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Eleventh Edition

The Handbook of Ocular Disease Management



Joseph W. Sowka, O.D., FAAO, Dipl.



Andrew S. Gurwood, O.D., FAAO, Dipl.



Alan G. Kabat, O.D., FAAO

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A Peer-Reviewed Supplement

The articles in this supplement were subjected to *Review of Optometry's* peer-review process. The magazine employs a double-blind review system for clinical manuscripts. Two referees review each manuscript before publication. This supplement was edited by the editors of *Review of Optometry*.



FROM THE AUTHORS

To Our Colleagues,

This year sees the publication of the eleventh edition of *The Handbook of Ocular Disease Management*. The years that we have been compiling this compendium have been professionally very rewarding to us. We are forever grateful to the management and editorial staff at *Review of Optometry*. We especially thank Amy Hellem for her work and contribution. We also thank Alcon for its continued support.

When we first envisioned this supplement, we wanted to provide a quick reference on the most commonly encountered ocular diseases and offer readers our perspectives and experience in dealing with these conditions. However, as the compendium evolved, we quickly saw the need to rely more heavily on evidence-based medicine. Simply put, evidence-based medicine is the conscientious, explicit, and judicious use of current best research in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. Good doctors combine individual clinical expertise with the best available external evidence. Without clinical expertise, practices risk becoming tyrannized by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, a practice risks becoming rapidly out of date, to the detriment of patients. We have gone back to the beginning. We want to ensure that every condition that we write about (or have written about) not only reflects our personal experience and perspective, but that our perspectives are backed through scrupulous research and reflect evidence based medicine.

Last year, we dedicated the Tenth Edition to our professors and mentors who helped shape our professional development. This year, we dedicate the Eleventh Edition of the *Handbook of Ocular Disease Management* to our students and residents. With their interactions and questions, they challenge us to remain current and practical and to stay on top of our game.

To them we dedicate the eleventh edition of the *Handbook of Ocular Disease Management*.

Joe
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Joseph W. Sowka, O.D., F.A.A.O., Dipl., is a professor of optometry at Nova Southeastern University College of Optometry, where he teaches Glaucoma and Retinal Disease. He is the director of the Glaucoma Service and chief of the Advanced Care Service. He is a diplomate of the Disease Section of the American Academy of Optometry (Glaucoma Subsection) and a founding member of the Optometric Glaucoma Society and the Optometric Retina Society. He can be reached at (954) 262-1472 or at jsowka@nova.edu.



Andrew S. Gurwood, O.D., F.A.A.O., Dipl., is a member of the attending staff of The Albert Einstein Medical Center Department of Ophthalmology. Involved in direct patient care, he also precepts students and medical residents teaching clinical practice, clinical medicine and its relationship to the eye and ocular urgencies and emergencies. He is a diplomate of the American Academy of Optometry's Primary Care Section, a founding member of the Optometric Retina Society, a member of the Optometric Glaucoma Society and member of the Optometric Dry Eye Society. He serves on the American Academy of Optometry's Program Committee and is the Chairperson of the American Academy of Optometry's Disease Section Written Examination for Retinal Disease Diplomate. He can be reached at (215) 276-6134 or at agurwood@salus.edu.



Alan G. Kabat, O.D., F.A.A.O., is an associate professor at Nova Southeastern University College of Optometry where he teaches several didactic courses and serves as an attending physician in The Eye Care Institute. He is a founding member of the Optometric Dry Eye Society and the Ocular Surface Society of Optometry. Dr. Kabat is also the newly appointed Diplomate Chair for the Disease Section (Anterior Segment Disease Subsection) of the American Academy of Optometry. He can be reached at (954) 262-1440 or at kabat@nova.edu.

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BLOWOUT FRACTURE

Signs and Symptoms

Blunt trauma to the orbital rim is the typical cause of orbital floor and medial orbital wall fractures.¹⁻³ Although there is no epidemiologic predilection for “blowout fracture,” there are some clinical trends regarding those individuals most likely to sustain these injuries: male, between the ages of 18–30, engaged in activities of poor judgment, with most incidents occurring in or near the home.^{3,4} The specific term “blowout fracture” is reserved to connote an isolated orbital floor or medial wall fracture in the setting of an intact orbital rim.¹⁻³ Patients present with a history of blunt-force trauma, such as being struck with a projectile, like a ball, bat or fist, or being a participant in a collision injury, such as those caused by the impact of an airbag or the contact of an object following a fall.⁵ Pain, photophobia and lacrimation associated with post-traumatic uveal inflammation (iritis or iridocyclitis), variable facial swelling secondary to fluid or air (orbital emphysema), crepitus (a crackling noise when tissue infiltrated with air is palpated), gaze-evoked diplopia and pain upon movement of the eyes are all common.⁶ Other associated collateral injuries may include subconjunctival hemorrhage, ruptured globe, corneal abrasion, conjunctival laceration, hyphema, iridodialysis, lenticular subluxation, retinal detachment, vitreous hemorrhage, choroidal rupture and optic nerve avulsion. If the eye settles inferiorly or medially into the exposed sinus, enophthalmos with restricted ocular motility will be present, with or without loss of facial sensation.

Pathophysiology

The seven bones of the orbit include the frontal, zygomatic, maxillary, ethmoid, sphenoid, lacrimal and pterygopalatine.⁷ The orbital roof includes the orbital plate of the frontal bone and the lesser wing of the sphenoid; the lat-

eral wall is composed of the zygomatic bone and the greater wing of the sphenoid; the floor of the orbit is composed of the orbital plate of the maxilla, the zygomatic and orbital process of the pterygopalatine bone; the medial wall



CT scan demonstrating a blowout fracture of the right orbital floor.

of the orbit is composed of maxilla, the lacrimal, the ethmoid and body of the sphenoid.⁷ The other critical anatomical players are the surrounding paranasal air sinuses.⁸ Several sinuses surrounding the orbit help to lessen the weight of the skull and aid in the resonance of the voice.⁸ Unfortunately, these structures leave the superior, medial and inferior walls of the orbit unsupported and vulnerable to catastrophic failure (blowout fracture, trap door fracture) from blunt-force trauma. The sinuses surrounding the orbit include the ethmoidal air cells (anterior, middle and posterior), the sphenoidal sinuses, the maxillary sinuses and the frontal sinuses.^{7,8}

There is some debate about the mechanism of blowout fracture. When a blunt force impacts the face, it may produce a combination of effects: 1) The force may strike the bone, producing a shock wave that causes “bone buckling”; 2) The force may be transmitted to the

eyeball, causing the globe to strike one of the orbital walls such that it fractures; or 3) The force may be transmitted by the globe via the principle of fluid incompressibility, causing generalized increased orbital content pressure or a “hydraulic” effect, resulting in bone fractures.⁹⁻¹² The point of breakage usually occurs along the axis of least support in an area where the tissue is weakest.⁹⁻¹² Since the orbital floor is not parallel to the horizontal plane, the vector of the striking force seems to affect the resultant fracture patterns.⁹ Although all three mechanisms are mentioned in the literature, the buckling mechanism and the hydraulic mechanism seem to have the most support.¹⁰⁻¹² Fractures produced by the buckling mechanism are often limited to the anterior part of the orbital floor.¹¹ In contrast, hydraulic fractures are often larger, involving both the anterior and posterior parts of the floor as well as the medial wall of the orbit.¹¹

The orbital floor has a lower threshold for fracture than the medial wall and other orbital bones and occurs most frequently. When it gives way, the globe and its attached components become unsupported, slipping down into the vacant sinus below, producing visible enophthalmos and gaze-evoked, symptomatic diplopia, along with degrees of extraocular muscle dysfunction and infraorbital nerve hypoesthesia.^{10,12}

Management

For the optometrist, the treatment of blowout fracture centers around ocular first aid. The most challenging aspect of beginning an examination on patients who have experienced facial blunt-force injury is getting the eye open to look. Facial and orbital swelling or orbital emphysema can literally force the eye closed. In such cases, a Desmarre lid retractor can be used as a speculum to lift the superior lid. The thin blade can be inserted between the lids and the superior lid elevated by pulling upward.

Since blunt ocular trauma involving the eye or face is the result of being

struck by an object at velocity; upon contact, a shock wave within the local area is generated. This produces what is known as the *coup* injury, from the French/Scottish meaning "to upset." Injuries may also be seen directly opposite the impact point, in line with the shock wave; these are known as the *contrecoup* effects, from the French derivation meaning occurring at a site opposite the area of impact. For these reasons, a dilated fundus evaluation to rule out vitreous hemorrhage, retinal tearing and retinal detachment is required.

Computed tomography (CT) scanning remains the gold standard for assessing orbital fractures.¹³ The CT technology (multislice CT) has improved the acquisition of coronal images of the orbit without the need for hyperextension of the neck.¹³ Treatment of blowout fracture may not be emergent. If there is a compressive threat to the optic nerve via swelling and retrobulbar hemorrhage, it requires referral for an emergent lateral canthotomy and orbital decompression. Typically, surgical intervention is postponed until orbital health is consistent with a good surgical environment, unless a large amount of soft tissue is incarcerated in the bony rupture.¹⁴

Management of orbital floor fractures traditionally has been accomplished through transconjunctival and subciliary incisions.¹⁵ However, postoperative lid malposition is a complication.¹⁵ Some surgeons have begun to evaluate an endoscopic approach to orbital floor fractures. This approach offers a hidden incision and improved fracture visualization.¹⁵ When the orbital floor requires replacement or reconstruction, ultra-thin porous polyethylene implants serve as durable substitutes that mimic the anatomy and avoid the morbidity of rejection.¹⁶

In cases of orbital fracture in which surgery is postponed or not considered, the patient can be prescribed a course of broad-spectrum oral antibiotics, such as cephalexin or amoxicillin, 500 mg b.i.d. p.o. while the osseous tissues heal.

Clinical Pearls

- Patients presenting after orbital blunt trauma should be discouraged from nose-blowing until orbital fractures can be positively ruled out via imaging (X-ray, CT or magnetic resonance imaging). This helps to avoid the unwanted complication of orbital emphysema.

- The only way to diagnose an orbital fracture is by neuro-imaging.

- Air from the external environment may enter the subcutaneous tissue surrounding the orbit or globe via a communication created by a fracture. This is often visible as soft or "puffy" swelling and is known as orbital emphysema.

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ACQUIRED PTOSIS

Signs and Symptoms

Ptosis is a condition that may be either congenital or acquired; however, it is typically those with acquired ptosis who present with symptomology. Most individuals with congenital ptosis have made adaptations, and they usually have only cosmetic concerns. Common symptoms associated with acquired ptosis involve an inability to open the eye(s), decreased vision and superior loss of field due to lid obstruction.¹ Non-specific symptomology may include fatigue, headache (from chronic compensatory contracture of the frontalis muscle), blurred vision or even pain.

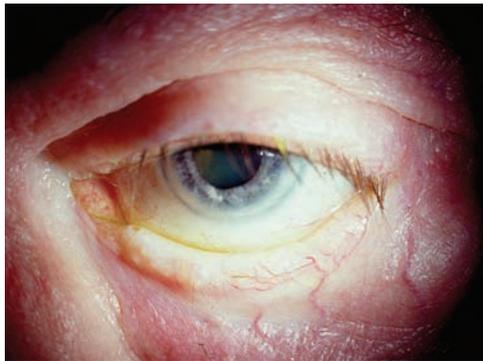
Examination of the patient with acquired ptosis reveals a narrowed palpebral aperture and notable lid droop. The condition may be unilateral or bilateral. The laterality may be indicative of the underlying etiology. Unilateral ptosis often stems from neurologic or mechanical disease, while bilateral ptosis is typically associated with generalized muscle disorders or aging. Associated signs may also help to identify the specific disorder. For example, Horner's syndrome involves a unilateral ptosis with a miotic pupil. A third nerve palsy demonstrates a ptosis with restriction of both upgaze and adduction. Additionally, the pupil may be dilated and unresponsive to light. Pain and swelling of the lid may point to an inflammatory or neoplastic disorder involving the lid, such as dacryocystitis or preseptal cellulitis. When ptosis is variable and intermittent, myasthenia gravis is often the cause.²

Pathophysiology

Acquired ptosis may present in a number of clinical disorders, but all can be ascribed to one of four categories:

aponeurogenic, myogenic, neurogenic or mechanical.¹

Aponeurogenic or involuntional ptosis is the most commonly encountered form of acquired ptosis, particularly in older



Involuntional ptosis in an elderly patient.

adults.¹ It involves local dehiscence, stretching and disinsertion of the levator aponeurosis from its attachments to the tarsus and pretarsal orbicularis muscle.² Histologic evaluation of the patient demonstrates atrophy, fatty infiltration and fibrosis of the levator muscle, as well as an attenuated levator aponeurosis.³ Although elderly patients are primarily affected, younger patients can develop this condition as a result of trauma, severe lid swelling, blepharochalasis, prior ocular surgery or long-term contact lens wear.⁴⁻⁶

Myogenic ptosis is less commonly encountered clinically than aponeurogenic ptosis. It results from one of a number of muscular debilities involving the levator palpebrae superioris. Etiologies include acquired mitochondrial dysfunction (chronic progressive external ophthalmoplegia), muscle fibrosis and degeneration (myotonic dystrophy and oculopharyngeal dystrophy) and dysfunction of neuromuscular junction signaling due to acetylcholine receptor autoantibodies (myasthenia gravis).^{1,7-10}

Neurogenic ptosis involves a disruption of innervation to the muscles of eyelid elevation. There are various etiologies, including vascular ischemia, inflammation, infection, demyelination and neoplasia. Most commonly, neuro-

genic ptosis implicates either the levator via oculomotor palsy (i.e., cranial nerve III palsy) or the muscle of Mueller via oculosympathetic dysfunction (i.e., Horner's syndrome). Occasionally, however, neurogenic ptosis results from a lesion to the supranuclear pathway, a condition referred to as apraxia of eyelid opening. This bilateral ptosis is characterized by inability to open closed lids voluntarily, and it may be seen in patients with extrapyramidal dysfunction, including progressive supranuclear palsy, Parkinson's disease, Shy-Drager syndrome, and Wilson's disease.¹¹

Mechanical ptosis can be caused by any condition that provides resistance to the action of the levator muscle. The most common etiologies include trauma, lid tumors, dermatocha-



Mechanical ptosis resulting from trauma to the lid.

lasis and conjunctival scarring (i.e., secondary to ocular cicatricial pemphigoid or Stevens-Johnson syndrome). Floppy eyelid syndrome also falls within this category. Excessive papillary responses, such as vernal keratoconjunctivitis or giant papillary conjunctivitis, can also result in mechanical eyelid ptosis.^{1,12,13}

Management

Without question, the most important aspect of managing a patient with acquired ptosis is determining the underlying cause. A thorough history is crucial. The clinician must consider laterality and check associated motility

function and pupillary responses. Pseudoptosis—any condition that gives the appearance of a drooped lid but actually involves no lid dysfunction in the involved eye—must be ruled out. Some examples of pseudoptosis include patients with small globes (e.g., microphthalmos, phthisis bulbi), enophthalmos, blowout fracture, contralateral lid retraction and ipsilateral hypotropia. Mechanical etiologies are the simplest to remedy, in principle: Removal of the cause creating the resistance should render improvement. In cases of extensive scarring from long-standing disease, a surgical consultation may be advised.¹⁴

Aponeurogenic ptoses may be treated by a variety of methods. The use of a prosthetic ptosis crutch attached to the spectacle frame can provide relief from some of the major symptoms encountered by these patients. The principle advantage of this modality is diminished cost without the risks of surgical intervention.¹⁵ Of course, surgery offers a more consistent and long-term solution for patients with ptosis. Procedures such as levator resection and aponeurosis tightening are principle considerations. All surgical patients should be followed closely for the development of secondary lagophthalmos and exposure complications.¹⁴

Ptosis that is neurogenic or myogenic in nature is best managed by a specialist with advanced training in neuro-ophthalmology. Such cases generally require imaging and other specialized testing (e.g. Tensilon® in myasthenia gravis) for confirmatory diagnosis.

Clinical Pearls

- Consider the lid crease when differentiating congenital ptosis from acquired ptosis. Acquired ptosis will maintain a lid crease; congenital ptosis will not. A high lid crease often heralds an aponeurogenic ptosis.
- Review of old photographs of the patient may also often help to differenti-

ate a congenital or long-standing ptosis from an acquired ptosis.

- The laterality of a ptosis can help determine its etiology. In general, unilateral ptosis may be due to Horner's syndrome, third nerve palsy, inflammation, trauma or infiltrative disease. Bilateral ptosis suggests damage to the supranuclear pathways of the brain or ocular myopathies. Age-related (senile or involutional) ptosis is typically bilateral but may be unilateral or asymmetric. A ptosis that is variable or "jumps" from one eye to the other is highly suggestive of myasthenia gravis.

- Ptosis is usually the initial and most common complaint in myasthenia gravis.¹ To confirm suspicions, clinicians can test sustained upgaze and/or conduct the "sleep or ice-pack test." Tensilon® testing confirms a diagnosis of systemic myasthenia.

- Third nerve palsies are variable in presentation and may or may not show pupillary involvement. Associated ipsilateral motility problems may be very subtle and are often overlooked. Remember that upgaze and adduction are affected most commonly. Third nerve palsies are unilateral except in cases involving the third nerve nucleus. In the latter, patients present with bilateral ptosis.

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ACQUIRED ENTROPION

Signs and Symptoms

Entropion represents a condition of eyelid malpositioning in which the lid margin rotates inward against the ocular surface.¹⁻⁵ This phenomenon may occur unilaterally or bilaterally and may involve the upper or lower eyelid, although the lower lids are affected most frequently.¹ Clinical features associated with entropion may be observed in and out of the slit lamp. The most obvious gross finding is a turning-in of the lid margin, with eyelid skin or eyelashes contacting the cornea. Associated hyperemia of the conjunctiva may also be noted. Biomicroscopy reveals variable corneal pathology, including superficial punctate epitheliopathy and, in severe or untreated cases, corneal ulceration and pannus formation.^{1,2} Symptoms associated with entropion may involve ocular irritation and/or foreign body sensation, tearing/epiphora and a persistent red eye. Vision may be variably affected, depending upon the extent and location of corneal damage.

Most commonly, entropion occurs as an involutional change in older patients; however, it can also represent cicatricial damage following blunt, chemical or thermal injury to the lids. A careful his-

tory should be elicited from all patients presenting with entropion to assess for prior trauma, particularly in those who are younger than 60 years.

