bladder dysfunction occurs in the majority of patients. Many patients with TM complain of a tight banding or girdle-like sensation around the trunk.

DIAGNOSTIC TESTS AND INTERPRETATION
Lab
Initial lab tests

There are no specific blood tests to diagnose TM, but the following tests should be obtained to identify potential underlying causes: CBC/differential, rapid plasma reagin (RPR), antinuclear antibody (ANA), double-stranded DNA, anti-Sjögren's syndrome A (SSA) and anti-Sjögren's syndrome B (SSB) antibody, serum vitamin B12 level, human immunodeficiency virus antibody, human T-cell leukemia virus (HTLV-1), and serum angiotensin-converting enzyme. A paraneoplastic antibody panel should be considered.

Follow-up & special considerations

Serum assay for the NMO-IgG antibody should be obtained if there are typical radiological features or recurrent episodes of TM.

Imaging
Initial approach

MRI with T2-weighted images and contrast enhancement of the entire spine should be performed urgently. If MRI is contraindicated, myelogram should be performed. The immediate purpose is to rule out a compressive lesion of the cord requiring surgical decompression. Normal spine MRI should prompt consideration of other disorders of the central or peripheral nervous system (1)[B].

Follow-up & special considerations

- Spinal lesions that span 3 or more vertebral segments of the cord are termed *longitudinally extensive TM* and are strongly associated with NMO.
- Brain MRI should be considered to investigate for the possibility of more disseminated demyelination such as MS or ADEM.

Diagnostic Procedures/Other
Lumbar puncture –CSF should be sent for cell count, differential, total protein, protein electrophoresis, IgG index, Gram stain and bacterial culture, cryptococcal antigen, fungal culture, acid-fast bacilli smear and culture, and viral titers and cultures. CSF examination typically shows a lymphocytic pleocytosis with normal or elevated total protein level. Oligoclonal bands are present in 20–40% of patients with TM.

Pathological Findings
Focal inflammation with aggregates of lymphocytes and monocytes as well as demyelination, axonal injury within the spinal cord.

DIFFERENTIAL DIAGNOSIS
- Extrinsic cord compression
- Spinal arteriovenous malformation and dural av fistula
- Epidural abscess
- Spinal cord infarction
- ADEM

TREATMENT

MEDICATION
First Line
Specific treatment should be given if any underlying cause of TM is detected. Examples include antibiotics for bacterial infections and antiviral agents for TM associated with varicella zoster or herpes simplex infection. Otherwise, high-dose intravenous methylprednisolone should be administered for idiopathic, autoimmune disease-related or post-infectious TM. Methylprednisolone 1 g IV daily for 3–5 days followed by an oral taper of prednisone is given for patients with no identifiable active infection. There is no standard taper.

Second Line
- Spasticity may be a subacute or chronic problem; it may be ameliorated by medications:
  - Lioresal at a dosage of 10 mg 1 to 2 times daily titrated up to an effective dose to maximum of 100 mg or sometimes more daily in divided doses 3–4 times per day.
  - Tizanidine may be used as an alternative agent if lioresal is not tolerated. Start with 2 mg daily and gradually increase by 2 mg every 3–4 days up to a maximum of 32 mg per day in 3 doses per day. Tizanidine may cause less weakness than lioresal. Liver function tests must be monitored.
  - Diazepam 2–10 mg given 1–3 times per day or clonazepam 0.5–1.0 mg up to 3 times per day. Benzodiazepines are often only tolerated at night due to associated sedation.

- Bladder dysfunction: Patients may develop several different patterns of bladder dysfunction. Checking postvoid residuals and cystometric studies may be helpful.
  – Hypertonic bladder: Oxybutynin 2.5–5 mg PO taken 2–3 times per day or tolterodine 1–2 mg PO b.i.d. (long-acting formulations are available).
- Constipation—in addition to increase in oral fluids to 2–2.5 L per day, bulking agents, stool softeners, rectal stimulation (e.g. with glycerin or Dulcolax suppositories), and Theravac mini-enemas may be helpful.
- Neuropathic pain: Many patients complain of neuropathic pain as a long-term residuum of TM. This should be managed with trials of agents such as gabapentin 100–900 mg 1–3 times a day, pregabalin 50–75 mg PO 2–3 times a day, amitriptyline 25–150 mg PO q.h.s., or carbamazepine 100–200 mg daily with gradual increase to 600–1600 mg daily in divided doses.

ADDITIONAL TREATMENT

General Measures

- Respiratory function should be monitored closely with forced vital capacity or negative inspiratory force assessment in the acute phase for high cervical TM. These patients may also require intubation for airway protection if they are not handling secretions adequately.
- Prophylactic treatment should be given for deep vein thrombosis (DVT) in patients who are immobilized with either air compression boots or SQ low-molecular-weight heparin. A high index of suspicion should be maintained for DVT and pulmonary embolism should suggestive symptoms arise.
- Urinary retention is frequent. Bladder function should be checked frequently in the acute phase. Intermittent catheterization is often required.
- A bowel program should be taught for patients with constipation/impaired defecation.
- Physical therapy with active and passive range or motion and occupational therapy should be started as soon as possible to prevent contractures and hasten functional recovery.
- Patients with immobilization should have attention to frequent repositioning and padding to prevent decubitus ulceration. Splints may be required to prevent joint contractures.

Issues for Referral

Consideration for follow-up with a neurologist and physiatrist should be considered for patients with significant residual deficits.

Additional Therapies

Rescue plasma exchange and/or cyclophosphamide should be considered for patients with severe deficits who do not respond to corticosteroid therapy.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

None specifically indicated.

SURGERY/OTHER PROCEDURES

There are no surgical procedures to treat TM. Rarely, presentation will be associated with significant cord swelling, and a spinal cord tumor cannot be excluded. Biopsy of the cord should be cautiously considered in that case.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

Immediate stabilization involves assessment of respiratory function and cardiovascular status.

Admission Criteria

Patients are generally admitted for acute evaluation and administration of intravenous steroid therapy.

IV Fluids

No specific recommendations.

Discharge Criteria

Patients with significant weakness should be evaluated for consideration of inpatient acute rehabilitation.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

In patients who have a significant residual myelopathy, long-term follow-up and symptomatic care may be needed for weakness, mobility issues, bowel, bladder and sexual dysfunction, spasticity and neuropathic pain.

Patient Monitoring

Patients should be followed to make sure that they stabilize and to detect recurrent episodes of myelitis or other neurological dysfunction.

DIET

As tolerated.

PATIENT EDUCATION

Transverse Myelitis Association, 3548 Tahoma Place West, Tacoma, WA 98466; phone 614-766-1806; website: www.myelitis.org

PROGNOSIS

Approximately 50–70% of patients have partial or complete recovery.

COMPLICATIONS

- Deep venous thrombosis/pulmonary embolism
- Decubitus ulcer
- Pneumonia

REFERENCE

1. Frohman EM, Wingerchuk DM. Transverse myelitis. *N Engl J Med* 2010;363:564–572.

ADDITIONAL READING

- Greenberg BM, Thomas KP, Krishnan C, et al. Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. *Neurology* 2007;68:1614–1617.
- Pidcock FS, Krishnan C, Crawford TO, et al. Acute transverse myelitis in childhood: center-based analysis of 47 cases. *Neurology* 2007;68: 1474–1480.
- Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol* 1999;46:878–886.

See Also (Topic, Algorithm, Electronic Media Element)

- www.myelitis.org

CODES

ICD9

- 052.7 Chickenpox with other specified complications
- 323.9 Unspecified cause of encephalitis, myelitis, and encephalomyelitis
- 323.42 Other myelitis due to infection classified elsewhere

CLINICAL PEARLS

- Test for NMO if there is a longitudinally extensive lesion by MRI in the spinal cord.
- Obtain brain MRI to assess for evidence of MS or other disorders with disseminated demyelination.

TRAUMA, INTRACRANIAL

Chad W. Farley, MD
Lori Shutter, MD

BASICS

DESCRIPTION
Intracranial trauma can be described in terms of mechanism and morphology of injury. Mechanism of injury refers to blunt versus penetrating trauma, whereas morphology describes the presence of focal or diffuse intracranial injury. The initial primary injury results in both global and focal disruption of neural networks and metabolism. Secondary injury is the vulnerable tissue at high risk for further insult. Prevention of secondary injury is the focus of in-hospital medical care.

EPIDEMIOLOGY
- Incidence
  - Estimate in the US is 200 per 100,000 (80% mild, 10% moderate, 10% severe).
  - 1.7 million in the US sustain a TBI each year; 80% treated and released from ER; traumatic brain injury (TBI) contributes to 30.5% of all injury-related deaths annually.
- Race
  - Higher incidence in African Americans; appears to be related to an increased exposure to firearms and higher rates of homicide.
- Age
  - Occurs in all ages; tri-modal distribution: <4, 15–24 (majority), and >65 years.
- Sex
  - Males-to-females ratio of 3:1.

RISK FACTORS
Alcohol and drug intoxication

ETIOLOGY
- Motor vehicle accidents, falls, assaults, and sports-related injuries that may lead to:
  - Diffuse axonal injury
  - Traumatic subarachnoid hemorrhage
  - Coup–contrecoup injuries
  - Cortical contusions and lacerations
  - Subdural, epidural, or intracerebral hematomas

DIAGNOSIS

- Immediate loss or alteration of consciousness
- Period of confusion and post-traumatic amnesia (retrograde and antegrade)
- Signs of trauma
  - Facial or scalp lacerations, abrasions, etc.
  - Raccoon's sign
  - Battle sign
- Glasgow Coma Scale (GCS): Defines severity of injury.
  - Ocular: Eyes open spontaneously = 4, to voice = 3, to pain = 2, no opening = 1
  - Verbal: Oriented = 5, disoriented = 4, inappropriate = 3, incomprehensible = 2, no response = 1
  - Motor: Follows commands = 6, localizes = 5, withdraws = 4, flexion posturing = 3, extensors posturing = 2, no response = 1
- Definitions
  - Severe injury: Initial GCS ≤8 or deterioration to this score
  - Moderate injury: Initial GCS 9–13 without subsequent deterioration
  - Mild injury: Loss of consciousness or alteration of awareness for <30 minutes; initial GCS 14–15 without neurosurgical pathology or subsequent deterioration. Concussions are a mild TBI

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
Platelet count, PT, PTT, international normalized ratio, glucose

Imaging
- Head CT: Initial study assesses for intracranial blood. Can be performed on anyone with loss of consciousness for >15 minutes.
- Brain MRI is useful for detecting brainstem involvement and diffuse axonal injury.

Diagnostic Procedures/Other
- EEG
  - Mandatory for induced barbiturate coma; useful to assess seizure activity; uncertain role in predicting outcome.
  - Consider continuous EEG monitoring for 48–72 hours for all severe TBI injuries or those with witnessed seizures.
  - Approximately 18–24% incidence of nonconvulsive status in severe TBI patients.
- Evoked potentials (EPs)
  - Combination of somatosensory, visual, and brainstem EPs has high correlation with 1-year clinical outcome.

DIFFERENTIAL DIAGNOSIS
Other causes of coma.

TREATMENT

MEDICATION
- Increased intracranial pressure (ICP)
  - Mannitol at 1 g/kg loading dose, then repeat maintenance boluses of 25–50 g.
  - Hypertonic saline—various concentrations are reported, can be used either as bolus dosing or maintenance infusions.
  - Barbiturates (pentobarbital, thiopental) at 5 mg/kg loading dose, then steady infusion of 1–3 mg/kg/hour to maintain burst-suppression with continuous EEG monitoring.
- Seizures
  - Acute period: Levetiracetam 500–1000 mg b.i.d. or phenytoin at 15–20 mg/kg loading dose, then maintenance dose for a therapeutic level; discontinue after 1 week if there are no witnessed seizures.
  - Long term: Carbamazepine, valproic acid, or levetiracetam are preferred anticonvulsants due to fewer adverse effects on cognition.
- Agitation
  - Agitation in ICU should be treated with short-acting sedatives, analgesics, and soft restraints.
  - Persistent agitation can be treated with dopamine agonists, anticonvulsants (valproic acid, carbamazepine), β-adrenergic antagonists, antipsychotics, or buspirone.
- Arousal
  - Arousal, motivation, and responsiveness increase with use of dopamine agonists, psychostimulants, and antidepressants.
- Contraindications
  - Hypotension and hypoxia worsen clinical outcome. Avoid glucose-containing IV fluids.
  - Steroids are contraindicated due to increased risk of death.
- Precautions
  - Rebound increased ICP has been reported with mannitol. Short-term used is ideal with subsequent taper. Intravenous forms of valproic acid should not be used in the acute phase after TBI. Avoid hyperthermia and hyperglycemia.

ADDITIONAL TREATMENT

General Measures
Appropriate emergency department/intensive care unit management is critical. Transfer to a level-one trauma center improves mortality. Following the Brain Trauma Foundation guidelines has also been shown to reduce mortality. Treatment differs based on severity of injury. Multidisciplinary teams consisting of trauma surgery, neurosurgery, orthopedic surgery, neurocritical care, and rehabilitation services frequently are necessary.

Severe TBI
- Monitor to prevent secondary injury
  - ICP monitors: Codman monitors, Camino bolts, ventriculostomy; ICP goal: <20 mm Hg.
  - Cerebral perfusion pressure = Mean arterial pressure (MAP) – ICP; goal: 50–70 mm Hg
- ICP control
  - Hyperosmotic agents (i.e., mannitol, 3% saline); monitor serum osmolality and sodium levels frequently.
  - Ventricular drainage
  - Limited use of hyperventilation secondary to risk for ischemia with prolonged use; prophylactic prolonged hyperventilation results in worse outcomes at 6 months
  - Barbiturate coma for refractory ICP
  - Hypothermia may assist in refractory ICP control, but recent studies found that prophylactic use did not improve outcome
  - Corticosteroids are contraindicated for improving outcome or ICP control
  - Identify and treat herniation syndromes
- Seizures
  - Immediate seizures at time of injury do not require anticonvulsant medications; initiate anticonvulsants if seizures are observed after initial resuscitation and stabilization
  - May contribute to ICP elevations
  - Avoid routine prophylaxis beyond 1 week

- Acute hydrocephalus
  - Usually secondary to intraventricular or subarachnoid hemorrhage
  - Signs: Neurological deterioration, increased ICP, nausea, vomiting, headache
  - Ventriculostomy provides acute treatment; may need ventriculoperitoneal shunting
  - Development of hydrocephalus may be delayed or chronic in nature
- Agitation
  - Subtype of delirium occurring during period of amnesia due to increased sympathetic drive; characterized by excessive behaviors
  - Managed with a combination of low-dose anxiolytics and antipsychotics
  - Light sedation is beneficial to ICP
- Electrolyte abnormalities
  - Hyponatremia
    - Cerebral salt wasting
    - Clinical signs: Hyponatremia with hypovolemia, high urine output, normal to increased serum osmolality
    - Treatment: Should focus on hydration and salt supplementation. Fludrocortisone is occasionally used
    - Syndrome of inappropriate secretion of antidiuretic hormone
    - *Treatment: Fluid restriction and avoiding hypotonic IV fluids. Refractory cases: Demeclocycline (300 mg every 6 hours), fludrocortisone (0.1–0.2 mg/day), hypertonic saline (500 cc over several hours), or oral salt replacement
  - Hypernatremia
    - Diabetes insipidus: Relatively uncommon
    - *Clinical signs: Hypernatremia with polyuria, polydipsia, hypovolemia, increased serum osmolality, low urine osmolality
    - *Treatment: Pitressin, vasopressin, fluid supplementation
    - Iatrogenic causes—may result from hypertonic saline infusions
- General care
  - Positioning—head elevated by 30–45 degrees
  - Prophylaxis for deep vein thrombosis
  - Meeting early nutritional needs decreases mortality
  - Early initiation of rehabilitation services

Moderate TBI

Generally ICP is not a concern in this group. Similar management as severe TBI for seizures, agitation, and general care. Observation for clinical deterioration should be warranted. Neurological decline may be delayed

Mild TBI

Treatment should focus on the symptomatic treatment of sequelae. Patients should not engage in activities placing them at risk for recurrent injury until they have been symptom-free for at least 1 week.

SURGICAL TREATMENT GUIDELINES

General surgical intervention guidelines:

- Traumatic intracerebral hemorrhage
  - Volume >50 cm^3
  - Attributable mass effect (midline shift or cisternal effacement)
- Epidural hematoma
  - Evacuate if >30 cm^3, regardless of GCS
  - Width above 1.5 cm
- Subdural hematoma
  - Maximal width of hematoma >1 cm
  - Midline shift greater than 5 mm
  - If width <1 cm and shift <5 mm evacuation should be considered with neurological decline
  - Chronic traumatic subdural hematoma can generally be evacuated less urgently. They are better tolerated with chronic development
- Depressed skull fractures
  - Elevate if depressed greater than thickness of calvaria
  - Resultant neurological deficit, CSF leak, or open contaminated wound. Considered for cosmesis or frontal sinus involvement
- Intractable ICP
  - May require hemispheric or bifrontal craniotomy with or without tissue resection though recent studies question surgical benefit in absence of mass effect lesions

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Discussed under Sub-Section 'General Measures'. Sequelae may require treatment of headaches, spasticity, cognitive deficits, and pain.
- Adjunctive treatment
  - Rehabilitation services: Physical, occupational, and speech therapy; neuropsychological testing and counseling.
  - Early percutaneous endoscopic gastrostomy and tracheostomy recommended.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with all severe and moderate injuries, as well as mild injuries with an abnormal CT, should be admitted. Discharge may be considered when responsive and clinically stable ≥24 hours.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Monitor patients through neurosurgery, neurology, and rehabilitation services for delayed complications

PATIENT EDUCATION

- Brain Injury Association, 105 North Alfred Street, Alexandria, VA 22314. Website: www.biausa.org
- Brain Trauma Foundation, 7 World Trade Center, 34th floor, 250 Greenwich Street, New York, NY 10007. Website: www.braintrauma.org

PROGNOSIS

- *Mortality:* Directly related to severity of injury, overall rate = 20/100,000. Higher mortality seen in ages <5 and >65. Severe injury carries a 30% mortality rate.
- *Morbidity:* Some degree of neurological impairment remains in 10% of patients with mild TBI, 67% with moderate, and 100% with severe. Annual disability rate is 35/100,000.
- Posttraumatic seizures
  - Risk is the greatest in the first year after injury. Recurrent seizures occur in >85% with an unprovoked late posttraumatic seizure.
  - Risk factors for posttraumatic seizures:
    - Cortical contusion, subdural or epidural hematoma
    - Depressed skull fracture
    - All penetrating injuries
    - Any injury with GCS <10
    - Immediate post-injury seizures
    - Prophylactic treatment generally reserved for severe TBI patients only
- Delayed hydrocephalus
  - Difficult to distinguish hydrocephalus ex vacuo from symptomatic hydrocephalus. Sequential head CTs are beneficial.
  - Presents any time, from >1 month to years after injury. Incidence is 4%.
  - Usually a communicating hydrocephalus. May see the classic triad of dementia, gait ataxia, and urinary incontinence.
  - Suspected in patients who deteriorate or fail to progress in their rehabilitation.
  - Treatment: Ventriculoperitoneal or lumboperitoneal shunt.
- Postconcussion syndrome
  - Diverse symptom constellation: Headaches, dizziness, visual blurring, tinnitus, fatigue, sleep disruption, mood changes, impairments in memory, and attention.
  - Usually improves over 3 months in >90%.
  - Persistence 6 months after injury raises concerns of psychological factors.
- Neuropsychological issues
  - 5 years after injury, 50% of severe, 14% of moderate, and 3% of mild injuries may still demonstrate neuropsychological impairments.
  - Neuropsychological testing can assist with planning of appropriate rehabilitation programs, prediction of functional recovery, and long-term prognosis.
- Rehabilitation
  - Majority of recovery following any brain injury occurs in first 6 months after injury.
  - Specialized postacute rehabilitation programs have been developed to address community reentry and vocational rehabilitation.

ADDITIONAL READING

- AANS and Brain Trauma Foundation. Guidelines for the management of severe head injury, 1999. Website: www.braintrauma.org
- Annengers J, Hauser W, Coan S, et al. A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 1998;338:20–24.
- Center for Disease Control and Prevention. Traumatic Brain Injury, 2010. Website: http://www.cdc.gov/TraumaticBrainInjury/index.html

See Also (Topic, Algorithm, Electronic Media Element)

- Head injury
- Concussion
- Trauma, spinal cord

CODES

ICD9

- 852.01 Subarachnoid hemorrhage following injury, without mention of open intracranial wound, with no loss of consciousness
- 854.00 Intracranial injury of other and unspecified nature, without mention of open intracranial wound, with state of consciousness unspecified
- 854.01 Intracranial injury of other and unspecified nature, without mention of open intracranial wound, with no loss of consciousness

TRAUMA, MILD BRAIN INJURY

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BASICS

DESCRIPTION

Various definitions have been proposed for mild traumatic brain injury (MTBI). One which is used frequently is as follows: A patient with MTBI is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: Any period of loss of consciousness; any loss of memory of events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: Post-traumatic amnesia not greater than 24 hours; after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; a loss of consciousness of approximately 30 minutes or less (MTBI committee 1993). Other definitions include patients with a head injury and GCS of 15 in the emergency room. Traumatic brain injury in general has recently been defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force. Such definitions are presently in flux and are likely to change as new data emerge on outcomes of various levels of traumatic brain injury. Despite the term *mild* TBI, approximately 15% of people with mild TBI have symptoms that last 1 year or more, causing disruption in school, work, and interpersonal relationships.

EPIDEMIOLOGY

- Incidence/Prevalence
  - It is estimated that 2 million persons in the US suffer closed head injuries each year. Approximately 80% of these are due to mild head injury.
  - Incidence of sports-related MTBIs has increased as much as 4-fold over the past 10 years, perhaps due to reporting, and may account for another 1.6–3.8 million MTBIs annually.
- Race
  - No known differences
- Age
  - Motor vehicle accidents are the most frequent cause of head injuries. Males between 15 and 24 years old are the group at highest risk.

RISK FACTORS

Motor vehicle accidents are the main cause in the young. Falls are more common in the elderly. Rates of head injury are higher for males at all ages. Females may have a higher rate of MTBI from sports-related injuries than males playing in the same sports.

ETIOLOGY

- Estimates of the relative causes of MTBI in the US are as follows:
  - Motor vehicle accidents (45%)
  - Falls (30%)
  - Occupational accidents (10%)
  - Recreational accidents (10%)
  - Assaults (5%)
- Mechanisms of head injury or MTBI include:
  - Direct contact injuries
  - Indirect or nonimpact injury (whiplash)
  - Soft tissue injuries
  - Probable cascade of metabolic changes that are known to occur in brain injury
- Most injuries may overlap, i.e., in acceleration/deceleration head movement, forehead collision on the steering wheel, and cervical strain. There is increasing evidence supporting an organic basis in the pathophysiology of MTBI. After both mild and severe head injuries, damage to nerve fibers and nerve fiber degeneration are evident. Cerebral circulation can be slowed and rotational forces may cause shearing of axons. Generally an injury sustained with the head free (such as an automobile accident) is more damaging than an injury sustained with the head fixed (such as sports injuries).

COMMONLY ASSOCIATED CONDITIONS

Alcohol intoxication has been found in almost two thirds of those tested following MTBI due to automobile accidents.

DIAGNOSIS

- Headaches are the most common symptom following MTBI. Headache prevalence is actually greater in people with mild head injury than in those with more severe trauma. The onset of headache usually occurs within 2 weeks. There may be more than one type of headache, i.e., they are often mixed with tension and vascular features.
- Neck injuries commonly accompany head injuries and can cause headache. Tension-type headaches may account for 75% of headaches. Recurring attacks of migraine with or without aura can occur. Cluster-type headaches are rare.
- Dizziness is reported by almost half of patients with MTBI. This is usually due to vestibular or labyrinthine dysfunction. The dizziness is usually triggered by head movement.
- Other common symptoms include difficulty with attention, concentration, and memory; depression; fatigue; and irritability.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Usually not significant

Imaging

The most common imaging study is CT scan, although MRI is probably superior in most circumstances. In MTBI, imaging studies are usually normal. Some have recommended CT brain scan for all patients with a GCS <15, an abnormal mental status examination, or any neurological deficit. Even mild lethargy or memory deficit justifies a CT scan. MRI sequences using magnetic susceptibility weighting (SWI or GRE) will show microhemorrhages well. Diffusion tensor imaging appears to predict recovery from MTBI.

Diagnostic Procedures/Other

- EEG evaluation in MTBI remains uncertain. The EEG may be abnormal, usually with slowing, in some patients shortly after a head injury, and this abnormality may decrease or disappear within days to weeks. Some studies have found no EEG abnormalities if there was not a period of amnesia or loss of consciousness.
- Brainstem auditory evoked potentials are useful for assessing the integrity of the auditory pathway. Abnormalities can be found in 10–20% of patients with post-traumatic syndrome or after MTBI. Approximately 30% of patients with mild MTBI and symptomatic dizziness will have abnormal studies. The degree of abnormality usually increases with the extent of injury.
- Electronystagmography (ENG) has been noted to be abnormal in 40–50% of patients with MTBI or even "whiplash." ENG may be more sensitive to traumatic abnormalities than the brainstem auditory evoked response.

DIFFERENTIAL DIAGNOSIS

Usually mild head injury has an apparent source as noted above. Other medical or neurological conditions may have been responsible for the head injury, such as a seizure disorder or syncope.

TREATMENT

MEDICATION

- Analgesics
- Nonsteroidal inflammatory medications
- Muscle relaxants
- Antidepressants
- Anticonvulsants
- There has been some success with treating chronic daily post-traumatic headache with divalproex sodium. Other anticonvulsant medications are currently being tried for various types of headache.

- Contraindications
  - Triptan medications are contraindicated in patients with ischemic coronary, cerebrovascular, or peripheral vascular artery disease and pregnancy.
  - Propranolol is contraindicated in cardiogenic shock and severe congestive heart failure; sinus bradycardia and greater than first-degree block; and bronchial asthma.
  - Valproate sodium is contraindicated in patients with significant hepatic disease.
- Precautions
  - Valproate sodium is associated with hepatotoxicity, pancreatitis, hyperammonemia, and thrombocytopenia. It is known to cause teratogenic effects such as neural tube defects. Liver function tests and platelet count should be monitored at drug initiation and at regular intervals.
- Alternative drugs
  - Not established for MTBI

ADDITIONAL TREATMENT

General Measures

Treatment is individualized for each of the problems diagnosed. Treatment for headaches is similar to treatment of headache in general. If there is a post-traumatic migraine syndrome, the triptan-type medications can be helpful. Education of the patient, family members, other physicians, and, when appropriate, employers and attorneys can be very helpful.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Patients with daily post-traumatic headache may need to be placed on some type of preventative medication, usually an antidepressant. Tricyclic antidepressants are usually given first, but selective serotonin reuptake inhibitors can also be tried. Dosing antidepressants for post-traumatic headache is essentially the same as for treatment of depression, although occasionally patients will respond to lower doses. Patients with post-traumatic migraine may benefit from propranolol or a calcium channel blocker (verapamil). Using analgesic medication to decrease pain levels may enable the patient to better concentrate and relax and obtain greater benefits from nondrug therapies. Care must be taken that analgesic rebound headaches do not occur. Anti-inflammatory medication and muscle relaxants may be useful for some patients, usually for a limited time frame, i.e., 1–2 weeks.
- Adjunctive treatment
  - Headaches associated with myofascial trigger points in the neck or upper back will often respond to trigger point injections of local anesthetic, with or without steroids. These are often helpful but typically last only 2–4 weeks. Other nondrug therapies include biofeedback, physical therapy, massage, and counseling. Psychotherapy may be helpful if there is significant depression, anxiety, frustration, excessive expectations, anger, and unresolved grief and loss. Depression should be treated with antidepressant medication.

SURGERY/OTHER PROCEDURES

Generally none for MTBI

IN-PATIENT CONSIDERATIONS

Admission Criteria

MTBI typically does not require neurosurgical intervention or hospitalization. If there is any uncertainty as to the degree of head injury, a brief hospitalization for observation is perfectly reasonable. Patients with MTBI may be admitted if there are concurrent injuries to other parts of the body. Patients with GCS scores <15, an abnormal mental status, or any neurological deficit should be considered for admission. The majority of patients with mild head injuries can be sent home and observed.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Outpatient follow-up is usually all that is necessary, but patients may take more time because of multiple symptoms and concerns. Follow-up should be individualized. Bed rest may not be generally helpful but may reduce dizziness at 2 weeks. Otherwise patients should be encouraged to return to normal activity at their maximal capacity. Patients with mild head injury should be reassured that condition is transient and full recovery expected.

Recommendations for return to sports vary depending on the extent of injury, number of head injuries, and type of sport. Current recommendations suggest no return to athletic or academic activities until the neurological symptoms clear. Return to these activities should be individualized and slowly advanced only as patient continues without symptoms.

PATIENT EDUCATION

Patients should be educated as to the expected outcome for MTBI. Patients should be cautioned they may be more susceptible to a second more severe concussion while in recovery. Most MTBI patients do not enroll in support groups or brain injury associations. If patients have symptoms that persist beyond 1 year, they may benefit from contacting the Brain Injury Association.

PROGNOSIS

- Approximately 80% of patients will recover without significant sequelae. 20% may continue to have symptomatic headache, neck pain, or dizziness. Some will continue to have difficulty with attention, concentration, and memory. Some guidelines exist to identify patients at risk for longer periods of incapacity. These include
  - Older patients
  - Patients with previous head injuries
  - Persons who have been high achievers or in demanding occupations
  - Patients who have family or social stressors
- Late encephalopathy has been seen in chronic repetitive MTBI.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Concussion
- Mild head injury
- Mild traumatic brain injury
- Postconcussion syndrome

CODES

ICD9

- 310.2 Postconcussion syndrome
- 850.9 Concussion, unspecified
- 854.00 Intracranial injury of other and unspecified nature without mention of open intracranial wound, unspecified state of consciousness

TRAUMA, SPINAL CORD

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Lori Shutter, MD

BASICS

DESCRIPTION
Spinal cord injury can be divided into complete or incomplete injuries. Extrication, stabilization, and transport guidelines are followed to prevent exacerbation of current injuries and increase rehabilitation potential.

EPIDEMIOLOGY
- Incidence
  - Between 30 and 50 per 1,000,000
  - Approximately 12,000 per year
- Injury levels
  - C-spine 55%, T-spine 30%, L-spine 15%
- Prevalence
  - Approximately 721 per 1,000,000
  - Estimated up to 300,000 in the US
- Age
  - All ages; majority 25–44 years; median age has increased to 40 as population shifts.
- Sex
  - Males outnumber females by a ratio of 2.5:1
  - More recently, 80% of spinal cord injury occurred among males.
- Race
  - Higher incidence in Caucasians

RISK FACTORS
Alcohol, drug intoxication, violence

ETIOLOGY
- Motor vehicle accidents 45%
- Falls 17%
- Acts of violence

DIAGNOSIS

Diagnosis is largely based on clinical assessment of motor, sensory function together with reflexes and rectal function.

- Depends on level of injury, which is defined as the lowest spinal cord segment with intact motor and sensory function.
  - Loss of motor control, tone, and reflexes.
  - Loss of sensory function within 3 levels of injury.
  - Hand paresthesias should raise concern for cervical injury.
  - Loss of bowel, bladder, and sexual function.
    - Testing involves voluntary motor control, sensory sparing, tone, and reflexes (bulbocavernosus reflex).
- Key levels:
  - Motor:
    - C5: Elbow flexors
    - C6: Wrist extensors
    - C7: Elbow extensors
    - C8: Finger flexors to the middle finger
    - T1: Small finger abductors
    - L2: Hip flexors
    - L3: Knee extensors
    - L4: Ankle dorsiflexors
    - L5: Long toe extensors
    - S1: Ankle plantar flexors
    - S4–5: Rectal tone
  - Sensory: T4-nipple line, T10-umbilicus
- Tetraplegia results from cervical region injury.
- Paraplegia results from injury to the thoracic, lumbar, or sacral segments; conus medullaris; or cauda equina.
- Spinal cord syndromes
  - Complete
    - Loss of all sensory and motor function.
    - Reflexes initially flaccid, but hyperreflexia develops over time.
    - Autonomic pathways are disrupted, resulting in urinary, rectal, and sexual dysfunction.
  - Incomplete syndromes
    - Brown–Séquard syndrome (hemisection of cord)
    - *Ipsilateral motor weakness and proprioception/vibration loss
    - *Contralateral pain and temperature loss
    - Central cord syndrome
    - *Weakness of arms greater than legs due to involvement of anterior horn cells. Limited bladder control may also result
    - *Pain/temperature loss at level of injury
    - *Reflexes decreased in arms; normal-to-hyperactive in legs
    - *Frequently occurs with hyperextension injuries in the elderly due to cervical spondylosis
    - Anterior cord syndrome
    - *Weakness from the involvement of corticospinal tracts and anterior horn cells
    - *Disruption of spinothalamic pathways results in loss of pain, temperature, and light touch, with sparing of proprioception/vibration
    - *Reflexes initially flaccid, but hyperreflexia develops over time
    - *Autonomic pathways are disrupted
    - Posterior cord syndrome
    - *Motor pathways are intact
    - *Dorsal column impairment resulting in proprioception/vibration loss and a sensory ataxia
    - Cauda equina syndrome
    - *Motor involvement results in rectal and bladder paralysis
    - *Sensory loss in area supplied by nerve roots
    - *Reflexes usually are flaccid
- American Spinal Injury Association (ASIA) Impairment Scale describes the extent of spinal cord injury:
  - A = Complete: No preserved motor or sensory function
  - B = Incomplete: Motor function absent, sensation preserved below the neurological level
  - C = Incomplete: Motor function below the neurological level with <50% key muscle grades ≥3/5
  - D = Incomplete: Motor function below the neurological level with ≥50% key muscle grades ≥3/5
  - E = Normal: Motor and sensory function

DIAGNOSTIC TESTS AND INTERPRETATION

Lab
CBC, PT, PTT, international normalized ratio, glucose

Imaging
- Spinal CT of bony structures if abnormalities are present on conventional imaging. Plain x-rays are felt to miss many spinal fractures. Trauma guidelines generally suggest CT as a first-line assessment.
- Spinal MRI of spinal cord and intervertebral and paravertebral soft tissue.

Diagnostic Procedures/Other
Cervical magnetic resonance angiography to assess integrity of vertebral arteries with cervical injury. CTA may also be considered.

- Head CT or MRI should be done if traumatic brain injury is suspected.
- Traction for cervical injury may be necessary depending on fracture morphology. There is no indication for traction in thoracic or lumbar spine.

DIFFERENTIAL DIAGNOSIS
- Transverse myelitis, myelopathy
- Spinal cord ischemia
- Brachial plexopathy
- SCIWORA—Spinal cord injury without radiographic abnormality; more likely to occur with pediatric population, often in a delayed fashion. Obtain full spinal CT and MRI imaging to assess for bony or soft tissue injury. Instability may be present requiring long-term immobilization with bracing. May be due to ligamentous laxity in children.

TREATMENT

MEDICATION
- Acute injury
  - Methylprednisolone—very controversial. Associated risks may outweigh any benefit.
  - Keep systolic blood pressure >90 mm Hg; use fluids or vasopressors for shock and hypotension.
- Pain
  - Neuropathic pain: Gabapentin, pregabalin, carbamazepine, phenytoin, or tricyclics.
  - Musculoskeletal pain: Narcotics acutely, nonsteroidal antiinflammatory drugs.
- Deep vein thrombosis
  - Prophylaxis: Enoxaparin (Lovenox) 30–60 mg b.i.d., SQ heparin 5,000 U b.i.d.
  - Treatment: Anticoagulation with heparin, then coumadin. If contraindicated, inferior vena cava Greenfield filter is necessary.
- Spasticity
  - Useful drugs: Gabapentin, baclofen, tizanidine, diazepam, dantrolene sodium.
  - Intrathecal baclofen pumps are helpful for excessive spasticity.
- GI issues
  - Ileus/gastric motility: Metoclopramide 10 mg q.i.d., erythromycin 250 mg b.i.d.
  - Ulcer prophylaxis: H2 receptor antagonists or sucralfate. Data unclear for this need.
  - Bowel program: Adequate fluid, diet, and activity level, stool softeners, and glycerin or bisacodyl suppositories.

- Contraindications: Hypotension worsens clinical outcome.
- Precautions: Monitor closely for pulmonary complications, deep vein thrombosis, infections, and skin care.

ADDITIONAL TREATMENT

General Measures

Early immobilization of the spine is mandatory. A detailed neurological examination, including rectal tone, is necessary to identify level and completeness of injury.

- High-dose steroids (very controversial): Methylprednisolone, initial bolus 30 mg/kg over 1 hour.
  - Follow with continuous infusion of 5.4 mg/kg/hour for 23 hours if treatment is started within 3 hours of injury. Continue for 48 hours if treatment is started 3–8 hours after injury.
  - No indication for high-dose steroids beyond the 8-hour time window.
  - The data suggests that associated risks (e.g., sepsis, pneumonia) outweigh any benefit.
- Neurogenic shock
  - Autonomic reflexes lost in high/mid cervical injury disrupting sympathetic tone.
  - Decreased peripheral vascular tone results in expanded vascular space and relative hypovolemia, with hypotension, bradycardia, and warm dry skin.
  - Monitor volume status carefully, with appropriate use of vasopressors.
- Spinal shock
  - Loss of tone and spinal reflexes below level of injury. Duration is 2–4 weeks.
  - Considered to be over upon return of bulbocavernosus reflex, after which persistent deficits are likely to be relatively permanent.
- Pulmonary complications
  - High tetraplegics require ventilatory support and/or phrenic nerve pacemakers.
- Pain management
  - Differentiation required between neuropathic and musculoskeletal pain.
  - Gabapentin rather than narcotics should be considered for neuropathic pain.
- Autonomic dysreflexia
  - Noxious stimuli below the lesion level result in sympathetic discharge with hypertension, reflex bradycardia, sweating, headache, flushing, and piloerection.
  - Noted in 45–85% of injuries at or above T6; onset $\geq$2 months after injury.
  - Common causes:
    - Bladder and/or bowel distention
    - Pressure ulcers, skin infections
    - Urinary tract infections
    - Uterine contractions during labor and delivery
  - Management:
    - Identify and treat underlying inciting factor
    - Raise head of bed and treat hypertension pharmacologically
- General care
  - Prophylaxis for deep vein thrombosis.
  - Early tracheostomy is usually needed for mid cervical or higher spinal cord injuries.
  - Gastrointestinal care: Nasogastric tube to manage ileus prior to return of GI motility; bowel program.
  - Monitor for spasticity; early ranging and medications may prevent contractures.
  - Prevent decubitus ulcers.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Sequelae of trauma may require treatment of orthopedic, internal, and pulmonary injuries; spasticity, and pain.
- Adjunctive treatment
  - Rehabilitation services: Physical, occupational, and speech therapy; neuropsychological counseling.
  - Hypothermia—experimental. To date, there is no conclusive data for or against its use.

SURGERY/OTHER PROCEDURES

- Immobilization or bracing is frequently used to facilitate fracture healing. Multiple brace options exist including Miami J, Aspen, Minerva, Jewett, and thoraco-lumbo-sacral orthosis braces.
- Cervical traction is generally warranted if misalignment results from injury. Traction is also needed for perched or fully dislocated facets. Must be undertaken with care to not cause further injury (extension of cord injury, hematomas, herniation of disks).
- Early surgery warranted for locked and dislocated facet joints or marked spinal instability or deformity that does not respond to closed realignment.
  - Decompress and prevent further injury to neural elements to maximize recovery.
  - Fusion procedures are often necessary to facilitate recovery.
  - Prevent delayed spinal instability and deformity.
  - Allow early mobilization and rehabilitation.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Any evidence of spinal cord injury warrants admission; transfer to specialized rehabilitation services when the patient is stabilized.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Long-term monitoring by neurosurgery, neurology, and rehabilitation for delayed complications

PATIENT EDUCATION

- American Spinal Injury Association, 2020 Peachtree Road, NW, Atlanta, GA 30309. Phone: 404-355-9772; website: www.asia-spinalinjury.org
- Foundation for Spinal Cord Injury Prevention, Care & Cure, 13426 Golden Circle, Genton, Michigan 48430. Phone: 800-342-0330; website: www.fscip.org

PROGNOSIS

- Clinical course is based on level of injury
  - High tetraplegia (C1–C4).
    - Requires long-term ventilatory support.
  - C5: Functional biceps allows greater independence through splinting and orthotics. Generally able to feed self and assist with upper body dressing.
  - C6: Presence of wrist extension allows use of tenodesis for greater hand use.
    - Generally able to feed self and perform oral–facial hygiene.
  - C7: Triceps function significantly increases independence.
    - Most are independent with dressing and bowel and bladder management.
  - Thoracic and lumbar paraplegia.
    - Should achieve full independence with self-care and wheelchair mobility.
- Prognosis for ambulation recovery based on assessment at 1 week:
  - ASIA A: 80–90% remain complete; only 3–6% recover functional leg strength.
  - ASIA B: 50% become ambulatory.
  - ASIA C: 75% become community ambulators.
  - ASIA D: 95% become community ambulators.
- Equipment needs
  - Proper wheelchair positioning, cushions
  - Bracing may assist with ambulation
- Sexual function
  - Education and counseling are essential.
  - Adaptive strategies, alternative techniques, mechanical devices, and medications may be useful.
- Psychological
  - Depression in 25–50%.
  - Chemical dependency in up to 50%.
  - Counseling should be available.

ADDITIONAL READING

- American Spinal Injury Association (ASIA). *Standards for neurological and functional classification of spinal cord injury*. Chicago, IL: ASIA, 1992.
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- Consortium for Spinal Cord Medicine. *Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals*. Paralyzed Veterans of America, Washington, DC, 1999.
- Yarkony GM. Spinal cord rehabilitation. In: Lazar RB, ed. *Principles of neurologic rehabilitation*. New York, NY: McGraw-Hill, 1998:121–141.

CODES

ICD9

- 952.00 C1-C4 level with unspecified spinal cord injury
- 952.9 Unspecified site of spinal cord injury without evidence of spinal bone injury
- 952.10 T1-T6 level with unspecified spinal cord injury

TRICHINOSIS

Barbara S. Giesser, MD

BASICS

DESCRIPTION

Trichinosis is the systemic illness that results from infestation with larvae of the nematode worm *Trichinella sp*. It may consist of general, gastrointestinal, neurological, cardiac, and respiratory manifestations.

EPIDEMIOLOGY

- Incidence in the US has been declining over the past 50 years.
- Currently, cases in the US occur in average <40 years of age.
- May be acquired by traveling in foreign countries.

RISK FACTORS

- Consumption of undercooked pork or wild game such as deer, bear, horse meat, or *crocodile* which contain larvae of *Trichinella sp*.

GENERAL PREVENTION

- Recommendations are to cook pork and game meats until well done (not pink), to reach internal temperatures of at least *71° C (160° F) for at least 1 minute*
- *Appropriate farming methods of pigs*
- *Appropriate freezing and curing methods to render at-risk meat safe*.

Pregnancy Considerations

- There are reports of trichinosis being transmitted *in utero* from mother to fetus.
- Maternal trichinosis has been associated with spontaneous abortion. Lactation has been reported to be suppressed in postpartum women with trichinosis.

ETIOLOGY

- Invasion of tissue by worm larvae

PATHOPHYSIOLOGY

- Inflammatory response to infection
- *Parasite promotes Th2 cytokine shift in host*
- After the ingested cyst wall is digested in the stomach, the larvae are released and enter the general circulation from the gut. Although they may invade multiple organ systems, they encyst in striated muscle and may persist there for many years. An allergic vasculitis may occur and is responsible for edema and hemorrhage.

DIAGNOSIS

HISTORY

- The diagnosis is suggested by the symptom complex of fever, malaise, *diarrhea, abdominal pain* myalgia, and periorbital edema.
- *History of ingesting undercooked pork or game*
- The incubation period for the appearance of generalized symptoms from time of ingestion varies from approximately 1 day to 7 weeks, with earlier appearance of symptoms generally presaging a more severe course.

PHYSICAL EXAM

- Fever, malaise
- Cramping, diarrhea
- Periorbital edema
- Subconjunctival hemorrhages
- Myocarditis
- Maculopapular rash
  – Neurological
- Myalgia
- Muscles painful to palpation
- Pain occurring at rest but worse with movement
- Limbs, extraocular muscles, tongue, respiratory, neck muscles
- Weakness and stiffness in affected muscles
- CNS involvement occurs in 10–20% of cases and may result from direct invasion of tissue by larvae, obstruction of blood vessels by larvae, toxic vasculitis, or acute host hypersensitivity reaction. In untreated patients with neurological manifestations, mortality may be as high as 50%.
- Headache
- Seizures
- Meningitis/encephalitis
- Cerebrovascular thrombosis/infarction
- Tinnitus/decreased hearing
- *Diplopia, facial paresis*
- Polyradiculoneuritis

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Blood tests

- Eosinophilia
  – Elevated muscle enzymes
  – Hypoalbuminemia
  – Leukocytosis
  – *ELISA test for Trichinella Ab; immunoblot to confirm + ELISA*

Imaging

Neuroimaging may reveal focal areas of infarction, hemorrhage, or thrombosis and in cases where there has been larval invasion of the brain. In some cases, larvae may be found in spun samples of CSF. In cases of pulmonary complications, there may be pneumonia or pleural effusion present on chest x-ray film. MRI of skeletal muscles may show cysts but has not been assessed as a diagnostic test for this indication.

Diagnostic Procedures/Other

- The definitive test for trichinosis is the presence of *Trichinella sp*. larvae in muscle biopsy of the affected individual. Biopsy may be positive as early as 2 weeks after infection. Serologic tests may become positive 2–8 weeks after initial infection.
- ECG
  – T wave changes, e.g., inversion
  – Decreased QRS voltage
  – ST-segment depression
  – Premature ventricular contractions
  – Conduction disturbances
  – *Echocadiogram can demonstrate pleural effusion*

DIFFERENTIAL DIAGNOSIS

- Typhoid fever
- Food poisoning
- Leptospirosis
- Periarteritis nodosa
- Dermatomyositis
- Poliomyelitis
- Meningitis/encephalitis

TREATMENT

MEDICATION

- Intestinal phase
  - Mebendazole (Vermox®) 200–400 mg PO t.i.d. for 3 days, followed by 400–500 mg PO t.i.d. for 10 days
  - Albendazole (Zentel®) 400 mg b.i.d. *for 8–14 days*
  - *Pyrantel (Combantrin®) may be used in pregnant women and young children at doses of 10–20 mg/kg/day for 2–3 days but only affects intestinal nematodes and not muscle larvae*.
  - Corticosteroids 0.5–2.0 mg/kg/day in divided doses for 4–10 days
  - *Repletion of proteins and electrolytes*
- Contraindications: Albendazole and mebendazole are contraindicated for use in pregnant women and not recommended for use in children less than 2 years of age.
- Precautions
  - Side effects include neutropenia, abnormal liver function tests, myalgia, and fatigue.
  - In patients who develop allergic vasculitis or hypersensitivity reactions, steroids may be combined with antihelminthic treatment.

ADDITIONAL TREATMENT

General Measures

Other than specific treatment of complications, therapy is directed at stopping infection and eradicating the parasite within the host *(vide supra)*. Management of complications is symptom specific, e.g., anticonvulsant therapy for seizures. Corticosteroids may be indicated in moderate-to-severe cases of allergic vasculitis, e.g., prednisone at doses of 60–120 mg/day or higher if needed. Steroids should not be used *without concomitant administration of antihelminthics* in early cases (<6 weeks after ingestion) because they may prolong the presence of adult worms in the gut.

- Symptomatic treatment
  - Symptomatic therapy is aimed at specific complications. Fluids may be needed for dehydration or diuretics in cases of severe edema. Antiarrhythmics may be indicated in cases of cardiac complications. Rarely, with severe pulmonary involvement, assisted ventilation may be necessary. Myalgia may respond to conventional doses of salicylates or nonsteroidal antiinflammatory drugs. After the acute phase, physical or occupational therapy may be indicated to restore function in affected muscle.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

N/A

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with moderate or severe trichinosis need to be admitted primarily for the management of systemic manifestations and complications, e.g., dehydration or cardiopulmonary or CNS manifestations. The most common cause of death in trichinosis is myocarditis/cardiac failure, which most frequently occurs in weeks 4–8 of infection.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients should be monitored in the first few weeks of the illness for the development of neurological, cardiac, pulmonary, and respiratory complications. Patients may develop hypersensitivity reactions (*Jarisch–Herxheimer reaction*) as the result of larval death due to antihelminthic therapy.

PATIENT EDUCATION

Patients should be warned against eating raw or undercooked pork or wild game products, particularly when traveling abroad. They should be instructed in proper cooking and freezing procedures when home processing pork and game products.

PROGNOSIS

- Recovery is complete *in 2–6 months* in most cases.
- Encysted larvae in muscle may persist for up to decades and be asymptomatic.
- Rarely, there is a chronic syndrome that consists primarily of fatigue *and myalgia*.
- *May have up to 5% mortality.*

ADDITIONAL READING

- Clausen MR, Meyer CN, Krantz T, et al. Trichinella infection and clinical disease. *QJM* 1996;89: 631–636.
- Gottstein B, Pozio E, Nockler K. Epidemiology, diagnosis, treatment and control of *Trichinellosis*. *Clin Microbiol Rev* 2009:22(1):27–145.
- Gould SE. Symptomatology and diagnosis. In: Gould SE, ed. *Trichinosis in man and animals*. Springfield, Illinois: Charles C. Thomas Publisher, 1970: 269–307.
- MacLean JD. Trichinosis. In: Hoeprich PD, ed. *Infectious diseases: a treatise of infectious processes*, 4th ed. Philadelphia: JB Lippincott, 1994:1377–1380.
- Pawlowski ZS. Clinical aspects in man. In: Campbell WC, ed. *Trichinella and trichinosis*. New York: Plenum Press, 1983:367–398.

See Also (Topic, Algorithm, Electronic Media Element)

Trichinellosis

CODES

ICD9

124 Trichinosis

TRIGEMINAL NEURALGIA

Benjamin Miller, MD
Thomas C. Chelimsky, MD

BASICS

DESCRIPTION

Trigeminal neuralgia is a clinical syndrome characterized by recurrent paroxysmal lancinating pain in the trigeminal distribution. The pathogenesis in most cases is idiopathic, but may be caused by a local lesion.

EPIDEMIOLOGY

- Incidence/prevalence
  - 4–5 per 100,000 population
- Age
  - Trigeminal neuralgia usually occurs after age 40 years
- Sex
  - Slightly greater incidence in females

RISK FACTORS

Pregnancy Considerations

Currently, there is no particular relation of trigeminal neuralgia with pregnancy.

ETIOLOGY

- The pathogenesis of trigeminal neuralgia is unclear and probably multifactorial.
- Cerebellopontine tumors, schwannoma, multiple sclerosis, or other lesion involving or near the trigeminal nerve or its nucleus may cause trigeminal neuralgia in a minority of cases.
- The proposed theories of pathogenesis for both the idiopathic and symptomatic cases focus on aberrant repetitive discharges that could arise from the involved nerve.
  - The vascular compression theory holds that a tortuous artery or vein near the trigeminal nerve compresses the nerve root. The compression increases with age and causes changes in the sensory root entry zone that result in prolongation of electrical impulses in the nerve and reexcitement of the axon leading to repetitive neuronal discharges.
  - Localized magnetic induction currents caused by the blood vessels around the nerve may cause focal irritation.
  - Inflammation near or in the trigeminal nerve.

COMMONLY ASSOCIATED CONDITIONS

- Multiple sclerosis
- Brainstem neoplasm
- Vascular compression/vertebrobasilar dolichoectasia
- Trigeminal schwannoma
- Cerebropontine angle tumors: Acoustic neuroma, meningioma
- Metastatic infiltration of the base of the skull
- Cavernous sinus lesions: Cavernous carotid aneurysm, meningioma, pituitary adenoma, Tolosa-Hunt syndrome, metastasis

DIAGNOSIS

- The characteristic pain in trigeminal neuralgia is a paroxysmal, sharp, shooting, or lancinating pain in the distribution of 1 or more divisions of the trigeminal nerve, most commonly in the second and third divisions.
- Pain classically consists of a burst of multiple very brief sharp jabs, each lasting <1 second but occurring in rapid succession repeatedly for a period of a few seconds to 1 minute. The pain may be excruciating to the point of deep depression or even suicide.
- The pain is triggered by sensory stimuli to the skin, mucosa, or teeth within the area innervated by trigeminal nerve. Pain sometimes can be initiated by chewing, brushing the teeth, or talking.
- In classic idiopathic trigeminal neuralgia, the neurological examination is normal. There is no sensory or motor impairment in the trigeminal distribution.
- When trigeminal neuralgia results from a lesion involving the trigeminal nerve roots or ganglion, the neurological examination may show sensory deficits in the trigeminal distribution, weakness or atrophy of the muscles of mastication, or abnormalities in the adjacent cranial nerves, depending on the location.
- Atypical trigeminal neuralgia is characterized by atypical characteristics of pain (e.g., no bursts, continuous pain) or an abnormal neurological examination that would prompt investigations for an associated structural lesion.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- In classic trigeminal neuralgia, there are no accompanying laboratory or radiographic abnormalities. Blink reflexes are normal.
- Additional laboratory tests may be required for other disorders in the differential diagnosis of facial pain such as ESR for temporal arteritis or x-ray film of sinus or temporomandibular joint.

Imaging

- Neuroradiologic imaging is recommended in patients undergoing surgical treatment for trigeminal neuralgia, those with atypical trigeminal neuralgia, or those with any associated neurological deficit compatible with an underlying structural lesion.
- In the case of trigeminal neuralgia due to structural lesions such as meningioma, schwannoma of the trigeminal nerve, or infiltration of the base of skull by malignant tumors, CT or MRI with contrast may reveal a lesion along the pathway of trigeminal nerve.
- In idiopathic trigeminal neuralgia, neuroimaging is normal.

DIFFERENTIAL DIAGNOSIS

- Need to differentiate from *other causes of pain or cranial pain*
  - Neuralgia
    - Glossopharyngeal neuralgia
    - Atypical neuralgia
  - Migraine headaches
  - SUNCT (sudden unilateral headache with nasal congestion and tearing)
  - Cluster headache
  - Temporal arteritis
  - Musculoskeletal pain
    - Temporomandibular joint pain
    - Myofascial pain syndrome
  - Local diseases
    - Ocular and periocular diseases, e.g., uveitis, orbital tumor, orbital cellulitis
    - Nasal and paranasal sinus diseases
    - Odontogenic diseases

TREATMENT

MEDICATION

Carbamazepine is the most effective medication, with pain relief achieved in 75% of patients.

- Dosage
  - Medication may be started at a small dose of 50–100 mg twice per day to prevent side effects and increased slowly as tolerated. Usual therapeutic doses range from 600 to–1,200 mg/day, with the therapeutic drug level of 40–100 g/mL.
- Side effects
  - Common side effects include drowsiness, vertigo, nausea, and ataxia.
- Contraindications: History of previous bone marrow depression, hypersensitivity to carbamazepine. Combination with monoamine oxidase (MAO) inhibitors is contraindicated. MAO inhibitors should be discontinued for 14 days before starting carbamazepine.
- Precautions: Hyponatremia can occur. In patients taking carbamazepine, CBC should be taken in the first few months and periodically because of increased risk for aplastic anemia and agranulocytosis. Liver function tests should also be periodically checked.
- Alternative drugs
  - Oxcarbazepine has been found to be as effective as carbamazepine and may become the preferred drug mainly because of the absence of aplastic anemia as a complication, starting at 150 mg b.i.d. and increasing by 300 mg total daily dose per week until optimal effect or to a maximum dose of 1200 mg/day.
  - Alternative medications are levitriacetam, pregabalin, phenytoin, baclofen, gabapentin, valproate, mexiletine, and clonazepam, which are generally less effective than carbamazepine but may be effective in particular individuals.
  - It is suggested that alternatives should only be tried after failure of a trial of both carbamazepine and oxcarbamazepine.

ADDITIONAL TREATMENT

General Measures

Initial management begins with a trial of carbamazepine or oxcarbazepine. Other agents listed in the "Medications" section can be tried alone or in combination. Approximately 25–50% of patients eventually will fail to respond to drug therapy and require intervention.