Pathophysiology

Etiologically, there are four commonly recognized forms of entropion: congenital, cicatricial, involutional and spastic.

Congenital entropion, by definition, is present at birth or develops soon thereafter. It is relatively rare and typically affects the upper eyelid, although the lower lid may be affected as well. The pathophysiology may involve structural defects in the tarsal plate, shortened posterior lamellae (tarsal plate and conjunctiva) or eyelid retractor dysgenesis.^{1,3} Congenital entropion must be differentiated from other developmental oddities such as epiblepharon (a fold of skin that overlaps the eyelid margin, pushing the eyelid margin inward) and prominent epicanthus (a fold of skin partially covering the inner canthus, caruncle and plica semilunaris), which are similar in presentation but different in etiology.¹

Cicatricial entropion results from scarring of the ocular tissues, resulting in a vertical shortening of the tarsus. Most commonly, cicatricial injury is associated with trauma (e.g., chemical, thermal or blunt injury) but it can also occur secondary to disorders such as Stevens-Johnson syndrome, ocular cicatricial pemphigoid, herpes zoster and trachoma.³

Involutional (formerly called senile) entropion is by far the most common form of entropion encountered clinically. It predominantly affects the lower eyelid and is associated with a variety of structural features. These may include medial and lateral canthal laxity or dehiscence, disinsertion or stretching of the lower lid retractor complex, override of the pre-septal orbicularis over the pretarsal component and extension of orbital fat anterior to the orbital rim.^{3,6}

Spastic entropion represents a very

different type of disease state compared with the other three categories. It occurs when the preseptal orbicularis muscle becomes overactive and hypertrophic secondarily to blepharospasm, inflammation, irritation or surgery.¹ In addition, some degree of eyelid edema is also present; this adds to the abnormal mechanical forces turning the margin inward. Unlike the other forms of entropion, spastic entropion typically resolves when the underlying inflammatory or irritative factors are eliminated.⁵

Management

While the treatment of choice should be guided by the underlying cause, the fundamental philosophies of entropion management include: 1) moving the lid margins and lashes away from the cornea, and 2) providing lubrication for the compromised ocular surface. A simple method for alleviating contact between the eyelid and ocular surface is to apply surgical tape to the lid to rotate it out and away from the globe. Unfortunately, this technique is neither precise nor permanent, and it requires cooperation and participation by the patient. It is typically employed as a stopgap measure for individuals who are not amenable to prompt surgical intervention. The liberal use of artificial tear products is recommended for all entropion patients, regardless of the etiology; gel-forming solutions, gels and ointments may provide greater and more sustained relief of symptoms than drops. Bandage contact lenses may also prove helpful in providing a barrier between the ocular surface and entropic lid margin.⁷ Prophylactic antibiotic coverage may be beneficial in cases of more severe keratitis. In lieu of bacitracin or erythromycin ointment q.i.d., AzaSite® (azithromycin 1% in DuraSite®) offers a similar antimicrobial spectrum and efficacy at just once-daily dosing.

Botulinum toxin has been shown in several series to provide temporary relief of entropion.⁸⁻¹⁰ By affecting a

transient paralysis of the eyelid protractor muscles, botulinum toxin may help to alleviate the inward turning of the lid margin for several weeks, until surgical intervention can be undertaken. In cases of spastic entropion, the injection of botulinum toxin into the orbicularis muscle may break the cycle of spasm and irritation.¹⁰

Surgery provides the longest-lasting solution and is ultimately the best therapeutic option in most cases of entropion. In cicatricial cases, surgical repair may include excision of the scar with a tarsal plate graft from preserved sclera, ear cartilage or hard palate (in most severe circumstances), along with conjunctival and mucous membrane grafting using fetal amniotic membrane tissue.² For involutional entropion, common surgical options include the Quickert suturing technique or a base-down triangular tarsal resection. If significant horizontal lid laxity is present, then a combination technique involving horizontal shortening of the eyelid and resuspension of the lower eyelid retractors may be performed.^{1,2,11}

Clinical Pearls

- A thorough history should be completed for all patients with entropion. Attention to previous eye surgery, trauma, chemical injury, chronic infection and changes in eyelid tonus should be provided.

- The differential diagnosis of entropion includes eyelash anomalies such as trichiasis (inward turning of the cilia) and distichiasis (multiple rows of eyelashes), neuro-ophthalmic blepharospasm, traumatic etiologies, scarring from chemical injuries and lid malposition secondary to previous ocular surgeries.

- Focused physical testing can aid in the diagnosis of entropion. One such examination technique is the “snap-back test,” in which the patient is asked to look upward slightly while the examiner pulls the lower eyelid inferiorly; if the eyelid fails to return to its normal

anatomical position within 1 or 2 seconds before blinking, it is indicative of pathological laxity.¹ Another diagnostic technique is the dislocation or distraction test. This is performed by grasping the lower eyelid and pulling it anteriorly away from the globe. If the lid can be pulled more than 7mm from the globe, then increased horizontal lid laxity is the source of the entropion.¹

- The easiest way to resolve spastic entropion is to remove the offending irritant. In cases that involve the seventh cranial nerve (essential blepharospasm, orofacial dyskinesia, hemifacial spasm, facial myokymia) a neuro-ophthalmic consult is indicated. In some instances, these conditions can be managed pharmacologically using anti-seizure medications.

- Thermal cautery of the lid was once a popular corrective procedure for the treatment of involutional entropion; however, this technique appears to have fallen out of favor over the last 10 to 20 years, particularly among oculoplastic surgeons.²

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VERRUCA & PAPILLOMA

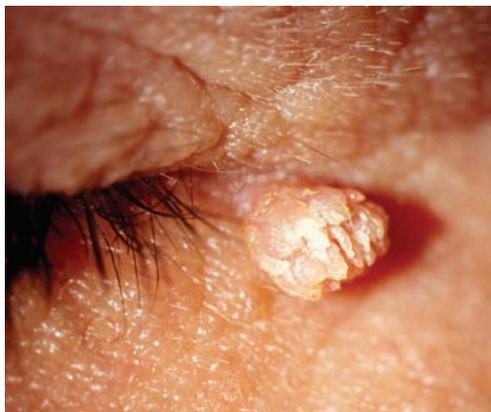
Signs and Symptoms

The term *papilloma* refers to a benign epithelial lesion of the skin or mucosa.¹ Papillomas affecting the eye primarily appear on the skin of the eyelid, but they are occasionally seen on the palpebral and bulbar conjunctivae. All papillomas have a similar characteristic configuration, consisting of lobular projections that can resemble mulberries or cauliflower. They may be flat or planar or they may be pedunculated (i.e., on a stalk). They may be solitary or multiple in presentation.

Verrucae are papillomas of viral origin. They are sometimes referred to in the literature as viral papillomas, *verruca vulgaris* or viral warts.² They may



Verruca plana.



Verruca filiformis.

vary in pigmentation from yellow to pink to dark brown or even black. At least two types of verrucae may be identified clinically. *Verruca plana* are gen-

erally round, flat-topped, slightly elevated lesions. Compared with other papillomas, their surface is remarkably smooth. *Verruca filiformis*, as the name implies, present with numerous “finger-like” projections from a larger base. Close inspection of all verrucae reveals that they are comprised of multiple stalks of fibrovascular tissue.³ Often, tiny red or black dots are evident near the surface of these projections, representing thrombosed, dilated capillaries.⁴ Verrucae of the lids may become quite large and often become keratinized over time; associated cutaneous horns are not uncommon. Verrucae of the conjunctiva are less common and tend to maintain a more “fleshy” appearance.⁵

Squamous papilloma is a generic term describing any papilloma of non-viral origin. Most often these lesions represent a benign dermatologic entity known as *acrochordon*, or “skin tag.”⁶ Clinically, squamous papillomas present as round or oval multilobular lesions. They may be sessile or pedunculated. Like verrucae, they may vary in pigmentation. Most commonly, the coloration approximates that of the patient’s skin; i.e., dark-skinned patients present with more densely pigmented papillomas. Upon close inspection, one may note a central vascular core within each lesion, which provides blood to the proliferating epithelium. The surface is typically roughened or granulated, reflecting the redundant epithelial cell growth.⁶

Patients with verrucae tend to be younger, typically between ages 5 and 20; less than 15% of patients are older than 35.⁷ Squamous papilloma, on the other hand, is more common in

those aged 30 and older, and the frequency increases steadily with age. There is no known race or gender



A large squamous papilloma on the lower lid.

predilection for either of these types of lesions, although *acrochordons* are encountered more commonly in obese and pregnant individuals.⁶ Patients with papillomas rarely present with symptoms beyond cosmetic concern, although in rare instances large lesions may induce mild lid dysfunction or discomfort.⁸ Patients who attempt to remove these lesions by “picking” at them may develop secondary, localized bacterial infections.

Pathophysiology

Papillomas represent benign overgrowths of normal epithelium, with varying levels of keratinization and pigmentation. Histopathologically, the lesions consist of multiple epithelial projections, the cores of which are vascularized, fibrous connective tissue. These are covered by acanthotic (i.e., thickened, prickle-cell layer of the skin) and hyperkeratotic epithelium.^{1,9}

Verrucae arise from viral infection; their cores represent inflammatory hypertrophy of tissue with viral inclusions.¹⁰ The causative agent in these lesions is the human papilloma virus (HPV), a double-stranded, non-enveloped DNA virus that is spread by direct contact.^{2-5,8,11} There are more than 60 strains of HPV, although most lesions are attributable to only a few of

the known serotypes.¹¹ As with many viral diseases, patients who are immunocompromised by chronic disease (diabetes, HIV infection, and so on) are more susceptible to infection.

Squamous papillomas may have numerous etiologies, but most often they arise *de novo* as a normal senescent skin change. The onset tends to be gradual rather than sudden. Lesions tend not to resolve spontaneously, nor is acute enlargement common. However, squamous papillomas may in rare instances represent precancerous lesions, so malignant conversion must remain a consideration.¹²

Management

Because of their benign nature, verruca and squamous papillomas typically warrant intervention only in cases of cosmetic concern, impairment of lid function or discomfort. Obviously, should any signs suggestive of malignancy develop, biopsy and removal are essential. Typical management involves patient reassurance, photodocumentation and periodic observation.

When warranted, papillomas may be removed via several methods. Electrocautery and surgical curettage are some of the oldest and still most widely practiced therapeutic options for both ocular and non-ocular lesions.¹³ The application of electric current results in iatrogenic necrosis and subsequent regression, usually within a week to 10 days. Unfortunately, both electrocautery and curettage can be painful unless local anesthesia is used, and they can result in cosmetically displeasing scarring. Additionally, physicians must take care when surgically removing verrucae to prevent spread of the virus by cutting across the stalk of pedunculated lesions. The virus may also spread if not enough of the adjacent tissue is removed.

Chemical cautery with trichloroacetic or dichloroacetic acid is a popular therapeutic alternative for periocu-

lar papillomas and other benign skin lesions. Application of these agents is simple and safe, provided the surrounding skin is coated with petroleum ointment and the chemicals are not applied on the lid margin or conjunctival surface. Cryotherapy with liquid nitrogen is another common treatment modality for papillomas, although this is typically not used outside of a dermatologist's office. Recently, however, over-the-counter cryogens such as Verruca-Freeze® (CryoSurgery, Inc., Nashville, TN) have made it possible for other health professionals to employ this technique. Again, exercise caution when using cryotherapy on periocular lesions; adverse effects can include hypo- or hyperpigmentation (especially in dark skin) as well as nerve damage when therapy is too aggressive.¹² Inadvertent application of cryogens to the ocular surface can result in corneal scarring, scleritis, uveitis and a host of other complications.

Other treatment options for periocular papillomas include laser ablation using the CO₂ laser, Nd:YAG laser or pulsed dye laser.¹³ Verrucae may also respond to a number of topical therapies, including cantharadin, podophyllin, bleomycin and imiquimod.

Clinical Pearls

- Although the nomenclature regarding papillomas is sometimes confusing and contradictory, the terms all refer to benign epithelial lesions.

- Whether the origin is hyperplasia or viral infection, recognition and differentiation from malignant skin lesions is the first concern. Red flags for malignancy include the following: asymmetry of shape, irregular borders, abrupt changes in coloration or size, crusting or bleeding with minimal manipulation. Rarely, malignant lesions may arise from or adjacent to benign papillomas.¹²

- Patients should be advised of the infectious nature of verrucae. They should be educated that these may

spread to form satellite lesions around the eye, affect skin in different regions of the body or be transferred to other individuals. HPV is often spread by sexual contact; patients should be asked whether similar lesions exist elsewhere on the body; if so, appropriate referrals should be made.

- Some states permit optometrists to remove benign skin lesions via chemical cautery. The Derma-Cauter-All® Chemical Cauterization Kit is available to eye-care practitioners and includes all of the necessary items to perform in-office chemical cautery (dichloroacetic acid, petrolatum, cleaning pads, acid receptacle, applicators, dropper and an instruction packet with a DVD).¹⁴ The kit may be ordered online from Sigma Pharmaceuticals, LLC (www.sigmapharmaceuticals.com) or from North Pine Enterprises (www.northpineenterprises.com).

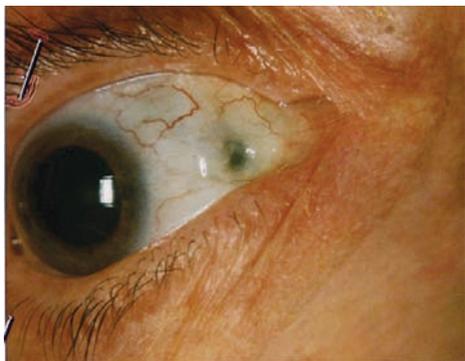
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SCLERAL MELT

Signs and Symptoms

Scleral melt, also known as scleral necrosis, is an uncommon condition that typically presents in older adults. In most cases, scleral melt represents a late complication of ocular surgery or trauma. Clinically, the condition may be seen as a focal area of scleral thinning between the corneal limbus and the insertion of the extraocular muscles, with the dark blue/black coloration of the underlying uvea visible beneath the lesion. A variable degree of adjacent conjunctival inflammation accompanies scleral melting, depending upon the etiology and associated pathology.

Individuals presenting with scleral melting generally report symptoms of mild-to-moderate discomfort. Foreign body sensation or stinging is common, as is excessive lacrimation and possibly photophobia. Blurred vision is another frequent symptom. Rarely do patients complain of intense ocular pain. No race predilection has been identified, but women do appear to be affected more often than men.¹ A history of systemic autoimmune disease is another common finding; some of the associated conditions may include rheumatoid arthritis,



Scleral melt.

systemic lupus erythematosus, polyarteritis nodosa, inflammatory bowel disease, Wegener's granulomatosis, relapsing polychondritis, diabetes mellitus and thyroid disorders.¹⁻³

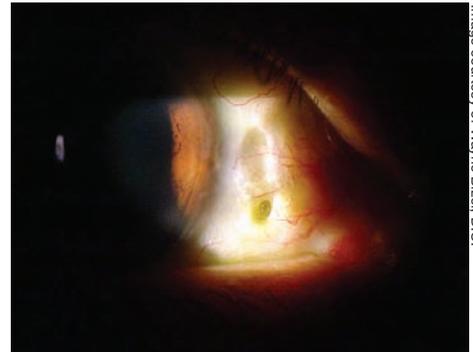
Pathophysiology

The most common predisposing factor in cases of scleral melting is prior ocular surgery. There is a particularly high association with bare sclera pterygium excision, particularly cases in which adjunctive radiation or chemotherapy was used.^{4,5} Scleral melt has also been described as occurring after cataract extraction, trabeculectomy, strabismus surgery, retinal detachment repair and orbital/ocular radiation.^{1,2} Alternatively, the patient may report a prior incident involving a severe chemical or thermal burn to the ocular surface. The condition may occur as soon as one day or as late as 40 years after the antecedent trauma.^{4,6} Less commonly, scleral melt is encountered as a sequela of severe ocular surface disease (e.g., keratoconjunctivitis sicca), ocular infection, systemic vasculitis or connective tissue disorders.^{7,8}

Scleral melting is presumed to represent a delayed-onset hypersensitivity response to localized ischemia involving the episcleral blood vessels.⁹ Such ischemia can be precipitated by surgical trauma (especially when accompanied by beta irradiation or mitomycin C therapy), chemical or thermal injury or, less commonly, by severe autoimmune disease or vasculitis.² The exact mechanism of damage is poorly understood, but enzymes produced by polymorphonuclear cells are likely implicated, leading to destruction of collagen and proteoglycans that comprise the scleral stroma.¹⁰ Evidence to support these hypotheses include the success of systemic immunosuppression in the treatment of scleral melts, as well as the presence of immune complexes in the episcleral vessel walls among such patients.¹¹ Research has identified elevated levels of both tumor necrosis factor alpha (TNF- α) and matrix metalloproteinase-9 (MMP-9) in patients with surgically induced scleral necrosis.¹²

Management

Therapeutic intervention in cases of scleral melt depends on a number of factors, most notably the disposition of the patient and the risk of globe perforation. For cases that are relatively asymptomatic and not in danger of perforation, simple periodic observa-



Scleral necrosis.

tion (e.g., every 4–6 months) along with liberal use of ophthalmic lubricants may be all that is required.² More severe cases may require the application of surgical patch grafts to maintain tectonic support of the globe.² Tenonoplasty—a surgical procedure involving excision of necrotic superficial tissue along with dissection and advancement of viable underlying Tenon's capsule—is performed initially to reestablish the blood supply to the ischemic sclera. Then, donor sclera tissue or a lamellar corneal graft is typically transplanted to the wound and covered with either amniotic membrane or a conjunctival flap.^{2,13,14}

Postoperatively, treatment with topical corticosteroids (e.g., 1% prednisolone acetate, q.i.d.) and prophylactic antibiotics (e.g., 0.5% moxifloxacin, t.i.d.) helps control subsequent inflammation and infection.² A variety of other surgical techniques have been piloted, with varying success.^{14,15} The concurrent use of immunosuppressive agents, such as oral cyclophosphamide, azathioprine, cyclosporin A and tacrolimus, may be helpful to prevent graft rejection in difficult cases.¹⁶

Clinical Pearls

- Scleral melt is a serious and challenging clinical problem, because it threatens the integrity of the eye. Even asymptomatic cases likely warrant a surgical consultation to assess the potential for perforation.

- Numerous conditions can masquerade as scleral melting. These include benign entities such as senile scleral plaques and dellen, as well as more serious conditions including ciliary body melanoma and scleromalacia perforans. Scleromalacia perforans can be differentiated from scleral melt in that patients with the former are generally asymptomatic and present with bilateral involvement. In addition, the eyes are usually otherwise quiet in the setting of the patient having a longstanding, chronic history of rheumatoid arthritis.