SURGERY/OTHER PROCEDURES

- Surgical measures are reserved for patients with
  - Surgical lesions
  - Inadequate response to nonsurgical treatment
  - High-dosage medication requirement with intolerable side effects
- Extracranial peripheral denervation
  - Temporary denervation or blocks of the peripheral branches of trigeminal nerve
  - Nerve block performed at supraorbital, infraorbital, or mental foramen with alcohol or lidocaine
  - Advantages: May be performed in the office. The area of denervation is focal and small. The corneal does not become denervated and permanent dysesthesias are unlikely. Major complications are rare
  - Disadvantages: The procedure is very painful when it is performed without sedation or analgesia in the office
  - Even with the more permanent peripheral denervations, pain commonly returns within 6–18 months
- Percutaneous denervation of gasserian ganglion and retrogasserian ganglion rootlets
  - Several methods may produce partial denervation of the trigeminal ganglion or its rootlets. A specially designed device is inserted under radiographic control into the cheek, through the foramen ovale, into the gasserian or retrogasserian ganglion. Partial destruction of the trigeminal nerve then is accomplished with radiofrequency thermocoagulation or glycerol. The procedure results in loss of sensation in the distribution of the trigeminal nerve. Return of pain may be worse than the original symptom complex
- Botulinum toxin injections
  - Injection of botulinum A toxin had been shown previously effective for migraine headaches, marginally effective in trigeminal neuralgia
  - Injection only to the subcutaneous sites of pain, no direct injection to the trigeminal nerve itself
  - Effect is only temporary and wears off requiring further intervention, currently requiring further study in the literature
- Gamma Knife radiosurgery
  - Less invasive than other modalities of direct intervention on the trigeminal nerve, must have identifiable lesion on contrast MRI to allow for proper procedural targeting of the trigeminal nerve
  - Complete pain relief in >60% in single study with long-term follow-up
  - Over half of the patients with complete relief had regression to pre-treatment pain levels over a 5-year period
- Percutaneous radiofrequency thermocoagulation
  - Initial pain relief occurs in >90% of the patients, with recurrence in 22% at 2–6 years and up to 80% with long-term (12 years) follow-up
  - Severe dysesthesia follows the procedure in 2–10% of the patients. Denervation of cornea and keratitis occur in 1–3% of patients
- Glycerol trigeminal rhizolysis
  - Injection of sterile glycerol into the gasserian ganglion and retrogasserian rootlets instead of radiofrequency thermocoagulation
  - Glycerol is a mild denervating agent producing milder denervation with presumably fewer complications such as dysesthesia or keratitis. With mild denervation, the recurrence rate is high (28% after 1 year and 50% after 47 months)
- Microvascular decompression
  - Procedure is based on the proposed mechanism that trigeminal neuralgia results from chronic vascular compression of the trigeminal nerve at the root entry zone.
  - Procedure is performed through a suboccipital retromastoid craniectomy. The trigeminal nerve then is decompressed by placing a synthetic material, usually a Teflon felt, between the nerve and the vessel.
  - One year after the procedure, 75% have pain relief and 9% have partial relief, After 10 years, 64% continue with excellent results and 4% with partial relief of pain
  - Death occurs in 0.2–2.4% of patients, and other major intracranial complications occur in 1–2% of patients. Hearing loss occurs in 1–2% of patients. Facial weakness occurs in approximately 1% of patients, and burning and aching facial pain occurs in 3.3–4.8% of patients.
- Choosing the surgical procedure
  - Due to the invasiveness of microvascular decompression, radiofrequency thermocoagulation or other less invasive procedures are preferred in patients with (i) older age, (ii) significant medical illness, (iii) contralateral hearing loss, (iv) previously good results with radiofrequency thermocoagulation, or (v) multiple sclerosis

IN-PATIENT CONSIDERATIONS

Admission Criteria

Admission may be required when pain is so severe that it has resulted in dehydration. Intravenous valproic acid or a lidocaine drip may be required to control pain. Opiates are usually ineffective and should not be tried.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Neurological examination should be performed periodically. A neurological deficit suggests an occult structural lesion.

PATIENT EDUCATION

- TNA Facial Pain Association, 408 W. University Avenue, Suite 602, Gainesville, FL 32601; phone: 800-923-3608 or 352-384-3600, fax: 352-384-3606; website: http://www.fpa-support.org

PROGNOSIS

- The clinical course is exacerbating and remitting over many years. Spontaneous remission may occur at any time and last for months or years.
- Medications should be tapered periodically to uncover a remission.

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CODES

ICD9

350.1 Trigeminal neuralgia

TUBERCULOSIS

Ersin Tan, MD

BASICS

DESCRIPTION

Tuberculous involvement of the nervous system occurs as meningitis, encephalitis, tuberculoma, spinal arachnoiditis, tuberculous brain abscess, or rarely in other forms such as acute disseminated encephalomyelitis.

EPIDEMIOLOGY

- Incidence/prevalence
  - CNS disease caused by mycobacterium tuberculosis is an uncommon yet highly devastating manifestation of tuberculosis. CNS tuberculosis accounts for approximately 1% of all cases of tuberculosis and 5–10% of extrapulmonary tuberculosis cases.
  - Tuberculous meningitis develops in 1–2% of tuberculosis cases. Immunodeficiency increases the incidence. From 5 to 10% of AIDS patients have tuberculosis, and up to 10% of these patients develop CNS involvement.
- Race
  - American Indians have higher rates than African Americans, who in turn have higher rates than Caucasians.
- Age
  - Seen at any age, but peaks in the pediatric and elderly populations.
- Sex
  - More common in males than females.

RISK FACTORS

- Immunodeficiency
- HIV infection
- Hematologic and reticuloendothelial malignancies
- Immunosuppressive therapy
- Malnutrition
- Chronic renal failure
- Alcohol and drug abuse

Pregnancy Considerations

A pregnant woman with tuberculosis should be treated because the infection is more hazardous to the patient and fetus than are the drugs. Isoniazid, rifampin, and ethambutol cross the placenta but have not demonstrated teratogenic effects. Streptomycin can cause congenital deafness. There are no adequate data on pyrazinamide. Tuberculosis during pregnancy is not an indication for therapeutic abortion.

ETIOLOGY

Mycobacterium tuberculosis is an aerobic, nonmotile, nonspore forming, acid-fast bacillus. Transmission of the disease from person-to-person is through air. Bacilli are expelled as droplet nuclei from patients while they are coughing, sneezing, and talking. Droplet nuclei can stay in the air for hours before they enter the body through the respiratory tract or rarely through the skin and gastrointestinal tract. Bacilli reach the central nervous system by hematogenous dissemination from a primary focus.

DIAGNOSIS

- CNS tuberculosis mainly presents as 4 different clinical pictures.
  - *Tuberculous meningitis* results from hematogenous dissemination or, more frequently, rupture of granulomas into the subarachnoid space. The cause of the neurological symptoms is the thick fibrous exudate that especially fills the basal cisterns. Inflammation and compression of blood vessels cause cerebral infarctions. Cranial nerves traversing the exudate are affected. A communicating type of hydrocephalus commonly develops.
    - The onset of symptoms is subacute. Signs of meningeal irritation (headache, vomiting, neck stiffness) are preceded by a prodromal phase lasting 2–3 weeks. Prodromal symptoms are fatigue, night sweats, low-grade fever, anorexia, malaise, and myalgia. Altered consciousness follows meningeal irritation signs. Cranial nerve palsies, especially involvement of cranial nerves III, IV, and VI, are seen in 20–30% of patients. Papilledema, seizures, and hemiparesis occur in 10–15% of patients. Signs of pulmonary or extrapulmonary tuberculosis are often present. If not treated, coma and death occur within 5–8 weeks.
  - *Tuberculomas* are slow-growing granulomas that can be found in the cerebrum, cerebellum, brainstem, subarachnoid, subdural and epidural spaces, and rarely within the spinal cord. They more commonly arise as solitary lesions, but multiple tuberculomas are seen. They cause headache, seizures, and focal neurological deficits.
  - *Spinal arachnoiditis* usually follows intracranial meningitis. Resultant root and cord compression causes pain, paralysis, sensory loss, and sphincter disturbances.
  - *Tuberculous brain abscess*, which is a rare manifestation, develops either from parenchymal tubercular granulomas or via the spread of foci from the meninges. Although clinic manifestations largely depend on their location, patients often present with headache, seizures, papilledema, or other signs of increased intracranial pressure.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- Routine blood tests are nonspecific. Mild anemia, leukocytosis, and increased erythrocyte sedimentation rate are seen. Inappropriate antidiuretic hormone secretion can lead to mild-to-moderate hyponatremia in about half of the patients.
- From 50 to –75% of patients with tuberculous meningitis have a positive tuberculin skin test (purified protein derivative).

Imaging

- Chest x-ray film shows findings of pulmonary tuberculosis in about 50–90% of patients with meningitis.
- Cranial CT with contrast and postgadolinium magnetic MRI demonstrate uniform and intense enhancement of basal cisterns and meninges early in the disease.
- Hydrocephalus is seen as the disease evolves, more commonly in children. Serial CT examinations help to follow the progression of hydrocephalus.
- Tuberculomas are seen as hypodense, avascular, solid, or ring-enhancing lesions on CT scans. Occasionally they may have central calcification surrounded by a hypodense area with ring enhancement (target sign). On MRI, tuberculomas appear isointense to gray matter on T1-weighted images and are either hyperintense (noncaseating lesions) or isointense to hypointense (caseating tuberculomas) on T2-weighted images. They may have surrounding edema. Tuberculomas tend to be infratentorial in children but supratentorial in adults.

Diagnostic Procedures/Other

- CSF examination is the most important investigation. CSF pressure is increased, usually over 300 mm H_2O, and there is pleocytosis. Polymorphonuclear leukocytes predominate in the earlier stages. Lymphocytic pleocytosis is seen within 24–48 hours. White cell count is between 100 and 400 cells/mm^3. CSF protein concentration is high (between 100 and 200 mg/dL) and glucose is decreased (<45 mg/dL). Acid-fast bacilli can be detected by Ziehl–Neelsen stain on CSF examination. The chance of detection of acid-fast bacilli increases with repeated examinations.
- CSF cultures reveal the microorganism in 50–60% of patients; however, it takes several weeks to obtain the results. Cultures are important for drug sensitivity studies.
- Detection of bacterial DNA with polymerase chain reaction amplification is more sensitive than cultures and provides results within 24–72 hours.
- The detection of mycobacterium tuberculosis-specific antibodies in the CSF is rapid, but the techniques are limited by the inability to differentiate acute infection from previous one and problems with cross-reactivity.
- In tuberculomas without meningitis, CSF is either normal or may show lymphocytic pleocytosis with elevated protein and normal glucose.

DIFFERENTIAL DIAGNOSIS

- Fungal or viral meningitis
- Partially treated bacterial meningitis
- Parasitic infections (cysticercosis, toxoplasmosis)
- Carcinomatous meningitis
- Neurosyphilis
- Sarcoidosis
- Pyogenic brain abscess

TREATMENT

MEDICATION

- Multiple-drug therapy is necessary because of the possibility of resistant strains of bacteria. Isoniazid and pyrazinamide are the key components of the regimen. Isoniazid penetrates the CSF freely and has potent early bactericidal activity. Rifampicin penetrates the CSF less well (maximum concentrations around 30% of plasma), but the high mortality from rifampicin-resistant tuberculous meningitis has confirmed its central role in the treatment of CNS disease. Penetration of rifampin, streptomycin, and ethambutol through noninflamed meninges is poor.
- British Infection Society guidelines for the treatment of CNS tuberculosis recommends 4 drugs (isoniazid, rifampicin, pyrazinamid, ethambutol) for 2 months followed by 2 drugs (isoniazid, rifampicin) for at least 10 months for all forms of CNS tuberculosis (1)[A].
  - Isoniazid: Daily dose 300 mg in adults, 10–20 mg/kg (maximum 500 mg) in children, oral, for 12 months).
  - Rifampicin: Daily dose 450 mg (<50 kg) and 600 mg (≥50 kg) in adults, 10–20 mg/kg (maximum 600 mg) in children, oral, for 12 months).
  - Pyrazinamide: Daily dose 1.5 g (<50 kg) and 2 g (≥50 kg) in adults, 30–35 mg/kg (maximum 2 g) in children, oral, for 2 months).
  - Ethambutol: 15 mg/kg in adults, 15–20 mg/kg (maximum 1 g) in children, oral, for 2 months.
  - Although it has been suggested that short-duration (6 months) treatment is as effective as long-duration treatment, it is recommended to continue for 12 months prompted by the uncertain influences of disease severity, CNS drug penetration, undetected drug resistance, and patient compliance on response to therapy.
- All patients with suspected or proven tuberculosis should be offered testing for HIV infection. The treatment principals for HIV-infected and -uninfected individuals are the same, however, since anti-retroviral treatment can complicate the management, a combined approach between HIV and tuberculosis experts is needed.
- British Infection Society guidelines recommend that all patients with tuberculous meningitis receive adjunctive corticosteroids regardless of disease severity at presentation.
- Adults (>14 years) should start treatment with dexamethasone 0.4 mg/kg/day with a reducing course over 6–8 weeks. Children (≤14 years) should be given prednisolone 4 mg/kg/day (or equivalent dose dexamethasone: 0.6 mg/kg/day) for 4 weeks, followed by a reducing course over 4 weeks. Although there is insufficient evidence to recommend routine corticosteroids for tuberculomas without meningitis or with spinal cord tuberculosis, they may be helpful when the symptoms are not controlled or are worsening under treatment or may help those who have acute spinal cord compression due to vertebral tuberculosis.
- Contraindications: Drug allergy
- Precautions
  - Side effects
    - Isoniazid causes an axonal sensorimotor polyneuropathy by interfering with pyridoxine metabolism. Supplemental pyridoxine should be administered. Slow acetylators of the drug are more susceptible to neuropathy, whereas fast acetylators are prone to hepatotoxicity. Rifampin causes orange discoloration of body fluids, leukopenia, thrombocytopenia, and hemolytic anemia. Streptomycin is ototoxic, and ethambutol carries a risk of optic neuropathy.
- Alternative drugs
  - If resistance or allergy to the standard regimen exists, susceptibility studies should guide treatment.

ADDITIONAL TREATMENT

General Measures

Routine supportive care of the unconscious or paralyzed patient, maintenance of fluid and electrolyte balance and nutrition, and care of urinary bladder are important.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Symptomatic treatment for headaches, vomiting, fever, and seizures is necessary.

SURGERY/OTHER PROCEDURES

- Indications for neurosurgical referral are hydrocephalus, tuberculous cerebral abscess, and vertebral tuberculosis with paraparesis.
- Early ventriculo-peritoneal shunting should be considered in noncommunicating hydrocephalus and in communicating hydrocephalus failing medical management. Communicating hydrocephalus may be initially treated with furosemide (40 mg/day adults) and acetazolamide (1–20 mg/kg adults) or repeated lumbar punctures.
- Urgent surgical decompression should be considered in all patients with extradural lesions causing paraparesis.
- Surgery for tuberculomas is indicated in the presence of intolerably high intracranial pressure or in medical failures.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Tuberculosis patients with neurological involvement must be hospitalized.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Repeat lumbar punctures are necessary to monitor response to treatment, and CSF pressure should be measured. Serial CT scans are used to follow hydrocephalus and resolution of tuberculomas. Patients receiving isoniazid should be followed monthly for hepatotoxicity. Color vision and visual acuity should be followed in patients receiving ethambutol, and patients should be asked to report any decrease in acuity.

PATIENT EDUCATION

- Centers for Disease Control and Prevention. Website: www.cdc.gov/nchstp/tb/faqs/qa.htm
- American Thoracic Society. Website: www.thoracic.org/statemnt.html

PROGNOSIS

- Tuberculosis of the CNS is associated with higher mortality rates than other forms of tuberculosis.
- Although discovery of antituberculosis agents increased survival, tuberculosis meningitis still carries a 20% mortality risk. The prognosis mainly depends on the severity of findings at the initiation of therapy. Empiric therapy should be started as soon as tuberculosis meningitis is suspected. Other factors that affect the prognosis are
  - Age of the patient (children and the elderly have worse prognosis)
  - Nutritional status
  - Presence of miliary tuberculosis
  - Presence of hydrocephalus or cerebral infarction

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CODES

ICD9

- 011.90 Pulmonary tuberculosis, unspecified, unspecified
- 013.00 Tuberculous meningitis, unspecified
- 013.60 Tuberculous encephalitis or myelitis, unspecified

TUBEROUS SCLEROSIS

S. Anne Joseph, MD
Sunila O' Connor, MD

BASICS

DESCRIPTION

The tuberous sclerosis complex is a multisystem autosomal dominant neurocutaneous syndrome that most commonly affects the brain, eye, skin, kidneys, and heart. The clinical manifestations of tuberous sclerosis can be identified in organs derived from all primary stem cell lines, e.g., ectoderm, endoderm, and mesoderm.

EPIDEMIOLOGY

Tuberous sclerosis occurs in about 1 in 5800 live births. An estimated 1 million individuals are affected worldwide.

RISK FACTORS

Genetics

Tuberous sclerosis is inherited in an autosomal dominant fashion, with a penetrance of almost 100%. The disorder is characterized by the presence of hamartomas in multiple organ systems caused by an inactivating mutation in 1 of the tumor suppressor genes, TSC1 or TSC2. TSC1, on chromosome 9q34, encodes for the protein harmatin. TSC2, on chromosome 16p13.3, encodes for the protein tuberin. Harmatin and tuberin work together to inhibit the pathway involving the mammalian target of rapamycin (mTOR) and a cascade of other factors that stimulate protein translation, cell growth and proliferation. mTOR exists as 2 complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), each with differing functions. When a tuberous sclerosis complex (TSC) mutation is present, a source of inhibition of mTORC1 is absent that causes abnormal cellular proliferation and differentiation, thus producing harmatomatous lesions. Approximately 50% of tuberous sclerosis families show genetic linkage to TSC2 and 50% to TSC1. Approximately 60% of patients have no prior family history and represent new mutations.

COMMONLY ASSOCIATED CONDITIONS

- Mental retardation: Mental function varies greatly among patients with tuberous sclerosis. Although mental retardation is a characteristic of the disease, approximately 30% of patients have normal intelligence. The cognitive difficulties can range from profound retardation to mild learning problems.
- Seizures: Seizures can be refractory and can start in infancy. Seizures represent the most common symptom seen in this condition. The majority of children have seizure onset in the first year of life, and up to one third of them develop infantile spasms. Many have intractable epilepsy. Epileptogenesis in tuberous sclerosis complex implicates molecular changes in gamma-aminobutyric acid (GABA) receptors and glutamate receptors in dysplastic neurons resulting in decreased inhibition and increased excitation. The following seizure types can be seen in tuberous sclerosis:
  - Neonatal seizures
  - Infantile spasms: The importance of the GABAergic inhibitory system in seizures in the tuberous sclerosis complex is underscored by the particular efficacy of vigabatrin, an inhibitor of GABA transaminase, to stop spasms in 95% of tuberous sclerosis complex infants
  - Lennox–Gastaut syndrome
  - Simple and complex partial seizures
- Behavioral abnormalities
  - Hyperactivity
  - Aggression
- Autism and pervasive developmental disorder
- Malignant transformation
  - Giant cell astrocytoma
  - Renal cell carcinoma

DIAGNOSIS

- The clinical manifestations in tuberous sclerosis are varied. Hamartomas are the pathologic hallmark of the tuberous sclerosis complex. These lesions contain cells that have undergone abnormal differentiation but generally behave as benign tumors. The following are the revised diagnostic criteria for tuberous sclerosis.
- Major features
  - Facial angiofibromas or forehead plaque
  - Nontraumatic ungual or periungual fibroma
  - Hypomelanotic macules (3 or more)
  - Shagreen patch (connective tissue nevus)
  - Multiple retinal nodular hamartomas
  - Cortical tuber
  - Subependymal nodules
  - Subependymal giant cell astrocytoma
  - Cardiac rhabdomyoma, single or multiple
  - Lymphangiomatosis
  - Renal angiomyolipoma
- Minor features
  - Multiple randomly distributed pits in dental enamel
  - Hamartomatous rectal polyps
  - Bone cysts
  - Cerebral white matter radial migrational lines
  - Gingival fibromas
  - Nonrenal hamartoma
  - Retinal achromic patch
  - "Confetti" skin lesions
  - Multiple renal cysts
  - Definite tuberous sclerosis complex: Either 2 major or 1 major and 2 minor features
  - Probable tuberous sclerosis: 1 major plus 1 minor feature
  - Possible tuberous sclerosis: Either 1 major feature or 2 minor features
- The diagnosis is made clinically. Once the diagnosis is suspected, then additional studies should be done to screen the organ systems that are usually affected.
- Neurological symptoms can include seizures, developmental delay, mental retardation, autism or pervasive developmental disorder, or obstructive hydrocephalus. Renal manifestations can include hypertension or painless hematuria. Cardiac rhabdomyomas tend to be silent unless they cause rhythm or flow problems. These tend to involute with age.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

- The following diagnostic studies are recommended in the evaluation of a new patient with tuberous sclerosis.
- *Electroencephalogram:* This test is recommended for patients who present with episodes suggestive of seizures but is not particularly useful in the routine evaluation of a patient with tuberous sclerosis.
- *Electrocardiography:* Cardiac arrhythmias sometimes occur even in patients without a cardiac rhabdomyoma. A baseline study is recommended at the time of diagnosis or before surgery.

Imaging

- *MRI/cranial CT:* MRI may be the more sensitive test to determine the presence of cerebral hamartomas, subependymal nodules, radial migrational lines, and giant cell astrocytomas. Larger calcified lesions can be seen on CT scan.
- *Renal ultrasonography* for renal angiomyolipomas.
- *Echocardiography* reveals 1 or more cardiac rhabdomyomas in more than half the younger individuals with tuberous sclerosis. These tumors tend to involute dramatically and often disappear by adulthood. The most rapid reduction in size occurs in the first 3 years of life.

Diagnostic Procedures/Other

- *Molecular diagnosis:* The addition of DNA testing complements clinical diagnosis and allows prenatal diagnosis in some cases. The 15% false negative rate for DNA testing and the occurrence of germline mosaicism in about 2% of individuals with tuberous sclerosis make it difficult to exclude this diagnosis in family members using this method in isolation.
- *Ophthalmologic evaluation* for retinal hamartomas.
- Dermatologic evaluation.

TREATMENT

ADDITIONAL TREATMENT

General Measures

There is no specific treatment as yet for tuberous sclerosis. Current management is targeted at symptomatic treatment of problems related to tuberous sclerosis, such as epilepsy, mental retardation, and autism, and for monitoring cardiac, renal, and dermatologic manifestations, as discussed below. However, with the evolving knowledge of the molecular pathology of tuberous sclerosis complex, several therapies are being explored that attempt to target the disease at this level (please see below)

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - Associated conditions such as epilepsy should be treated with the appropriate antiepileptic agents. Infantile spasms are present in 30–40% of patients with tuberous sclerosis. Vigabatrin has a 95% response rate for infantile spasms in patients with tuberous sclerosis. However, the risk of visual field restriction from this drug has limited its use.
  - Given the lack of curative treatment for tuberous sclerosis, the current understanding of the pathophysiology of the disorder has led to the exploration of mTOR pathway inhibitors such as rapamycin to treat and possibly prevent certain clinical aspects of tuberous sclerosis complex. There have been reports of the use of pharmacological inhibitors of mTOR such as rapamycin in patients with neurological as well as kidney and lung manifestations. These agents work by dissociating mTORC1 from its co-factor, thereby inactivating it. Although initial clinical results appear encouraging, potential side effects from chronic exposure to such agents in young children are not known.

SURGERY/OTHER PROCEDURES

Patients with refractory epilepsy may be epilepsy surgery candidates. Large lesions that obstruct cerebrospinal fluid flow should be surgically removed. Occasionally, if skin lesions are continually irritated or subjected to trauma, they can be removed surgically or by other dermatologic therapeutic measures.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Once the diagnosis has been established and the extent of organ involvement determined, management includes ongoing monitoring and treatment of associated conditions. Long-term surveillance testing should concentrate on complications that are significant, relatively common, and more easily managed when found early. The following guidelines are designed for long-term clinical management of an asymptomatic patient. Additional studies may be necessary and tailored to clinical symptoms.

- Cranial CT and MRI
  - Children should undergo neuroimaging once every 1–3 years to monitor for subependymal giant cell astrocytomas and cerebral hamartomas. If cerebral lesions are already present, more frequent neuroimaging may be needed to monitor progression.
- Renal ultrasonography
  - By the age of 10 years, nearly 75% of children with tuberous sclerosis have sonographic evidence of 1 or more renal angiomyolipomas. During the first decade, the number and size of these lesions tend to increase. The current recommendation is for renal ultrasonography to be done once every 1–3 years. The frequency depends on the results of previous examinations. Patients with large or numerous renal tumors may require referral to a urologist, as well as either CT or MRI of the kidneys to better define the extent of kidney disease.
- Echocardiography
  - Most patients with tuberous sclerosis who have a cardiac rhabdomyoma remain asymptomatic. It is unusual for patients to become symptomatic after the neonatal period. Occasionally, asymptomatic patients may need follow-up echocardiography because the original study raised specific concern about the size and location of a cardiac rhabdomyoma.
- Lung disease
  - Pulmonary function tests should be reserved for patients with suspected lung dysfunction.

PATIENT EDUCATION

- Education with regard to the long-term nature of this disease, as well as the potential for multiple organ involvement, should be outlined in detail.
- Genetic counseling, as well as screening of family members, is an important part of management.
- Seizure care should be explained, and seizure precautions should be followed by patients with seizures.
- Tuberous Sclerosis Alliance offers a comprehensive website for patients and professionals. Website: www.tsalliance.org/default.asp

PROGNOSIS

Course and prognosis depend on the organ systems involved and the extent of involvement.

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See Also (Topic, Algorithm, Electronic Media Element)

- Bourneville's cerebral sclerosis

CODES

ICD9

759.5 Tuberous sclerosis

VASCULITIS, CENTRAL NERVOUS SYSTEM

John N. Ratchford, MD

BASICS

DESCRIPTION

Central nervous system (CNS) vasculitis is a syndrome of subacute onset caused by inflammation of small- and medium-sized blood vessels of the brain, spinal cord, and leptomeninges. Primary angiitis of the central nervous system (PACNS) exclusively involves the CNS. PACNS is also referred to as primary CNS vasculitis, isolated CNS vasculitis, or granulomatous angiitis of the nervous system. Secondary CNS vasculitis is the result of a systemic vasculitis involving the CNS.

EPIDEMIOLOGY

Incidence

- PACNS
  - Very rare with no epidemiologic studies of its incidence
  - Mean age of onset is 45, range 3–71 years
  - Males and females approximately equally affected
- Secondary CNS vasculitis
  - Annual incidence of systemic vasculitis is 39 per million with only 1–2 per million involving the CNS.

Prevalence

Unknown

RISK FACTORS

Risk factors are associated with specific conditions that can cause a systemic vasculitis.

Genetics

No known genetic associations

GENERAL PREVENTION

None

PATHOPHYSIOLOGY

- In most cases the inflamed vessels cause tissue ischemia and necrosis, resulting in small infarcts or hemorrhages which present with focal neurologic symptoms.
- Headache and encephalopathy are common.

ETIOLOGY

- Etiology of PACNS is unknown. Infectious agents have been proposed as a cause, but not proven.
- CNS vasculitis can occur as a complication of infection by varicella zoster virus (VZV), HIV, West Nile virus, and other viruses.
- Many systemic vasculitides can cause secondary CNS vasculitis. Deposition of antigen–antibody immune complexes containing activated complement in blood vessel walls has been implicated in initiating the vascular injury.

COMMONLY ASSOCIATED CONDITIONS

- Systemic vasculitis: Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome, polyarteritis nodosa, Behçet's disease, Takayasu's arteritis
- Infections: VZV, HIV, West Nile virus, others
- Toxic: Cocaine
- Some cases of PACNS have occurred together with cerebral amyloid angiopathy or lymphoma.

DIAGNOSIS

HISTORY

- Commonly presents with subacute onset headache, confusion, and focal neurologic findings due to ischemic or hemorrhagic stroke.
- Symptoms can include hemiparesis, aphasia, ataxia, movement disorders, visual changes, and brainstem syndromes.
- Seizures occur in about 30%.
- Should be considered when stroke (especially recurrent) is seen in a young patient without identifiable stroke risk factors or a hypercoagulable state.
- Patients should be queried for symptoms suggestive of a systemic syndrome, including fever, malaise, weight loss, rash, arthritis, and peripheral neuropathy.

PHYSICAL EXAM

- A detailed examination of the CNS should be performed.
- Examination of the skin, eyes, sinuses, lungs, testicles, and peripheral nervous system should be undertaken to look for signs of a systemic syndrome.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- CBC with differential, hepatic function panel, ESR, ANA, c-ANCA, p-ANCA, SSA/SSB, cryoglobulin, complement, syphilis serology, anticardiolipin antibody, lupus anticoagulant, Lyme serology, and an HIV test will help to evaluate for a systemic syndrome.
- In PACNS, CSF generally shows an elevated protein. A lymphocytic pleocytosis is present in 68%, but CSF can be normal. CSF testing should help rule out infection or leptomeningeal metastases.

Follow-up & special considerations

None

Imaging

Initial approach

- Brain MRI generally shows single or multifocal infarcts and/or hemorrhages. Nonspecific T2-weighted lesions are commonly present.
- MR angiography is insensitive in small-vessel vasculitides, but could identify abnormalities in vasculitides involving large vessels.

Follow-up & special considerations

- Catheter angiography classically demonstrates multifocal areas of stenosis or "beading" in small- and medium-sized vessels, but this is not specific to vasculitis.
- Reported sensitivity of angiography ranges from 10% to 60% in proven cases, so a negative angiogram does not rule out CNS vasculitis (1).

Diagnostic Procedures/Other

- In PACNS a biopsy of the cortex and leptomeninges is generally required to make the diagnosis and rule out other possibilities prior to initiating intensive immunosuppression. In one series of suspected PACNS, biopsy revealed an alternate diagnosis in 50% of cases (2).
- In a suspected systemic vasculitis, biopsy of skin, peripheral nerve, muscle, or other affected organs may confirm the diagnosis.
- Electromyography and nerve conduction studies may show mononeuritis multiplex or a diffuse sensorimotor polyneuropathy in a systemic vasculitis.

Pathological Findings

- The classic pathology of PACNS is a segmental granulomatous vasculitis with multinucleated giant cells, but this is not constant.
- Monocytes, histiocytes, lymphocytes, and plasma cells can be found infiltrating the walls of small vessels.
- Specific other pathological findings may suggest polyarteritis nodosa, Churg–Strauss, Wegener's granulomatosis, or sarcoidosis.
- Stains for infectious agents and neoplasm should be done.

DIFFERENTIAL DIAGNOSIS

- PACNS
- CNS vasculitis secondary to polyarteritis nodosa, Wegener's granulomatosis, Churg–Strauss, Behçet's disease
- Temporal arteritis or Takayasu's arteritis
- Neuropsychiatric lupus and related conditions
- Reversible cerebral vasoconstriction syndrome (causes acute, severe headache, focal neurologic symptoms; normal CSF; reversible angiographic findings; can be drug-induced, migraine-related, postpartum, or idiopathic)
- Antiphospholipid antibody syndrome
- Infection: Bacterial, fungal, or TB meningitis; encephalitis; vasculitis due to VZV; neurosyphilis; CNS Lyme; HIV; progressive multifocal leukoencephalopathy
- Atherosclerosis or cerebral emboli
- Neurosarcoidosis
- Multiple sclerosis
- Moyamoya disease
- Cocaine-related vasculopathy
- Intravascular lymphoma
- Leptomeningeal metastases
- Hashimoto encephalopathy

TREATMENT

MEDICATION

First Line

- Treatment should be specific to the syndrome causing CNS vasculitis.
- PACNS, induction phase (3,4)
  - – Prednisone 1 mg/kg/day, tapered slowly
  - – When needed, oral cyclophosphamide 1–2 mg/kg/day (maintain hydration; risks include myelosuppression, hemorrhagic cystitis, infection, infertility, and malignancy)
  - – Alternatives:
    - ○ An initial IV methylprednisolone 15 mg/kg/day pulse × 3 days, followed by oral steroids
    - ○ Monthly IV cyclophosphamide pulses
- PACNS, maintenance phase
  - – Continue cyclophosphamide 6–12 months after remission
  - – Could then switch to azathioprine or mycophenolate mofetil
  - – Taper prednisone slowly
- Similar regimens have been used in pediatric patients (5)

Second Line

Experience with other treatments is limited; methotrexate can be considered.

ADDITIONAL TREATMENT

General Measures

- Trimethoprim/sulfamethoxazole 3 times weekly for pneumocystis carinii prophylaxis while immunosuppressed.
- In patients on corticosteroids consider GI prophylaxis and monitor for osteoporosis and other potential complications.

Issues for Referral

Management often requires involvement of neurology, rheumatology, radiology, neurosurgery, and others.

Additional Therapies

Physical, occupational, and speech therapy may be needed.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

None

SURGERY/OTHER PROCEDURES

Brain biopsy is often required for diagnosis.

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Initial management generally focuses on ruling out neurologic emergencies such as stroke or CNS infection.
- Patients with an intracerebral hemorrhage or large stroke may require ICU monitoring.

Admission Criteria

Patients often will be admitted following a stroke or transient ischemic attack, or for workup of progressive neurologic symptoms (e.g., encephalopathy).

IV Fluids

IV fluids should be administered when appropriate. Do not use hypotonic IV fluids in patients with a large stroke or intracerebral hemorrhage as this could exacerbate cerebral edema.

Nursing

Nurses should periodically evaluate the patient's neurologic status

Discharge Criteria

Per physician judgment

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients should be followed closely for a change in neurologic status and for response to treatment.
- Repeat brain MRI may be useful to evaluate for treatment responsiveness.

Patient Monitoring

- Cyclophosphamide requires frequent blood monitoring and should only be prescribed by providers familiar with its use.
- Patients receiving chronic corticosteroids should continue to be monitored and treated for potential steroid side effects.

DIET

No restrictions

PATIENT EDUCATION

- Patients should be educated about common symptoms and signs of stroke and the importance of urgent evaluation if a stroke develops.
- Reinforce the importance of adhering to the recommended schedule for blood testing in outpatients on cyclophosphamide and other immunosuppressants.
- Advise immunosuppressed patients to contact their provider if symptoms of infection develop.
- A strategy for avoiding pregnancy should be developed for those taking teratogenic medications.

PROGNOSIS

Prognosis is poor in PACNS with a significant number of patients dying within 6 weeks and most dying within 1 year. However, the course can be more benign with periods of remission in some. Prognosis in secondary CNS vasculitis depends on the success of treating the underlying disorder.

COMPLICATIONS

- Patients can experience disease progression or recurrences despite treatment.
- Infection can occur in patients being treated with immunosuppressive medications.
- Immunosuppression can rarely result in secondary malignancies.

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ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Cerebrovascular disease, ischemic infarcts
- Intracerebral hemorrhage

CODES

ICD9

- 437.4 Cerebral arteritis
- 446.4 Wegener's granulomatosis
- 447.6 Arteritis, unspecified

CLINICAL PEARLS

- PACNS exclusively involves the CNS and is very rare; whereas secondary CNS vasculitis is the result of a systemic vasculitis involving the CNS.
- Typical symptoms include subacute onset of headache, encephalopathy, and focal neurologic symptoms.
- CNS vasculitis particularly should be considered in younger stroke patients without traditional stroke risk factors.
- History, exam, blood testing, and CSF analysis should be used to evaluate for a systemic disorder or CNS infections.
- Catheter angiography has low sensitivity and specificity in PACNS, and biopsy of the brain and leptomeninges is often needed for diagnosis.

VERTEBROBASILAR INSUFFICIENCY

Alan B. Sanderson, MD

BASICS

DESCRIPTION

- Vertebrobasilar insufficiency (VBI) refers to a transient or intermittent diminished blood flow in the posterior cerebral circulation, causing ischemia in areas of the brain supplied by these arteries and their branches.
- Major symptoms are referable to areas of the brain supplied by the posterior circulation, including the occipital lobes, thalamus, brainstem, and cerebellum.
- Occasionally VBI can be elicited by certain neck positions or postures, such as hyperextension. There are case reports of VBI in women having their hair washed at a salon.
- VBI can be the first warning of impending ischemic stroke in the posterior cerebrovascular territories.
- Systems affected: CNS, cardiovascular system
- Synonyms: An episode of VBI may be termed a transient ischemic attack (TIA).

EPIDEMIOLOGY

Incidence

20% of stroke/TIA events involve the posterior circulation. Of these, about 25% have >50% stenosis involving the vertebrobasilar system (1).

Prevalence

The age and gender profiles mimic that of atherosclerosis, with increasing prevalence with age and in the male gender.

RISK FACTORS

VBI shares risk factors for atherosclerosis and stroke, namely smoking, hypertension, diabetes, dyslipidemia, heart disease, hypercoagulable states, and age.

Genetics

No genetic syndromes reported.

GENERAL PREVENTION

- Smoking cessation, medical management of vascular risk factors, including hypertension, diabetes, and dyslipidemia.

PATHOPHYSIOLOGY

- Atherosclerotic stenosis of the vertebral artery most commonly occurs at the origin of the vessel from the subclavian artery, sometimes related to atherosclerosis also involving the parent vessel.

ETIOLOGY

- The most common causes are atherosclerosis of the vertebral or basilar arteries, embolism, and penetrating small vessel disease.
- Many different processes can contribute to VBI, including mechanical compression of the arteries related to neck positioning, subclavian steal syndrome, intrinsic vessel diseases, and embolic phenomena.
- VBI may be a manifestation of dolichoectasia of the basilar artery.

COMMONLY ASSOCIATED CONDITIONS

Vascular disease in other locations, including carotid artery stenosis, coronary artery disease, and peripheral vascular disease.

DIAGNOSIS

HISTORY

- Patients will often describe vertigo, nausea, lightheadedness, diplopia, nystagmus, and other symptoms which relate to brainstem ischemia. More severe presentations can include coma, paralysis, or death.
- Symptoms typically will last several minutes at a time.

PHYSICAL EXAM

- Vital signs: Check blood pressure in both arms to screen for subclavian steal syndrome.
- Cardiovascular: Take note of murmurs or abnormal rhythms. Listen for bruits in the neck.
- Neurologic: A full screening neurologic exam should be performed, with special attention to the cranial nerves and the visual system. Usually the neurologic exam is normal between episodes unless the patient has had a stroke.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- There are no specific laboratory tests.
- Screen for dyslipidemia and diabetes.

Follow-up & special considerations

- Consider screening for less common causes of vascular disease, including vasculitis.
- Consider screening for hypercoagulable states, especially in younger patients with fewer risk factors.

Imaging

Initial approach

- MRI with diffusion-weighted imaging is the preferred initial study to evaluate for many conditions which can cause symptoms of VBI.
- Noninvasive angiography using CT and MRI can often identify a structural cause of VBI, but may be insensitive to stenosis at the origin of the vertebral arteries (1)[A].

Follow-up & special considerations

Consider conventional angiography when noninvasive imaging is equivocal and a high index of suspicion remains, especially if the patient may be a candidate for intervention (2)[C].

Diagnostic Procedures/Other

Carotid Doppler ultrasound may be useful to evaluate the carotid arteries or to screen for subclavian steal syndrome (3)[C].

Pathological Findings

There is no significant role for biopsy in the diagnosis of VBI. Histology typically shows atherosclerosis at the site of occlusion.

DIFFERENTIAL DIAGNOSIS

- Other causes of neurologic symptoms: Vertebral or basilar artery stenosis, thromboembolic disease, basilar migraine, infectious, inflammatory, or neoplastic disease involving the brainstem, toxic or metabolic conditions such as hypo- or hyperglycemia, syncope, seizure, trauma
- Presyncope
- Other causes of vertigo: Vestibulitis, vestibular neuronitis, Meniere's disease, etc.

TREATMENT

MEDICATION

First Line

Aspirin (3)[A]

Second Line

- Clopidogrel or aspirin plus dipyridamole (3)[A]
- Warfarin (3)[A]

ADDITIONAL TREATMENT

General Measures

- Optimal medical therapy including management of underlying vascular risk factors, including hypertension, diabetes, dyslipidemia, and smoking (3)[A]

Issues for Referral

Patients should be followed by a stroke neurologist or vascular neurosurgeon.

Additional Therapies

Where applicable, patients can be counseled to avoid neck positions or postures which reproduce symptoms.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

There are case reports of successfully using Chinese herbal remedies and acupuncture to treat VBI (4)[C].

SURGERY/OTHER PROCEDURES

- Various surgical bypass procedures have been reported, and generally have high morbidity and mortality (2)[B].
- Endovascular approaches with angioplasty with or without stenting generally have low morbidity and mortality, but have a high restenosis rate of about 30–40%. Restenotic patients are symptomatic only 1/3 of the time (2)[B].
- Endovascular approaches have not been shown to be superior to medical therapy alone (5)[B].

IN-PATIENT CONSIDERATIONS

Initial Stabilization

- Once ischemic stroke has been ruled out, patients should be stabilized with blood pressure normalization.
- In cases of impaired consciousness or other causes of poor airway protection, patients should be intubated to prevent aspiration.

Admission Criteria

- Most patients can be managed as outpatients.
- Reasons for admission may include TIA, stroke, or planned intervention.

IV Fluids

If indicated for hypotension in the setting of active symptoms. There is no preference for one type of IV hydration.

Nursing

- Assure glucose control in diabetic patients.
- Manage accurate administration of medications.
- Provide patient education on VBI and comorbid conditions.

Discharge Criteria

Asymptomatic patients may be discharged as soon as a diagnostic workup is complete and outpatient follow-up plans have been made.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients should be followed by a stroke neurologist or vascular neurosurgeon.
- Primary care doctors or medical specialists should provide treatment for underlying medical risk factors.

Patient Monitoring

- There are no recommendations for follow-up imaging in asymptomatic patients.

DIET

- Diets shown to be helpful in other atherosclerotic vascular diseases are likely to be helpful in VBI, but there are no research studies addressing this topic.
- Diabetic diet as applicable.

PATIENT EDUCATION

- Patients should be educated regarding the cause of their symptoms and treatment options.
- Patients should be informed of underlying risk factors for VBI and counseled regarding smoking cessation and compliance with medical therapies for hypertension, dyslipidemia, and diabetes.
- Patients should know what symptoms should prompt them to seek medical care.

PROGNOSIS

- Variable, depending on the etiology and presence of associated infarction.
- After posterior circulation stroke the risk of death is about 3–4%, and major disability is about 20%.

COMPLICATIONS

The most important complication of VBI is ischemic infarction in the posterior cerebrovascular territories.

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See Also (Topic, Algorithm, Electronic Media Element)

- Subclavian steal syndrome
- Cerebrovascular disease, ischemic infarcts
- Cerebrovascular, TIA

CODES

ICD9

- 435.0 Basilar artery syndrome
- 435.3 Vertebrobasilar artery syndrome
- 435.9 Unspecified transient cerebral ischemia

CLINICAL PEARLS

- Vertebrobasilar insufficiency refers to transient or recurrent ischemia in the posterior circulation, usually caused by atherosclerosis in the vertebral or basilar arteries.
- Common symptoms are vertigo, nausea, diplopia, sensory loss, and visual loss.
- VBI almost never causes a single symptom or sign in isolation, but will cause a constellation of findings related to the localization of ischemia.
- VBI is a major risk factor for stroke.

VITAMIN B_{12} DEFICIENCY

Vicki A. Ramsey-Williams, MD, PhD

BASICS

DESCRIPTION

Vitamin B_{12} (B_{12}) deficiency results in a variety of neurological and non-neurological symptoms, including cognitive impairment, ataxia, myelopathy, anemia, neuropathy, and paresthesias (1). Subacute combined degeneration (SCD) is the name given to spinal cord dysfunction that arises from usually severe B_{12} deficiency. SCD usually develops over a few weeks and involves both the corticospinal tracts (resulting in motor weakness) and the dorsal columns (resulting in vibratory and proprioceptive loss).

EPIDEMIOLOGY

- Race
  - Recent studies show higher B_{12} deficiency rates among Caucasians and Hispanics as compared to Asian and African Americans.
- Sex
  - No difference
- Age
  - B_{12} deficiency is more common in the elderly, possibly due to comorbid gastric atrophy.

Incidence

Increases with age

Prevalence

Up to 15% of the elderly may have B_{12} deficiency, depending on definitions and assays used.

RISK FACTORS

- Pernicious anemia (PA)
- Infiltrative gastric carcinomas
- Gastric resection or bariatric surgery
- Strict vegetarian (vegan) diet
- Malnutrition
- Alcoholism
- Inflammatory bowel disease
- Gastric atrophy
- Achlorhydria/hypochlorhydria
- Autoimmunity, e.g., Graves' disease, thyroiditis, Sjögren's syndrome, and vitiligo
- Age

Genetics

- Mutations in the gastric intrinsic factor (IF) gene are associated with hereditary juvenile B_{12} deficiency.
- *CUBN* gene mutation causes impaired recognition of the IF–B_{12} complex and are associated with megaloblastic anemia 1 (MGA1), a rare disorder causing neurological symptoms and juvenile megaloblastic anemia.
- *AMN* mutations are also associated with MGA1 and selective B_{12} malabsorption.

GENERAL PREVENTION

Consumption of adequate B_{12} will prevent the deficiency state in patients with normal absorption, but may not be adequate for those with impaired B_{12} absorption.

PATHOPHYSIOLOGY

- B_{12} is a cofactor and coenzyme in many biochemical reactions, including DNA synthesis, methionine synthesis from homocysteine, and formation of succinyl coenzyme A (2).
- B_{12} is released from food in the stomach and bound first to haptocorrin, then IF. B_{12}–IF complex travels to the distal ileum, where it is absorbed at the brush border membrane via an endocytic receptor for IF–B_{12} containing cubilin, a peripheral membrane glycoprotein, encoded by the *CUBN* gene and the amnionless protein encoded by the *AMN* gene. After absorption, B_{12} dissociates from IF and binds to transcobalamin II (2).
- B_{12} deficiency may not manifest for years after the deficiency develops due to the ability to draw upon liver stores of the vitamin.
- B_{12} deficiency results in hyperhomocysteinemia, which may be associated with increased cardiovascular events and amyloid deposition. The precise relationship between B_{12} deficiency and these processes is not clear.

ETIOLOGY

- Insufficient intake
  - Strict vegans may develop B_{12} deficiency.
  - Insufficient intake is not a common cause of B_{12} deficiency in the industrial world.
- Malabsorption of B_{12}
  - PA is a cause of B_{12} deficiency, resulting from insufficient IF release from the gastric mucosa. PA may also result from antibody formation to IF, reducing the free IF available to bind B_{12}, or from gastric achlorhydria, most often seen in the elderly, in which increased stomach pH prevents the release of bound B_{12} from food.
  - Rarely B_{12} deficiency results from insufficient precursors of the pathway that processes B_{12} [methylmalonic acid (MMA) and homocysteine (HC)].
  - Food-cobalamin malabsorption syndrome occurs in the absence of PA. B_{12} is not released from food or binding proteins in this syndrome. In recent studies, this is a more common etiology of B_{12} deficiency in the elderly than is PA.
  - Malabsorption of B_{12} from the distal ileum may occur from either resection or chronic inflammation of the stomach or ileum, such as sprue or inflammatory bowel disease.
  - Intestinal bacteria or parasites occasionally may compete for dietary B_{12}, most notably the fish tapeworm (*Diphyllobothrium latum*).
  - Nitrous oxide (NO_2) abuse irreversibly inactivates B_{12} by oxidizing the cobalt moiety, causing deficiency.
  - Pancreatic insufficiency may cause B_{12} deficiency due to lack of enzymes needed to free B_{12} from haptocorrin, a protein that initially binds ingested B_{12}.
  - Medications may reduce intestinal absorption of B_{12}, including proton pump inhibitors, histamine receptor antagonists, or biguanides.

COMMONLY ASSOCIATED CONDITIONS

- NO_2 abuse
- Pernicious anemia/macrocytic anemia
- Gastric carcinomas may be the underlying etiology for PA.
- Terminal ileal resection
- Inflammatory bowel disease
- Polyneuropathy
- SCD
- Atrophic gastritis (associated with food-cobalamin malabsorption)

DIAGNOSIS

- Uncomplicated B_{12} deficiency may present with relatively minor symptoms such as paresthesias or forgetfulness (3)[C].
- The signs and symptoms of SCD develop over days to weeks and may vary. Patients complain of weakness and imbalance. They may complain of sensory disturbance and even may have a "sensory level," i.e., sensory changes ascending to, and ending at, a certain spinal dermatome. Sensory abnormalities include decreased sensation and paresthesias. The imbalance may present as falling, impaired gait (ataxia), or inability to stand upright without assistance. The weakness may be mild or profound. The neurological examination may reveal a combination of upper and lower motor neuron signs. Spasticity and positive Babinski's signs may coexist with hyporeflexia.

HISTORY

- Paresthesias/numbness
- Ataxia
- Sore tongue
- Anorexia
- Diarrhea
- Cognitive impairment/dementia
- Fatigue
- Irritability
- Depression
- Psychosis

PHYSICAL EXAM

- Glossitis
- Decreased proprioception
- Ataxia
- Weakness
- Cognitive impairment
- Upper and lower motor neuron signs
- Polyneuropathy

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Laboratory reference values for plasma B_{12} vary. Generally, <250 pmol/mL B_{12} is considered below normal. Some labs separate borderline low as 125–250 pmol/mL with clear deficiency <125 pmol/mL. Folic acid levels should also be obtained (3)[C].
- If plasma B_{12} is low normal or normal in a patient with suspected deficiency, then serum MMA and HC levels may be checked. MMA and HC are precursors in the B_{12} metabolic pathway and accumulate in B_{12}-deficient states, but elevated HC lacks specificity (4)[C].
- If folate is taken to excess in a B_{12}-deficient state, HC levels may normalize, whereas MMA levels will remain high.
- Antibodies to IF are found in 70% of those with PA.
- Shilling's test for B_{12} absorption, using radiolabled B_{12} and IF, is not widely available due to lack of labeled human IF.

Follow-up & special considerations

For patients with anemia, reticulocyte count and/or plasma hemoglobin concentration to monitor appropriate response to B_{12} replacement.

Imaging

Initial approach

- MRI of the spinal cord is indicated to exclude other pathological processes (e.g., abscess, tumor, or compression). In SCD, high signal on T2-weighted images in the dorsal columns is indicative of ongoing degeneration.
- Brain MRI is usually done to evaluate those patients with cognitive decline.

Follow-up & special considerations

Patients with PA have increased risk of developing gastric cancer, and should be screened with endoscopy every 5 years.

Pathological Findings

- Spongy vacuolation of the spinal cord white matter > brain white matter.
- Increased production and levels of CSF myelinotoxic cytokines and growth factors such as tumor necrosis factor alpha, nerve growth factor and the soluble CD40 ligand.
- Decreased spinal cord synthesis and levels of myelinotrophic interleukin-6 and epidermal growth factor.

DIFFERENTIAL DIAGNOSIS

- Myelopathy
- Syringomyelia
- Epidural abscess
- Tabes dorsalis

TREATMENT

MEDICATION

First Line

- For patients with malabsorption, cyanocobalamin 1,000 mcg IM daily for 7 days followed by weekly injection for 4 weeks; then monthly is a common dosing algorithm in the US. Hydroxycobalamin and methylcobalamin are used in other countries.
- For those with normal absorption (vegans), a daily oral vitamin containing at least 6 mcg of B_{12} may serve as effective maintenance therapy, but is not adequate for rapid replacement of severe deficiency.

Second Line

- Oral hydroxycobalamin is sometimes used as a maintenance drug when GI absorption of vitamin B_{12} is intact.
- B_{12} gel for intranasal administration (500 μg intranasally every week) is indicated for long-term maintenance after a course of replacement with intramuscular B_{12}.

ADDITIONAL TREATMENT

General Measures

- Management of B_{12} deficiency depends upon the underlying etiology. If B_{12} malabsorption is the cause, the vitamin must be replaced parenterally.
- Currently, some researchers are making a case for use of large doses of oral B_{12}, particularly in the case of food-cobalamin malabsorption. This is unacceptable to rapidly replace diminished B_{12} levels. Oral B_{12} may have a role in maintenance therapy. If the underlying etiology is distal ileal dysfunction, oral treatment may be ineffective.
- Patients should be questioned regarding NO_2 abuse or "whippets." Those in the dental field and the food industry have access to NO_2.

Issues for Referral

- In patients with clear gastric malabsorption, esophagogastroduodenoscopy may be indicated to evaluate for cancerous lesions.
- In patients suspected of possible inflammatory bowel disease, colonscopy is indicated.

Additional Therapies

Physical therapy may be helpful in the management of gait abnormalities and ataxia.

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients are admitted if they are unable to safely ambulate or care for themselves.

Discharge Criteria

Discharge considerations after evaluation and treatment include ability to perform activities of daily living upon discharge. Discharge to inpatient rehabilitation may be necessary.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

B_{12} levels should be followed lifelong after diagnosis of deficiency. Periodic evaluations (once per year) are adequate. Patients with a history of NO_2 abuse should be offered counseling and observed for possible relapses.

DIET

The US recommended daily allowance of B_{12} is 2.4 mcg. In states of malabsorption, this amount may not prevent deficiency from developing.

PATIENT EDUCATION

Patients should be counseled regarding the necessity of lifelong therapy in case of B_{12} malabsorption.

PROGNOSIS

Treatment should begin promptly after B_{12} deficiency is diagnosed. Ongoing degeneration is halted by B_{12} replacement to normal levels, but acquired abnormalities may not be reversible.

COMPLICATIONS

- Infections, muscle soreness, focal muscle atrophy from repeated injections.
- Iron, potassium, and folic acid deficiencies may develop after B_{12} replacement, and should be monitored.

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See Also (Topic, Algorithm, Electronic Media Element)

- Subacute combined degeneration
- Vitamin B_{12} deficiency
- Pernicious anemia
- Hyperhomocysteinemia

CODES

ICD9

- 266.2 Other B-complex deficiencies
- 281.0 Pernicious anemia
- 336.2 Subacute combined degeneration of spinal cord in diseases classified elsewhere

CLINICAL PEARLS

- B_{12} deficiency may not manifest for years after insufficient levels are established.
- Parenteral B_{12} is recommended for replacement in most patients.

WERNICKE–KORSAKOFF SYNDROME

Alexander D. Rae-Grant, MD

BASICS

DESCRIPTION

- Wernicke–Korsakoff syndrome (WKS) is a disorder of the CNS in which a lack of thiamine causes an initial acute illness (Wernicke syndrome) followed occasionally by a chronic illness (Korsakoff syndrome). Classic signs of Wernicke syndrome include nystagmus, ataxia, and confusion. Korsakoff syndrome is characterized by a disorder of memory.
- Early replacement of thiamine may abort the acute syndrome, but delay in diagnosis and treatment can cause permanent injury.
- Recent literature has emphasized that dosing of thiamine may have been inappropriately low in the past and gives recommendations for higher dose treatment.

EPIDEMIOLOGY

Wernicke syndrome is frequently underdiagnosed. In one series, only 20% of autopsy cases were suspected in life. Autopsy series frequency for Wernicke syndrome ranges from 0.8% to 2.8%. A high level of clinical suspicion is necessary. It is likely that the disease is underreported and underdiagnosed. An estimated 25% of WKS cases were missed when the brains were not examined microscopically. Mortality rates vary but have been estimated at about 17% of patients with acute WKS.

RISK FACTORS

Any condition causing reduced thiamine intake, absorption, or excessive utilization of thiamine can cause WKS. Alcoholics are most commonly affected by WKS based on inadequate intake of thiamine. Other risk factors are listed below.

Pregnancy Considerations

Hyperemesis gravidarum may precipitate WKS.

Genetics

Transketolase in cultured fibroblasts from alcoholics with WKS binds thiamine pyrophosphate less well than control lines. This finding may implicate a hereditary basis for WKS in this population. Recent research suggests that the genetic marker APOE4 is a significant predictor of global intellectual deficits in people with WKS.

ETIOLOGY

- WKS occurs in the setting of thiamine deficiency. Various states with nutritional deficits may cause this syndrome. Chronic alcoholism with deficient nutritional intake is the most common cause, but other causes include recurrent vomiting such as in hyperemesis gravidarum, systemic malignancy, chronically ill patients, anorexia nervosa, AIDS, and after various GI surgical procedures such as gastric bypass surgery.
- Thiamine (Vitamin B1) is a vitamin cofactor in many enzymatic reactions important for energy metabolism. Thiamine's active form, thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain. Specific areas of the brain susceptible to injury include the paraventricular regions of the thalamus and hypothalamus, the mammillary bodies, the periaqueductal region of the midbrain, the floor of the fourth ventricle, and the superior cerebellar vermis. These areas may show necrosis and gliosis, petechial hemorrhage, with vacuolation of the affected brain. There may be spongiosis between hemorrhages without capillary proliferation.
- Fibroblasts from patients with WKS showed that transketolase had a reduced affinity for thiamine pyrophosphate, suggesting that such patients may be more predisposed to WKS on a diet low in thiamine.
- With fasting the time necessary to deplete body stores of thiamine is about 18 days, so that fasts well within the range of hospital stays can cause WKS.