- When scleral melting occurs as a complication of ocular surgery, the term “surgically-induced necrotizing scleritis” (SINS) is often used.

- In cases of scleral melt that do not have an obvious traumatic or iatrogenic etiology, and especially in those cases that involve the limbal and peripheral corneal regions, a medical workup to examine for collagen vascular disease is highly advised. Contributory systemic disorders are present in as many as 40% of scleral melt cases, and 62% of subjects carry serologic markers for connective tissue disease.^{4,6}

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GIANT PAPILLARY CONJUNCTIVITIS

Signs and Symptoms

Patients with giant papillary conjunctivitis (GPC) present clinically with ocular irritation and itching, increased mucus accumulation and variable palpebral conjunctival redness. By definition, the condition is always associated with an object interacting with the ocular surface, such as an exposed suture, extruded scleral buckle, cyanoacrylate glue, a contact lens or ocular prosthesis.¹⁻⁶ Since the condition is most commonly associated with contact lens wear, some distinguish the etiology of that specific cause and effect as contact lens papillary conjunctivitis (CLPC).² Patients with CLPC generally report symptoms of lens discomfort and intolerance, increased lens movement and surface coating and ocular itching after lens removal. The initial presentation may occur months or even years after lens wear has been initiated. Biomicroscopic examination reveals large papillae along the upper tarsal conjunctiva; these papillae are generally

between 0.3–1.0mm and are typically uniformly shaped.⁶ Additionally, tarsal conjunctival hyperemia and thickening may be observed. Vision can be affected due to deposits on the lens, as the result of contact lens displacement secondary to superior lid papillary hypertrophy or from repetitive mechanical corneal abrasion (shield ulceration).

Pathophysiology

GPC is loosely classified as a form of ocular allergy, mostly because it is known to involve mast-cell degranulation.^{1,2} Patients with GPC are also likely to have a history of atopy (e.g., asthma, allergic rhinitis, hayfever).^{2,3} However, this condition differs from the more common clinical presentations such as seasonal and perennial allergic conjunctivitis in that GPC has a greater eosinophil and basophil response than other acute forms of allergic conjunctivitis. Additionally, GPC shows comparatively low tear histamine levels.^{1,4}

From a pathophysiological perspective, GPC does not appear to be triggered by a foreign antigen-like typical allergic reactions; rather, it is believed to result from a combination of traumatic and autoimmune elements. The chronic mechanical “hammering” of the tarsal surface by a contact lens or other object, combined with proteinaceous surface deposits on these substrates has been hypothesized to induce a cell-mediated response, which results in papillary hypertrophy and other elements of surface inflammation.⁵ GPC seems to involve both a Type I (immediate) and a Type IV (delayed) hypersensitivity reaction, implicating a response by both mast cells and inflammatory T-cells.²

Management

The initial treatment of GPC involves removing the allergic/inflammatory stimulus whenever possible. In cases of CLPC, this means suspending contact lens wear for an indeterminate length of time. Numerous topical medications have been advocated for adjunctive therapeutic relief.

Perhaps the oldest and most well-known therapeutic agents to be used in this capacity are the mast-cell stabilizers. Historically, cromolyn sodium 4% was widely accepted as the gold standard in



Giant papillary conjunctivitis in a contact lens wearer.



managing GPC throughout the 1980s and early 90s.⁷⁻⁹ Today, however, many prefer the antihistamine/mast-cell stabilizer combinations, such as olopatadine and epinastine, because these agents provide more rapid and complete symptomatic relief, less frequent dosing (once or twice daily) and greater comfort upon instillation than the older treatment.^{2,10} In lieu of anti-allergy therapies, topical corticosteroids likely represent the most comprehensive option in GPC management. Steroids completely inhibit the arachidonic acid pathway, preventing both prostaglandin and leukotriene synthesis. In addition, these drugs have the capacity to stabilize cell membranes and hence may diminish mast-cell degranulation.¹¹

Resolving GPC may be a long and arduous process. For those with CLPC, lens wear may resume when symptoms are diminished and the hyperemic response lessened. The papillary response may never fully abate, so com-

plete elimination is not a realistic goal. Upon reinitiating lens wear, a decreased wearing schedule, increased frequency of contact lens cleaning, enzymatic removal of proteins and/or frequent replacement becomes paramount.

Clinical Pearls

- CLPC has been noted to occur with all types of contact lenses, although it is most common with HEMA-based soft lenses.^{1,6,12} Silicone hydrogels have also been implicated in the development of CLPC; however, the presentation in these patients may be somewhat atypical, inducing a localized presentation in which the papillae are confined to just one or two areas of the tarsal conjunctiva near the lid margin.^{13,14}

- The use of topical steroids as first-line agents in GPC remains controversial, primarily due to the potential side effects of long-term steroid use. These include elevated

intraocular pressure, cataractogenesis and increased susceptibility to ocular infection. For this reason, most sources stress that corticosteroids should be used only for short-term management of GPC, if at all.

- Ester-based steroids such as loteprednol have also been widely advocated over ketone-based steroids (e.g., prednisolone acetate or fluorometholone) in GPC because they enjoy the reputation of having a greater safety profile than the latter.^{11,15,16}

- Topical cyclosporine A offers a long-term immunomodulatory option without the potential side effects of corticosteroids. Although no peer-reviewed data currently exists in the literature supporting cyclosporine for GPC management, its utility in the treatment of other forms of allergic conjunctivitis is well established.¹⁷ Similarly, another immunomodulatory agent, topical tacrolimus ointment, has

recently been proved effective in refractory GPC.¹⁸

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CONJUNCTIVAL LYMPHOMA

Signs and Symptoms

Conjunctival lymphomas present as

rapidly growing mass lesions of the superficial ocular surface. They can be seen as isolated entities or they may occur as a localized manifestation of systemic lymphoma.^{1,2} The typical appearance is that of a pink, “fleshy” mass that arises from within the fornix and extends toward the cornea; classically, they are described as “salmon-colored patches.” They may present bilaterally in 20% to 38% of patients.²⁻⁴ Individuals with conjunctival lymphoma are usually between 60 to 68 years; the condition predominantly affects female patients.²⁻⁵ These patients may have cosmetic concerns regarding chronic redness, and they occasionally report dryness and irritation, but they rarely experience substantial ocular discomfort. Vision may be variably impacted, depending upon the location and extent of the lesion.

Pathophysiology

Lymphoid tissue is present in most organs throughout the body. It is connected by channels and conduits to lymph nodes, located primarily in the neck, axillae, groin and abdomen. Lymphoma is an abnormal, malignant growth of lymphoid tissue; a cancer of the various elements of the lymphatic system. In the eye, lymphoma typically manifests as a conjunctival or orbital mass; less common presentations include choroidal infiltration with secondary uveitis and infiltrative optic neuropathy.³

Over the years, a number of classification systems have been developed to describe lymphoid tumors. These include the Rappaport, Kiel, Lukes-Collins, Working Formulation, British National Lymphoma Investigation, and Revised European-American Lymphoma (REAL) classifications.⁶ These systems were based on the histological appearance of tumor growth (nodular or diffuse), size of cells (small, medium or large) and cell immunophenotype (B, T, NK or null).⁶ Today, the accepted standard is the World Health

Organization (WHO) classification, established in 2001.^{6,7} This system recognizes three broad categories: precursor cell lymphomas, peripheral B-cell neoplasms and peripheral T and NK cell neoplasms. It further subdivides these into numerous specific entities based upon morphologic, immunologic and genetic characteristics.^{6,7}



MALT lymphoma.

Most conjunctival lymphomas fall into the category of B-cell neoplasms of the non-Hodgkin's variety.^{6,8} These are frequently broken down further into mucosa-associated lymphoid tissue (MALT) lymphomas and non-MALT lymphomas. MALT lymphomas generally follow a more indolent course; non-MALT lesions are considered highly malignant and invasive.⁹

Management

Although conjunctival lymphomas often have a characteristic appearance, it is important to differentiate them from other benign tumors of the ocular surface, such as squamous papilloma, pyogenic granuloma and lymphangiectasis. Furthermore, it is not possible to differentiate between benign and malignant lymphoid tumors (or MALT vs. non-MALT lymphomas) simply on the basis of clinical presentation. Hence, excisional biopsy is crucial to establish a definitive diagnosis. In addition, any patients with biopsy-

proven lymphoma deserve a complete medical evaluation to determine whether systemic lymphoma is present. This includes basic hematology (CBC with differential) as well as evaluation by an oncologist. Radiographic imaging of the head, chest and abdomen should also be obtained if systemic involvement is suspected.⁹

Therapy for conjunctival lymphoma depends on the disposition of the tumor and whether there is disseminated lymphoma elsewhere in the body. Isolated conjunctival lymphoma (i.e., involving the conjunctiva but not other ocular or systemic structures) is often treated with external beam irradiation, on the order of 2,000–4,000cGy.^{2,10} Dosage and exposure tends to be higher for more

aggressive non-MALT lymphomas, although care must be taken to minimize long-term complications of ocular radiation such as xerophthalmia or cataract formation.¹¹ Other therapeutic options for these patients may include brachytherapy, cryotherapy, intralésional interferon-A, rituximab or simple observation.^{10,12,13} Those with invasive or disseminated lymphoma may require systemic chemotherapy in addition to local treatment. The standard regimen for non-Hodgkin's lymphoma is a combination of cyclophosphamide, doxorubicin, vincristine and prednisone, referred to in oncologic circles as CHOP.^{14,15}

Clinical Pearls

- Conjunctival lymphoma should be part of the differential in all cases of sudden-onset rapidly growing lesions of the fornix, particularly those that are highly vascularized and fleshy. Never assume that these lesions are benign; the most prudent course of action is to obtain a prompt biopsy.

- Though conjunctival lymphoma may be associated with systemic lymphoma, the ocular lesions have not been shown to metastasize to any significant degree. The five-year survival rate for MALT lymphomas is excellent.¹⁵

- Localized therapy for conjunctival lymphoma may not be required in individuals with disseminated lymphoma who are already undergoing systemic chemotherapy.

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BLUE SCLERA

Signs and Symptoms

Blue sclera is not a diagnosis but a sign of imperfect connective tissue, collagen and collagen-vascular construction and assemblance.¹⁻⁴ The etiology of the blue hue comes from the pigmentation of the uveal tunic showing through beneath an abnormally thin scleral coat.¹⁻⁴ This is in contradistinction to ocular melanosis, which produces a brown scleral hue. Although the blue coloration may be apparent to examiners, in most instances, unless there is accompanying ocular inflammation or vision loss secondary to an associated vascular occlusion or choroidal neovascularization (CNV), there are no symptoms. The ocular signs and symptoms that accompany the findings of blue sclera will be consistent with the underlying syndrome producing it. The systemic diseases frequently associated with blue sclera include Nevus of Ota, Ehlers-Danlos syndrome (EDS), Marfan's syndrome, osteogenesis imperfecta and rheumatoid arthritis.¹⁻⁴

Pathophysiology

Nevus of Ota is a benign dermal melanocytosis.⁴ It involves the facial skin as a macular discoloration and can involve the ocular structures such as the episclera, sclera, conjunctiva, cornea, retina and uveal tract. Melanocytes are derived from neural crest cells that migrate to the conjunctiva and uvea. When these cells invade the episclera and sclera they can produce patchy areas of bluish subconjunctival discoloration. Open-angle

glaucoma and malignant melanoma are two known ocular complications.⁴

Ehlers-Danlos syndrome is a heterogeneous group of connective tissue disorders characterized by joint hypermobility, skin hyperelasticity, tissue fragility, easy bruising and poor wound healing.⁵ Abnormal bruising and bleeding with skin extensibility are cardinal features.⁶ The vascular complications seen in Type IV disease may affect all anatomical areas, with a



Two examples of blue sclera.



tendency toward large and medium diameter arteries.⁷ In addition to a blue sclera via scleral thinning, dissections of the vertebral arteries and the carotid arteries are typical.⁷ Patients with EDS may present with blue sclera and dilated and tortuous conjunctival vessels with pulsatile proptosis.⁸ Patients experiencing vascular dissection (a stretching and tearing of the affected vessels) may present with variable headache along with fleeting

visual symptoms such as transient vision loss and transient visual blur.⁹ Ehlers-Danlos syndrome may produce radiating angioid streaks, which are known to induce choroidal neovascularization (CNV).¹⁰

Marfan's syndrome is an autosomal-dominant multisystem connective tissue disorder resulting from mutations in the gene for fibrillin, FBN1.¹¹⁻¹³ The clinical diagnosis is based on a set of well-defined clinical criteria (long face, cardiac issues, dental issues, ocular issues and lumbosacral dural ectasia).^{11,12} Ocular complications include blue sclera, lens subluxation (typically superiorly, a common diagnostic feature), vitreous degeneration and angioid streaks which also predispose the potential for CNV.^{14,15}

Osteogenesis imperfecta (OI) is a rare heritable condition characterized by bone fragility and reduced bone mass.^{16,17} OI produces systemic complications that include dentinogenesis imperfecta, hearing loss, joint laxity, restrictive pulmonary disease and short stature. Its ocular complications include blue sclera, fragile cornea, decreased ocular rigidity, myopia, glaucoma, keratoconus, corneal opacity, small corneal diameter and congenital Bowman's layer agenesis.¹⁸⁻²⁰

Rheumatoid arthritis (RA) is a systemic disease with manifestations in many organ systems.²¹ While the articulating surfaces are a focus, extra-articular manifestations occur in almost every organ system with varied incidence.²¹⁻²³ Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia and immune mechanisms such as T-cell activation. Ophthalmic presentations may include blue sclera, Sjögren's syndrome (autoimmune rheumatic variant characterized by fatigue, dry eyes and dry mouth), episcleritis, scleritis, scleromalacia perforans (inflammation and thinning of the wall of the eyeball), artery and vein occlusion.²¹⁻²³

Management

There is no management for blue sclera. The key is recognizing its appearance and referring for the proper medical workup. Because the management of a discovered systemic disease and its potential complications will rest within the domain of the internist or specialist, the role of the primary eye-care provider is to discover undiagnosed cases and monitor ocular health for the abovementioned conditions.

Medical testing may be required to determine potential causes for blue sclera. The laboratory testing potentially includes complete blood count with differential and platelets (CBC, c Diff and PL), X-rays of the chest and hands, sacrolumbar/iliac X-ray, erythrocyte sedimentation rate, rheumatoid factor (RF), human leukocyte antigen (HLA-B27), rapid plasma reagin (RPR), venereal disease research lab test (VDRL), fluorescent treponemal antibody absorption test (FTA-Abs), blood urea nitrogen (BUN), total serum protein, homocysteine, skin biopsy and genetic analysis.²⁴

Clinical Pearls

- Blue sclera may be associated with Ehlers-Danlos syndrome and these patients' angioid streaks may also be produced by sickle cell anemia, pseudo-xanthoma elasticum, high myopia, age-related causes and Paget's disease of the bone. Any patient with blue sclera should be monitored for angioid streak formation and subsequent CNV.
- Corneal thickness has been reported to be reduced in patients with OI and blueness of the sclera. This may be of importance because these patients may exhibit artificially low intraocular pressure measurements.
- Scleritis occurring in RA has the potential to produce blinding consequences. Systemic and ocular treatment is required.

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CORNEAL LACERATION

Signs and Symptoms

Corneal lacerations are invariably accompanied by a recent history of ocular trauma. Typically, this involves a sharp object such as a knife, hand tool or glass shard, although cases have been documented involving some very obscure etiologies, including such odd items as fish hooks, plastic toys, ninja stars and the talons from a bird of



Repaired corneal laceration with interrupted sutures.

prey.¹⁻⁴ Lacerations may also result from penetration by a high-velocity projectile or may occur secondary to severe blunt injury.⁵ Patients with corneal laceration typically report intense pain at the onset, although this may diminish over time due to severing of the corneal nerves. Additional symptoms may include photophobia, excessive lacrimation and variably reduced vision.

Inspection of the eye reveals pronounced ocular injection, secondary blepharospasm and pseudoptosis secondary to pain and photophobia. The corneal laceration may be obvious if it is large or irregularly shaped. One may observe a jagged defect that extends from the corneal epithelium into and through the underlying stroma. Small, linear breaks may be more difficult to visualize, because the opposing surfaces of the wound may close like a “flap-valve” under the sustained intraocular pressure of the eye. If the laceration is full thickness, the anterior chamber may be shallow or even flat, again depending upon the extent of the injury. Aqueous can be visualized percolating from the edge of the wound when fluorescein is applied (Seidel’s sign). The intraocular pressure will be substantially reduced in cases of full-thickness laceration, sometimes reaching as low as 0-2mm Hg depending upon the timing of the evaluation compared to the time of injury.

One finding that is particularly diag-

nostic of a perforating corneal injury is the presence of air bubbles within the anterior chamber. Other key signs include corectopia (i.e., irregularity of the pupil) and iris prolapse into or through the wound. Accompanying pathology related to the inciting trauma is also common; subconjunctival hemorrhage, hyphema, iridodialysis, lens dislocation, cataract, vitreous hemorrhage and vitreous incarceration are all possible findings.⁴

Pathophysiology

The cornea possesses great tensile strength and is generally resistant to penetration by blunt perpendicular forces; however, tangential injuries of sufficient force—particularly those induced by sharp objects—have the potential to cause the lamellar sheets of the corneal stroma to separate, allowing for entry into the tissue. By definition, a laceration refers to a wound produced by the tearing of a bodily tissue; it is usually traumatic, irregularly shaped and induced unintentionally by a foreign object.⁶ Lacerations may vary in thickness. When the cornea is penetrat-



Acute corneal laceration due to screwdriver injury.

ed through all layers into the anterior chamber, it is referred to as a full-thickness laceration. A cleft that does not completely traverse the stroma and endothelium is considered a partial-

thickness laceration.

The obvious danger in a full-thickness corneal laceration is the subsequent extrusion of intraocular contents through the wound or introduction of harmful debris. As the pressure in the anterior chamber drops, the pressure from the vitreous body forces the lens and iris forward. Excessive manipulation or further trauma may induce a prolapse of these tissues through the laceration. An additional risk is the transmission of potential pathogens into the eye, resulting in infection. Numerous cases of endophthalmitis have been documented, in some cases involving highly unusual organisms.⁷⁻⁹

Management

From a primary care point of view, the management of corneal laceration involves first aid. The clinician must make a definitive diagnosis as quickly as possible using the least amount of manipulation or intervention. It is most important to differentiate corneal abrasions and partial-thickness lacerations from full-thickness lacerations. This is facilitated by using the Seidel’s test. Here sodium fluorescein is applied directly to the wound, and then carefully inspected under cobalt blue illumina-

tion. In cases of corneal perforation, aqueous will slowly percolate from the lesion, creating a dark-appearing area with a steady flow of fluid to the inferior fluorescent tear lake. Tonometry, gonioscopy and other procedures requiring pressure on the globe should be deferred if there is any suspicion of potential ocular perforation.