COMMONLY ASSOCIATED CONDITIONS

- Alcoholism
- Alcoholic polyneuropathy
- Alcoholic beriberi
- Alcoholic myopathy
- Marchiafava–Bignami disease
- Alcoholic cerebellar degeneration

DIAGNOSIS

- The triad of ophthalmoplegia, ataxia, and confusion is classic, but only 19% of patients determined to have Wernicke syndrome show all of these signs. Oculomotor signs: Horizontal nystagmus on lateral gaze, bilateral lateral rectus palsies, conjugate gaze palsies, ptosis. Other signs: Paresis of vestibular function (which may be shown by absent cold water calorics), confusion with reduced attention, indifference to environment, and unsteady gait due to ataxia. Korsakoff syndrome is diagnosed in the presence of appropriate risk factors, and a defect in learning new material (anterograde amnesia) and a loss of prior memories (retrograde amnesia). Signs of peripheral neuropathy, an associated nutritional disorder, are common. Postural hypotension and syncope are common and related to autonomic insufficiency.
- Fundoscopic examination may show swelling of the optic disks and retinal hemorrhages.
- Uncommon symptoms at presentation include stupor, hypotension and tachycardia, hypothermia, bilateral visual symptoms, epileptic seizures, hearing loss, and hallucinosis.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

WKS is a clinical diagnosis. Laboratory testing usually is not helpful. Blood pyruvate levels are elevated in untreated cases of Wernicke syndrome. Blood transketolase activity is reduced to as low as one third of normal values, but assays are not readily available.

Imaging

- CT scanning is not helpful in WKS per se. It may help rule out concurrent syndromes causing altered consciousness, such as subdural hematomas, intracerebral hemorrhage, or ischemic disease.
- MRI studies typically show an increased T2 signal which is symmetric in the paraventricular regions of the thalamus, the hypothalamus, mammillary bodies, periaqueductal region, the floor of the fourth ventricle, and the midline cerebellum. Unusual lesions may occur in the cortex and the splenium of the corpus callosum. Diffuse weighted imaging may also be abnormal in WKS.

DIFFERENTIAL DIAGNOSIS

Diagnosis is based on a high index of suspicion in the appropriate clinical situation. Consider in patients with alcoholism, chronic disease, or poor nutritional intake who show evidence of nystagmus, diplopia, ataxia, confusion, or ophthalmoplegia. Patients with cerebellar or thalamic infarction may have some of the same symptoms. Head-injured patients may have unrecognized WKS. Rarely Creutzfeldt–Jacob syndrome may mimic WKS. Paraneoplastic or toxic cerebellar disorders may mimic WKS.

TREATMENT

MEDICATION

The treatment of WKS is a medical emergency and should be instituted as soon as the diagnosis is suspected.

- Recent experimental studies have suggested that traditional dosing for WKS may be inadequate.
- Recent recommendation for thiamine therapy: 500 mg of thiamine hydrochloride IV (dissolved in 100 ml normal saline) given over 30 minutes 3 times a day for 2–3 days, followed by 250 mg IV or IM daily for 3–5 days or until clinical improvement ceases. Doses of 100–250 mg IV may not restore vitamin status, improve clinical signs, or prevent death.
- There are no randomized trials of such therapy, but a controlled study of thiamine replacement in alcohol-dependent patients without clinically apparent Wernicke's encephalopathy showed that at least 200 mg daily was required to improve neurological symptoms.
- Parenteral thiamine is generally safe.
- Contraindications: Hypersensitivity to thiamine
- Precautions: Rare cases of angioedema, cyanosis, or anaphylaxis may occur. Common reactions include pruritus, urticaria, and injection site pain.
- Patients who have concurrent hypomagnesemia may be unresponsive to thiamine until the magnesium deficit is normalized.

ADDITIONAL TREATMENT

General Measures

- Care must be taken to stabilize the patient medically, particularly noting the presence of hypothermia or hypotension and treating if present. Appropriate fluid resuscitation is key because patients may be dehydrated. Patients should be examined for trauma and assessed for the presence of alcohol intoxication or withdrawal, as well as concurrent drug intoxication or withdrawal. Concurrent pneumonia, subdural hematoma, GI bleeding, pancreatitis, and other sequelae of alcoholism may be present and need to be considered and treated.
- Thiamine should be instituted prior to IV glucose, though there is some controversy as to whether the actual sequencing is critical. Traditional concepts that glucose may drive the pathology of WKS have not been proven. However, thiamine should be administered with or soon after glucose in any case.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Symptomatic treatment
  - See "Medication"
- Adjunctive treatment
  - Treatment for alcohol withdrawal or delirium tremens may be necessary (see appropriate sections).

IN-PATIENT CONSIDERATIONS

Admission Criteria

Patients with Wernicke syndrome are usually acutely ill and require admission. Patients with Korsakoff syndrome may require long-term care and supervision.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

Patient Monitoring

Patients with WKS are acutely ill and need to be monitored in an ICU or other monitored setting until they are stable.

PATIENT EDUCATION

When stable, patients should be counseled on avoiding alcohol intake (if appropriate) and maintaining good dietary intake.

PROGNOSIS

Although treatable if caught early enough, the death rate from WKS is relatively high, about 10–20%. Ataxia improves > nystagmus > cognitive dysfunction.

ADDITIONAL READING

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See Also (Topic, Algorithm, Electronic Media Element)

- Alcohol, neurological complications

CODES

ICD9

- 265.1 Other and unspecified manifestations of thiamine deficiency
- 291.1 Alcohol-induced persisting amnestic disorder

WHIPPLE'S DISEASE

Hongyan Li, MD, PhD

BASICS

DESCRIPTION

- Whipple's disease is a rare bacterial infection that involves small intestine and many other organs and tissues, including central and peripheral nervous systems. George Hoyt Whipple first reported this disease in 1907.
- Whipple's disease is clinically characterized by diarrhea, steatorrhea, malabsorption, hypoalbuminemia, weight loss, arthralgia, abdominal pain, lymphadenopathy, and anemia. Focal and diffuse neurological deficits occur in 10–40% infected patients.
- Whipple's disease results from chronic infection by *Tropheryma whipplei*.
- Effective treatments with antibiotics are available for Whipple's disease. However, the disease is fatal when there is a delay in diagnosis and treatment.

EPIDEMIOLOGY

Incidence

Rare (1:1,000,000)

Prevalence

All age groups worldwide may contract Whipple's disease. Meanwhile, it predominantly affects middle-aged Caucasian males (86%).

RISK FACTORS

Farmers, urban sewage workers, and those exposed to contaminated soil and animals are at higher risk.

Genetics

- Not hereditary
- Certain genetic disposition (such as HLA-B27)

GENERAL PREVENTION

Contraction of Whipple's disease is likely by the entry of pathogenic bacteria through mouth into the GI tract. Therefore, personal hygiene and protections can be effective means of prevention, especially for those at risk.

PATHOPHYSIOLOGY

- Bacterial invasion, colonization, and propagation interrupt the physiological functions of small intestine mucosa. Reactive macrophages may limit but are unable to stop the infection from spreading into blood stream. Persistent and recurrent infections, together with the resultant tissue reactions, cause structural damage of the intestinal mucosa and lead to clinical symptoms.
- After invading intestine, the bacteria then travel in blood flow to other tissues and organs, including CNS, and result in similar damage at the new sites.
- Bacteria-containing macrophages infiltrate the brain and spinal cord parenchyma and form granulomas. Focal tissue and cellular damage by these granulomas and their degenerations are responsible for the neurological complications. About 50% patients with brain infection may be neurologically asymptomatic.

ETIOLOGY

- Infection by *T. whipplei*, a rod-shaped gram-positive bacterium, and one of the *actinomycetes*.
- Unknown reservoir (likely in soil and animals).
- Infection is likely through ingestion of contaminated sources. The bacteria are in the free lumen and mucosa of small intestine.
- Those with defected macrophage functions may be more susceptible.

COMMONLY ASSOCIATED CONDITIONS (1)

- GI symptoms: Diarrhea (76%), steatorrhea (91%), and abdominal pain (50%)
- Malnutrition from malabsorption: Weight loss (92%), wasting, hypoalbuminemia (91%), and deficiencies
- Systemic spread: Lymphadenopathy (60%), anemia (85%), joint pain (67%), fever and chills (38%), endocarditis, pericarditis, etc.
- CNS symptoms: Headaches (10%), visual loss, supranuclear ophthalmoplegia (32%), myorhythmia (8%), ataxia (10%), dementia (28%), memory loss (25%), confusion (24%), apathy (21%), psychiatric changes (19%), seizures (14%), myoclonus (16%), focal deficits, hydrocephalus, hypothalamic–pituitary dysfunctions (diabetes insipidus, hypogonadism), sleep disorders, etc.

DIAGNOSIS

HISTORY

- Early stage: Diarrhea and signs of malabsorption are most common. Other symptoms include fatigue, weight loss, normochromic or hypochromic anemia, low fever, intermittent polyarthralgia (legs and spine), and skin hyperpigmentation after exposure to light (2)
- Chronic stage: Epigastric pain and bloating, fetid and watery stool, steatorrhea, signs of deficiencies (fat-soluble vitamins, minerals, fat, proteins, carbohydrates)
- Advanced stage:
  - CNS complications: Headache, lethargy, chronic and recurrent meningitis, focal deficits from brain and spinal cord lesions, cerebellar ataxia, supranuclear ophthalmoplegia, papilledema, insomnia, personality changes, memory loss, frontal and subcortical dementia, confusion, reduced level of consciousness, coma, and seizures. Oculomasticatory and oculofacial–skeletal myorhythmias are seen in about 20% patients and are considered as pathognomonic for Whipple's disease.
  - Other manifestations: Pericarditis and endocarditis, uveitis, impotence, etc.

PHYSICAL EXAM

Findings corresponding to the aforementioned bacterial infections and complications.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

Selected screening laboratories for infections and inflammation (RBC sedimentation rate, C-reactive protein, WBC count with differential) as well as for malnutrition and deficiencies (serum levels of fat-soluble vitamins, albumin, minerals cholesterol, etc.)

Follow-up & special considerations

Microbiology of blood, stool, and CSF

Imaging

Initial approach

- Brain and spine MRIs with gadolinium are preferred. MRI provides good anatomical resolution and may demonstrate enhancing or unenhancing focal lesions in the cortical and subcortical brain parenchyma and in the spinal cord. Surrounding edema is usually minimal. T2 and FLAIR hyperintensity lesions are common.
- Head CT may show enhancing lesions.
- Small bowel x-ray may show irregular thickening of mucosal folds in jejunum and duodenum.

Follow-up & special considerations

- Follow-up brain MRI is usually required to monitor disease progression, responses to treatment, and possible recurrent infections.
- MRI and other neuroimaging studies may also help with differential diagnosis from other causes of parenchymal lesions.

Diagnostic Procedures/Other

- Duodenal or jejunal biopsy shows PAS-positive macrophages, which contain engulfed bacteria, in mucosa. Immunohistochemistry, using antibodies against *T. whipplei*, is more sensitive than PAS stain (1).
- PCR with specially designed primers based on the bacterial genome is highly sensitive but not very specific (1). Positive result indicates presence of bacterial infection. DNA specimen may be from blood, CSF, stool, or tissues.
- Other techniques, such as bacterial culture, serology, and immunopathology, are not commonly used clinically.

Pathological Findings

- Small intestine is always infected.
  - The infection rate is highest in ileum followed by jejunum and duodenum. However, duodenal biopsy is always positive (2).
  - The infected intestine appears enlarged and mucosa becomes thick.
  - Under microscope, the infected mucosa appears edematous with distended and flattened villi and dilated lymphatic tubules. PAS-positive foamy macrophages are found infiltrating lamina propria. Inflammatory cellular reactions are minimal. Secondary amyloidosis may occur in chronic infections.
  - Electromicroscopy shows structures formed by the degenerated bacterial remnants inside the PAS-positive macrophages.

- PAS-positive macrophages also appear in organs and tissues outside intestines (lymphatic tissues, spleen, kidney, lung, pancreas, liver, joints, myocardium, bone marrow, and neural tissues) (2).
- In CNS, these macrophages form granulomas in cortical and subcortical brain parenchyma (3). Granulomatous encephalitis results in destruction of brain structures and surrounding reactive gliosis. Perivascular lymphocytic infiltrations may present and granulomatous inflammation may extend to leptomeninges.

DIFFERENTIAL DIAGNOSIS

- Other causes of progressive dementia, ataxia, infectious and noninfectious meningitis and encephalitis, focal brain and spinal cord lesions from tumors and strokes, inflammatory and autoimmune vasculopathies, etc.
- Other conditions that cause chronic abdominal pain, diarrhea, malabsorption, weight loss, wasting, deficiencies, and arthralgia, such as celiac disease and irritable bowel syndrome.

TREATMENT

MEDICATION

First Line

- Initial therapy: Consider using one of the following antibiotics for 2 weeks (1,2)
  - – Procaine penicillin 1.2 million units IM plus streptomycin 1 g IM daily
  - – Ceftriaxone 2 g IV daily
  - – Penicillin G 2 million units IV q4h
  - – Trimethoprim-sulfamethoxazole DS PO b.i.d.
- Maintenance therapy: Consider using one of the following antibiotics for 12–18 months (1,2)
  - – Cefepime 400 mg PO b.i.d.
  - – Trimethoprim-sulfamethoxazole DS PO b.i.d.
  - – Tetracycline 1 g PO daily
  - – Doxycycline 100 mg PO b.i.d. plus hydroxychloroquine 200 mg PO t.i.d.
- Treatment for relapses (1):
  - – Ceftriaxone 2 g IV b.i.d. or penicillin G 4 million units IV q4h for 4 weeks, then
  - – One of the followings for at least 1 year: Trimethoprim-sulfamethoxazole DS PO b.i.d., or doxycycline 100 mg PO b.i.d. plus hydroxychloroquine 200 mg PO t.i.d.
- Treatment for CNS infection: Doxycycline 100 mg PO b.i.d. and hydroxychloroquine 200 mg PO t.i.d. (or add trimethoprim-sulfamethoxazole) for 1 year or until negative DNA test and biopsy (1)

Second Line

Alternative antibiotics are chosen from the above-listed antibiotics in the presence of allergy, poor tolerance, or drug resistance.

ADDITIONAL TREATMENT

General Measures

- Supportive treatments based on symptoms and laboratory findings
  - – Fluid and electrolyte replacements
  - – High-calorie and protein-rich diet
  - – Supplements of other nutrients [folic acid, iron, fat-soluble vitamins (A, D, E, K), and minerals (calcium, magnesium)]
- Symptomatic treatments for debilitating discomforts such as fever, seizures, myoclonus, headaches, and arthralgia

Issues for Referral

- Infectious disease consultation
- Nutritional counseling
- Psychiatric and neuropsychological evaluations

Additional Therapies

Physical therapy for neurological deficits

COMPLEMENTARY AND ALTERNATIVE THERAPIES

- Immunotherapies for those with immune deficiencies (1)
- Corticosteroids for those with extensive cerebral lesions and prolonged fevers to reduce inflammatory reactions (1)

SURGERY/OTHER PROCEDURES

- Early small intestine biopsy for diagnosis
- Early lumbar puncture and CSF testing for bacteria-containing macrophages
- Insertion of catheters for parental infusion of nutrition or antibiotics as needed

IN-PATIENT CONSIDERATIONS

Initial Stabilization

May be necessary as clinically determined

Admission Criteria

- Inpatient observation and treatment of severe complications
- To carry out special procedures for diagnosis

Discharge Criteria

N/A

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- Patients who receive treatments must be evaluated in 2 weeks for clinical response. If improvements are confirmed, further follow-up visits in 3, 6, and 12 months are recommended. Afterward, annual visits are still necessary to ensure complete cure of the disease (1).
- Follow-up visits also include evaluation and treatment for complications.
- Repeating diagnostic tests:
  - – PCR is more convenient than biopsy. PCR of CSF needs to be repeated at 2 weeks after treatment. If negative, it should be repeated further in 6 and 36 months.
  - – Repeating brain and spine MRIs with contrast when determined as necessary for monitoring neurological complications.
  - – Repeating small bowel biopsy and PCR when determined as clinically necessary.

Patient Monitoring

As discussed above

DIET

As discussed above

PATIENT EDUCATION

- National Organization for Rare Disorders (55 Kenosia Avenue, P.O. Box 1968, Danbury, CT 06813-1968. Tel: 1-800-999-6673 or 203-744-0100; Fax: 203-798-2291; Email: orphan@rarediseases.org; Website: www.rarediseases.org)
- National Digestive Diseases Information Clearinghouse (2 Information Way, Bethesda, MD 20892-3570. Tel: 1-800-891-5389, TTY: 1-866-569-1162; Fax: 703-738-4929; Email: nddic@info.niddk.nih.gov; Website: www.digestive.niddk.nih.gov)

PROGNOSIS

- Whipple's disease is curable with antibiotic treatment, especially if treatments begin before the CNS invasion. It is fatal if not treated.
- Relapses can still be treated once identified.
- Reversal of neurological deficits is difficult especially when symptoms have become evident.

COMPLICATIONS

As discussed above

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2. Singer R. Diagnosis and treatment of Whipple's disease. *Drugs* 1998;55:699–704.
3. Ludwig B, Bohl J, Haferkamp G. Central nervous system involvement in Whipple's disease. *Neuroradiology* 1981;21:289–293.

CODES

ICD9

040.2 Whipple's disease

CLINICAL PEARLS

- Whipple's disease is a rare bacterial infection caused by ingestion of *Tropheryma whipplei*. Infiltration of PAS-positive macrophages in the small bowel mucosa is the feature of biopsy finding.
- Diarrhea and wasting from malabsorption are the most prominent symptoms. CNS infection results in focal and diffuse neurological deficits.
- The disease is fatal but curable.

WILSON'S DISEASE

D. Joanne Lynn, MD

BASICS

DESCRIPTION

Wilson's disease (WD) is an inherited disorder of copper metabolism with a wide spectrum of system involvement (also known as hepatolenticular degeneration). CNS manifestations include dystonia and psychiatric symptomatology. Other organs prominently affected include the liver and kidneys.

EPIDEMIOLOGY

Incidence

Estimates of prevalence vary widely (10–30 per million), with a heterozygous carrier rate of 1 in 90.

Prevalence

The average worldwide prevalence has been estimated to be 30 per million.

RISK FACTORS

Genetics

WD is inherited as an autosomal recessive disease due to the mutation of the ATPase *ATP7B* gene on chromosome 13. The risk of WD is 40% in a sibling of an index case and 0.5% in a child of an index patient.

GENERAL PREVENTION

Since this is a rare disorder, prevention efforts focus on identification of affected family members and prevention of organ injury once an index patient is identified.

PATHOPHYSIOLOGY

The *ATP7B* gene codes for a metal-transporting P-type ATPase which is primarily expressed on hepatocytes. It functions in the transmembrane transport of copper within hepatocytes. In WD, decreased ATP7B protein leads to decreased transport of copper into the bile and resultant hepatic copper accumulation and injury. Decreased ATP7B protein function is also associated with decreased incorporation of copper into ceruloplasmin (protein synthesized by liver which is the major carrier of copper in the blood). Copper eventually spills into the bloodstream and is abnormally deposited into various organs including brain, kidney, and cornea, causing tissue damage.

ETIOLOGY

Genetic – autosomal recessive disorder caused by mutations of the *ATP7B* gene on chromosome 13.

COMMONLY ASSOCIATED CONDITIONS

- Hepatic
  - Chronic active hepatitis
  - Cirrhosis
  - Fulminant hepatic failure
- Hematologic
  - Coombs-negative hemolytic anemia
  - Hypersplenism
  - Coagulopathy due to liver disease
- Renal
  - Fanconi's syndrome
  - Urolithiasis
  - Hematuria
  - Proteinuria
  - Peptiduria
  - Nephrocalcinosis
- Ophthalmologic
  - Sunflower cataracts
  - Night blindness
- Other
  - Osteopenia
  - Cardiomyopathy/cardiac arrhythmias
  - Arthritis
  - Amenorrhea
  - Hypoparathyroidism

DIAGNOSIS

HISTORY

- Neurologic symptoms of WD generally present later than hepatic manifestations – typically in the third decade although pediatric neurologic presentations of WD do occur. Neurologic presentations include bulbar symptoms such as dysarthria and difficulty swallowing, dystonia, and a wide spectrum of neuropsychiatric manifestations. Patients may give a history of deteriorating handwriting or micrographia.
- The spectrum of hepatic presentations of WD includes acute hepatitis or liver failure, cirrhosis, or isolated splenomegaly due to portal hypertension associated with occult cirrhosis. Coombs-negative hemolytic anemia may be associated with acute liver and/or renal failure. Transient episodes of jaundice may occur due to hemolysis.

Pediatric Considerations

Many children are without symptoms but hepatic enlargement or elevated serum transaminases may be found incidentally. Early subtle findings in pediatric patients may include behavioral changes, deterioration in school performance, or poor hand–eye coordination.

PHYSICAL EXAM

The classic triad of WD is cirrhosis, neurologic manifestations, and Kayser–Fleischer (KF) pigmented corneal rings but the majority of patients with WD do not have all of these presenting conditions. Common neurologic findings include tremor, motor incoordination, dysarthria, dystonia, and spasticity. Dysautonomia and pseudobulbar palsy with dysphagia may be present. Psychiatric manifestations may include depression, anxiety, and psychosis. Seizures are rare.

DIAGNOSTIC TESTS AND INTERPRETATION

Lab

Initial lab tests

- Serum aminotransaminase levels
- Serum ceruloplasmin (level $<$200 mg/L consistent with WD, but it is an acute phase reactant, so levels may be falsely normal with inflammatory states)
- Serum non-ceruloplasmin bound copper level often elevated above 25 μg/dL in untreated patients
- 24-hour urine copper (usually $>$100 μg/24 hours in WD but lesser amounts can still be consistent with diagnosis)
- Slit-lamp examination

Follow-up & special considerations

Interpretation of many laboratory tests for WD can be obscured by other conditions.

Imaging

Brain MRI frequently shows hyperintensity of the basal ganglia on T2 imaging. Other abnormal findings may include abnormal signal of the gray and white matter, cerebellar hemispheres, and the dorsal and central regions of the pons. Generalized and focal atrophy and ventricular dilation may also be present.

Initial approach

MRI should be obtained in all patients with neurologic WD prior to initiation of treatment.

Follow-up & special considerations

The diagnosis of WD in patients who present with hepatic disease is more complex. Because no single test establishes the diagnosis, a combination of laboratory features is required to firmly establish the diagnosis.

Diagnostic Procedures/Other

- Slit-lamp ophthalmologic examination for KF rings: Despite a clinical tradition that KF rings must be present once neuropsychiatric signs are present in WD, there are reports of a small percentage of patients with neuropsychiatric signs without KF rings.
- Hepatic copper content via liver biopsy is increased in most patients with WD, typically $>$250 μg/g dry weight. Other hepatic diseases can be associated with increased hepatic copper.

Pathological Findings
The lenticular nuclei of the brain grossly appear brown due to copper deposition. Early pathology includes astrocytic proliferation. Necrosis, gliosis, and cystic changes later develop in the thalamus, brainstem, cerebellum, and cerebral cortex. The KF ring is caused by copper deposition in Descemet's membrane.

DIFFERENTIAL DIAGNOSIS
- Huntington's disease
- Essential tremor
- Parkinson's disease
- Neurologic complications of chronic hepatic encephalopathy
- Multiple sclerosis

TREATMENT

MEDICATION
First Line
- The primary treatment approach to WD is to remove copper from the various tissues and to prevent reaccumulation. Copper-chelating agents are the first-line medications for WD therapy. Penicillamine (dimethylcysteine), the traditional mainstay of WD treatment, avidly chelates copper; the complexed copper is excreted in urine. The traditional dosage is 1–2 g/day PO but many recommend starting with 250–500 mg/day and increasing by 250 mg increments every 4–7 days to a maximum of 1,000–1,500 mg/day in 2–4 divided dosages. Penicillamine should be administered 1 hour before or 2 hours after a meal as food inhibits its absorption. The usual maintenance dose is 750–1,000 mg/day in 2 divided doses. Pediatric dosing is 20 mg/kg/day in 2 or 3 divided doses.
- Zinc acetate or zinc sulfate interferes with uptake of dietary copper from the GI tract. It should be administered at a dose of 50 mg elemental zinc 3 times per day on an empty stomach. It has been used as first-line therapy for asymptomatic and presymptomatic WD.

Second Line
- Trientine (triethylenetetramine dihydrochloride) is another copper chelation therapy. It should be taken on an empty stomach. A typical daily dose is 750–2,000 mg in 3 divided doses. Trientine is less toxic than penicillamine, but it has been associated with lupus nephritis and sideroblastic anemia.
- Ammonium tetrathiomolybdate (TM) is an experimental therapy which complexes copper in the GI tract to prevent absorption and in the bloodstream to reduce tissue deposition. TM is administered in a regimen of 6 doses daily: 3 with meals and 3 between meals, at starting doses of 20 mg gradually titrated upward (20–60 mg/dose). TM is associated with reversible bone marrow depression and hepatotoxicity.

ADDITIONAL TREATMENT
General Measures
Patients are initially treated with decoppering agents, zinc, and dietary restriction. After several years of therapy, stable patients may be treated with lower maintenance doses of a chelating agent or zinc alone.

Issues for Referral
Individual multidisciplinary specialty approaches are needed to improve quality and longevity of patients. Dietary counseling is necessary. Various specialist referrals may be required dependent upon disease manifestations (neurologist, hepatologist, hematologist, etc.).

Additional Therapies
Serum and hepatic vitamin E levels are often low in WD. Symptomatic improvement has been reported with supplemental vitamin E but no rigorous studies are available.

SURGERY/OTHER PROCEDURES
Orthoptic hepatic transplantation is recommended for patients with progressive liver failure unresponsive to chelation therapy or acute liver failure due to fulminant hepatitis. Hepatic transplantation results in improvement of neuropsychiatric symptoms.

IN-PATIENT CONSIDERATIONS
Initial Stabilization
Patients who present with acute inflammatory hepatic or neurologic disease or one of the other potential organ involvements of WD may require hospitalization.

Admission Criteria
Admission is required if symptoms are life-threatening (e.g., hepatic failure) or if hydration, mobility, or nutrition is compromised.

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS
Patient Monitoring
Blood counts and urinalysis should be followed closely during penicillamine therapy because hypersensitivity reactions are not uncommon. Copper concentrations in 24-hour urine collections can be used to guide titration of therapy. A 24-hour cupriuresis may exceed 1,000 μg immediately after starting treatment; during maintenance treatment, urinary copper excretion should be around 200–500 μg/day.

DIET
Dietary copper restriction is not recommended as the primary therapy but is an important component of disease management. Foods with high copper content, such as shellfish, nuts, chocolate, mushrooms, and organ meats, should be avoided. Water in households with copper content should be assessed for copper content and copper containers/cookware should not be used for food.

PATIENT EDUCATION
- Compliance with long-term chelation therapy must be encouraged because rapid deterioration has been reported after abrupt discontinuation of penicillamine.
- Wilson Disease Organization. Website: www.wilsonsdisease.org

PROGNOSIS
Symptomatic WD patients require chronic lifelong therapy. Interrupted or inadequate therapy may lead to death, most often due to hepatic failure. If treatment is begun in a timely fashion, most patients will become asymptomatic or nearly so. Residual dystonia and dysarthria are often seen in neurologic cases. Long-term follow-up and monitoring is required to ensure adequate treatment.

COMPLICATIONS
- Initiation of treatment with decoppering agents can be associated with a worsening of neurologic deficits which may require discontinuation of treatment. This is most frequent with penicillamine.
- Penicillamine: Adverse events include fever, rash, proteinuria, lupus-like reaction, thrombocytopenia, leukopenia, gastritis, hepatotoxicity. Each of the decoppering agents is associated with additional potential risks.

ADDITIONAL READING

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- Roberts EA, Schilsky ML. Diagnosis and treatment of Wilson disease: an update. *Hepatology* 2008;47(6): 2089–2111.
- USDA National Nutrient Database. Listing of copper content in various foods. Available at http://www.ars.usda.gov/Services/docs.htm?docid=17477. Accessed on May 30, 2011.

CODES

ICD9
275.1 Disorders of copper metabolism

CLINICAL PEARLS

First-degree relatives of an index patient with WD should be screened for WD. No single laboratory assessment is sufficient. Mutation analysis is the only reliable screening tool. Disease symptoms may be prevented in presymptomatic patients identified through family screening by treatment with chelating agents and/or zinc.