To facilitate examination in cases of corneal trauma, it is often advantageous to instill a topical anesthetic. This helps to alleviate patient discomfort and permits the clinician to perform a more thorough

evaluation of the eye, including visual acuity assessment, pupillary evaluation and biomicroscopy. The downside of using a topical anesthetic—or any topical agent—in cases of corneal laceration is the potential for deep tissue toxicity or introduced infection. With a compromised cornea, topically applied drugs achieve intraocular concentrations much greater than normally intended. This can lead to unwanted sequelae. Hence, any topical agents should be used sparingly if at all, and preservative-free options, where available, are preferred.¹⁰

Once the diagnosis is established, the primary goal is to stabilize the eye and ensure that no further damage occurs. An eye shield should be gently placed to protect the globe; however, the use of a pressure patch or bandage contact lens is ill-advised, primarily due to the manipulation required to apply these measures. In the event that material is lodged in the wound, it should not be removed. Immediately refer to a corneal specialist to initiate surgical repair of the laceration. Patients must be instructed not to eat or drink before the surgical consultation, because this may delay the procedure. If the patient is nauseous or overly anxious, consider prescribing an antiemetic agent such as meclizine 25 mg p.o. to prevent vomiting.

Repair of corneal lacerations involves a variety of measures. Partial-thickness and self-sealing lacerations may be treated with nothing more than topical antibiotics, cycloplegics and a bandage contact lens. Larger wounds or those that are prone to leakage may sometimes be managed with cyanoacrylate tissue adhesive in lieu of surgical repair.¹¹ However, most corneal lacerations—certainly most full-thickness lacerations—require suturing to restore corneal integrity.

Clinical Pearls

- According to the database of the United States Eye Injury Registry (USEIR), corneal injuries are five times

more likely in males than females, and are also more common in younger age groups.¹¹

- Although fingernail scratches typically do not generate enough force to lacerate the cornea, at least one case of this has been documented in the literature; hence, it is important to rule out laceration in all cases of corneal trauma.¹²

- With a corneal laceration, the patient may be lacrimating so heavily as to render the Seidel test inaccurate. In these cases, a shallow or flat anterior chamber or the presence of bubbles within the anterior chamber indicates a breach in the corneal integrity.

- For full-thickness corneal lacerations, the less done in the office the better. Assess the injury, arrange for the appropriate referral and shield the eye gently for protection while the patient is in transit to the surgeon.

- The patient should be educated that the initial entering acuity may represent the best vision that can be expected after surgical repair. Of course, visual acuity may improve following surgery; however, it is best not to elevate a patient's expectations.

- A fresh, previously unopened bottle of topical anesthetic is preferred when a full thickness corneal laceration or globe rupture is suspected.

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TERRIEN'S MARGINAL DEGENERATION

Signs and Symptoms

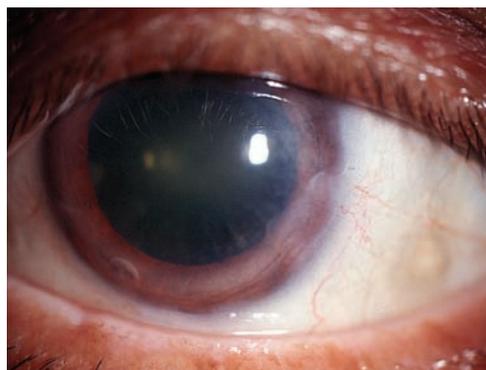
Terrien's marginal degeneration (TMD) is a rare, slowly progressive thinning disorder of the cornea. The condition is typically bilateral and predominantly affects men aged 40 years and older, although women and younger patients may also present with a variant of this condition.¹⁻³ Individuals with TMD generally do not exhibit pain, photophobia, lacrimation or conjunctival redness upon presentation. In fact, aside from possible visual changes (resulting from increased regular and irregular astigmatism), these patients are often asymptomatic.

In its earliest stages, TMD presents as a fine, white punctate opacification of the peripheral cornea. As in arcus senilis, a clear zone is preserved between the limbus and the affected region of the cornea, although this area may be bridged by fine vascularization resembling pannus. The proximal edge of the degeneration is demarcated by a circumferential yellow line, representing lipid infiltration.⁴ Although these changes can be noted anywhere along the corneal periphery, the superior and superonasal aspects of the cornea are characteristically involved. Over time, the region undergoes stromal thinning such that the area resembles a sloping "gutter" with a peripheral lip defined by the corneal limbus.^{2,5} Despite the loss of corneal tissue, the overlying epithelium remains intact.⁵ Late changes may include localized corneal ectasia, hydrops and opacification. Perforation is a rare sequela, encountered in only about 15% of cases; although the major-

ity of these complications are due to coincident trauma, spontaneous perforation has been encountered in TMD.^{1,3}

Pathophysiology

The precise etiology of TMD has never been fully elucidated; however, the disorder has been loosely associated with vernal keratoconjunctivitis, posterior polymorphous dystrophy and ery-



Terrien's marginal degeneration.

thema elevatum diutinum (a rare chronic skin disease with cutaneous vasculitis), suggesting a possible autoimmune mechanism.⁶⁻⁸ Studies have demonstrated evidence of increased lysosomal activity.^{9,10} Histopathologically, the principle findings include fibrosis, vascularization and phagocytosis of corneal stromal collagen by histiocytes.⁹ The epithelium remains intact, but there is degeneration of basal epithelial cells and an abnormal basement membrane-like layer. Bowman's membrane is typically lost; Descemet's membrane may be intact, thickened or thinned, and sometimes appears wavy. The endothelium may be normal or attenuated.⁹

Management

The most important aspect of managing patients with TMD is recognizing the condition and differentiating it from other peripheral corneal degenerations. In questionable cases, corneal topography can be a helpful diagnostic technique, demonstrating corneal flattening at the juncture of the furrow and

corneal steepening 90° away from the area of flattening, with a relatively spherical and regular central area.¹¹

Therapeutic management of Terrien's marginal degeneration is largely supportive, as the majority of patients remain asymptomatic. TMD patients are known to suffer from periodic episodes of red, irritated eyes secondary to mild adjacent conjunctival inflammation. In addition to lubrication with artificial tears, these cases often respond effectively to topical corticosteroid therapy (e.g., prednisolone acetate 0.12 % or 1%, loteprednol 0.5% q.i.d.). Refractive correction is paramount to compensate for the acquired astigmatism, although this can be difficult because of the irregularity and severity of the disturbance. Contact lenses may offer a better option for visual success, but they often require

complex fitting techniques (e.g., piggyback lens systems) by trained specialists. Because patients with severe TMD are at risk for corneal perforation, polycarbonate spectacles are highly recommended, even in cases where contact lenses are the primary refractive correction. When vision cannot be corrected or the risk of perforation is high, surgical intervention may need to be considered. A variety of procedures have been employed with modest success, including thermokeratoplasty, annular full thickness penetrating keratoplasty, lamellar penetrating keratoplasty, and large eccentric corneal grafts.¹²⁻¹⁴

Clinical Pearls

- Suspect Terrien's marginal degeneration in cases of bilateral or asymmetrical peripheral corneal thinning in a non-inflamed, otherwise asymptomatic eye.
- Key differential diagnoses of TMD include the following:
 - **Peripheral corneal melting (keratolysis)** secondary to collagen vascular disease (e.g., rheumatoid arthritis or

polyarteritis nodosa)—bilateral, typically painful and progressive to perforation

- **Mooren's ulcer**—unilateral or bilateral, painful corneal thinning with neovascularization.

- **Pellucid marginal degeneration**—painless, inferior, peripheral corneal thinning, a variant of keratoconus.

- **Furrow degeneration**—painless, peripheral corneal thinning adjacent to corneal arcus, without vascularization.

- **Dellen**—reversible, painless oval thinning secondary to corneal dehydration.

- **Marginal keratitis** secondary to staphylococcal hypersensitivity—painful, infiltrate present, inset from limbus.

- **Fuch's Marginal Keratitis**—peripheral corneal inflammation marked by pannus and thinning.

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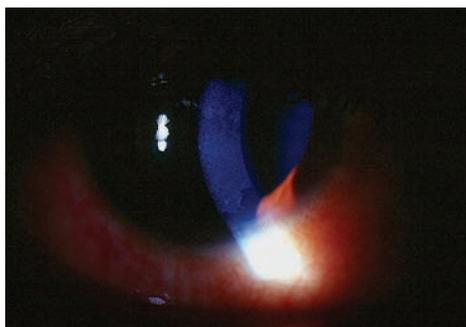
CHEMICAL/TOXIC KERATO-CONJUNCTIVITIS

Signs and Symptoms

Toxic keratoconjunctivitis, sometimes referred to as chemical keratitis or toxic follicular conjunctivitis, results when the cornea, palpebral and bulbar conjunctiva and surrounding tissue are exposed to any number or combinations of foreign substances.¹⁻⁴ The process may occur unilaterally or bilaterally. Symptoms occurring from chronic exposure include ocular itching, burning and tearing, corneal punctate epitheliopathy, injection of the bulbar and palpebral conjunctivae, chemosis of the conjunctiva and adnexa and inferior and/or superior conjunctival follicles and papillae in the absence of lymphadenopathy.¹⁻⁴ If the reaction is substantial, involves a large area or the exposure is diffuse, an anterior chamber reaction is possible. The severity of the external damage and internal inflammation depends upon the nature of the offending substance (caustic, bland, acid, base, solid, liquid, gas or light) along with the duration (long time vs. short time) and type of contact (direct or indirect).⁵ It is important to recall that phototoxicity (exposure to ultraviolet light, typically from a welder's arc or sunlight reflected by snow) is a keratitis-producing source.^{4,6} When exposure to an agent or combination of substances or irritants (mechanical included) continues without treatment or antidote, a fibrovascular adaptation of the conjunctival tissue may ensue.⁷ This finding is known as pannus.⁷

Typically, patients present in one of two ways: either they report with an unexplained red eye, oblivious to a causative vector, or they report that their eye was accidentally exposed to something noxious. In the case of the phenomenon known as medicamentosa, there will be a history of starting a new ocular medication, preparation (i.e., contact lens solution, rewetting drop) or contact lens.⁸ Diagnosis is typically straightforward. The keratitis is

termed punctate epitheliopathy and exactly resembles its description (diffuse, dot-like compromise either confined to the area of contact or distributed equally throughout the entire tissue). The conjunctivae, while injected, will appear elevated, boggy and



Chemical keratitis: note the "ground glass" appearance of the cornea.

chemotic without being firm, warm or painful to the touch. In some instances, the term "watch glass" is employed because the domed appearance of the conjunctiva, as it is juxtaposed against the cornea, resembles the way a watch's crystal interfaces with its casing. Likewise, the skin and adnexa may be involved, with a response ranging from itching to full-blown urticaria or boggy edema.

Pathophysiology

The toxic/allergic response is classically considered an overreaction of the body's immune system to immunogens or allergens.⁷⁻¹³ The reaction can be innate or acquired. This overaction is manifested when the body responds hyperactively to any exogenous material. The chemical may be overtly destructive (such as gasoline, ammonia or chlorine) or may be a topical medicine, a contact lens, contact lens solution, dust or dander.¹⁻¹³ The resultant tissue response is generated by the release of cytokines and chemoattractants. When researchers analyzed the tissue response that produces pannus following chemical injury, they found that the tissue contained epithelial hyperplasia in 62% of cases, active

fibrosis in 66% of cases, severe inflammation in 21% of cases, giant cell reaction in 28% of cases and stromal calcification in 14% of cases.⁷ Further, goblet cell absence was associated with squamous metaplasia of the conjunctiva and associated with long duration of insult, indicating that chemical injuries may produce lasting effects, even after the event has passed.⁷

The immune system has two divisions, each containing several components. The cellular immune system has a cellular component (leukocytes and other supportive cells) and a humoral component (antibodies).¹³ The system relies primarily on the cellular system to recognize foreign substances and initiate the first attack.^{13,14} The

components of the cellular system include granulocytes (neutrophils, basophils, eosinophils) and macrophages (which phagocytize antigen and present it to T-cells). It also includes T-helper lymphocytes, which recognize foreign proteins presented by macrophages and bind to them, causing the release of lymphokines and alerting other lymphocytes to the presence of foreign antigens and cytotoxic T-cells that destroy abnormal host cells. Suppressor T-cells also play a role by suppressing the immune response. B cells differentiate into plasma cells, producing antibodies against foreign invaders. An antibody is a complex glycoprotein produced by plasma cells that are highly specific for the antigen that stimulated their production. Mast cells are also included as members of the cellular immune team.^{13,14}

Notwithstanding the other elements of the response, the key component to the ocular allergic response is the mast cell. When mast cells interact with specific allergens, it is like a lock being opened by a key. They open (degranulate), discharging chemical substances called mediators into the surrounding tissues.¹¹ The primary chemical mediators include histamine (responsible for

increased vascular permeability, vasodilatation, bronchial constriction and increased secretion of mucous), neutral proteases (which generate other inflammatory mediators) and arachidonic acid (a crucial component of the cyclooxygenase pathway leading to production of prostaglandins and leukotrienes).¹⁵

Pathophysiologically, there are four types of hypersensitivity reactions.¹³ Type I reactions are immediate hypersensitivity or anaphylactic reactions. They produce sudden mass degranulation of mast cells mediated by the antibody IgE.¹³ Type II reactions are classified as autoimmune and involve a body's impaired ability to distinguish self from non-self.¹³ Abnormalities in this element of the system give rise to diseases in which auto-antibodies are produced and directed against the host.¹³ Type III reactions involve combined formations of antigen and antibody known as immune complexes.¹³ Offending triggers may be intrinsic (e.g., a protein molecule) or extrinsic (a penicillin molecule) producing a significant tissue response.¹³ Type IV reactions, sometimes referred to as cell-mediated hypersensitivity reactions, involve the T lymphocytes and lymphokines.¹³ The reaction is classically delayed until a sufficient volume of antigens stimulate the chemical cascade.¹³ Here, the individual has the potential to respond when the appropriate levels of antigen become present. This may take one exposure or 100 exposures. Classically, following the response, which is rarely life-threatening, the patient is bewildered, recognizing that he or she had been engaged with that substance a number of times without any complication whatsoever. The Type I and IV reactions govern toxic/allergic keratoconjunctival disease.

In the ocular tissues, the result of these chemical exchanges appear as conjunctival and adnexal vasodilation, producing chemosis and edema.^{12,14} Conjunctival follicles are hyperplasia of lymphoid tissue within the eyelid stroma and papillae are hyperplastic palpe-

bral conjunctival epithelium infiltrated by lymphocytes and plasma cells.^{13,15}

The keratitis that occurs may be secondary to the agent itself or may be cytokine expression. Absorption of excessive amounts of ultraviolet light (UVA, UVB) can overwhelm the corneal endothelial pump, inducing corneal edema with all its concomitant signs and symptoms.⁴

Another type of corneal toxic/allergic reaction has recently been reported.⁸ Researchers have discovered a potential long-term inflammatory upregulation within the cornea and conjunctiva secondary to the preservative benzalkonium chloride.⁸ It has been postulated that other preservatives may also produce this response. In a report outlining two combined studies, histopathological effects of antiglaucoma drugs on the conjunctiva and trabecular meshwork demonstrated toxic/immunoinflammatory effects on both tissues.⁸ This data supports other findings, and together they illuminate a mechanism by which surgical glaucoma treatment (trabeculectomy) may fail in young patients. Evidence has been gathered citing the upregulated inflammatory processes, created by placing some individuals on these preparations for a long period, as inducing increased, aggressive healing that renders some of the surgical corrective procedures ineffective.⁸

Management

Since there are many strata of ocular allergic reactions, management is primarily aimed at eliminating the causative substance and reducing symptomatology.¹⁻¹⁷ In the event of an acute injury, lavage should be completed with single and double lid eversion. If patients call to report that they have been involved in an accidental chemical exposure, they should be advised to copiously lavage immediately before coming to the office. Patients who require over-the-phone first aid should be advised to brush off all powdered chemicals before attempting lavage and to make sure the recommended anti-

dote for the exposure is irrigation. This information should be on the product label or material safety data sheet (MSDS). The procedure for self-lavage is to run water from a tap or nozzle into cupped hands, placing the eye into the formed receptacle. Copious blinking enables the rinse.^{5,16} In the office, irrigation can be augmented manually by using a sterile ophthalmic saline applied forcefully and directly to all surfaces or by flushing the eye with a sterile intravenous saline solution run through a Morgan lens apparatus.^{5,16}

Following any necessary first aid, cold compresses, artificial tears and ointments can soothe and lubricate the conjunctiva, skin and cornea as needed. Topical decongestants (naphazoline, phenylephrine, and so on, b.i.d.-q.i.d.) produce vasoconstriction, which reduces hyperemia, chemosis and other symptoms by retarding the release of the chemical mediators into the tissues from the bloodstream. Topical antihistamines along with antihistamine/mast-cell stabilizing combinations (Pataday, Patanol, Zaditor, Optivar) and oral antihistamines (Benadryl, 25-50 mg, p.o., t.i.d.) are also excellent therapies for acute signs and symptoms.¹⁵ The nonsteroidal anti-inflammatory drugs (NSAIDs; Acular, Voltaren, Xibrom, Nevanac b.i.d.-q.i.d.) may offer significant pain relief in moderate cases, with topical steroidal preparations (Alex, Lotemax, Pred Mild and Forte, Inflammase Mild and Forte, FML and FML Forte suspensions b.id.-q.i.d.) reserved for the most severe presentations.¹⁻¹⁵ In instances in which the cornea is sufficiently tattered, topical antibiotic coverage may be prudent. Bandage contact lenses and cycloplegia can also be included as needed.¹⁷ Finally, oral analgesics such as aspirin or ibuprofen can be used to settle excessive discomfort and referred pain.¹⁷ If corneal edema is significant, topical hypertonic drops and ointments can be used q.d.-q.i.d. to restore normal levels of hydration.