Section IV
Short Topics

Herbert B. Newton, MD, FAAN
Jacob J. Mandel, MD

Abetalipoproteinemia: Bassen–Kornzweig syndrome; autosomal recessive; disorder of lipid metabolism, develops in the first decade of life; symptoms and signs consist of steatorrhea, distal sensorimotor neuropathy, retinitis pigmentosa, ataxia, areflexia, and dysarthria. Mutations in the microsomal triglyceride transfer protein (MTTP) gene have been associated with this condition. The MTTP gene provides instructions for making a protein called MTTP, which is essential for creating beta-lipoproteins. The inability to synthesize beta-lipoprotein reduces the concentration of chylomicrons and causes deficiencies of fat-soluble vitamins A, K, and E; neurological syndrome resembles vitamin E deficiency in other situations; treatment consists of vitamin E supplementation, restricted intake of long-chain fats, substitution with polyunsaturated fats, and rehabilitation.

Adie's syndrome: Tonic Pupil Syndrome; incidence of 4.7/100,000; usually sporadic in origin; female preponderance with typical onset between 20 and 50 years of age; unilateral in 80% of cases; usually develops acutely, with pupillary dilatation and poor reaction to light but better with accommodation; results from parasympathetic denervation at the level of the ciliary ganglion and postganglionic nerves; over time, the pupil often becomes miotic; symptoms include difficulty with dark adaptation and reading, photophobia, blurred near vision, and anisocoria; reduced or absent deep tendon reflexes are often noted; cholinergic denervation supersensitivity can be demonstrated with a 0.1% pilocarpine solution; the cause of Adie's syndrome remains unclear; symptomatic treatment is not required for most patients.

Adrenoleukodystrophy (ALD): X-linked recessive disorder with variable expressivity; ALD gene encodes an ATP binding cassette transporter protein; childhood onset most common (between 5 and 10 years of age), may develop in adolescence or adulthood; clinical symptoms are progressive and include withdrawal, dementia, visual loss with optic atrophy, spastic gait, dysphagia, deafness, and seizures; adrenal failure variable; patients enter vegetative state within 1 to 10 years of onset; MRI shows diffuse demyelination, which predates clinical symptoms; diagnosis requires presence of elevated levels of very long chain fatty acids (VLCFA) in plasma and cultured fibroblasts; the diagnosis should be confirmed by molecular genetic testing of the ABCD1 gene locus; treatment includes replacement and stress steroids, methods to reduce VLCFA, and bone marrow transplantation. Gene therapy of autologous hematopoietic stem cells is currently under investigation.

Adrenomyeloneuropathy: Most common phenotypic variant of ALD; accounts for 25% of phenotypes associated with mutations at ALD locus; onset between 18 and 36 years of age; main clinical features include spastic paraparesis, peripheral neuropathy, and adrenal insufficiency; other commonly noted signs are hypogonadism, impotence, cerebellar dysfunction, and dementia; MRI reveals demyelination, which always predates symptoms; diagnosis requires presence of elevated levels of VLCFA in plasma and cultured fibroblasts; treatment is similar to ALD and includes replacement and stress steroids, methods to reduce VLCFA, such as dietary restriction of VLCFA and Lorenzo oil (glycerol trierucate oil, glycerol trioleate oil), and bone marrow transplantation.

Adult polyglucosan body disease: Glycogenosis type IV; a form of glycogen storage disease with adult onset in the fifth or the sixth decade; usually associated with a deficiency of the branching enzyme, but there appear to be other biochemical variants; inheritance is autosomal recessive associated with mutations in the GBE1 gene located at 3p14; glycogen branching enzyme catalyzes the attachment of short glucosyl chains to a naked peripheral chain of nascent glycogen with deficiency resulting in abnormal structure of glycogen; characterized by progressive upper and lower motor neuron dysfunction, sensory loss, sphincter abnormalities, neurogenic bladder, and dementia (50% of patients); electrodiagnostic testing demonstrates axonal sensorimotor neuropathy; polyglucosan bodies are PAS-positive, diastase-resistant cellular inclusions; pathology reveals polyglucosan bodies in processes of neurons and astrocytes of gray and white matter, and in the axoplasm of peripheral myelinated fibers; there is no specific therapy.

Aicardi's syndrome: Disorder of cerebral cortical development, with abnormal neuronal migration; only noted in females, probably due to X-linked dominant transmission (lethal to males); presents with severe mental retardation, early seizures (infantile spasms), agenesis or hypoplasia of the corpus callosum, periventricular and subcortical band heterotopias, chorioretinal lacunae, cerebellar abnormalities, fused vertebrae, and hemivertebrae; associated with an increased incidence of choroid plexus papillomas; there is no specific therapy except anticonvulsant treatment; supportive care.

Alexander disease: Degenerative disease of unknown etiology that affects astrocytes; autosomal inheritance may be noted in some families; usually occurs in childhood; infantile form most common, presents with severe psychomotor retardation, progressive spasticity, seizures, megalencephaly, and frequent hydrocephalus; juvenile and adult variants are less severe; CT and MRI demonstrate diffuse demyelination with a frontal predominance; the pathological hallmark is diffuse presence of Rosenthal fibers within astrocytic footplates; alpha B-crystallin and HSP27 levels may be elevated in CSF; therapy is nonspecific and consists of seizure medications and other supportive care.

Alpers' syndrome: Progressive infantile poliodystrophy; grouped into diseases of mitochondrial enzyme defects; exact gene and enzyme defect remains unclear; age of onset before one year, with death by age 5; presents with initial psychomotor delay, abrupt onset of seizures, multifocal myoclonus, areflexia, and hypotonia; ataxia, spasticity, and blindness may occur later; 40% incidence of hepatic dysfunction; damage noted in cerebral cortex, cerebellum, basal ganglia, and brain stem; biochemical abnormalities include decreased pyruvate dehydrogenase activity and dysfunction of the citric acid cycle; MRI shows progressive atrophy; diagnosis is by exclusion; no specific treatment exists, except for anticonvulsants; a trial of pyridoxine may be helpful.

Andersen syndrome: Type of familial periodic paralysis; autosomal dominant inheritance; linked to mutations of potassium channel Kir2.1 subunit on chromosome 17q23 in some families; attacks may be associated with high, low, or normal potassium levels; administration of potassium may provoke attacks of weakness or arrhythmias; presentation is in childhood or adolescence with dysmorphic features (low-set ears, broad nose, hypertelorism), short stature, periodic paralysis, potassium sensitivity, myotonia, and cardiac disease (prolonged QT interval, ventricular arrhythmias); electromyogram (EMG) demonstrates progressive drop in CMAP amplitude during exercise, without myotonic discharges; serum CK shows mild to moderate elevation; high incidence of death from arrhythmia and cardiac arrest; acetazolamide may control periodic weakness; anti-arrhythmics.

Angelman's syndrome: Genetic disease that is usually sporadic, but may be familial; associated with DNA deletion within chromosome 15q11–13, inherited maternally in most cases; mouse models suggest UBE3A is a strong candidate gene within 15q12; infants are typically normal at birth, with rapid onset of feeding abnormalities and failure to thrive; other features include small head circumference, severely delayed motor development and hypotonia, early onset of seizures, lack of speech development, wide-based and ataxic gait, hyperactivity, rounded facies with a protruding tongue, delayed puberty, and very short adult height; no specific treatment except anticonvulsants.

Apert syndrome: Acrocephalosyndactyly; a sub-type of craniosynostosis; autosomal dominant; abnormal skull development with coronal suture closure, shortening of the head in the anterioposterior dimension, prominent forehead, and flat occiput; typical facies includes shallow orbits and proptosis of eyes, hypertelorism, maxillary hypoplasia, small nose, low-set ears, and narrow or cleft palate; osseous and cutaneous syndactyly noted often; occasional cardiac, gastrointestinal, and genitourinary malformations are present; mental deficiency often noted; hydrocephalus may develop; maldevelopment of the limbic structures, corpus callosum, and gyri may occur; no specific therapy.

Ataxia-telangiectasia: Early onset ataxia syndrome; autosomal recessive inheritance; involves mutations of ATM gene on chromosome 11q22–23, results in dysfunction of DNA repair processes and impaired cell cycle control; clinical features include truncal ataxia, delayed motor development, dysarthria, conjunctival and cutaneous telangiectasias, immune dysfunction with reduced concentrations of IgA and IgG2, recurrent respiratory and cutaneous infections, growth retardation, premature aging, and delayed sexual development; mild mental retardation, oculomotor abnormalities, myoclonus, and peripheral neuropathy may be noted; 15–20% incidence of malignancies, especially leukemias and lymphomas; serum alpha-fetoprotein level is elevated; median age at death is 20 years, from respiratory infections and cancer; treatment is supportive (i.e., antibiotics).

Balint's syndrome: Symptom complex due to bilateral damage to posterior parietal lobes (e.g., angular gyrus and superior parietal cortex); most commonly caused by watershed infarction; cerebral control of precise eye movements is impaired; clinical features include optic ataxia (defect in reaching under visual guidance), simultanagnosia (inability to recognize a whole picture despite perceiving its parts), and ocular apraxia (defect in voluntary eye movements); inferior altitudinal visual field defects and bilateral hemineglect may be present; patients may deny having any visual dysfunction or deficits.

Behçet's disease: Inflammatory disorder of unknown etiology, characterized by relapsing/remitting uveitis and recurrent genital and oral ulcers; CNS involvement occurs in 25 to 30% of patients; age of onset is the third and the fourth decades; men are more frequently affected than women; neurological signs and symptoms include headache, cranial nerve palsies, seizures, mental confusion, dementia, aphasia, hemiparesis, and papilledema; low-grade fevers are common; laboratory data may include elevated sedimentation rate, anemia, mild leukocytosis, elevated CSF pressure and protein, CSF pleocytosis; CNS involvement may be multifocal (similar to multiple sclerosis); CT/MRI

demonstrate focal CNS lesions; immunosuppressive therapy may be of benefit for CNS involvement.

Brill–Zinsser disease: Recrudescent typhus; flare-up of epidemic louseborne typhus fever in mild form months to years after the primary attack; infectious agent is obligate intracellular parasite, Rickettsia prowazekii, which has remained latent in the tissues; symptoms and signs are similar to epidemic typhus fever, lasts 7 to 12 days, and may include the characteristic rash (often absent), mild fever, headache, malaise, myalgias, photophobia, dizziness, stroke, and mild somnolence or encephalopathy; diagnosis is made by Weil–Felix test (may be negative) or specific rickettsial antibody titers; treatment is with tetracycline antibiotics (i.e., doxycycline) or chloramphenicol, and supportive care.

Carnitine deficiency: Carnitine is essential cofactor to transport long-chain fatty acids into mitochondria for beta oxidation; muscle carnitine concentration is decreased or absent; primary carnitine deficiency presents in the first or the second decade as progressive, proximal muscle weakness and hypotonia, reduced or absent reflexes, normal motor milestones, mentation and sensation preserved, atrophy of extremities may be noted; EMG shows diffuse myopathic process; secondary carnitine deficiency occurs with short and medium chain acyl-coenzyme A dehydrogenase deficiencies, Reye syndrome, and valproate therapy; primary carnitine deficiency is diagnosis of exclusion; treatment consists of oral carnitine, with or without prednisone.

Cerebrotendinous xanthomatosis: Cholestanol storage disease; caused by mutations in the CYP27A1 gene on chromosome 2q33-qter that encodes the mitochondrial enzyme sterol 27-hydroxylase; deficiency of the enzyme sterol 27-hydroxylase causes the accumulation of cholesterol and cholestanol in virtually all tissues; autosomal recessive inheritance often noted; clinical features become apparent in early adolescence and include cataracts, tendon xanthomas, progressive spasticity and ataxia, dysarthria, mental deterioration (in most cases), sensorimotor neuropathy, distal muscle wasting, and Babinski signs; pseudobalbar palsy, dementia, and myocardial infarction may be noted in late stages; cholestanol levels are increased in plasma, brain, bile, and tendon xanthomas; cholesterol level usually normal in serum; chenodeoxycholic acid level is reduced or absent in bile; treatment with chenodeoxycholic acid replacement therapy or a low cholestanol diet may be of benefit.

Chagas disease: South American Trypanosomiasis (*Trypanosoma cruzi*); infection is transmitted by an animal host (e.g., rodents, cats) to humans by blood-sucking reduviid bugs (i.e., "kissing bug"); clinical features include an acute febrile stage with conjuctivitis, facial edema, lymphadenopathy, and hepatosplenomegaly; chronic infection may lead to diffuse (encephalopathy, seizures, chorea) or focal (hemiplegia, ataxia, aphasia) neurologic involvement; disease is slowly progressive without treatment; laboratory abnormalities may include elevated ESR and anemia, CSF lymphocytic pleocytosis with elevated protein and gamma globulins; diagnosis made by demonstration of organisms in blood, CSF, or biopsy materials, or by serologic and CSF antibody testing; treatment with nifurtimox or benznidasole usually effective in acute stage.

Chediak–Higashi syndrome: Autosomal recessive inheritance; characterized by partial oculocutaneous albinism, immunologic defects, hepatosplenomegaly, pancytopenia, and progressive neurological dysfunction, including psychomotor retardation, seizures, nystagmus, spinocerebellar disorder, and peripheral neuropathy; linked to mutation of CHS1 gene on chromosome 1q42–44; results in defective transport of intracellular proteins, leading to giant peroxidase-positive granules and reduced function of leukocytes and other granule-containing cells (e.g., monocytes, hepatocytes, renal tubular cells); neurons and schwann cells may have inclusions; predisposition to frequent pyogenic infections; increased risk of lymphoreticular malignancies; therapy consists of anticonvulsants, antibiotics and other supportive care; no specific therapy exists.

Chorea-Acanthocytosis: Neuroacanthocytosis; McLeod's syndrome; Huntington's disease-like 2; pantothenate kinase-associated neurodegeneration (PKAN); Levine–Critchley syndrome; characterized by acanthocytes, normal plasma lipids and lipoproteins; and variable neurologic involvement; inheritance usually autosomal dominant, but may be recessive or sporadic; conditions are caused by genetic mutations of several different genes including XK, JPH3 and pantothenate kinase 2 (PANK2); chorea acanthocytosis is passed in an autosomal recessive manner and linked to VPS13A located on chromosome 9q21; McLeod syndrome is inherited in an X-linked recessive manner and caused by mutation of XK gene; onset in the second to the fourth decade; clinical features include hyperkinetic movement disorder (chorea, orofacial dyskinesias, dystonia), personality changes such as obsessive-compulsive disorder, dementia in late stages, axonal neuropathy with muscle wasting and weakness, reduced deep tendon reflexes, pseudobulbar palsy, and seizures in 40% of patients; MRI shows generalized atrophy and atrophy of caudate nuclei; treatment is symptomatic and supportive.

Cockayne syndrome: Progressive multisystem disease with autosomal-recessive inheritance pattern; caused by mutations in the ERCC6 and ERCC8 genes as the proteins made by these genes are involved in repairing damaged DNA via transcription-coupled repair mechanism; clinical features include extreme dwarfism, dysmorphic facies, cachectic habitus, and neurological deterioration; children are normal at birth, then develop failure to thrive and decreased height, weight, and head circumference by 24 months; cognitive development and speech are rudimentary, gait is limited by progressive spasticity and ataxia, deafness and impaired vision occur frequently, peripheral neuropathy may develop; the brain is small, with atrophic white matter and calcification of the basal ganglia; patchy demyelination is noted in the white matter and peripheral nerves; no specific treatment is available.

Corticobasal ganglionic degeneration: Corticodentatonigral degeneration; degenerative dementia syndrome characterized by the diffuse accumulation of pathologic tau proteins within neurons; clinical features reflect dysfunction predominantly of frontal and parietal cortices and include progressive memory loss, dysphasia, psychomotor slowing, apraxia, alien hand syndrome, asymmetric rigidity, dysphagia, postural instability, frontal release signs, oculomotor impairment, asymmetric hyper-reflexia, myoclonus, and hypokinetic dysarthria; pathology demonstrates asymmetrical frontoparietal atrophy with neuronal loss and gliosis, substantia nigra degeneration, and swollen achromatic neurons; MRI shows asymmetrical cortical atrophy most severe in the parietal lobes; positron emission tomography (PET) and single photon emission computed tomography reveal hypoperfusion and hypometabolism in affected areas; treatment involves symptomatic and supportive care; levodopa may occasionally result in modest reduction of rigidity.

Cowden's syndrome: Gingival multiple hamartoma syndrome; familial cancer syndrome with autosomal-dominant inheritance; linked to mutations of PTEN gene on chromosome 10q23; symptoms in young children include progressive macrocephaly, mental retardation, mild to moderate delay in motor development, lingua plicata; adults present with facial trichilemmomas, oral papillomas, lingua plicata, and hamartomatous lesions like lipomas, fibromas, and hemangiomas; increased risk at a young age of developing benign and malignant tumors of the thyroid, GI tract, breast, retina, and ovary; frequent occurrence of Lhermitte-Duclos disease; management is directed toward surveillance and treatment of the various hamartomatous and neoplastic lesions.

Crouzon's syndrome: Craniofacial dysostosis; disorder caused by premature fusion of the cranial sutures; autosomal-dominant inheritance pattern; linked to mutations in fibroblast growth factor receptor types 2 and 3 genes located on chromosome 10; coronal, sagittal, and lambdoid sutures affected most often; other clinical features include ocular proptosis caused by shallow orbits, visual impairment in 50% of cases, traction and compression in the optic canals can cause optic atrophy and blindness, conductive hearing loss in 55% of patients, headaches, and seizures in up to 12% of patients; mental deficiency is rare; CT with three-dimensional reconstruction is necessary for evaluation and planning of neurosurgical repair.

Crow–Fukase syndrome: POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes); characterized by progressive, symmetrical demyelinating sensorimotor neuropathy in association with osteosclerotic and multiple myeloma, Waldenstroms macroglobulinemia, plasmacytoma, or angiofollicular lymph node hyperplasia; pathophysiology unknown, probably mediated by immune effectors with elevation of serum or plasma vascular endothelial growth factor levels; mean onset in the fifth decade, often in males; clinical features include moderate to severe weakness affecting distal more than proximal muscles, less prominent sensory loss (mostly large fiber), uncommon autonomic symptoms, and cranial nerve involvement; common systemic features include hepatomegaly, diabetes mellitus, hypothyroidism, skin hyperpigmentation, and peripheral edema; treatment of underlying disease may stabilize or improve the neuropathy.

Cysticercosis: Most common parasitic disease of the CNS; acquired by ingestion of food contaminated by Taenia solium eggs (often undercooked pork); hatched eggs spread via blood to eyes, skeletal muscles, and CNS (brain parenchyma, subarachnoid space, ventricles, or spinal cord); parasites may live for years within cysts or die and leave calcified granulomas; cysts in subarachnoid space may incite intense inflammation, causing fibrosis, and hydrocephalus; clinical features include new onset seizures, cognitive impairment, confusion, headache; gait disturbance, focal neurological deficits, and signs of elevated intracranial pressure; cysts well visualized by CT and MRI; CSF ELISA and complement fixation tests are diagnostic; treatment consists of albendazole and praziquantel, and anticonvulsants.

Dandy–Walker syndrome: Dandy-Walker malformation; 1 in 30,000 births; posterior fossa malformation characterized by complete or partial agenesis of the cerebellar vermis, cystic dilatation of the fourth ventricle, enlarged posterior fossa, elevation of the torcula and straight sinus, and hydrocephalus;

atresia of the foramina of Luschka and Magendie may be present; patients display delayed motor development, nystagmus, spasticity, titubation, and abnormal cognition; treatment consists of shunting of the ventricles or posterior fossa cyst, or both; early shunting and decompression of the cyst may allow more normal development of the cerebellar hemispheres.

Dejerine–Sottas syndrome: Progressive hypertrophic neuropathy; form of hereditary peripheral neuropathy (HSMN type III); autosomal dominant or recessive inheritance patterns can occur; presentation in infancy with progressive generalized muscle weakness, severe sensory loss, limb ataxia, muscular atrophy, and marked hypertrophy of peripheral nerves; appears to be more severe phenotype of Charcot-Marie-Tooth disease; mutations within several different genes involved in peripheral nerve myelination result in a similar phenotype, including PMP22 (17p11.2), myelin P0 (1q22.3), and EGR2 (10q21); treatment is supportive and consists of physical and occupational therapy, orthotic devices, genetic counseling.

Denny–Brown, Foley syndrome: Benign fasciculation with cramps; disorder characterized by frequent muscle cramping, often accompanied by muscle fasciculations; cramps can occur during sleep or after ordinary physical activity; EMG and nerve conduction testing are benign, without evidence of muscle denervation or peripheral nerve dysfunction; symptoms do not progress to include muscle weakness or atrophy; not accompanied by an increased risk for Amyotrophic lateral sclerosis (ALS) or motor neuron disease; treatment is symptomatic and consists of quinine, phenytoin, or carbamazepine.

Dentatorubral-pallidoluysian atrophy (DRPLA): Degenerative trinucleotide repeat disorder that is usually autosomal-dominant, occasionally sporadic; occurs mainly in Japan; caused by unstable expanded CAG repeats within the DRPLA gene, on chromosome 12p12 and presents with anticipation; DRPLA gene produces a cytoplasmic protein called atrophin-1; intergenerational instability occurs; onset at any age, usually in early fourth decade; constant clinical features include cerebellar ataxia, dysarthria, and progressive dementia; less common findings consist of progressive myoclonic epilepsy, opsoclonus, chorea or dystonia, psychiatric abnormalities, and oculomotor disturbances; EEG demonstrates a slow background and frequent epileptiform activity; MRI reveals atrophy of the superior cerebellar peduncles and high-signal abnormalities in the pallidum; no specific therapy available except for anticonvulsants.

DiMauro syndrome: Carnitine palmitoyl transferase (CPT 1 or CPT 2) deficiency; enzymes involved in fatty acid oxidation and energy metabolism within mitochondria; autosomal recessive inheritance pattern; CPT1 caused by mutations in the CPT1A gene; CPT 1 deficiency manifests in infancy with nonketotic hypoglycemic coma, hepatomegaly, hypertriglyceridemia; and abnormal liver function, including hyperammonemia (similar to Reye's syndrome); condition may improve with medium-chain triglycerides; CPT 2 deficiency caused by mutations in the CPT 2 gene on chromosome 1p32; CPT 2 deficiency is lethal in infants but more benign in adults; clinical features include metabolic myopathy with recurrent pain and myoglobinuria; diagnosis is confirmed by a combination of enzyme assay and genetic testing and symptoms; provoked by fasting, prolonged exercise, cold exposure, infection, or emotional stress; permanent weakness in 10% of cases; dietary management with no specific treatment available. Benzafibrate currently under investigation for mild CPT 2 deficiency.

Distal myopathies: Several distinct clinical entities cause a distal myopathy syndrome. These include Welander (late adult type I), Markesbery-Udd (late adult type II), Nonaka or familial inclusion body myopathy (IBM) (early adult onset type I), Miyoshi or limb-girdle muscular dystrophy (early adult onset type II), Laing (early adult onset type III), and myofibrillar (Desmin) myopathy with onset varying from childhood to the seventh decade. Rare. Inheritance varies depending on syndrome. Some types with associated cardiac involvement. EMG is consistent with myopathic process. Biopsy varies depending on etiology. No specific treatment, bracing, aides for mobility.

Dystonia musculorum deformans: Idiopathic torsion dystonia; primary torsion dystonia; mostly an inherited disorder of the basal ganglia with autosomal dominant inheritance though may be sporadic; DYT1 dystonia is caused by a mutation in the TOR1A gene on the 9q34 locus that encodes torsinA, an ATP-binding protein; mutant torsinA may interfere with VMAT2 expression and dopamine release; early onset between 5 and 15 years of age; clinical features include initial dystonic involvement of the legs, with rapid progression to involve the arms, neck, head, and trunk; torticollis, lordosis, and scoliosis often develop; pain with movements is unusual; over time, axial musculature may become more impaired than limb muscles; affected muscles often become hypertrophic; MRI usually unremarkable; PET scans may demonstrate reduced glucose metabolism in the basal ganglia; treatment with anticholinergic agents, levodopa, bromocriptine, baclofen, carbamazepine, tetrabenezine, or botox injections occasionally improve symptoms.

Emery–Dreifuss muscular dystrophy: Inherited as an X-linked recessive, autosomal dominant, or autosomal recessive disorder; muscular dystrophy syndrome characterized by an unusual pattern of weakness: Humeroperoneal that predominantly affects the biceps and triceps in the arms and distal musculature of the legs; severity of myopathic weakness is quite variable; early onset of severe contractures of elbows, knees, ankles, fingers, and spine; a rigid spine typically develops, with limited neck flexion; prominent muscular wasting occurs; heart block is common and often requires a pacemaker; linked to mutation of EDMD gene, localized to the Xq28 locus; expression of the EDMD gene product, emerin, which is normally present in the nuclear membrane of muscles and other tissues, is absent; autosomal dominant and recessive forms of EDMD are linked to mutations of the LMNA gene that encodes for lamin A/C; treatment is symptomatic.

Encephalitis lethargica: von Economo disease; disease of unknown etiology, presumed to be viral, responsible for worldwide epidemic from 1917 to 1928; epidemic form possibly extinct; now occurs sporadically; affects patients of all ages and sexes; clinical features include acute stage (3–4 week duration) with onset of fever, headache, lethargy, impairment of eye movements and oculomotor control, motor symptoms characteristic of basal ganglia dysfunction, and acute organic psychosis; CSF demonstrates lymphocytic pleocytosis with elevated protein in 50% of patients; parkinsonian syndrome common in post-encephalitic phase, unusual features include early age of onset, torticollis, torsion spasms, myoclonus, and facial tics; no specific treatment.

Encephalotrigeminal angiomatosis: Sturge–Weber–Dimitri Syndrome; a form of neurocutaneous disorder characterized by a cutaneous vascular port-wine nevus of the face (follows distribution of trigeminal nerve), contralateral hemiparesis and hemiatrophy, glaucoma, seizures, frequent homonymous hemianopsia, and mental retardation; inheritance usually sporadic, may be dominant or recessive; seizures are early onset and difficult to control, they can be focal motor, generalized, or partial complex; occipital lobe most often affected, also involves the temporal and parietal lobes; atrophy noted ipsilateral to facial nevus; calcification involves the cortex and small vessels; skull radiographs reveal trolley-track curvilinear calcifications; treatment includes cosmetic surgery, anticonvulsants, physical and occupational therapy, and supportive care.

Eosinophilia-myalgia syndrome: An interstitial form of eosinophilic myositis and fasciitis; characterized by severe myalgias, muscle cramps, edema and induration of the skin, pulmonary symptoms (e.g., cough, dyspnea), and peripheral blood eosinophilia; in one-third of cases, an associated inflammatory polyneuropathy can occur and cause neuropathic symptoms (may be painful); myokymia, myoclonus, and movement disorders occur in some patients; in most cases, related to patients taking certain preparations of L-tryptophan that contained a chemical contaminant (e.g., 1,1′ethylidenebis); the condition has been most prevalent in the USA; symptoms respond well to glucocorticoids, nonsteroidal anti-inflammatory agents and rehabilitation may also be beneficial.

Erb-Duchenne syndrome: Upper radicular syndrome; weakness of the upper extremity caused by damage to the upper nerve roots (fourth, fifth, sixth cervical roots or upper trunks) of the brachial plexus; weakness affects the deltoid, biceps, brachioradialis, pectoralis major, supraspinatus, infraspinatus, subscapularis, and teres major muscles; flexion of the forearm, abduction and internal and external rotation of the arm, and apposition of the scapula are all severely affected; sensory loss is variable and consists of hypesthesia on the outer surface of the arm and forearm; the biceps reflex is absent; recovery is likely if complete avulsion has not occurred; rehabilitation is of benefit.

Fabry disease: X-linked disorder of the skin (angiokeratoma corporis diffusum), kidney, blood vessels, neurons, and peripheral and autonomic nervous systems; caused by defective enzyme, α-galactosidase A, with abnormal storage of ceramide trihexoside in affected tissues; incompletely recessive, since some female heterozygotes may be affected; clinical features include paroxysmal burning pains in the limbs, paresthesias, anhydrosis, fever, priapism, hemiplegia, hemianesthesia, dysphasia, and seizures; psychosis and dementia may occur in older patients; cardiac abnormalities may include myocardial ischemia or infarction, congestive heart failure, and aortic stenosis; progressive renal failure is common and kidney transplant may be lifesaving; enzyme replacement therapy is recommended in all patients with renal manifestations or asymptomatic hemizygous males with the classic form of disease although extremely expensive; antiplatelets are recommended for secondary stroke prophylaxis; phenytoin or carbamazepine may improve neuropathic pain.

Familial amyloidotic polyneuropathy: Inherited neuropathy characterized by amyloid deposition into peripheral and autonomic nerves; pathological evaluation reveals both demyelination and axonal damage; autosomal dominant inheritance pattern; linked to mutations of transthyretin gene, mapped to chromosome 18q11.2–q12.1; onset is between ages 20 and 35 years; initial clinical features

include acral sensory loss, chronic diarrhea, and impotence; followed by progressive weakness, sphincter dysfunction, and orthostatic hypotension; cardiomyopathy with heart block may occur, requiring a pacemaker; nephrosis is a late manifestation; the disease is inexorably progressive, no specific therapy exists; liver transplantation and plasma exchange have had little impact on the neuropathy; symptomatic treatment.

Familial dysautonomia: Riley-Day syndrome; autosomal recessive, slowly progressive condition that affects children, typically of Jewish heritage; caused by mutations in I kappa B kinase complex-associated protein gene on chromosome 9, which encodes for the IKAP protein; clinical features include diminished lacrimation, lack of reflexes, hyperhidrosis, abnormal blood pressure regulation, postural hypotension, intermittent skin blotching, poor temperature control, subnormal growth, and multiple sensory deficits; in addition, children have poor motor coordination, emotional instability, frequent vomiting, and relative insensitivity to pain; seizures, frequent breath-holding episodes, and abnormal EEG's may be noted; overall intelligence is preserved; pathology reveals progressive loss of neurons in sympathetic and parasympathetic ganglia; diazepam, clonidine can provide relief from crises; bethanecol chloride may improve crises, GI motility, increase tearing, and reduce the incidence of aspiration.

Farber lipogranulomatosis: Recessive lysosomal storage disease; associated with a deficiency in ASAH1 gene; onset in first few weeks to months of life; clinical features include painful swollen joints, hoarseness, vomiting, respiratory difficulties, and limb edema; subcutaneous nodules develop near joints, tendon sheaths, and at pressure points; less common findings include cardiac enlargement, lymphadenopathy, hepatosplenomegaly, macroglossia, and difficulty swallowing; mental development may be impaired; syndrome caused by severe deficiency of acid ceramidase, with accumulation of ceramide and related materials in foam cells within affected tissues; diagnosis is clinical and finding deficiency of acid ceramidase in cultured fibroblasts or leukocytes; no specific treatment.

Fatal familial insomnia: Prion disease (spongiform encephalopathy) with autosomal dominant inheritance and onset between 18 and 60 years of age; clinical features include progressive insomnia, dysautonomia (hyperhidrosis, tachycardia, tachypnea, hyperthermia, hypertension), dementia, myoclonus, and motor dysfunction (pyramidal tract and cerebellar signs); EEG shows diffuse slowing with infrequent periodicity; pathology reveals prominent neuronal loss and gliosis in the thalamus, with minimal spongiform change; the neocortex, basal ganglia, cerebellum, and brainstem are variably affected; syndrome caused by mutation within PrP gene at codon 178, coupled with a methionine at codon 129; no specific treatment available; family genetic counseling is indicated.

Fazio-Londe syndrome: Form of juvenile spinal muscular atrophy, with onset in late childhood or early adolescence; inheritance is usually autosomal recessive, although sporadic cases can occur; clinical features include progressive bulbofacial weakness, dysarthria, dysphagia and, in some cases, less severe weakness of the arms and legs; wasting of the tongue with visible fasciculations is noted; upper motor neuron signs are absent; respiration may be affected in patients with long-standing disease; symptoms typically remain restricted until end-stage disease; death occurs within 2 years of presentation in most patients, usually from respiratory failure.

Foster Kennedy syndrome: Defined as ipsilateral optic nerve atrophy and contralateral papilledema; caused by tumors that arise in the retro-orbital region, anterior skull base (e.g., medial sphenoid wing), or inferior frontal lobe and compress the optic nerve; initial tumor growth causes optic nerve damage and atrophy, further growth elevates intracranial pressure and leads to papilledema in the contralateral, intact optic nerve; ipsilateral anosmia may be noted; a central scotoma is often present ipsilateral to the tumor; typically occurs with frontal tumors and meningiomas of the olfactory groove and sphenoid wing.

Friedreich's ataxia: Autosomal recessive inheritance; prevalence is 2/100,000; GAA triplet repeat expansion found in first intron of X25 gene, located on chromosome 9q13–21, codes for conserved protein, frataxin; onset in early teen years; clinical symptoms include progressive gait ataxia, areflexia of lower limbs, impaired vibration and position sense, diffuse weakness, dysarthria, nystagmus, frequent Babinski sign, and hypertrophic cardiomyopathy; MRI is usually normal, may show mild cerebellar atrophy; most patients become non-ambulatory within 15 years of symptom onset; treatment is symptomatic (e.g., physical therapy), no specific treatment is available; antioxidants such as idebenone (a free radical scavenger), coenzyme Q10, or vitamin E are under investigation but of unclear clinical benefit; death from infection or cardiac disease occurs between 40 and 60 years of age.

Frontotemporal dementia: Group of rare progressive dementia syndromes, Pick's disease is the best characterized subtype; the clinical features of Pick's disease include initial mild memory impairment, with more pronounced dysphasia (reduced speech output), personality changes, apathy, inattentiveness, and extrapyramidal motor dysfunction; dementia become severe later in the disease; MRI demonstrates focal atrophy of the frontal and temporal lobes; pathology reveals argyrophilic intraneuronal inclusion bodies (Pick bodies) and gliosis in affected areas; associated with mutations in tau gene (involved in microtubule assembly and stabilization) on chromosome 17, with accumulation of abnormal tau proteins in Pick bodies; no disease modifying treatment has been identified yet; treatment is supportive with selective serotonin reuptake inhibitor's (SSRI) and/or atypical antipsychotics for behavioral symptoms.

Fucosidosis: Storage disease with onset during the first two years of life; clinical features include progressive intellectual and motor deterioration, initial hypotonia that gradually evolves into spastic quadriplegia, decorticate rigidity, anhydrosis, cardiomegaly, failure to thrive, and recurrent respiratory infections; other findings are coarse facies and angiokeratoma corporis diffusum of the skin; autosomal recessive lysosomal storage disease caused by mutation of α-L-fucosidase gene on chromosome 1p34.1–36.1; enzyme levels are severely reduced in serum, leukocytes, and cultured fibroblasts; pathology reveals accumulation of fucose-containing oligosaccarides and glycoproteins into vacuoles within affected regions of brain; no specific treatment is available.

Fukuyama congenital muscular dystrophy: Autosomal recessive disorder linked to mutations in the FKTN gene located on chromosome 9q31; common in Japan and rare elsewhere; infants demonstrate significant hypotonia, muscular weakness and contractures, in combination with moderately severe psychomotor retardation; mild developmental and functional abnormalities of the eyes can be occasionally noted (e.g., myopia and optic atrophy); seizures occur in approximately 50% of patients; MRI demonstrates areas of pachygyria and polymicrogyria, with regions of high-signal abnormality in the white matter; EEG is abnormal in this disorder and shows epileptiform activity; the cerebellum may be mildly affected; there is no specific treatment; anticonvulsants and physical therapy are of benefit.

Gaucher disease: Lysosomal storage disease with autosomal recessive inheritance; caused by mutations in the glucocerebrosidase (GBA) gene located on chromosome 1q2; glucocerebroside accumulates within affected tissues because of a deficiency of β–glucosidase; infantile, juvenile, and adult neuronopathic forms exist, as well as an adult non-neuronopathic form; the infantile form has onset in the first 6 to 12 months, with poor suck and swallow, dementia, strabismus, opisthotonus, spasticity, organomegaly, and seizures; the clinical features of the juvenile and adult forms include dementia with variable onset, seizures, incoordination, splenomegaly, and tics; diagnosis made by demonstration of reduced β–glucosidase in leukocytes or presence of a mutation in the β–glucosidase gene; treatment includes enyzme replacement therapy (ERT) with recombinant GBAs (imiglucerase or velaglucerase alfa) for all symptomatic children or substrate reduction therapy with miglustat, an inhibitor of glucosylceramide synthase, in adult patients who are unwilling or unable to receive ERT; hematopoietic cell transplantation can provide a definitive cure but has been replaced by ERT due to its substantial morbidity and mortality.

Hallervorden-Spatz disease: Pantothenate kinase-associated neurodegeneration (PKAN); neurodegeneration with brain iron accumulation 1 (NBIA 1); autosomal recessive disorder with onset in childhood and adolescence; caused by mutations in the gene encoding PANK2 located at the chromosomal locus 20p13–p12.3; symptoms typically begin with stiffness of gait, distal extremity wasting (hands may become useless), pes cavus, toe-walking, risus sardonicus, spasticity and rigidity (painful spasms can develop), speech difficulty with eventual anarthria (comprehension is maintained), hyperactive reflexes, and occasional mild dementia; dystonia, ataxia, and tremor may occur; MRI demonstrates low-signal abnormality in the globus pallidus ("eye-of-the-tiger sign"); pathology reveals neuronal loss and thinning of myelin in the medial segment of the globus pallidus; no specific treatment.

Hand–Schüller–Christian Disease: Multifocal form of Langerhans cell histiocytosis; caused by proliferation of antigen-presenting dendritic cells and antigen-processing phagocytic cells; core features are calvarial lesions, exophthalmus, and diabetes insipidus; short stature; otitis media, constitutional symptoms (fever, weight loss), visual loss, and other endocrine manifestations may occur; symptoms linked to granuloma formation within skull, orbits, and hypothalamic-pituitary axis; MRI reveals multifocal intra-parenchymal lesions that may enhance; diagnosis is made by demonstration of Langerhans cells in brain or calvarial biopsy tissue, with a consistent immunohistochemical analysis; treatment consists of corticosteroids with or without vinblastine; radiotherapy can be used for bone lesions of the vertebrae or femoral neck which are at risk of collapse; chemotherapy is reserved for refractory disease.

Hepatolenticular degeneration: Wilson's disease; inborn error of copper metabolism with autosomal recessive inheritance, due to mutations and deletions of P-type ATPase located on chromosome 13q14.3; onset variable in late childhood or adolescence; accumulation of copper in liver leads to

cirrhosis; neurologic features are quite variable, but can include rigidity, tremor (often "wing beating"), dystonic movements, dysarthria, unsteady gait, reduced dexterity, hypophonic speech, seizures, behavioral abnormalities (affective disorder or psychosis), drooling, and dysphagia; Kayser–Fleischer ring noted in 75% of patients; MRI demonstrates diffuse atrophy, especially of the basal ganglia, and ventricular dilatation; initial therapy involves penicillamine, tetrathiomolybdate, triethylene tetramine, or zinc; optimum maintenance treatment is with zinc.

Hereditary spastic paraplegia: Genetically diverse group of disorders, usually autosomal dominant, may be recessive, X-linked, or sporadic; age of onset variable, symptoms may be mild or severe, all cases are slowly progressive; symptoms of "pure" disorder include spastic gait, with poor coordination, overactive reflexes, Babinski signs, and ankle clonus; sensation usually normal; leg strength may be normal; "complicated" cases present similar to "pure" patients, but have additional features, such as amyotrophy, ataxia, myoclonic epilepsy, dementia, optic atrophy, macular degeneration, or choreoathetosis; sphincter dysfunction may occur in late-onset forms; MRI of the spinal cord usually normal; no specific treatment; management is symptomatic.

Hirayama syndrome: Monomelic muscular atrophy; disorder of unknown origin, often diagnosed in Japan, that usually affects young males; onset at approximately 20 years of age in most patients; initial symptoms are progressive weakness and muscular atrophy affecting one limb, typically an arm and hand; patients are often athletes, but the disorder is not clearly related to cervical trauma; symptoms usually stabilize after several years; EMG consistent with a lower motor neuron process; patients must be followed closely even after stabilization of symptoms, to rule out other signs of motor neuron disease; no specific treatment, physical therapy may be of benefit.

Hunter syndrome: X-linked recessive lysosomal storage disease, with accumulation of mucopolysaccharides (dermatan sulfate, heparan sulfate) within affected tissues; caused by deficiency of iduronate-2-sulfatase; two forms, mild and severe; clinical features of the severe form include juvenile onset of joint stiffness, coarse facies, dysostosis multiplex, hepatosplenomegaly, mental deterioration, growth retardation, diarrhea, and occasional pigmentary retinal deterioration; the mild form may be asymptomatic, with short stature, joint stiffness, coarse features, normal intelligence, and hepatosplenomegaly; neither form has corneal clouding; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of iduronate-2-sulfatase in cultured fibroblasts; treatment is with weekly infusions of Elaprase (recombinant human iduronate sulfatase).

Hurler syndrome: Autosomal recessive lysosomal storage disease, with accumulation of mucopolysaccharides (dermatan sulfate, heparan sulfate) within affected tissues; caused by reduced expression of α–L-iduronidase gene (chromosome 4p); most severe form of the mucopolysaccharidoses; onset in infancy with stiff joints, corneal clouding, periarticular swelling, claw hands, chest deformity, dwarfing, coarsening of facial features, hypertelorism, enlarged tongue, mental retardation and deterioration, minimal speech development, and deafness; cardiac disease, abdominal distention, visual loss, and cervical cord compression may occur; zebra bodies containing lipids are noted in the brain; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of α–L-iduronidase in cultured fibroblasts; treatment is symptomatic and cannot prevent the inevitable decline in function but may alter the natural history; typically most effective when initiated before two years of age and before the onset of significant mental regression; options available include hematopoietic stem cell transplantation, umbilical cord blood transplantation, and enzyme replacement therapy with laronidase (recombinant human α-L-iduronidase); gene therapy is currently under investigation.

Hyperekplexia: Form of exaggerated startle response; associated with a variety of gene mutations usually affecting the glycine receptor or can result from a brainstem disorder; can be inherited as an autosomal dominant trait with mutations of the α_1 subunit of the glycine receptor (chromosome 5q); clinical features include a sudden motor response to unexpected auditory, tactile, or visual stimuli; the motor response involves a blink, contraction of the face, flexion of the neck and trunk, and abduction and flexion of the arms; the response can be brief or prolonged, falling can occur; in infancy may result in "stiff-baby syndrome", due to prolonged tonic spasms; excessive startle syndromes can be regional, such as the "jumping Frenchman of Maine" in Quebec; may respond to clonazepam or valproic acid.

Hyperviscosity syndrome: Can develop in all forms of leukemia with significant leukocytosis (most severe in myeloid forms), as well as in IgM paraproteinemia; clinical features include headache, blurred vision, tinnitus, vertigo, ataxia, somnolence, severe lethargy and fatigue, and cerebrovascular events (transient ischemic attacks or stroke); encephalopathy, reduced level of consciousness and coma, subarachnoid hemorrhage, spinal cord dysfunction, and seizures may develop; acute treatment consists of leukapheresis or plasmapheresis; definitive treatment of the underlying disease with chemotherapy is beneficial.

Isaacs syndrome: Neuromyotonia; slowly progressive myokymia (visible and continuous muscle twitching) that affects children, adolescents, or young adults; clinical features include slowed movements, clawing of the fingers, toe-walking, stiffness of muscles, abnormal postures of the limbs (similar to carpal spasm), pseudomyotonia, frequent cramps, and hyperhidrosis; percussion myotonia is not present; oropharyngeal and respiratory muscles may be affected; stiffness and myokymia is present during rest and sleep; rarely occurs as a paraneoplastic syndrome (antibodies to potassium channels); Thymoma, small cell lung carcinoma (SCLC), and Hodgkin lymphoma are the most commonly associated neoplasms; muscle activity abolished by botulinum toxin; disorder may be due to peripheral neuropathy or dysfunction of nerve terminals; phenytoin and carbamazepine usually control symptoms; plasmapheresis and intravenous immunoglobulin (IVIG) may be beneficial.

Jumping Frenchman of Maine: Regional form of hyperekplexia. See above.

Kennedy disease: Spinobulbar muscular atrophy; X-linked recessive inheritance pattern; onset usually after age 40; clinical features include slowly progressive dyarthria, dysphagia, tongue fasciculations, twitching of limb muscles, and delayed limb weakness, which is more severe proximally; reflexes are lost; upper motor neuron signs and dementia may occur, but are extremely rare; gynecomastia is common; disorder caused by CAG expansion mutation within the androgen receptor gene, linked to chromosome Xq11–12; expansion mutation probably causes toxic gain of function of gene product; inverse relationship between the number of repeats and the severity of the disease; no specific therapy is available.

Kleine–Levin Syndrome: Recurrent hypersomnia; a form of sleep disorder that consists of recurrent episodes of hypersomnia and binge eating that last up to several weeks; interval of 2 to 12 months between episodes; usually affects boys in early adolescence, rare in girls or adults; behavioral and psychological changes can occur, such as disorientation, forgetfulness, depression, depersonalization, hallucinations, irritability, aggression, and sexual hyperactivity accompany episodes of hypersomnia; episodes decrease in frequency and severity with age, uncommon after the fourth decade; patients may have limited improvement with amphetamines, methylphenidate, or lithium; no definitive treatment is available.

Klippel–Feil syndrome: Congenital fusion of two or more cervical vertebrae (usually C2/C3 or C5/C6); embryonic failure of segmentation of chordamesoderm that form cervical vertebrae; can be part of other syndromes (i.e., Turner's, Noonan's, Wildervanck's), sporadic, or inherited as autosomal dominant; radiographic evaluation of cervical spine is diagnostic; patients have a short neck, limitation of head and neck movement; frequent kyphosis, scoliosis, platybasia, and hearing loss; may have weakness and atrophy of arm muscles, mental retardation; craniocervical instability may lead to spinal cord compression and progressive paraplegia; laminectomy is indicated for cord compression.

Klumpke syndrome: Lower radicular syndrome; weakness of the upper extremity caused by damage to the lower nerve roots (eighth cervical and first thoracic roots or lower trunk) of the brachial plexus; weakness affects the flexor carpi ulnaris, flexor digitorum, interossei, and the thenar and hypothenar muscles; the pattern of weakness is similar to a combined lesion of the median and ulnar nerves, with a flattened or simian hand; the sensory deficit consists of hypesthesia on the inner side of the arm and forearm, and on the ulnar side of the hand; the triceps reflex is absent; Horner syndrome may occur if the inferior cervical ganglion is injured; rehabilitation is of benefit.

Krabbe leukodystrophy: Autosomal recessive lysosomal storage disease with deficiency of glalactocerebrosidase (GALC) and accumulation of galactocerebroside and psychosine in affected tissues; caused by mutations in the GALC gene located on chromosome 14q31; typical onset in infancy, can occasionally develop in juvenile or adult years; patients are normal at birth, then have progressive irritability, inexplicable crying, fevers, limb stiffness, seizures, feeding difficulty, vomiting, and slowing of mental and motor development; followed by psychomotor deterioration, marked hypertonia, extensor posturing, and optic atrophy; reflexes eventually decrease or disappear, with loss of tone and flaccidity; death by 2 years in most cases; CSF protein is elevated; nerve conduction velocities are reduced; globoid cells are noted in demyelinated regions of affected brain; diagnosis is made by measurement of GALC activity in leukocytes isolated from whole blood or cultured skin fibroblasts; treatment with hematopoietic stem cell transplantation is recommend for the infantile form of Krabbe disease as long as transplantation is performed prior to the development of neurologic symptoms and for symptomatic children with the late onset form of Krabbe disease.

Kugelberg–Welander syndrome: Spinal muscular atrophy type III; inheritance can be autosomal recessive or dominant; onset is usually in middle to late childhood, with slow progression into

adult middle age; clinical features include proximal weakness of the extremities (most often the legs), with variable amounts of muscle wasting, fasciculations, and occasional elevation of serum creatine kinase activity; the bulbar musculature is usually spared; corticospinal tract signs, sensory deficit, autonomic involvement, and mental deterioration do not occur; linked to mutations of SMN gene, located on chromosome 5q11.3-13.1; no specific treatment exists; multidisciplinary supportive care and genetic counseling are of benefit.

Laurence–Moon–Biedl syndrome: Congenital disorder of development with an autosomal recessive inheritance pattern; characterized by early onset obesity, mental retardation, retinal dystrophy, hypogenitalism and hypogonadism (mostly in males), and coloboma; polydactyly, syndactyly, or both may occur; less common features include renal dysfunction, hypertension, cardiac abnormalities, and liver defects; night vision is impaired early by retinitis pigmentosa, patients are often blind by age 20; lifespan may be normal, although frequently shortened by cardiac and renal disease; no specific neuropathological changes have been described yet; treatment is symptomatic, with supportive care.

Landau–Kleffner syndrome: Disorder of childhood that is characterized by an acquired aphasia, typically in association with a seizure disorder; that occurs in children with previously normal language and motor development, between the ages of 4 and 7; occasionally the disorder can affect very young children, so that speech never develops properly; the disorder can precede or follow the occurrence of seizures and often persists, even though seizures may be well controlled; EEG shows temporal or temoporoparietal spikes, or spike and wave discharges, that may be almost continuous in some cases; MRI is normal; etiology unknown, possibly a focal encephalitis; valproic acid, ethosuxumide, and benzodiazepines may improve the condition; a trial of prednisone is recommended if there is no response to antiepileptic drugs (AEDs); a surgical technique called multiple subpial transection may also benefit children who have failed treatment with AEDs.

Leber hereditary optic neuropathy: Maternally inherited disorder of the optic nerve, caused by mutations in mitochondrial DNA; mutations have been noted in several genes of complex I of the respiratory chain (e.g., ND1, ND4, ND6); clinical features include onset in adolescence or early adulthood, with progressive, painless cloudiness of central vision (may be asymmetric) that results in bilateral loss of vision (20/200 or finger counting) within several months; optic atrophy is always present; possible associated findings include cardiac pre-excitation, postural tremor, dystonia, motor tics, and peripheral neuropathy; treatment remains unclear; corticosteroids, hydroxycobalamin, optic nerve sheath fenestration, and craniotomy with lysis of optic nerve/chiasm adhesions are of unproven value; avoidance of tobacco and alcohol is recommended.

Leigh syndrome: Subacute necrotizing encephalomyelopathy; disorder of cerebral oxidative metabolism usually caused by mutations of nuclear DNA in genes of complex I, II, or IV of the respiratory chain; rarely due to mutations of mitochondrial DNA; inheritance can be sporadic, X-linked, autosomal recessive, or maternal; affected infants develop normally then display poor feeding, feeble crying, respiratory difficulty, impaired vision and hearing, ataxia, nystagmus, weakness, seizures, and intellectual deterioration; late onset form is characterized by external ophthalmoplegia, dystonia, and ataxia; MRI reveals high-signal abnormalities in the basal ganglia, putamen, and medulla; cell necrosis, demyelination, and vascular proliferation noted in affected regions of brain; no treatment is available.

Leprosy: Hansen disease; chronic infection by *Mycobacterium leprae*, which has a predilection for the skin and peripheral nerves (i.e., cooler areas of body); lepromatous and tuberculoid forms occur; transmitted by direct contact, with long incubation period (3 to 4 years); clinical features include anesthetic skin nodules, cranial nerve palsies (usually V, VII), extremity weakness and distal muscle atrophy (fasciculations and contractures may develop), patchy cutaneous sensory impairment, and late loss of reflexes; arthropathies and resorption of the finger bones are common; treatment consists of dapsone for at least 6 months, supplementation with rifampin and clofazimine may be necessary.

Lesch–Nyhan syndrome: Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency; X-linked recessive; HPRT necessary for re-cycling of purine bases into nucleotide forms during DNA and RNA synthesis; leads to accelerated synthesis of uric acid and hyperuricemia; onset by 6 months of age with developmental delay, axial hypotonia, appendicular spasticity, mental retardation, choreoathetoid movements, self-mutilation, dysarthria; diagnsosis by demonstrating reduced tissue levels of HPRT; allopurinol reduces serum uric acid but does not effect neurological symptoms; not effective treatment, supportive care.

Letterer–Siwe disease: Disseminated form of langerhans cell histiocytosis; caused by proliferation of antigen-presenting dendritic cells and antigen-processing phagocytic cells; affects children under 2 years of age; clinical features include a granulomatous rash, lymphadenopathy, hepatomegaly, splenomegaly, fever, and weight loss; pulmonary and bone involvement is common; granulocytosis is usually present; pancytopenia may occur with severe hypersplenism; neurologic involvement is usually absent; the course is often fulminant, with a poor prognosis; symptoms may improve with corticosteroids; focal lesions may respond to radiotherapy; chemotherapy may be required to achieve clinical remission.

Levine–Critchley syndrome: Neuroacanthocytsis; familial multisystem neurodegenerative disorder with autosomal dominant or recessive inheritance linked to chromosome 9q21, sporadic cases are rare; onset is usually in the fourth or the fifth decade, juvenile onset is uncommon; clinical features include acanthocytosis, hyperkinetic movement disorder (chorea, orofacial diskinesias, dystonia), psychiatric symptoms (obsessive-compulsive disorder, personality changes), dementia, and axonal neuropathy; the neuropathy causes muscle wasting, weakness, and absent reflexes; epileptic seizures occur in 40% of patients; MRI shows atrophy of the caudate nuclei and high signal within the striatum; pathology reveals neuronal degeneration and gliosis within the basal ganglia and substantia nigra; no specific treatment is available.

Lhermitte–Duclos disease: Dysplastic gangliocytoma of the cerebellum; rarely noted in hypothalamus and spinal cord; associated with Cowden syndrome; age of onset typically in the third or the fourth decade; usually sporadic in origin; clinical features include cerebellar dysfunction (ataxia, dysdiadochokinesia, nystagmus), and symptoms of increased intracranial pressure secondary to hydrocephalus; may be associated with CNS malformations such as hydromyelia, brain heterotopia, and megalencephaly; MRI shows low signal lesion on T1 images, with minimal enhancement; pathology demonstrates altered cerebellar architecture, with pleomorphic ganglion cells replacing the granule cell layer; treatment is surgical resection, the role of radiotherapy and chemotherapy is unclear.

Lowe syndrome: Oculocerebrorenal syndrome; X-linked (long arm) recessive disorder of amino acid metabolism; caused by mutation in OCRL gene resulting in an enzyme inositol polyphosphate 5-phosphatase not being produced; clinical features include severe mental retardation, delayed physical development, myopathy, and congenital glaucoma or cataracts; general aminoaciduria of the Fanconi type occurs, with renal tubular acidosis and rickets; lysine is the predominant amino acid in the urine; MRI shows various patterns of white matter damage; CNS pathology is inconsistent; the gene encodes a protein similar to inositol polyphosphate-5-phosphatase; there is no specific treatment available.

Lytico–Bodig disease: Parkinson-dementia-ALS complex of Guam; syndrome indigenous to the Chamorro natives of Guam; also noted in emigrants from Guam; clinical features include those of Parkinson's disease and dementia, often in combination with ALS; a supranuclear gaze palsy may be present; pathology reveals the presence of neurofibrillary tangles in degenerating neurons of the substantia nigra and locus ceruleus, loss of anterior horn cells, and scattered granulovascular bodies; Lewy bodies and senile plaques are absent; possibly related to exposure to a neurotoxin, 2-amino-3-(methylamino)-propanoic acid, present in seeds of the plant, Cycas circinalis; parkinsonian symptoms may respond to levodopa.

Marinesco–Sjögren syndrome: Early-onset ataxia syndrome; autosomal recessive inheritance pattern; associated with mutations of the SIL1 gene in 50% of cases; clinical features include ataxia, bilateral cataracts (congenital or can develop in infancy), mental retardation, limited sexual maturation, and short stature; cerebellar dysfunction is manifested by dysarthria, nystagmus, and ataxia of the trunk and limbs; developmental delay always occurs, but can vary from mild to severe; other associated features that may be noted are strabismus, hypotonia, pes valgus, and scoliosis; disease progression is slow, with most patients being wheelchair bound by the third or the fourth decade; underlying cause is unknown, possibly a lysosomal storage disorder; MRI shows cerebellar atrophy, usually more pronounced in the vermis than the hemispheres; no specific treatment is available.

Maroteaux–Lamy syndrome: Mucopolysaccharidosis type VI; autosomal recessive inheritance; caused by mutations in the gene encoding arylsulfatase B on chromosome 5q11-q13; form of lysosomal storage disease, with deficiency of N-acetylgalactosamine-4-sulfate sulfatase or arylsulfatase B; accumulation of dermatan sulfate within affected tissues; disease severity can be variable, with mild, intermediate, and severe forms; manifestations of the severe form include growth retardation by 2 or 3 years of age, coarse facial features, corneal clouding, severe skeletal abnormalities, short stature, valvular heart disease, and heart failure; intelligence remains normal; hydrocephalus and cervical cord compression can develop from hypoplasia of the odontoid process; patients may survive into the second or the third decade; treatment options include hematopoietic stem cell transplantation, cord blood transplantation, and enzyme replacement therapy with galsulfase (human recombinant N-acetylgalactosamine-4-sulfatase).