Clinical Pearls

- The diagnosis of toxic/allergic conjunctivitis can be made based upon history and course. Patients who receive a chemical splash should be asked to bring the material safety data sheet (MSDS) or the product itself so that the chemical can be identified and referenced with poison control.

- Some clinicians prefer the convenience of prescribing combination antibiotic/steroid preparations to prescribing two separate agents. However, if therapy is required over a longer period, titration and tapering can become an issue, because the antibiotic and steroid in a combination drop cannot be tapered independently.

- Even if left untreated, uncomplicated injuries resolve within eight days.

- In true toxic keratoconjunctivitis, there will not be a palpable preauricular lymph node. Toxic substances related to acts of terrorism, such as mustard gas, may necessitate the use of the American Association of Poison Control Centers. If the circumstances surrounding the exposure are suspicious, the patient should be quarantined and the authorities called immediately after first aid has been administered.

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BACTERIAL KERATITIS

Signs and Symptoms

A patient with bacterial keratitis will generally present with a unilateral, acutely painful, photophobic, intensely injected eye. Visual acuity is often reduced and profuse tearing is common. There will be a focal stromal infiltrate with an overlying area of epithelial excavation. Often, the patient will have a history of contact lens wear, which is the most common precipitating condition in developed nations.¹⁻³ Corneal trauma or pre-existing keratopathy are also common precipitating conditions.¹⁻³

Mucopurulent discharge may emanate from the lesion. The cornea is often edematous. The conjunctival and episcleral vessels will be deeply engorged and inflamed, often greatly out of proportion to the size of the corneal defect. In bacterial keratitis, injection is typically 360° rather than sectoral as seen in non-infectious keratitis. A pronounced anterior chamber reaction, often with hypopyon, is present in severe cases. Intraocular pressure may be either reduced due to secretory hypotony of the ciliary body or elevated due to inflammatory cell blockage or direct inflammation of the trabecular meshworks. Often, the eyelids will also be edematous and ptotic.^{1,4}

Pathophysiology

Once defenses are breached, the

cornea is prone to colonization by pathogenic bacteria. Factors known to compromise corneal defenses include direct corneal trauma, chronic eyelid disease, systemic immune disease, tear film abnormalities affecting the ocular surface and hypoxia induction from contact lens wear.¹⁻⁴

Pathogenic bacteria colonize the corneal stroma and immediately become antigenic, both directly and indirectly, by releasing enzymes and toxins. This sets up an antigen-antibody immune reaction with chemotactic factors inducing an inflammatory reaction. The body mobilizes polymorphonuclear leukocytes (PMN), which aggregate at the area of infection, creating an infiltrate. The PMNs phagocytize and digest the bacteria and also damage stromal tissue by releasing numerous collagenolytic enzymes that directly impact stromal tissue.^{1,4}

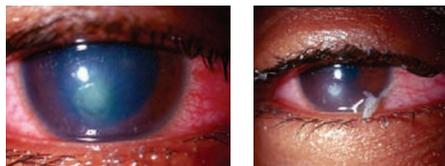
The collagen of the corneal stroma is poorly tolerant of the bacterial and leukocytic enzymes and undergoes degradation, necrosis and thinning. This leads to scarring of the cornea. As thinning advances, the cornea may perforate, thus introducing bacteria into the eye with ensuing endophthalmitis.

The most commonly occurring organisms in bacterial keratitis vary depending on the precipitating factors of the ulcer and the geographic location of the patient. In cases involving contact lens wear and cosmetic mascara, the most common infective organism is *Pseudomonas aeruginosa*.^{1,5} Throughout North America, the most common infective organism in bacterial keratitis is *Staphylococcus aureus*, and it appears that there is an increased incidence of Gram-positive recovery in infectious keratitis.^{1,5}

Management

Proper diagnosis and prompt therapy are essential to preserve vision in bacterial keratitis. Microbial identification and antibiotic sensitivity studies will aid in management. The first step in management should be to obtain

corneal scrapings for microbiologic studies. The standard of care supports culturing most, if not all, suspected infectious ulcers using a platinum spatula with plating directly onto blood and chocolate agar medium.



Bacterial keratitis with mucopurulent discharge.

Certainly, culturing is mandated when the infiltrate is in the visual axis, if the depth of the infiltrate approaches 25% or 50% of the corneal thickness, if there is scleral extension, if the infiltrate is not responding in a seemingly appropriate fashion to therapy, or if the infiltrate occurs in an immunocompromised or hospitalized patient. Additionally if a rare infection is suspected or atypical infiltrate is seen, cultures are also mandated. An alternative for culturing of less-threatening keratitis involves a mini-tip calcium alginate culturette and transport-media-containing carrier. However, the effectiveness of the fluoroquinolone antibiotics has led many practitioners away from this standard. Microbiologic identification is most crucial for central lesions that threaten vision, cases in which perforation is a risk, and in institutionalized patients in nursing homes and hospitals where methicillin-resistant *S. aureus* (MRSA) infections are possible.⁶

Empirical broad-spectrum antibiotic therapy must be initiated prior to obtaining culture results. Monotherapy with fluoroquinolone eye drops was shown in one report to result in shorter duration of intensive therapy and shorter hospital stay compared to that of combined fortified therapy (tobramycin-cefazolin). This finding may have resulted from quicker clinical response of healing as a result of less toxicity in the patients treated with fluoroquinolones. However, as some poor outcomes due to

resistance were encountered more commonly in the fluoroquinolone group, caution should be exercised in using fluoroquinolones in large, deep ulcers in elderly patients.^{7,8}

Despite clear efficacy of fluoroquinolones in managing bacterial keratitis, consideration must be given to the increasing resistance to these drugs.^{4,9-11} Since their inception, there has been a rise in the incidence of bacterial isolates in keratitis that exhibit resistance to the early-generation fluoroquinolones, especially among the Gram-positive organisms.^{4,5,12-15} Even cephazolin, commonly employed in fortified form, has seen increasing bacterial resistance.¹⁴

One method of combating the increasing problem of fluoroquinolone resistance and rising level of Gram-positive infections are the fourth-generation topical fluoroquinolones. Two fourth-generation fluoroquinolones—moxifloxacin (Vigamox, Alcon) and gatifloxacin (Zymar, Allergan)—have a greatly lowered resistance rate, while providing much greater Gram-positive activity than previous-generation fluoroquinolones.¹⁵⁻²¹ Gatifloxacin was shown to have a significantly better action against Gram-positive cocci both in vitro and in vivo compared with ciprofloxacin.²²

Another study examining the efficacy of moxifloxacin compared with standard therapies in patients with bacterial keratitis reported no difference in healing rate, cure rate or complications between



Bacterial keratitis with hypopyon.

fortified cephazolin and tobramycin, ofloxacin or moxifloxacin, although it must be noted that the concentration of moxifloxacin used in this study was double that available commercially.²³ In this study, moxifloxacin was instilled every hour, day and night, for 48 hours, and on the third day, every hour by day

and every two hours at night. For days 4 and 5, one drop every two hours by day and every four hours at night, and for days 6 and 7, one drop every four hours. After day 7, the antibiotic was tapered to every six hours and stopped when appropriate.²¹

Although fourth-generation fluoroquinolones have assisted greatly in managing bacterial keratitis, it must be noted that they are not without fail. There are now reports of patients developing resistance to these medications.^{24,25} Recently approved by the FDA is a higher-dose formulation of levofloxacin, 1.5% (Iquix), for treating bacterial keratitis. This formulation is the highest concentration available for any ocular antibiotic.²⁶

Strong cycloplegia is also recommended, in the form of homatropine 5% or scopolamine 0.25% b.i.d.. If this is insufficient, then atropine 1% b.i.d. is indicated. Adjunctive use of cold compresses will also help to reduce inflammation.

The patient should be followed daily until the infection is well under control. If the results of cultures and sensitivities show that the initially pre-



Bacterial keratitis.

scribed antibiotic is appropriate for the infective organism, or if the patient shows signs of clinical improvement (the ulcer does not worsen and pain and photophobia are reduced) at the 24–48 hour follow-up visit, a topical corticosteroid, such as prednisolone acetate 1% or loteprednol etabonate 0.5% q.i.d.-q2h can be added with caution to speed resolution and decrease corneal scarring. Although steroids have historically been avoided in managing infectious keratitis, judicious use can be beneficial. Antibiotics can suppress the infective organism, and corticosteroids can inhibit the corneotoxic inflammatory response. It has been feared that the

immunosuppressive effects of steroids could enhance bacterial replication and worsen infection. However, if the chosen antibiotic is effective against the organism, the concurrent use of steroids will not inhibit the bactericidal effect of the antibiotic.²⁷⁻³³

Steroids should not be employed until the antibiotic has been given enough time to sterilize the ulcer. A minimum 24-hour loading period is recommended. One must also be certain that the infection observed is not of herpetic viral, fungal or protozoan origin before initiating topical steroids. Steroids should be used only in conjunction with true bactericidal antibiotics, such as fluoroquinolones or fortified antibiotics. A recent report noted improved visual outcomes for eyes with bacterial keratitis from 1995–2005, commensurate with increased use of topical corticosteroids in conjunction with topical antibiotics. The authors speculated that increased emphasis on management of inflammation in conjunction with the infectious process may have contributed to the improved outcomes.³⁴

Clinical Pearls

- If a patient presents with a corneal infiltrate without overlying epithelial staining, then the condition is likely not infectious bacterial keratitis.

- Using strong bactericidal antibiotics will eliminate the infective organisms and sterilize the ulcer, but it will do nothing to quell the inflammatory reaction. In such instances, the inflammatory reaction is as damaging to the cornea as is the infective organism. If evidence exists that the antibiotic is suppressing the infective organism, then corticosteroid use will inhibit the inflammatory reaction and speed healing and reduce corneal scarring.

- For steroids to be most beneficial, prescribe them while the ulcer bed is still open, usually within the first 24–48 hours after you initiate antibiotic therapy. Waiting until the ulcer re-epithelializes before adding a steroid

reduces beneficial effects. A cautionary note: Be comfortable that the antibiotic has sterilized the ulcer before instituting the steroid.

- Oral doxycycline and high-dose vitamin C may reduce stromal damage in conditions such as bacterial keratitis.

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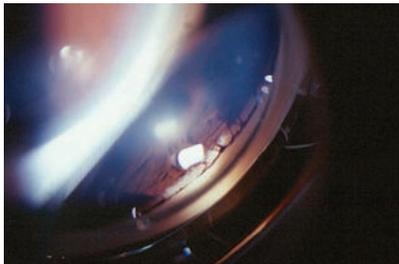
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AXENFELD-RIEGER SYNDROME

Signs and Symptoms

Axenfeld-Rieger syndrome (ARS) is a rare inherited disorder affecting the development of the eyes, teeth and abdomen.¹ The ocular component of ARS often garners the most clinical attention.¹ The spectrum of developmental eye disorders affecting the iris and angle include Rieger's anomaly (peripheral iris strands, prominent Schwalbe's line, stromal atrophy of the iris), Peter's anomaly (corneal leukoma with adhesions and anterior segment anomalies but no cataract), and Axenfeld's anomaly



Gonioscopic view of patient with Axenfeld-Rieger Syndrome.

(prominent Schwalbe's line and peripheral iris strands). If glaucoma occurs with these anomalies, then they are termed Rieger's syndrome, Peter's syndrome, or Axenfeld's syndrome, respectively. The glaucoma that occurs is an aggressive form with an early onset that poses a challenge for diagnosis and management.¹⁻⁶

Patients with ARS possess malformed irido-angular structures that are readily visible upon biomicroscopic and gonioscopic examination. Prominent bilateral forward-positioned Schwalbe's rings (posterior embryotoxon), peripheral contractile iridocorneal strands, iris hypoplasia and corectopia (decentered pupil) are all observable anatomic variations.⁶⁻⁸ Dental abnormalities are considered a definitive differentiating feature for the diagnosis of the Rieger type.⁹ Genetic variations have the ability to alter the clinical phenotype, producing individuals with variable amounts of hearing loss, congenital heart disease, dental anomalies, developmental delay

and a characteristic facial appearance.¹⁰

Pathophysiology

ARS is the result of developmental arrest in the third trimester of gestation.¹¹ At this point, tissues derived from the neural crest cells falter, accounting for the ocular and most non-ocular abnormalities.¹¹ The mesodermal dysgenesis and anterior chamber cleavage syndromes have not been found to be consistent with recent observations, resulting in the suggestion for the alternative nomenclature, Axenfeld-Rieger syndrome.¹¹ The autosomal dominant inheritance is characterized by complete penetrance with variable expressivity, producing ocular and extra-ocular malformations.¹⁻¹¹ Mutations in several chromosomal loci have been implicated including PITX2, FOXC1 (fork-head transcription factor gene-alterations in this gene are known to induce anterior segment abnormalities) and PAX6.⁸⁻¹² Full-spectrum ARS is caused primarily by mutations in the PITX2 gene.^{8,12} A 6p25 microdeletion has the capability of inducing the additional non-ocular findings of hearing loss, developmental delay and cardiac complications.^{9,13,14}

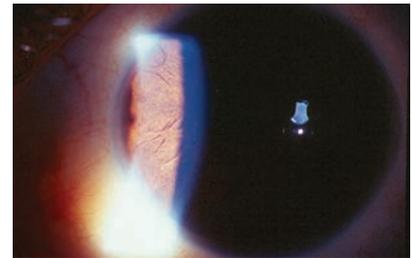
Since the principle ocular abnormality includes an interruption of the iris-angle relationship, faulty aqueous outflow produces a secondary open-angle glaucoma.¹⁵ Additional data has uncovered a relationship between the genetic markers that produce ARS (PITX2, FOXC1) and decreased central corneal thickness, a highly speculated independent marker for the risk of glaucoma.^{16,17} Other investigations have shown direct common linkage between the genetic mutations implicated in both ARS and glaucoma (PITX2 and CYP1B1 genes).^{18,19}



Axenfeld-Rieger Syndrome, showing correctopia and posterior embryotoxon.

Management

ARS is typically diagnosed in early childhood. If it has not yet been discovered by that time, a primary eyecare physician may play a role in identifying its unique characteristics, resulting in



Axenfeld-Rieger Syndrome, showing iris strands and posterior embryotoxon.

diagnosis. Managing the systemic effects of ARS requires a team approach. Dental, auditory and cardiovascular specialists are all required.¹⁻¹⁴ The ocular effects of ARS may also require specialists. The cosmetic and functional correction of iris atrophy and corectopia can be accomplished using specialty opaque/painted contact lenses. The open-angle glaucoma induced by ARS can be managed initially as with its primary open-angle counterpart. Topical prostaglandin medications and aqueous suppressants are reasonable choices. In advanced cases or those exhibiting a rapid progression, surgical intervention may be required.²⁰

Clinical Pearls

- Truncus arteriosus is a cardiac anomaly associated with ARS, characterized by a large defect in the ventricular septum (separating the ventricles), where one large single vessel (truncus) arises to carry blood both to the body and the lungs. Appropriate cardiovascular history should be gathered from patients with ARS.
- Genetic counseling is recommended, given the disease's known heritability.
- Posterior embryotoxon has been documented to exist in as many as 15% of normal eyes having no connection with ARS. Conversely, patients may have ARS without having posterior embryotoxon.
- The irido-corneal-endothelial syndromes known as Chandler syndrome, iris nevus syndrome and Cogan-Reese

syndrome are among the differential diagnoses. In these cases, there are no systemic complications.

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MALIGNANT GLAUCOMA

Signs and Symptoms

Malignant glaucoma, sometimes referred to as aqueous misdirection syndrome or ciliary block glaucoma, has no race or gender predilection. Patients typically have hyperopic and small or nanophthalmic eyes. Most significantly, there is a history of antecedent ocular surgery (typically glaucoma surgery) shortly after complications begin. It is most commonly encountered after trabeculectomy, glaucoma drainage device implant surgery, peripheral iridectomy or iridotomy or cataract surgery¹⁻⁶ Frequently, a period of hypotony may have occurred as a result of overfiltration following glaucoma surgery, and initially malignant glaucoma may present with statistically normal, though rising, intraocular pressure (IOP) with concurrent anterior chamber shallowing.^{1,7}

Biomicroscopically, a shallow or non-existent anterior chamber will be evident in the presence of an intact iridectomy or iridotomy.⁸⁻¹⁰ Frequently there is a preoperative history of anatomically narrow angles along with miotic therapy.⁹ Patients who develop significant inflammation, such as that seen with scleritis, may also develop malignant glaucoma. In rare cases, trauma can precipitate malignant glaucoma. Retinal detachment surgery, panretinal photocoagulation and central retinal vein occlusion have also been reported in association with the development of malignant glaucoma.¹¹

Predisposing factors such as hyperopia, a narrow iridocorneal angle, plateau iris configuration and a history of miotic use are risks for malignant glaucoma development, especially after the patient has corrective ocular surgery.⁹ Progressive flattening of the anterior chamber following surgery with progressive IOP rise is the hallmark of malignant glaucoma.⁹ Further, there will be no iris bombe or evidence of supraciliary effusion.^{1,9,12,13} Should IOP elevate abruptly, classic signs and symptoms similar to those of acute angle-closure glaucoma may occur.

Pathophysiology

Malignant glaucoma is actually an inappropriate term, since no malignancy is associated with the condition. The term arose because the condition was historically difficult to treat and typically resulted in significant visual morbidity. Likewise, aqueous misdirection syndrome is also somewhat of a misnomer in that it is not universally accepted that the aqueous is actually misdirected in every case. There is evidence, however, that this does happen in many instances.^{9,12-14}

Malignant glaucoma often occurs following ocular surgery (typically for angle-closure glaucoma) in an eye with a pre-existing narrow angle and shallow chamber. Certainly, eyes with shallow anterior chambers undergoing surgery are at risk for the condition.

The widely accepted theory holds that following surgery or through a natural predisposition, the ciliary body and ciliary processes form a tight apposition to the peripheral lens and the anterior vitreous. This prevents the aqueous from flowing into the anterior chamber and diverts it instead into the vitreous cavity, increasing the volume inside the cavity. An abnormally impermeable anterior hyaloid face may play a role by preventing aqueous from diffusing through the vitreous into the anterior chamber, and thus causes an increase in the volume of the vitreous. This expansion of the vitreous secondarily pushes the lens and iris towards the cornea, with subsequent shallowing of the anterior chamber and closure of the angles. The classic appearance that occurs is that of a shallow anterior chamber axial depth (lens-corneal distance) along with an accompanying shallow peripheral anterior chamber depth (iris-corneal distance).^{1,14,15} In contradistinction, a patient with acute pupil block primary-angle closure will have a normal axial depth and a shallow peripheral depth. In pupil block glaucoma, a peripheral iridotomy will lead to deepening of the chamber. In malignant glaucoma, there will be no effect by iridotomy, and indeed, the hallmark is a closed angle with a shallow chamber and narrow axial depth that remains despite patent iridotomy or iridectomy.