Meige's syndrome: Oromandibular dystonia; a form of oral-facial dyskinesia; characterized by the combination of blepharospasm and other cranial

dystonias; clinical features include forceful blinking and sustained eye-closure (with or without spasms of the orbicularis oculi), spasms of the jaw muscles that cause slow forceful involuntary opening of the mouth, deviation of the jaw to one side, protrusion of the tongue, spasms may be forceful enough to dislocate the mandible or fracture teeth; dystonia may spread over time to include the cervical and shoulder musculature; treatment with anticholinergic agents may give partial relief of symptoms and botulinum toxin injections may also provide temporary symptomatic relief.

Menke's syndrome: X-linked, localized to ATP7A gene at Xq13.3, in family of cation-transporting ATPases which transport ions across membranes; lack of gene causes insufficient intestinal absorption of copper and dysfunction of copper-containing enzymes; develops in first few months of life; symptoms and signs consist of male infants with developmental arrest and regression, hypotonia, seizures, failure to thrive, wiry and friable hair, recurrent infections, and hypothermia; very low serum copper levels; treatment with subcutaneous injections of copper histidine or copper chloride before 10 days of age may normalize developmental outcome or improve the neurologic outcome in some individuals; otherwise supportive care.

Metachromatic leukodystrophy: Group of autosomal recessive disorders characterized by degeneration of central and peripheral myelin; several forms are known, late-infantile is most common; caused by deficiency of arylsulfatase A (ARSA), with accumulation of sulfatide in affected tissues; infants between 12 and 30 months develop difficulty with gait, which progresses to flaccid paresis and reduced reflexes (spastic paresis may occur instead); other features include mental deterioration, dysarthria, intermittent pain in the extremities, feeding difficulties, bulbar and psuedobulbar palsies, and optic atrophy; progression to blindness and a vegetative state over 5 to 10 years; juvenile and adult cases are similar with slower progression; metachromatic lipids are noted on sural nerve biopsy; diagnosis is established by demonstrating deficient ARSA activity in leukocytes or cultured skin fibroblasts; no curative treatment is available. Bone marrow transplantation, hematopoietic stem cell transplantation, and gene therapy are currently under investigation.

Miller–Dieker syndrome: Autosomal dominant inheritance; linked to deletion of chromosome 17p13.3 in most cases; associated with abnormal neuronal migration and development of the CNS; distinctive facial dysmorphism occurs, with bitemporal hollowing, short nose with upturned nares, long and thin upper lip, low-set and posteriorly rotated ears, and small chin; other features include lissencephaly, microcephaly and agenesis of the corpus callosum, cardiac anomalies, and severe cerebral dysfunction; death usually occurs in the first decade; diagnosis by cytogenetic analysis and by FISH for a microdeletion at LIS1 gene; no specific treatment is available; supportive care.

Miller–Fisher syndrome: Miller–Fisher variant of Guillain–Barre syndrome (GBS); consists of the triad of ophthalmoplegia, gait ataxia, and areflexia occurring in isolation; pupillary abnormalities may be noted; limb weakness does not develop; similar to GBS, the disorder is often preceded by a respiratory infection; typically benign course with progression over weeks, followed by improvement; antibodies against GQ1b (a ganglioside component of nerve) are present in 85 to 90% of patients; CSF protein is usually elevated; nerve conduction testing is unremarkable; MRI may show high-signal abnormalities within the brainstem; treatment is supportive care to monitor for respiratory failure or autonomic instability; no specific immune therapy is required in most cases but plasma exchange or IVIG may be beneficial depending on duration of patient's symptoms and amount of disability.

Möebius syndrome: Developmental anomaly of the posterior fossa; core features include the combination of congenital facial diplegia and bilateral abducens nerve palsies; associated findings may include other cranial nerve deficits (hearing loss, dysarthria, dysphagia, ptosis, complete ophthalmoplegia), congenital anomalies of the limbs or heart, hypogonadism and anosmia, and mental retardation; facial weakness is more severe in the upper face than below (i.e., more difficulty with eye closure than lip movement); infants have difficulty sucking and lack facial expression when they cry; association with the Poland anomaly, which consists of absence of the pectoralis major muscle on one side of the body and limb abnormalities; two genetic loci one at 13q12.2-q13 and the other at 3q21–q22; etiology unclear, may be due to congenital absence of cranial nerve nuclei or vascular damage within the brainstem; also noted as possible result of in utero exposure to misoprostol.

NCL—adult variant: NCL type 4; Kuf's Disease; a form of lysosomal storage disease with adult onset in the third or the fourth decade; abnormal auotofluorescent lipopigments are present in granular cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive, may be dominant or sporadic; patients present with either late-onset epilepsy and progressive dementia or progressive motor deficits (ataxia, rigidity), myoclonus may be present; MRI may show cortical and/or cerebellar atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment is available; anticonvulsant therapy and supportive care; disease progression is slow over several decades.

NCL—juvenile variant: NCL type 1; Batten's disease; a form of lysosomal storage disease with onset between the ages of 5 and 15 years; abnormal auotofluorescent lipopigments are present in fingerprint cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive; early symptoms include behavioral changes, visual dysfunction, and learning difficulty; symptoms progress to dementia and blindness, with the addition of seizures, myoclonus, and motor dysfunction (pyramidal and extrapyramidal); reduced or absent electroretinogram; MRI may show cortical atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment is available; anticonvulsant therapy and supportive care.

Neuronal ceroid lipofuscinosis (NCL)—late-infantile variant: NCL Type 2; Jansky–Bielschowsky disease; a form of lysosomal storage disease with onset between ages 1.5 and 4 years; abnormal auotofluorescent lipopigments are present in curvilinear cytosomes within nervous system tissues and other organs; inheritance usually autosomal recessive; clinical features include severe seizures, psychomotor deterioration, and ataxia; seizures are often refractory to anticonvulsant treatment; progressive retinal deterioration, optic atrophy, and visual loss occur, with abolition of the electroretinogram; rapid progression to a vegetative state or death in a matter of months to several years, MRI may show atrophy; diagnosis is made by light and electron microscopic examination of tissue specimens and by enzyme and mutation testing; no specific treatment; anticonvulsant therapy and supportive care.

Opsoclonus-Myoclonus syndrome: A form of paraneoplastic syndrome, most often noted in children with neuroblastoma and adults with solid tumors (e.g., breast, small cell lung); clinical features consist of constant, arrhythmic motion of the eyes, irregular in direction or tempo, in combination with myoclonus affecting the facial muscles, limbs, or trunk; in adults, may be associated with the presence of anti-Ri antibodies and encephalomyelitis or a cerebellar disorder; eye movement disorder attributed to dysfunction of the paramedian pontine reticular formation; pathology occasionally reveals Purkinje cell loss, neuronal loss in the dentate nucleus, and demyelination of the cerebellar white matter; no specific treatment but may respond in part to antitumor treatment and/or immunosuppression.

Parinaud syndrome: Dorsal rostral midbrain syndrome; characterized by supranuclear paralysis of upgaze, defective convergence, convergence-retraction nystagmus, and light-near dissociation; lid retraction (Collier's sign) and skew deviation may be noted; most often caused by compression of the dorsal midbrain and superior colliculi from tumors of the pineal region (e.g., pinealoma, germ cell tumor, glioma); other causes include ischemia and stroke, and demyelinating disease; symptoms are caused by impairment of fiber connections between the oculomotor nuclei; treatment is directed towards the initiating disease process.

Pelizaeus–Merzbacher disease: X-linked recessive degenerative disease of childhood; linked to defects in the proteolipid gene on Xq22; two forms exist, one that is present at birth (connatal variant) and an infantile variant; both forms present with nystagmus and head tremor; the connatal form also has floppiness, head lag, psychomotor retardation, ataxia, spasticity, and failure to thrive; the classic infantile form shows initial slowing of motor and speech development, in association with ataxia, spasticity, hyperreflexia, optic atrophy, choreoathetotic movements, and eventual regression of psychomotor skills; patients often develop kyphoscoliosis, joint contractures, and incontinence; hearing is preserved; sensory loss does not occur; Brain MRI has patchy or diffuse leukodystrophy with increased signal intensity in the cerebral hemispheres, cerebellum, and brainstem on T2-weighted and fluid-attenuated inversion recovery sequences; pathology reveals tigroid changes of the white matter; diagnosis based on clinical suspicion and MRI Brain findings with confirmation by genetic testing; no specific treatment.

Platybasia: Autosomal dominant congenital malformation, affecting the base of the skull; defined as a skull base in which the angle between the planes of the anterior cranial fossa and the clivus are greater than 140 degrees; the foramen magnum is narrowed; patients generally remain asymptomatic; if symptoms do occur, the onset is in the second or the third decade, related to progressive compression of the cervical spinal cord; clinical features include spasticity, incoordination, nystagmus, and lower cranial nerve palsies; can occur in Paget's disease and other syndromes, such as Chiari types I and II, and aqueductal stenosis; treatment requires surgical decompression of the posterior fossa and upper cervical cord.

POEMS syndrome: Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; associated with osteosclerotic myeloma or plasmacytoma; electrodiagnostic testing of the neuropathy is consistent with demyelination and axonal degeneration, which may be similar to chronic

inflammatory demyelinating polyneuropathy; see Crow–Fukase syndrome.

Pompe's disease: Infantile acid maltase deficiency; glycogenosis type 2; lysosomal storage disease with autosomal recessive inheritance; caused by mutations in the gene encoding lysosomal α-1,4-glucosidase (GAA) located at 17q25.2-q25; combination of a metabolic myopathy and motor neuron disease; clinical features include initial normal development (for several weeks to months), followed by severe hypotonia, retained mental alertness, generalized weakness, weak cry, dysphagia, areflexia, enlarged tongue, cardiomegaly with congestive failure, and hepatomegaly; respiratory weakness will usually develop, along with an inability to handle oropharyngeal secretions; cardiac failure is the usual cause of death by 12 to 18 months of age; treatment is enzyme replacement therapy with Myozyme (a recombinant human acid maltase derived from Chinese hamster ovary cells) and supportive care for cardiac and respiratory complications.

Prader–Willi syndrome: Sporadic cytogenetic disorder affecting chromosome 15q11-q13, deletions of this region may occur in up to 50% of cases; clinical features include decreased fetal movement in utero, infants will have a feeble suck and severe hypotonia; older children have short stature, small hands and feet, narrowed cranial bifrontal diameter, almond-shaped eyes with strabismus, hypopigmentation of the skin, delayed speech development, hypogonadism, hyperphagia and obesity, mild mental retardation; MRI may show anomalous cortical growth around the Sylvian fissure, possibly due to misrouting of long projection axons; may be due to defective hypothalamic function; diagnosis confirmed by genetic testing; growth hormone treatment is indicated for children with growth failure; supportive care.

Quadriplegic myopathy: Critical illness myopathy; syndrome of acute quadriparesis that occurs in critically ill patients; usually develops after the administration of high-dose corticosteroids, non-depolarizing neuromuscular blocking agents, or both; most often under treatment for status asthmaticus, organ transplantation, and trauma; clinical features include onset of severe, diffuse extremity weakness, loss of reflexes, and persistent respiratory weakness; ophthalmoparesis and facial weakness may occur; serum creatine kinase levels are often elevated; diagnosis can be confirmed with nerve conduction studies and EMG; muscle biopsies reveal myopathic changes with fiber atrophy, fiber necrosis, loss of thick filaments (myosin); treatment consists of discontinuation of offending agents and supportive care.

Raeder syndrome: Cluster headache; more common in males; characterized by 1 to 3 brief attacks of severe periorbital or temporal pain each day for 4 to 8 weeks, followed by pain-free intervals that may last up to a year; a chronic form may develop; the onset of pain is very rapid, unilateral, and peaks within 5 minutes; the pain is constant, excruciating, deep, and non-pulsatile; attacks last from 30 minutes to 2 hours, associated symptoms include ipsilateral scleral injection, lacrimation, nasal stuffiness, ptosis, and nausea; may be due to abnormal serotonergic activity within the hypothalamus; acute treatment consists of oxygen or triptans and prophylaxis with verapamil or prednisone.

Ramsay Hunt syndrome: Early-onset ataxia syndrome; etiologically heterogeneous, consists of progressive ataxia in combination with myoclonus (action or intention); in most patients, the progressive ataxia develops first, followed by the onset of myoclonus, in other patients myoclonus may be the initial manifestation; the myoclonus may be a manifestation of another disease, such as mitochondrial encephalomyopathy with ragged red fibers (MERRF), Unverricht–Lundborg disease, or progressive myoclonus epilepsy; MERRF is the most common cause, and consists of ataxia, myoclonus, seizure activity, myopathy, and hearing loss; no specific treatment is available; myoclonic activity may respond to valproic acid or clonazepam.

Rasmussen encephalitis: Disorder of childhood and pre-adolescence characterized by a unilateral focal seizure disorder, including epilepsia partialis continua, and a progressive hemiplegia induced by focal cortical inflammation and destruction; the seizures manifest as repeated clonic or myoclonic jerks that may remain focal or regional; MRI shows focal or hemispheric atrophy; the underlying etiology is a chronic focal encephalitis, although an infectious agent is not consistently identified; an autoimmune etiology has also been postulated; treatment with anticonvulsants such as valproic acid or clonazepam is often unsuccessful, but may give partial relief; surgical hemispherectomy should be considered for intractable seizures.

Refsum's disease: Heredopathia atactica polyneuritiformis; autosomal recessive lipidosis with a deficiency of phytanoyl-coenzyme A hydroxylase and accumulation of phytanic acid in affected tissues; most cases caused by mutations in the PhyH gene located on chromosome 10pter-p11.2; the phytanic acid is exclusively of dietary origin; onset usually in childhood, manifested by progressive night blindness (granular pigmentary retinopathy), limb weakness, gait ataxia, peripheral neuropathy, loss of reflexes, and muscle wasting; less common features include deafness, cataracts, miosis, pes cavus, cardiac arrhythmias, and bone deformities; symptoms are progressive, but may have exacerbations with intercurrent illness; elevated CSF protein concentration without an increase in cells; diagnosis is confirmed by elevated plasma concentration of phytanic acid and mutation analysis; treatment with dietary reduction of phytanic acid and phytol may improve symptoms; exacerbations may respond to plasmapheresis.

Rendu–Osler–Weber syndrome: Hereditary hemorrhagic telangiectasia (HHT); autosomal dominant inheritance; mutations in at least five genes can cause HHT with the two major genes being the ENG gene on chromosome 9 and ACVRL1 gene on chromosome 12; presence of telangiectasias within multiple organs, including the brain; telangiectasias are collections of engorged capillaries or cavernous spaces that can originate anywhere in the brain, but have a predilection for white matter; brain telangiectasias are associated with similar lesions of the skin, mucous membranes, respiratory system, gastrointestinal tract, and genitourinary system; on occasion the telangiectasias can hemorrhage within the brain or other organs, leading to disability or death; they cannot be identified on angiography or CT; diagnosis based on the Curacao diagnostic criteria consisting of at least two of the following features: spontaneous and recurrent epistaxis, multiple mucocutaneous telangiectasia, a first degree relative with HHT, and visceral involvement; no specific treatment is available.

Rubella: Infection by rubella, a single-stranded RNA virus, acquired by droplet inhalation; neurological syndromes include congenital infection, acute encephalitis, post-rubella polyradiculoneuritis, and progressive panencephalitis; congenital rubella infection manifests as intrauterine growth retardation, deafness, cataracts, glaucoma, microcephaly, and mental retardation; rubella encephalitis is rare, symptoms include headache, dizziness, lethargy, seizures, behavioral changes, and coma; the polyradiculoneuritis presents similar to GBS, but has a brief course; rubella panencephalitis presents with dementia, cerebellar syndrome affecting gait and extremity function, spasticity, optic atrophy and retinopathy, lymphocytic CSF pleocytosis, and occasional seizures and myoclonus; no specific treatment is available.

Scheie's syndrome: Milder version of Hurler syndrome; autosomal recessive lysosomal storage disease, with accumulation of dermatan sulfate and heparan sulfate within affected tissues; caused by deficiency of α–L-iduronidase; juvenile onset of stiff joints, claw hands, deformed feet, corneal clouding, pigmentary degeneration of the retina, coarse facial features, glaucoma, carpal tunnel syndrome, and deafness; stature and intelligence are normal; psychological disturbances and cardiac dysfunction may be noted; diagnosis via demonstration of excess urinary dermatan sulfate and heparan sulfate, and deficiency of α–L-iduronidase in cultured fibroblasts; treatment is symptomatic and cannot prevent the inevitable decline in function but may alter the natural history; typically most effective when initiated before two years of age and before the onset of significant mental regression; options available include hematopoietic stem cell transplantation, umbilical cord blood transplantation, and enzyme replacement therapy with laronidase (recombinant human α-L-iduronidase); gene therapy is currently under investigation.

Schwartz–Jampel syndrome: Chondrodystrophic myotonia; three forms are recognized; the most common is the late infantile variant, which is autosomal recessive and mapped to 1p34-p36.1; a neonatal variant, which is more severe and often fatal, is not linked to chromosome 1; and an autosomal dominant variant, which is unmapped; muscles are stiff, especially in the face and thighs; muscle hypertrophy may be noted; EMG demonstrates continuous myotonia, with minimal waxing and waning; other associated features include facial abnormalities (narrow palpebral fissures, pinched nose, micrognathia) and skeletal anomalies (short neck, flexion contractures, kyphosis); treatment is symptomatic, improvement may occur with membrane stabilizing drugs (i.e., phenytoin).

Serotonin syndrome: Iatrogenic disorder caused most often by the use of serotonin-reuptake inhibitor drugs, either alone or in combination with other medications; clinical features include altered mental status and confusion, agitation, myoclonus, hyperreflexia, tremor, incoordination, nausea and diarrhea, low-grade fever, autonomic instability, diaphoresis, and rigidity; occurs after a serotoninergic drug is started or the dosage increased; also may be induced by the use of a SSRI in combination with a monoamine oxidase inhibitor or tricyclic antidepressant; other etiologies must be ruled out (i.e., infection, metabolic alteration, substance abuse); treatment consists of drug withdrawal and supportive care.

Sjögren's syndrome: Vasculitic and inflammatory disorder of unknown etiology, defined by two or more of the following symptoms: Xerostomia, xerophthalmia, or keratoconjunctivitis sicca (diagnosed by Shirmer test, SS-A/SS-B antibodies, and salivary gland biopsy); most common neurologic complications are sensorimotor peripheral neuropathy and polymyositis; oculomotor and trigeminal sensory neuropathies may occur; CNS involvement can manifest as aseptic meningitis, focal cerebral deficits, seizures, cognitive decline, personality changes, and

optic neuropathy; spinal cord may present as myelopathy, transverse myelitis, or intraspinal hemorrhage; CSF may show pleocytosis and elevated protein; MRI can demonstrate high-signal regions of ischemia; symptoms related to vasculitis respond well to corticosteroids; supportive care.

Subacute sclerosing panencephalitis: Dawson disease; chronic viral infection caused by a defective measles virus (deficient viral M protein); pre-adolescent children and young adults are affected (males more often than females); initial clinical features include the gradual onset of forgetfulness, difficulty with homework, and restlessness; followed in weeks to months by incoordination, ataxia, myoclonic jerks of the trunk and extremities, apraxia, loss of speech, and seizures; late stage disease reveals loss of vision, hearing, dementia, and a rigid quadriplegia; pathology demonstrates neuronal degeneration, perivascular infiltration, demyelination, and gliosis in the cortex, white matter, and deep nuclei; no definitive treatment; stabilization may occur with intrathecal interferon alfa and antiviral therapy with ribavirinor or inosine pranobex.

Sydenham chorea: St. Vitus dance; rhuematic chorea; acquired chorea of childhood caused by an autoimmune reaction to infection with group A β-hemolytic streptococcus; clinical features include the onset of rapid, irregular, aimless, involuntary movements of the muscles of the limbs, face, and trunk; patients appear to be very restless; other findings include muscular weakness, hypotonia, emotional lability, irritability, and obsessive-compulsive symptoms; less common manifestations are speech impairment, headache, seizures, and cranial neuropathy; EEG reveals diffuse slowing; CSF often normal, may show pleocytosis; MRI normal or may demonstrate enlargement of the basal ganglia; course benign, with improvement in 4 to 8 weeks; symptoms may improve with benzodiazepines, valproic acid, or corticosteroids.

Tay-Sachs disease: GM2-gangliosidosis type I; caused by mutations in the HEXA gene on chromosome 15; infantile variant of storage disease with deficiency of hexosaminidase A; autosomal recessive inheritance pattern; normal development until onset of symptoms by 6 months of age; clinical features include irritability and hyperexcitability, exaggerated startle response, delayed cognitive development, motor retardation with hypotonia, hyperactive reflexes, clonus, extensor plantar responses, progressive visual impairment, complete blindness by 1 year in most cases, presence of macular cherry-red spot, and occasional myoclonic seizures; a vegetative state occurs by the second year; pathology reveals ballooned neurons in brain, cerebellum, and spinal cord; no specific treatment is available; supportive care.

Thoracic outlet syndrome: Group of disorders that cause compression of the nerves or blood vessels of the brachial plexus; the C-8 and T-1 nerve roots and lower trunk of the plexus can be compressed by cervical ribs, fibrous bands, and hypertrophic scalenus muscles; pain is present in the shoulder, arm, and hand (fourth and fifth digits); use of the limb may exacerbate the pain and induce fatigue; hypesthesia of affected areas may be noted; wasting and weakness of muscles in the hand occurs; EMG is consistent with the appropriate nerve injury; MRI may show distortion or impingement along the pathway of nerves or vessels; surgery and physical therapy are the appropriate treatment.

Tolosa-Hunt Syndrome: Painful ophthalmoplegia syndrome; non-caseating granulomatous disorder of unknown etiology that is characterized by severe retro-orbital and supra-orbital pain, diplopia, paralysis of cranial nerves III, IV, and VI; less frequent involvement of cranial nerves II, V_1, and V_2; inflammation involves the superior orbital fissure and cavernous sinus region; visualized clearly on enhanced MRI scans; typical onset in middle to late life; dramatic clinical response to oral prednisone (60–80 mg/d); pain improves rapidly with treatment, ophthalmoplegia may take weeks to months to resolve; differential diagnosis includes syphilis, temporal arteritis, sarcoidosis, and systemic lupus erythematosis.

Trypanosomiasis: see Chagas disease; African form of Trypanosomiasis (Trypanosoma brucei); infection is usually transmitted person to person by the tsetse fly, occasionally by other flies or insects; clinical features include an acute febrile stage with rash, lymphadenitis, splenomegaly, arthralgias, asthenia, and myalgias; the chronic stage involves the CNS and includes tremor, seizures, confusion, incoordination, headache, paralysis, and eventual coma; laboratory abnormalities may include elevated ESR and anemia, CSF lymphocytic pleocytosis with elevated protein and gamma globulins; diagnosis made by demonstration of organisms in blood, CSF, or biopsy materials, or by serologic and CSF antibody testing; treatment with pentamidine, suramin or eflornithine is effective in the acute stages, melarsoprol for infections of the CNS.

Turner syndrome: Chromosomal anomaly associated with a 45,X karyotype (X-chromosomal monosomy); major clinical features are female phenotype, short stature, a shieldlike chest, a short and sometimes webbed neck, low-set ears, high-arched palate, small mandible, and sexual infantilism; associated findings include cardiac and renal defects, skeletal anomalies, nerve deafness, and congenital lymphedema; psychological testing reveals poor visuospatial and intellectual function, difficulty with attention, and impaired social behaviors; MRI may reveal volumetric loss in the parietal lobes, hippocampus, thalamus, caudate, and lenticular nuclei; diagnosis confirmed by karyotype analysis; treatment consists of hormone replacement therapy to improve growth retardation (recombinant growth hormone) and sexual infantilism.

Vogt–Koyanagi–Harada syndrome: Characterized by uveitis, retinal hemorrhages and detachment, depigmentation of the skin (i.e., vitiligo) and hair (i.e., poliosis and canities), alopecia, and neurological symptoms, which are caused by an inflammatory adhesive arachnoiditis; clinical features include headache, dizziness, somnolence, fatigue, ocular palsies, and meningeal signs; sensorineural deafness, hemiplegia, and psychosis are noted less frequently; CSF has elevated pressure and moderate lymphocytic pleocytosis, minimal increase in protein, normal glucose, intermittent elevation of gamma globulin; symptoms last for 6 to 12 months before improvement; etiology unknown, although a virus is suspected; no specific therapy, although steroids may be beneficial.

Von Hippel–Lindau disease: Characterized by the coexistence of multiple hemangioblastomas of the CNS, angiomas of the retina, cysts of the kidney and pancreas, capillary nevi of the skin, and systemic neoplasms such as renal cell carcinoma and pheochromocytoma; autosomal dominant inheritance, linked to mutations of tumor suppressor gene on chromosome 3p25.5; onset usually between ages 15 and 50 years; hemangioblastomas are vascular neoplasms that typically develop in the midline cerebellar hemispheres, less often in the medulla and spinal cord; clinical presentation includes headache, ataxia, nausea, emesis, and dizziness; hydrocephalus is common; treatment of choice is surgical resection; radiotherapy may be of benefit.

Wegener granulomatosis: Systemic vasculitis syndrome that primarily attacks the respiratory system and kidneys; diagnostic criteria include oral ulcers, purulent bloody nasal discharge, pulmonary infiltrates or nodules, glomerulonephritis with microhematuria, and biopsy evidence of granulomatous inflammation of arteries or perivascular tissue; neurological complications include peripheral neuropathy (typically mononeuritis multiplex), stroke, cranial neuropathies, headache, ophthalmoplegia, and ischemic optic neuropathy; most patients have an elevated ESR and are cANCA positive; MRI may be normal or reveal ischemic high-signal lesions; angiography is usually normal; brain or lung biopsy may be necessary for diagnosis; treatment consists of prednisone and cyclophosphamide.

Wolman disease: Storage disease characterized by a deficiency of the enzyme, acid lipase, which has been mapped to a gene on chromosome 10q23.2; accumulation of cholesterol esters and triglycerides in affected tissues; infants are normal at birth, but have rapid onset of severe vomiting, abdominal distention, malabsorption with diarrhea, poor weight gain, jaundice, fever, diffuse rash, hepatosplenomegaly, and adrenal insufficiency; adrenal calcification is noted on radiographs; neurological involvement is generally mild and includes delayed intellectual development and mild spasticity; the course is generally quite rapid, death occurs within 3 to 6 months in most cases; no treatment is available.

Xeroderma pigmentosum (XP): DeSantis Cacchione syndrome; group of autosomal recessive disorders characterized by loss of genes required for excision of damaged DNA and for replication past regions of damaged DNA; mutations can occur in genes mapped to several loci, depending on type of XP (9q34.1, 2q21, 3p25.1, and others); cells are hypersensitive to ultraviolet light and chemical carcinogens; clinical features include early sensitivity to light with blistering and erythema, dwarfism, increased risk of skin cancer, microcephaly, mental retardation, chorea, ataxia, spasticity, peripheral nerve dysfunction (motor neuron disorder, segmental demyelination), hearing loss, and supranuclear ophthalmoplegia; no specific treatment; management includes avoidance of sunlight, reduced exposure to environmental carcinogens, and surveillance for malignancies.

Zellweger syndrome: Cerebrohepatorenal syndrome; autosomal recessive peroxisomal disorder; caused by mutations in at least 11 different genes; mutations in the PEX1 or PEX6 genes that encode ATPases needed to import protein from the cytosol into peroxisomes are the most common mutations; symptoms are present at birth, including hypotonia, reduced activity, poor infantile reflexes (Moro, stepping, placing), hypoactive reflexes, characteristic facies (high narrow forehead, round cheeks, wide-set eyes, high-arched palate, small chin), other features include pigmentary retinopathy, optic atrophy, poor suck and swallow, congenital heart disease, cystic renal dysplasia, liver cirrhosis, splenomegaly, genital and skeletal anomalies, and seizures; MRI shows atrophy, poor myelination, pachygyria, and polymicrogyria; caused by dysfunction in multiple enzyme pathways, with increased levels of VLCFA, bile acid intermediates, pipecolic acid, and phytanic acid; no specific treatment available, supportive care.

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