Management

Management of malignant glaucoma begins medically with the goal of breaking the apposition of the ciliary body and ciliary processes to the lens and anterior vitreous. This is accomplished by relaxing the ciliary body and lens zonules to allow the lens to release posteriorly. This can be achieved with a potent cycloplegic such as atropine.^{1,7} Aqueous suppressants can be used to temporize the IOP, and topical steroids will ameliorate any inflammation. Miotics are contraindicated because they can precipitate or worsen the condition. Oral carbonic anhydrase inhibitors and hyperosmotic agents can be used to dehydrate and shrink the vitreous, adding additional room for the lens to settle. Medical control can be effective in a moderate number of cases, and represents the safest first option.^{1,14}

Should medical control be ineffective, there are surgical options. Treating malignant glaucoma and aqueous misdirection caused by increased resistance to aqueous flow anteriorly through the ciliary body-zonule-lens capsule complex requires the establishment of a conduit to allow fluid passage.¹⁶ The first of the surgical options is hyaloidotomy with disruption of the anterior hyaloid face to allow aqueous to escape from the ballooning vitreous cavity. This option attempts to facilitate aqueous redirection into the anterior chamber rather than the posterior chamber. The most common method involves Nd:YAG laser photodisruption of the anterior vitreous face through an iridectomy or iridotomy hole or through the pupil. This may create an opening for aqueous to reach the anterior chamber.^{1,9}

A more invasive method of surgically correcting malignant glaucoma is through vitrectomy.¹⁶⁻¹⁹ Here, the anterior vitreous is “debulked,” the iris is given a chance to relax and the anterior chamber to deepen. Further, pockets of aqueous within the vitreous are removed and the anterior vitreous face is disrupted, potentially rectifying the blockage that prevented the misdirected aqueous from ultimately getting through the pupil. All surgical options are designed to establish a communication between the vitreous cavity and anterior

chamber.^{18,19} Diode laser cyclodestruction has been used as a complementary treatment in managing the IOP in cases of refractory malignant glaucoma.^{2,20}

Unfortunately, after successful treatment of malignant glaucoma, the angle may remain closed from extensive peripheral anterior synechiae. If more than one-half of the angle remains closed, IOP will remain permanently elevated, despite successful treatment of the underlying cause. In such cases, the surgeon may try to break the peripheral anterior synechiae with a goniosynechialysis, or the patient may require a form of permanent medical therapy.

Clinical Pearls

- Pupillary block is the most common condition mimicking malignant glaucoma. Laser iridotomy will relieve pupil block angle closure, but it will have no effect on malignant glaucoma. However, laser iridotomy must be performed to differentiate the two conditions.

- Choroidal effusion with a shallow anterior chamber, particularly after glaucoma filtration surgery, is the second most-common differential diagnosis for malignant glaucoma. Large effusions will be seen ophthalmoscopically. Small suprachoroidal effusion can cause an anterior rotation of the ciliary body and precipitate this condition. Small effusions are typically detected only with ultrasound biomicroscopy.

- After glaucoma surgery such as trabeculectomy, a flat anterior chamber and low IOP are suggestive either of overfiltration or bleb leakage. If the anterior chamber is flattening and shallowing and the IOP is rising, malignant glaucoma should be considered the cause.

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CRYSTALLINE LENS SUBLUXATION

Signs and Symptoms

While subluxation of the crystalline lens can occur in any patient, it is common in three distinct situations. The first is a patient who has received significant blunt trauma to the eye, or in some cases to the head.¹⁻⁴ The second is in patients who have a systemic condition known to be associated with lens subluxation, such as Marfan's syndrome, homocystinuria, hyperlysinemia, familial ectopia lentis, sulfite oxidase deficiency, Weill-Marchesani syndrome, aniridia and Ehlers-Danlos syndrome.⁵⁻¹³ The third situation is a patient with a hypermature cataract in which zonular support has been lost.¹³ Additionally, crystalline lens subluxation can occur idiopathically and spontaneously.^{14,15} Other potential causes include ocular surgery, exfoliation syndrome and vigorous eye rubbing.¹⁶⁻¹⁷

Symptoms of lens subluxation include visual disturbance from extreme hyperopic or myopic shift, astigmatism or acquired aphakia. Occasionally, the vision fluctuates dramatically as the patient may alternate between phakic and aphakic vision.¹⁸ There may also be monocular diplopia. In most cases, there are no physical sensations unless the lens blocks the pupil leading to pupil block and secondary angle closure. In this scenario the patient may manifest the symptoms of acute angle-closure glaucoma including a steamy cornea, blurred vision, headache, pain, photophobia, lacrimation, nausea and vomiting.¹⁹⁻²¹

Although secondary glaucoma is commonly associated with crystalline lens subluxation, the cause is not always pupil block; open-angle glaucoma can occur as well, presumably from lens-induced inflammation.¹⁰

Biomicroscopically, there will be a displaced crystalline lens. This appears as a black crescent at the edge of the lens against a red reflex from the fundus. The lens can be dislocated up and out, down and in, down and out, nasally or temporally, or completely displaced into the posterior or anterior chamber. There may also be phacodonesis (tremulousness of the lens due to loss of zonular support) and iridodonesis (tremulousness of the iris).¹³

Pathophysiology

Subluxation implies displacement of the crystalline lens. Luxation refers to a lens that is totally dislocated. The term *ectopia lentis* has been used interchangeably with subluxation. However, this should be a term reserved for bilateral cases. Subluxation of the crystalline lens has been described as being either acquired or congenital. Better terminology would be that subluxation of the lens can be either acquired (such as from trauma) or due to congenital systemic causes. Rarely are infants born with displaced lenses; instead the phenomenon develops during life due to a predisposing systemic condition.²²

Traumatic subluxation is slightly more common than lens displacement associated with underlying systemic disorders.¹² Traumatic mechanical stretching of the zonules is the cause of the subluxation. This occurs as the eye is compressed in an anterior-posterior direction (such as with impact by a fist or other projectile) and the subsequent distention of the globe in the medial-lateral plane ruptures the zonular fibers.

Spontaneous lens subluxation associated with congenital conditions varies in pathophysiologic mechanism depending upon the condition. The direction of dis-

placement in each case is characteristic but by no means completely diagnostic. Marfan's syndrome is the most commonly encountered underlying condition in patients with crystalline lens subluxation. More than 70% of patients with Marfan's syndrome have displacement of the crystalline lens.²³ In Marfan's syndrome, the lens tends to be displaced superior temporally. This results from a predominance of abnormally constructed collagen vascular tissue and faulty lens zonules and is typically non-progressive. Further, as the zonules are still attached to the lens, some degree of accommodation exists.

Homocystinuria, a defect in amino acid metabolism, results in brittle zonules that rupture.^{5,13} This allows the lens to displace inferior nasally or even into the anterior chamber. There is no accommodation in this case and the condition may be progressive.^{5,13} Two other conditions that should be mentioned are simple *ectopia lentis* and *ectopia lentis et pupillae*.

Simple *ectopia lentis* is an autosomal dominant condition in which the lenses are dislocated superotemporally, but there are no other associated systemic abnormalities. *Ectopia lentis et pupillae* is likewise an isolated inherited condi-

tion, albeit autosomal recessive, in which the lenses are displaced temporally in opposing directions.²⁴⁻²⁶

The main concern with lens subluxation is the development of secondary angle-closure glaucoma. Any time the crystalline lens displaces, the possibility exists that the lens can come into firm apposition with the back surface of the iris. When the pupil is obstructed, there is pupil block, iris bombé and secondary angle closure.¹⁹⁻²¹ Should a lens completely dislocate into the anterior chamber, concern must be for the lens touching the cornea, irreversibly damaging the endothelial cells with subsequent chronic corneal edema and decompensation.¹³ Displacement of

the lens into the anterior chamber can also result in a reverse pupil block angle-closure glaucoma.²⁷

Management

Extraction of a dislocated lens can prove to be difficult. For that reason, lens subluxation alone is not sufficient to mandate surgery.⁹ It is recommended that, in the absence of pupil block glaucoma, corneal decompensation, inflammation or intractable visual disability, a subluxed lens should be left alone in favor of less invasive options.⁹ For induced refractive errors that are stable, visual correction with glasses or contact lenses should be investigated.

If the lens dislocates into the posterior chamber but the posterior capsule remains intact and no inflammation is induced, it can be monitored.⁹ However, if inflammation that cannot be managed topically is induced or retinal damage is threatened, then vitrectomy and lens extraction are necessary. Late onset inflammation is always possible. Patients require life-long, timely and periodic observation.⁹

In cases where there is suspected loss of zonular adherence (often with hypermature cataracts) with subsequent risk of dislocation into the anterior chamber, pharmacological dilation should be avoided until surgical consultation can be obtained. In cases where the lens has already dislocated into the anterior chamber, the patient can be reclined and

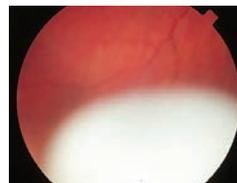
dilated, to attempt repositioning by carefully manipulating the head until the lens falls back into place. Following this, pilocarpine solution can be instilled to stabilize the structure, and a surgical consultation can be obtained.

In cases in which pupil block angle-closure glaucoma develops, laser peripheral iridotomy should be performed as soon as possible. However, this rarely manages the condition successfully. Patients frequently require lens extraction with intraocular lens implantation.

Phacoemulsification with posterior chamber intraocular lens and capsular



Crystalline lens subluxation.



Crystalline lens subluxation as seen on funduscopy.

tension ring implantation has been a very successful surgical management of crystalline lens subluxation.²⁸⁻³⁰ More recently, a modified capsular tension ring and capsular tension segment has improved capsular stability and intraocular lens centration via scleral-suture fixation.³⁰

Clinical Pearls

- In any case of lens dislocation, there exists a strong possibility of pupil block and secondary angle-closure glaucoma.
- More than 70% of patients with Marfan's syndrome develop lens subluxation.
- The mere fact that a lens is subluxed is not sufficient reason for surgical extraction.
- Symptomatic subluxation can be managed effectively with opaque contact lenses or long-term pilocarpine therapy.
- Patients with crystalline lenses that dislocate into the vitreous are at risk of chronic and severe inflammation, sometimes occurring years later.

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IRIDODIALYSIS

Signs and Symptoms

Iridodialysis is defined as a rupture of the iris at its thinnest area, the iris root.¹ Patients with iridodialysis present with a history of jarring blunt-force trauma, such as being struck with a projectile or being a participant in a collision injury such as those caused by the impact of an

automobile airbag or the contact with an object during a fall.² Pain, photophobia and lacrimation associated with post-traumatic uveal inflammation (iritis or iridocyclitis), variable facial swelling secondary to fluid accumulation, pain upon movement of the eyes and diplopia secondary to incidental corectopia are all common.³ The prominent sign is the classic D-shaped pupil, with the flat pupillary margin observed at the pupillary margin opposite the point of iris release. Other associated collateral injuries may include subconjunctival hemorrhage, ruptured globe, corneal abrasion, conjunctival laceration, hyphema, angle recession (with glaucoma), raised intraocular pressure (IOP), lens subluxation, orbital bone fracture, blowout fracture, retinal detachment, vitreous hemorrhage, choroidal rupture and optic nerve avulsion.⁴⁻⁶

Pathophysiology

The anterior chamber is defined by the boundaries of the iris, lens cornea and limbal-scleral junction where the thin iris root forms an "angle" just below the trabecular meshwork as it inserts into the ciliary body.^{1,7} Upon direct contact with an object or secondary to a sudden acceleration or deceleration, energy is perpetuated inside the eye by a hydraulic shock wave.⁸ This wave travels through the ocular media transferring sufficient forces to the contrecoup region (area 180° from or directly opposite the site of impact) to detach the iris at its thinnest and most vulnerable location. This peripheral anchor, which connects the iris to the ciliary body/muscle, is known as the iris root.⁸ As the tissue becomes freed, it creates an alternate, oval pupil confined by its points of attachment, and causes the iris body adjacent to the separation to become slack, creating a flat iris border. This results in the D-shaped pupil. Since the trabecular meshwork is also susceptible to the hydraulic effects of the shock wave, it too may incur damage, altering aqueous egress either acutely or on a delayed time line.^{9,10} Cases of iridodialysis involving more than 180° have a

greater statistical risk for the development of late glaucoma.¹¹

Management

Because iridodialysis involves the traumatic (injurious or surgical) dissection of well-vascularized and innervated iris tissue, an accompanying secondary iridocyclitis and hyphema should be anticipated during the acute phase of the trauma.¹² In such cases, topical cycloplegics such as atropine 1% q.d.–t.i.d. can provide pain relief by mitigating the spasmodic response both of the iris and ciliary body, while the aggressive use of topical steroidal and nonsteroidal anti-inflammatory preparations can be employed to reduce the incited immune response. In the event that IOP becomes acutely raised secondary to obstruction of the trabecular meshwork by blood or inflammatory debris, topical brimonidine, beta-blocker or carbonic anhydrase therapy can be used until the injury is healed.

Because the consequence of angle recession and of late or post-traumatic glaucoma exists in all patients sustaining ocular blunt trauma—whether or not visible damage is evident—following the repair and recovery from all acute sequelae, the entire angle in both eyes (for comparison) should be inspected with gonioscopy.¹² Patients with an ocular blunt-force history should be periodically assessed for rising IOP to exclude a delayed traumatic effect on aqueous drainage.⁹⁻¹² In the event that late or post-traumatic glaucoma develops, it can be treated using the same algorithm as with primary open-angle glaucoma.

Iridodialyses not requiring surgical repair and not producing ill cosmetic effects require no additional ophthalmic management. Those patients upset by the shape of their pupil or the appearance of the iris or suffering from any secondary effects of having an additional iris opening may be fit with large diameter painted/opaque contact lenses. In cases requiring surgical remediation, one

has several options. Microsurgical repair using a 22.0-mm plastic-handled 27-gauge straight needle through a 1.0-mm distal hole can serve as a passage for 9–0 or 10–0 mm polypropylene or nylon sutures.¹³ Alternately, a sutureless technique (for the repair itself) involves a limbal peritomy, multiple sclerostomies to gain access to the iris base at multiple clock hours of the iridodialysis (using a microvitrectomy blade) and placement with incarceration of the peripheral iris through these ports using a vitreoretinal forceps with conjunctival closure using absorbable sutures can be performed.¹³



Partial iridodialysis.

The latter technique is suitable for use in simple iridodialysis repair in conjunction with other intraocular procedures.¹⁴ Surgical repair of this



Complete iridodialysis.

injury is not emergent and often accomplished following the resolution of all resultant acute traumatic complications.

Clinical Pearls

- Any trauma capable of producing iridodialysis is capable of producing contrecoup posterior segment complications. In all instances, the posterior segment of both eyes should be evaluated.

- Since a frequent complication of iridodialysis is hyphema, gonioscopy at the time of acute presentation may not be desirable. The procedure will not provide information that improves treatment and may move a well-formed clot, promoting bleeding.

- The topical prostaglandins are not an effective choice for reducing IOP in the wake of any acute injury. They are chemically similar to our own

prostaglandins (a mediator of the immune response), so they may worsen inflammation. Also, they take too long to reach a therapeutic effect.

- The D-shaped pupil caused by iridodialysis should not be confused with the “peaked” or “pointed” pupil found in penetrating injuries.

- Following a severe injury with substantial peripheral iris release, the structure may appear floppy or tremulous as the eye moves. This is known as iridodonesis. If the zonules are involved and the lens appears unstable as the eye moves, the phenomenon is known as phacodonesis.

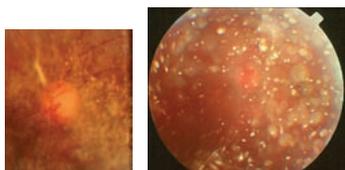
- Iris coloboma is the result of an arrested developmental syndrome associated with the PAX6 gene. Here, portions or entire sectors of the iris may be missing, with or without affecting pupil shape. However, the patient will provide a history of having had that defect since birth.

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ASTEROID HYALOSIS

Signs and Symptoms

Asteroid hyalosis is primarily a unilateral disorder that occurs in patients aged 60 years or older.¹ Although there is no known race predilection, men appear to be more frequently affected.¹ This condition is typically asymptomatic, with only the most severe cases causing a mild decrease in visual acuity. Some patients report glare; curiously, floaters are rarely reported.^{2,3} In two large population studies, asteroid hyalosis was present in 1% of surveyed people.^{4,5} Ophthalmoscopically,



Two views of asteroid hyalosis.

asteroid hyalosis appears as multiple, discrete, refractile yellow or yellow-white particles (asteroid bodies, Benson's bodies) suspended within the vitreous. In early stages, these bodies are less numerous and tend to accumulate in the inferior vitreous. Advanced cases can be so dense that the examiner's view of the posterior fundus is impaired. Asteroid hyalosis has been reported to have a strong positive association in patients with diabetes mellitus.⁶⁻¹⁰ Additionally, systemic arterial hypertension and atherosclerotic vascular disease have been associated with asteroid hyalosis.^{8,10} However, a number of reports refute the associations between asteroid hyalosis and systemic diseases.^{4,6}

Pathophysiology

Asteroid bodies represent small calcium soaps (calcium-laden lipids) suspended within and attached to the hyaluronic acid framework of the vitreous body. Chemically, they have been found to contain calcium oxalate monohydrate and calcium hydroxyphosphate. There are structural and elemental similarities of asteroid bodies with hydroxyapatite. Calcium may also be bound to phosphate groups in the

phospholipids.¹¹⁻¹⁵ Proteoglycans and their glycosaminoglycan side chains are implicated in regulating the biomineralization process.¹⁵

Determining the exact composition has been difficult as research scientists have yet to reproduce this condition experimentally in laboratory subjects. Although we understand the composition of the asteroid bodies, the exact genesis remains unclear. The large quantity of complex lipids and calcium in asteroid bodies suggests a derivation from sources exogenous to the vitreous.¹¹

Management

Asteroid hyalosis is considered a benign condition. Although it is progressive, it never leads to severe vision loss, and even the mild symptoms mentioned above are infrequent. The vast majority of cases merely require documentation. More often than not, this disorder poses a greater challenge to the physician's conducting a thorough examination, since it can obscure details of the underlying retina. Hence, intervention is considered only in patients being managed for glaucoma or retinal disease (e.g., those who have diabetic retinopathy, retinal tear or detachment). Vitrectomy is typically performed in these instances.^{1-3,16}

Clearly, asteroid hyalosis is more problematic to the examiner than the patient. Asteroid hyalosis changes the optical quality of the vitreous and can cause an incorrect reading from automated technologies such as autorefraction and A-scan ultrasonography.¹⁷ Thus, in addition to compromising ability to visualize fundus details, the presence of asteroid bodies can lead to erroneous axial length measurements, refractions, and intraocular lens power calculations.¹⁷⁻¹⁸ Also in consideration of intraocular lens implantation, it has been documented that silicone lenses can calcify when implanted in eyes with asteroid hyalosis, making silicone an unacceptable material choice for these subjects.¹⁹⁻²¹

Fortunately, there are options for fundus examinations in cases in which

dense asteroid hyalosis obscures ophthalmoscopic views. Fluorescein angiography optically "removes" the asteroid bodies from the vitreous, allowing detailed angiographic evaluation.^{22,23} Additionally, optical coherence tomography allows for anatomic visualization and detection of maculopathies, in spite of dense asteroid hyalosis.^{24,25}

Clinical Pearls

- Asteroid hyalosis presents a classic picture akin to "stars in the night sky." Upon eye movement, the asteroid bodies "sway" within the vitreous, but they always return to their origin.

- Two conditions are often confused with asteroid hyalosis: synchysis scintillans and amyloidosis.

- Synchysis scintillans (a.k.a. cholesterol bulbi) is an extremely rare condition that occurs in severely diseased eyes. This condition also presents with refractile crystals in the vitreous, although these particles are actually composed of cholesterol. They are not attached to the vitreal framework and therefore tend to settle out inferiorly after eye movement. Because this condition occurs in end-stage eye disease, pathologists, rather than clinical optometrists or ophthalmologists, typically make the diagnosis of synchysis scintillans.

- Amyloidosis of the vitreous is also quite rare and occurs typically after age 40. Those with a positive familial history of amyloidosis usually present earlier than those without family history (as much as 20 years earlier on average). Patients characteristically demonstrate bilateral involvement, with granular, strand-like opacities that are concentrated within the central vitreous. These strands or membranes are anchored to the posterior lens surface in about half of all patients. Small, yellow-white bodies dot the vitreal strands.

- The density of asteroid hyalosis does not correlate with visual dysfunction. If a patient presents with significantly diminished acuity (e.g., 20/40 or worse), asteroid hyalosis is not to blame. Continue examining the patient until the actual etiology is found.

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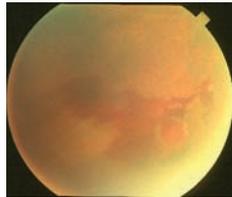
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RETINAL ARTERIAL MACROANEURYSM

Signs and Symptoms

Most patients developing retinal arterial macroaneurysms (RAMs) are older, typically between 50 and 80 years old.¹⁻⁶ RAMs rarely occur in younger patients, but when they do, there is often an associated systemic disease.⁷ There appears to be a female preponderance.⁴⁻⁶ The most common comorbidity is systemic arterial hypertension, occurring in approximately 80% or more of patients.^{3,5,8,9} There is also an increased incidence of cardiovascular disease and arteriosclerosis.^{5,6}



Retinal arterial macroaneurysm with notable vascular dilation and hemorrhage.

Ophthalmoscopically, there will be a dilatation of a major arterial branch within the first three bifurcations. Retinal arterial macroaneurysms are typically unilateral, but may be multifocal.^{3,5} In many cases of unruptured retinal arterial macroaneurysms, the patient remains asymptomatic and the discovery is made during a routine fundus examination. Often, however, by the time the patient presents, significant leakage has occurred and the surrounding area manifests exudates and extensive pre-, intra- and/or subretinal hemorrhage. Vitreous hemorrhage also may occur upon rupture.¹⁰⁻¹⁷ Occasionally, spontaneous pulsation of an unruptured aneurysm may be noted. When there is extensive hemorrhage, it is often difficult to identify retinal macroaneurysm as the cause. In such cases, neovascularization is often misdiagnosed as the source.

If the focal dilatation is not ophthalmoscopically apparent, fluorescein angiography can illuminate the RAM.

With fluorescein angiography, the aneurysm will hyperfluoresce early in the angiogram, showing a characteristic balloon-appearance with late-phase leakage.⁵ In cases of extensive hemorrhage, indocyanine green (ICG) angiography can better identify the focal aneurysmal dilatation.¹⁰

Several causes of vision loss may occur from retinal arterial macroaneurysm. Of course, leakage and rupture leading to macular edema, exudation and hemorrhage are the most obvious. However, retinal arterial macroaneurysm rupture also has been strongly associated with the development of macular holes and retinal detachment, which can leave patients with profound vision loss despite complete resolution of the leakage from aneurysmal rupture.¹⁸⁻²⁴ Additionally, retinal arterial macroaneurysms have been seen in association with retinal telangiectasias, arterial emboli and retinal vein occlusion.^{5,25}

Pathophysiology

Retinal arterial macroaneurysms are acquired out-pouchings of the retinal arterioles.⁵ These balloon-like formations are caused by a break in the internal elastic lamina of the arteriole wall through which serum, lipids and blood exude into the surrounding retina.²⁶ However, there is no associated microvasculopathy as typically seen in diabetic retinopathy. Aging arterioles demonstrate an increase in intimal collagen and replacement of medial muscle fibers by collagen, making them less elastic. It has been postulated that this loss of elasticity makes arterioles more susceptible to dilatation from elevated hydrostatic pressure occurring in hypertension.⁵ The strong association of retinal macroaneurysm with hypertension points to this systemic disease as a possible contributory mechanism affecting the vessel wall.



A small, almost subclinical RAM.

Management

The natural course of RAM typically

involves spontaneous sclerosis and occlusion, particularly after hemorrhaging.^{5,6,26-30} Periodic observation is indicated if there is no vision loss or threat of macular hemorrhage. Asymptomatic, non-leaking macroaneurysms may be monitored at four- to six-month intervals. If there is leakage in the form of exudation and/or hemorrhage that does not threaten the macula, then monitoring at one- to three-month intervals is indicated.

However, if hemorrhage threatens or involves the macula, or persistent macular edema exists, then direct photocoagulation of the macroaneurysm is indicated.^{1,4-6,27,29} In these cases, moderately intense photocoagulation is applied directly to the macroaneurysm so as not to produce complete occlusion of the involved artery. Alternately, to avoid potential arterial occlusion, perianeurysmal laser application can be performed. In the event a non-hemorrhagic macroaneurysm is observed to be spontaneously pulsating, immediate direct photocoagulation is indicated, since rupture is likely.

The visual prognosis for eyes with ruptured or leaking retinal arterial macroaneurysm depends on the degree and type of macular involvement. In most cases, gradual and spontaneous involution is concurrent with hemorrhage resorption.^{5,6,12,31} Eyes with vitreous hemorrhage or premacular subhyaloid hemorrhage typically recover good vision, but the vision in those with submacular hemorrhage with or without premacular hemorrhage generally remains poor.¹² Early vitrectomy is recommended for RAM-related vitreous hemorrhage, to allow for observation of the fundus, particularly the macula.¹⁰

In cases where significant preretinal hemorrhage has occurred, resolution and drainage can be greatly assisted by Nd:YAG laser rupture of the internal limiting membrane in front of the hemorrhage.^{12,19,32,33} Laser photodisruption of the posterior hyaloid membrane releases the preretinal hemorrhage into the vitreous space, where it can be more easily resorbed or surgically removed. More concerning and urgent are submacular hemorrhages that develop from retinal arterial macro-

aneurysm rupture as they have the greatest potential for residual visual morbidity.³¹ Submacular surgery to remove accumulated hematoma should be performed within several days of the development of submacular hemorrhage to prevent permanent photoreceptor damage. Alternately, pneumatic displacement of the submacular hematoma can help reduce permanent vision loss. Evacuation of the submacular hemorrhage through surgery must be done as soon as possible, since permanent vision loss will develop within several days.^{10,12,17,34}

Clinical Pearls

- In cases of unexplained vitreous pre-, intra- or subretinal hemorrhage, consider retinal macroaneurysm as the cause. If the characteristic balloon appearance is not readily observable ophthalmoscopically, fluorescein or ICG angiography may aid diagnosis by more clearly identifying the aneurysm. If the diagnosis is not in question, then angiography is not indicated.

- Retinal arterial macroaneurysm, along with exudative macular degeneration and polypoidal choroidal vasculopathy, can cause hemorrhage anywhere from the subretinal strata to the vitreous. Consider retinal arterial macroaneurysm when multiple layered hemorrhages are present.

- There is a high rate of mortality in patients with retinal arterial macroaneurysm due to cardiovascular disease. Patients discovered to have RAM should be referred for systemic evaluation. At the very least, a fasting blood glucose, complete blood count with differential, fasting lipid profile, blood pressure evaluation and electrocardiogram are indicated.

- Retinal macroaneurysms can occur also in a venule, but this is much rarer than occurrence in an arteriole.

- Physical exertion can cause rupturing of retinal arterial macroaneurysms.

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RETINAL EMBOLI

Signs and Symptoms

Patients observed to have retinal emboli are typically elderly and often have a concurrent history of hypertension, diabetes, carotid artery disease, peripheral vascular disease, hypercholesterolemia, hyperlipidemia, smoking and atherosclerosis.¹⁻⁴ The patient is often asymptomatic, and the plaques are often found upon routine eye exam. However, the patient may have previously experienced transient episodes of monocular vision loss (amaurosis fugax).^{5,6} Rarely, patients will have experienced a transient ischemic attack with hemiparesis, paresthesia, and/or aphasia. These episodic bouts of amaurosis fugax may be quite frequent, and may last from several seconds to several minutes. Rarely does the patient have any lasting visual deficits. Frequently, patients who describe experiencing amaurosis fugax will not exhibit retinal emboli upon examination, but may have arteriolar narrowing and sheathing.⁵

Ophthalmoscopically, an intra-arteriolar plaque will be evident. Emboli can occur along the course of the vessel in the retina or at the optic disc or at a vessel

bifurcation.^{5,7} Bilateral involvement is uncommon, but there may be multiple emboli within the same eye. The emboli can have a reflective or refractile appearance; a dull, bulky, chalky appearance; or may appear long and white within a vessel.^{1,5,7} Over time, retinal emboli tend to dislodge and move down the vascular tree.

One large population study found the 10-year cumulative incidence of retinal emboli was 1.5%.² Another large popu-



Examples of retinal emboli lodged in the arterial system.

lation based study found asymptomatic retinal emboli in 1.4% of the study population. There was an increase in prevalence associated with age, with a prevalence of 0.8% in persons aged younger than 60 years, 1.4% for those aged 60 to 69 years, 2.1% for those aged 70 to 79 years, and 1.5% for those aged 80 years or older.⁸ There is a greater prevalence in men than women.⁸ Another report noted a 3% incidence in retinal emboli in an older population.⁹ Notably, these large population studies involved primarily whites; there is a lower prevalence of asymptomatic retinal emboli in Hispanic and Asian peoples.^{1,10} However, the transient nature of retinal emboli makes it difficult to determine the true prevalence, and most population studies likely underestimate the actual prevalence.

Pathophysiology

Retinal emboli are heterogeneous. One type of embolus is composed of cholesterol and typically lodges at a vessel bifurcation. These cholesterol emboli are refractile in appearance and are sometimes known as Hollenhorst plaques.¹¹⁻¹³ Another type of embolus is long and dull and appears similar to toothpaste within the arteriole lumen. This type of emboli is composed of fibrin and platelet aggregates.⁴ The third type of retinal emboli is calcific and

appears chalk-like.⁴ Cholesterol emboli are the most commonly encountered (80% of all emboli); fibrin-platelet emboli represent 14% of emboli, while calcific emboli account for just 6% of visible retinal emboli.⁸

Patients frequently have concurrent hypertension, a history of smoking and elevated cholesterol levels. The stress on the arteries induced by hypertension leads to reduced elasticity of the vessels.

Cholesterol deposition then occurs within the vessel walls and an atheroma forms, with subsequent arterial narrowing. Turbulent blood flow over the atheroma can lead to plaque ulceration, which allows small particles to break off and flow within the bloodstream. This

accounts for the majority of cholesterol emboli. The origin of most cholesterol emboli is thought to be ulcerated atheromatous plaques in the internal or common carotid artery. Fibrin-platelet emboli typically arise from a mural thrombus, and calcific emboli are thought to arise from cardiac valvular structures.^{4,14}

Once an embolus has broken off from its point of origin, it travels the arterial system until it encounters a vessel whose



A rarely captured view of a plaque at the optic nerve head, which can induce a central retinal vein occlusion.

caliber is too small to allow it to flow any farther. This causes the plaque to lodge within that vessel. If blood flow is significantly impaired distal to the blockage, then ischemia to that tissue will ensue. If the embolus lodges within a retinal arteriole, then retinal ischemia with corresponding loss of vision occurs. The result may be a retinal artery occlusion. In the

case of cholesterol emboli, however, the blockage often quickly dislodges without permanent impairment of vision. Instead, the patient may experience a brief interruption of vision and/or visual field (amaurosis fugax).⁵ Multiple bouts of amaurosis fugax may indicate multiple emboli. In cases where the patient is asymptomatic, yet a retinal embolus is visible, there is unlikely permanent ischemia. This is because many emboli, particularly cholesterol, are malleable permitting blood flow.

Management

There is no direct treatment for asymptomatic visible retinal emboli. In fact, because blood flow is often uninterrupted, flowing around or through an apparently complete blockage, ocular intervention is not necessary. The proper approach to managing asymptomatic retinal emboli is truly unknown. Retinal emboli causing acute arterial occlusion, if detected in time, can be vaporized or dislodged by Nd:YAG laser; however, this procedure is still being refined.¹⁵ For all cases of retinal emboli, the concern must be subsequent embolization with ensuing permanent retinal infarct or cerebrovascular accident with the permanent sequelae of stroke.

A retinal embolus is an indication of significant systemic vascular disease. The most common associated systemic diseases are hypertension, cardiovascular disease and stroke.^{2-4,7-10} In many studies, the prevailing risk factor for retinal emboli is smoking.^{1,3,4,7-10} In that the presence of asymptomatic retinal emboli indicate potential risk for further embolic disease, a preventative approach dictates that all modifiable risk factors—especially smoking—be altered. Patients should be evaluated by an internist, vascular surgeon or cardiologist for hypertension, coronary artery disease, diabetes and carotid artery disease. A complete physical with stress echocardiogram, fasting glucose, lipid levels, blood chemistry with cardiac enzymes, magnetic resonance angiography, transthoracic and transesophageal echocardiography may be indicated, especially for patients

with symptomatic retinal emboli.⁶ Interestingly, there is no consensus on the need for carotid ultrasonography in patients with asymptomatic retinal emboli, since the majority of these patients do not have high-grade carotid stenosis.^{4,7,11,13,16}

There is increased risk of stroke and decreased survivorship with the appearance of a retinal embolus. A large population study collecting data over 10 to 12 years found that 30% of patients with retinal emboli died, with 4% dying from stroke-related complications and 16% from cardiovascular causes.¹⁶ These death rates were higher than those for age-matched people not having retinal emboli. Most available data suggests that retinal emboli in otherwise asymptomatic people are associated with a higher risk of stroke and stroke mortality, independent of conventional risk factors.⁷

There is no clear indication for carotid endarterectomy in patients with asymptomatic retinal emboli, even with concurrent high grade carotid stenosis.^{4,7,17-19} For these patients, carotid endarterectomy is generally not considered. There does seem to be a benefit to carotid endarterectomy in patients with symptomatic retinal emboli and high-grade carotid stenosis.²⁰

Clinical Pearls

- Asymptomatic retinal emboli can be difficult to detect ophthalmoscopically. Older male patients with a history of hypertension and smoking are at the greatest risk for retinal emboli. The retinal arterial tree should be examined most closely in these patients.
- Asymptomatic retinal emboli are not highly associated with severe carotid stenosis. Carotid ultrasonography is not an especially vital test for these patients.
- Patients with asymptomatic retinal emboli are typically not surgical candidates, especially if they are older than 70.
- The most significant modifiable risk factor for retinal emboli is smoking. Smoking cessation is crucial in reducing the risk of future embolic phenomenon in patients with asymptomatic retinal emboli.

tomatic retinal emboli.

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HYPERTENSIVE RETINOPATHY

Signs and Symptoms

A patient with hypertensive retinopathy suffers from hypertension, although

the condition may be unknown to the patient and the eye exam may yield the first clue to this potentially asymptomatic systemic disease.¹ Most commonly, the patient is middle-aged or older.² In addition, hypertension is more common and severe in African Americans than in whites.³ Patients with only hypertensive retinopathy and no other hypertensive ocular complications are nearly always visually asymptomatic.

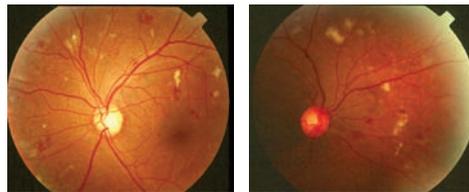
Findings in hypertensive retinopathy include arteriolosclerosis (artery narrowing with increased arteriole light reflex, secondary to thickening within the blood vessel wall, arteriovenous crossing changes with venous constriction and banking, arteriolar color changes and additional vessel damage with scar formation), cotton wool spots and flame shaped hemorrhages within the nerve fiber layer. Intraretinal hemorrhages occur less commonly. Rarely will there be retinal or macular edema, and then only in the most severe cases. In advanced cases, there will be a macular star or circinate pattern (ring of exudates from the disc to the macula) and disc edema.⁴⁻⁷ One study noted a greater incidence of hypertensive retinopathy in women and 40% of hypertensive patients demonstrating some degree of retinopathy.⁸ There may also be concomitant comorbidities in the form of subclinical and clinical stroke, cognitive impairment, renal dysfunction and cardiovascular mortality.⁹⁻¹³ Severe and atypical cases of hypertensive retinopathy have been associated with pheochromocytoma.^{14,15}

Pathophysiology

The findings in hypertensive retinopathy all stem from hypertension-induced changes to the retinal microvasculature. Hypertension leads to a lying down of cholesterol into the tunica intima of medium and large arteries. This leads to an overall reduction in the lumen size of these vessels. Arteriolosclerosis leads to focal closure of the retinal microvasculature. This gives rise to microinfarcts (cotton wool spots) and superficial hemorrhages. Cotton wool spots represent occlusions of the terminal retinal arteri-

oles, resulting in acute focal inner retinal ischemia.^{4,5} Acute elevation in blood pressure causes smooth muscle necrosis and breakdown of the blood-retina barrier, resulting in retinal hemorrhages.^{6,16,17}

In extreme cases, a macular exudative star and disc edema develops. The mechanism behind this phenomenon is poorly understood, but it may be associated with a hypertension-related increase in



Two examples of hypertensive retinopathy.

intracranial pressure and is therefore considered true papilledema.^{1,3,17}

Arteriolosclerotic changes in the retinal microvasculature will persist even if systemic blood pressure is reduced. Some hypertensive retinopathy classification schemes do not include the arteriolosclerotic changes as these vessel findings can occur in non-hypertensive people.⁹ The other hypertensive retinopathy changes will resolve over time with the reduction of systemic blood pressure (BP).¹⁸ Cotton wool spots will develop in 24–48 hours with the elevation of BP, and will resolve in two to 10 weeks with the lowering of BP.^{4,5}

Management

Management of hypertensive retinopathy involves appropriate treatment of the underlying hypertension. A large population study indicated that pharmacologic BP reduction resulted in a lower incidence of retinopathy.¹⁸ Medical co-management with the primary physician is paramount. The ophthalmic examination may be the first time that a patient is discovered to have retinopathic changes consistent with hypertension. In that patients demonstrating hypertensive retinopathy also have a greater risk of subclinical and clinical stroke, cognitive impairment, renal dysfunction and cardiovascular mortality, independent of blood pressure levels and control, referral for additional evaluation may be appropriate.⁹⁻¹³

Managing patients with severe hypertension and extremely elevated BP has led to an algorithm in which patients are classified as having either hypertensive emergency or hypertensive urgency. Patients with extremely elevated BP but no evidence of end organ damage are said to have a hypertensive urgency; oral antihypertensive medications are used to lower BP over 24 to 48 hours by a primary care physician. Patients with extremely elevated BP and acute end organ damage (cardiovascular, cerebrovascular, or renal) are diagnosed as having hypertensive emergency and require immediate treatment with a titratable short-acting IV antihypertensive agent.^{19,20}

In that the eye is considered an “end organ,” the presence of retinopathy and extremely elevated BP would technically be considered a hypertensive emergency. Most clinicians don’t equate retinal hemorrhages and cotton wool spots as a crisis situation. However, a patient presenting with disc edema and macular exudative star is suffering from malignant hypertension and should be considered as being in medical crisis. This patient needs immediate consult with a primary care physician and, most likely, immediate transport to a hospital emergency room. It must be reiterated, though, that there are many causes of papilledema. Other causes, such as an intracranial mass lesion, must also be considered in the patient with hypertension. However, in a case in which BP is extremely elevated (e.g., 250/150mm Hg) and there is disc edema with a macular star, malignant hypertension is the likely cause.

Clinical Pearls

- For cotton wool spots to develop from hypertension, autoregulatory mechanisms must first be overcome. The patient must have at least some chronic readings of 110mm Hg diastolic or high.
- Fluorescein angiography is not indicated in cases of hypertensive retinopathy, since it will yield little diagnostic information.
- Hypertensive retinopathy presents

with a “dry” retina (i.e., few hemorrhages, rare edema, rare exudates and multiple cotton wool spots), whereas diabetic retinopathy presents with a “wet” retina (multiple hemorrhage, multiple exudates, extensive edema, and few cotton wool spots).

• The presence of hypertensive retinopathy or disc edema in a poorly controlled hypertensive patient are important findings, because they indicate end organ damage. For this reason, comprehensive ophthalmic evaluation complete with dilation is mandatory. We do not defer dilation on patients with markedly elevated BP. Standard dilation with 2.5% phenylephrine and 1% tropicamide will not affect a patient’s BP.

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IDIOPATHIC JUXTAFOVEAL RETINAL TELANGIECTASIA

Signs and Symptoms

Patients with idiopathic juxtafoveal retinal telangiectasia (IJRT) are typically 40 years of age or older. They may have a coincident history of ischemic vascular diseases such as diabetes or hypertension, but these do not appear to be causative factors.¹⁻⁴ IJRT may present with a wide range of visual impact, from totally asymptomatic to substantially



Fundus photo of idiopathic juxtafoveal retinal telangiectasia.

impaired; in most cases however, patients retain functional acuity of 20/200 or better.¹ Metamorphopsia may be a subjective complaint. The key fundus findings in IJRT involve a focal area of diminished retinal transparency (i.e., gray-ing) and/or small retinal hemorrhages just temporal to the fovea. Dilated capillaries may also be noted within this area, and while this is often difficult to visualize ophthalmoscopically, the abnormal capillary pattern is readily identifiable with fluorescein angiography.¹⁻³

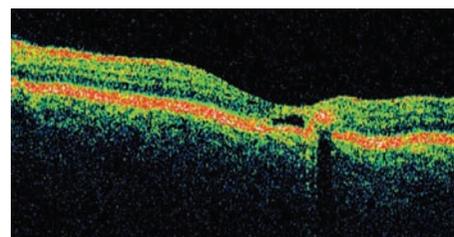
Areas of focal RPE hyperplasia, i.e. pigment plaques, often develop in the paramacular region as a response to these abnormal vessels. Other signs of IJRT include right angle venules, representing an unusual alteration of the vasculature in the paramacular area, with vessels taking an abrupt turn toward the macula as if being dragged.¹ Also, retinal crystals—fine, refractile deposits in the superficial retinal

layers—may be seen within the affected area.^{1,3,5} In some forms of the disease, lipid exudates are present.¹⁻⁴

Although a variety of complex classification schemes are described in the literature, there are essentially two forms of idiopathic juxtafoveal retinal telangiectasia (IJRT): unilateral and bilateral. The unilateral form, described by Yanuzzi as Type 1 or aneurysmal telangiectasia, occurs almost exclusively in males and is asymptomatic until after age 40.⁴ In this group, lipid exudate is common, while pigment plaques and retinal crystals are rare. The bilateral form, also known as Type 2 or perifoveal telangiectasia, occurs equally in males and females.¹⁻⁴ Type 2 IJRT is typically discovered between the ages of 40 and 60 years, with a mean age of 55-59 years.^{3,4} In this form of the disease, parafoveal atrophy, right-angle venules, RPE pigment plaques and retinal crystals are the prevailing signs.⁴

Pathophysiology

IJRT is probably best defined as an acquired capillary ectasia (i.e., a focal expansion or outpouching) and dilation in the parafoveal region, leading to vascular incompetence. The telangiectatic vessels develop microaneurysms, which subsequently leak fluid, blood, and occasionally, lipid. Some have described IJRT as a variant of Coat’s disease, although this is a more accurate depiction of the Type 1 form than the Type 2 form.^{4,6} While the precise etiology is unknown, it has been speculated that chronic venous congestion caused by obstruction of the retinal veins as they cross retinal arteries at the horizontal raphe may be a contributory factor.^{2,3,7} Histopathologically, the affected vessels



OCT of IJRT; evident is an intraretinal cystic area adjacent to an abnormal blood vessel, enhanced by accumulation of retinal pigment.

have been observed to display diffuse pericyte degeneration, as their lumens become occluded by abnormal basement membrane material.⁸ These findings are very similar to those seen in diabetic retinopathy, although there is no established link between IJRT and diabetes.⁹

In recent years, optical coherence tomography has been helpful in identifying more detailed fundus morphology associated with IJRT. One such finding is that there is often progressive foveal atrophy through the late stages of this disease.¹⁰ It is thought that this collective loss of retinal cells may induce intraretinal neovascularization and, ultimately, subretinal or choroidal neovascularization (CNV). However, it should be noted that not all patients will develop CNV, as IJRT often spontaneously arrests.¹¹

Management

The most crucial aspect of managing patients with IJRT is recognition of the clinical signs. This condition is relatively uncommon and has only been described in the literature during the past 25 years; hence, many practitioners may not be familiar with or experienced in diagnosing the disorder. IJRT must be part of the differential in any case of idiopathic paramacular hemorrhage, vasculopathy, macular edema or focal pigment hypertrophy, especially in those patients without a history of retinopathy or contributory systemic disease.

Diagnosis of IJRT may be aided by the use of ancillary testing. OCT can help to identify the abnormal vessels, pigment plaques, retinal crystals, foveal atrophy and intraretinal cysts associated with this disorder.^{6,7,10} Likewise, fluorescein angiography is beneficial in identifying the anomalous vasculature, particularly in the early stages of Type 2 disease. While some have argued that angiography is essential in making a definitive diagnosis, others suggest that such testing may be unnecessary when a diagnosis is apparent via less invasive means.^{1-4,6}

The natural history of IJRT suggests a slowly progressive disorder. A retrospective series of 20 patients over 10 to

21 years showed deterioration of vision in more than 84% of eyes, either due to intraretinal edema and serous retinal detachment (Type 1) or pigmented RPE scar formation or CNV (Type 2).¹¹ Historically, laser photocoagulation has been the recommended treatment early in the course of Type I IJRT to help suspend the exudative process and diminish macular edema.^{2,3} In contrast, laser therapy is not considered a viable treatment option for Type 2 IJRT, unless frank neovascularization is evident on fluorescein angiography.^{2,3,12} In fact, laser therapy may actually enhance vessel ectasia and promote intraretinal fibrosis in these individuals.¹²

Today, additional therapies include surgical removal of CNV, photodynamic therapy with verteporfin and treatment with anti-VEGF drugs such as bevacizumab.¹⁴⁻¹⁶ However, these treatment modalities should be considered only in cases of marked and rapid vision loss secondary to macular edema or CNV. Otherwise, a conservative approach is recommended, since many of these patients will stabilize without intervention.

Clinical Pearls

- IJRT may also be referred to by various names, including idiopathic juxtafoveal, macular, perifoveal or parafoveal telangiectasis, depending on the source. All refer to the same syndrome.

- IJRT is commonly underdiagnosed. The findings may appear very similar to diabetic retinopathy, and many cases have been incorrectly ascribed to diabetic retinopathy. Unfortunately, this misdiagnosis has also occurred in patients who were not diabetic. Recognition of this condition can save a patient from unnecessarily undergoing extensive medical testing.

- Consider IJRT in cases of mild paramacular dot and blot hemorrhages in patients without ischemic vascular disease such as diabetes and hypertension. Also, consider this diagnosis in cases of macular and paramacular RPE hyperplasia where no other cause can be identified.

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OCULAR ISCHEMIC SYNDROME

Signs and Symptoms

As the name implies, ocular ischemic syndrome (OIS) results when the blood supply to eye is diminished.¹⁻⁴ It is a progressive disorder in which chronic hypoperfusion to the eye and orbit produces poor ocular hemodynamics, resulting in a plethora of anterior and posterior segment findings, including loss of vision, exfoliation syndrome (with the possibility of exfoliation glaucoma), premature cataractogenesis, corneal edema, anterior chamber cellular response, ocu-

lar hypotony, dilated but non-tortuous retinal vessels, mid-peripheral intra-retinal hemorrhages secondary to venous stasis, cotton wool spots, spontaneous retinal arterial pulsation, cherry red macula and ischemia inciting the growth of neovascularization in both the posterior and anterior segment.¹⁻⁶

Impaired blood flow in the ophthalmic and central retinal artery can induce lenticular stress, which may incite premature cataractogenesis, true lens exfoliation syndrome and exfoliation glaucoma.⁵ Severe carotid stenosis may be associated with reduced ocular perfusion, which can be quantitatively evaluated by observing arterial pulsation upon ophthalmodynamometry (ODM).⁷ Induced rubeosis irides and neovascularization of the angle may or may not produce raised intraocular pressure (IOP) with variable amounts of cornea edema and iritis, ectropion uvea (eversion of the papillary margin), painful vision loss with eye and head pain, photophobia and lacrimation (secondary to ocular and arterial nociceptor stimulation via inflammation and ischemia).^{8,9} As the condition develops and the ciliary body becomes hypoxic, aqueous production often reduces, causing the IOP in the affected eye to drop, producing a relative hypotony despite angle closure from neovascularization. As the condition unfolds and worsens, inflammatory debris in the anterior chamber and neovascularization of the iris and angle may impede aqueous egress to the point where IOP rises well above normal levels.¹ Since the syndrome is associated with systemic age-related vascular processes, its presence carries an increased risk both of cardiovascular complications and cerebrovascular disease.²

Pathophysiology

OIS is traditionally caused by atherosclerotic stenotic processes of the ipsilateral internal carotid artery or ophthalmic artery.¹⁻¹⁰ These changes are produced by classic age-related vascular changes or vascular-inflammatory disease.^{2,8,10} External carotid stenosis is a rare but reported alternate etiology.^{5,8} The mechanism of damage results from a combi-

nation of markedly reduced ocular blood flow coupled with increased vascular resistance within the retrobulbar circulation of the central retinal and posterior ciliary circulation.¹⁰ Chronic hypoxia affects the iris and ciliary body producing hypoperfusion leading to relative ocular hypotony, secondary to decreased aqueous production.^{5,8} Further, a histopathologic study has demonstrated that ciliary body atrophy, derived from chronic ischemia, is plausible.⁵

Giant cell arteritis (GCA) is a systemic vasculopathy in which an excessive fibroproliferative response leads to vascular luminal narrowing.⁹ Alternately, this vascular closure can be distinguished from the typical OIS atherosclerotic



Mid-peripheral retinal hemorrhages and dilated, non-tortuous veins in ocular ischemic syndrome.

occlusion suggesting that it has a different response pattern to arterial injury.⁹ In GCA, macrophages at the vessel's tunica media/tunica intima border secrete platelet derived growth factors (PDGF), which drive the process.⁹ As the affected vessels lose their ability to support perfusion, ischemic optic neuropathy and ocular ischemic syndrome occur distal to the event.^{5,9}

The underlying ischemia encourages the release of ocular neovascular growth factors.⁴⁻¹¹ This initiates new vessel growth in the form of fibrovascular proliferative membranes, which form on both the retina and the iris surface.^{8,12} When iris neovascularization reaches the angle, its contractile nature pulls the iris into tight apposition with Schwalbe's ring, covering the trabecular meshwork and occluding the angle.^{8,12} This secondary angle closure is often called "zippering" and may eventually result in elevated IOP and neovascular glaucoma. However, anterior chamber rubeosis and neovascular angle closure secondary to

OIS does not often lead to increased IOP.^{5,10} Rather, because of the low perfusion pressure and propensity for ciliary body anoxia, poor aqueous secretion will result in relative hypotony.^{5,10} New iris vessels are weak and leaky, promoting a cellular inflammatory response with the potential to worsen any developing neovascular glaucoma.¹⁰ Diabetes mellitus is also known to aggravate carotid occlusive disease and can hasten the progression of developing ocular ischemic syndrome (OIS) and retinopathy.⁸

Management

The acute ocular management of OIS includes gonioscopy to obtain angle status, topical and oral steroidal and nonsteroidal anti-inflammatory preparations to quell inflammation, topical cycloplegics to reduce pain, topical ocular hypotensive medications if IOP is raised and ocular laser surgical therapy to address neovascular proliferation. A systemic evaluation is also critical to identify additional impending associated cardiovascular or cerebrovascular complications.^{3,13} In patients suspected of having OIS, evaluation should include a complete blood count with differential and platelets, an erythrocyte sedimentation rate, c-reactive protein, lipid panel, carotid artery evaluation using transcranial Doppler, magnetic resonance imaging, magnetic resonance angiography and vascular angiography.³

Anticoagulant and antiplatelet medications are a staple of managing systemic cardiovascular and cerebrovascular disease.² If giant cell arteritis is the suspected cause, immediate treatment or prompt referral to a neurologist or neuro-ophthalmologist is indicated for induction of appropriate anti-inflammatory therapy (intravenous methylprednisolone or high-dose oral prednisone).^{5,14} Patients with giant cell arteritis will require long-term oral steroid regimens with plans for extended monitoring for ocular and non-ocular complications.^{5,14} Generally, vision is not recovered. Treatment is geared toward recognizing OIS as a possible result of

GCA and preventing additional loss in the fellow eye.

In patients with OIS who develop neovascularization, panretinal photocoagulation (PRP) can be used to decrease the retinal demand for oxygen, thereby indirectly reducing the need for the faulty vascular supply.¹⁵



External view of OIS; note congestion of conjunctival vasculature and dense lenticular opacification.

New research in the area of combination treatment using PRP and the vascular endothelial growth factor inhibitor bevacizumab resulted in rapid decrease

of IOP and swift regression of neovascularization, possibly identifying a new approach to the problem.¹⁵

Percutaneous carotid angioplasty with stenting has been successfully developed for treating OIS resulting from intracranial carotid artery stenosis.^{3,16} Another modality for relieving the effects of reduced ocular circulation from carotid artery disease is carotid endarterectomy.¹⁷⁻¹⁹ Although it has had mixed support as a treatment for OIS, most reports in the literature support its position in the armamentarium of procedures designed to improve outcomes for OIS.^{6,18,19} In instances in which OIS is caused by non-giant cell vasculostenotic pathology, reestablishing the appropriate vascular supply reduced ocular sequelae and symptoms.^{12,15,17-19}

Clinical Pearls

- Intracranial carotid artery stenosis is a rare cause of ocular ischemic syndrome. Carotid angioplasty and stenting now permits lesions to be treated that were previously not amenable to endarterectomy.

- Giant cell arteritis must always be considered as the cause of ocular ischemic syndrome cases in patients older than 60 years.

- Lack of perfusion creates a stagnant blood in the peripheral retinal microvascular circulation. This leads to mid-peripheral dot and blot hemorrhages, the hallmark of OIS.

- Because of its appearance, OIS is often mistaken for diabetic retinopathy. Unilateral, asymmetric presentation in the absence of lipid should create suspicion for OIS over diabetic retinopathy.

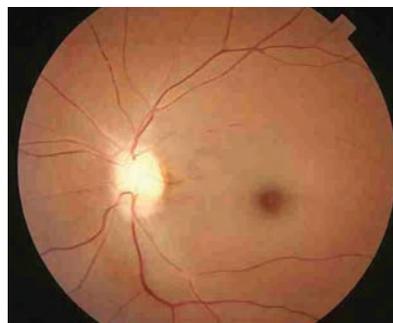
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RETINAL ARTERY OCCLUSION

Signs and Symptoms

Acute retinal artery occlusion is a potentially blinding ophthalmic emergency.^{1,2} Artery occlusions are categorized into branch, central, cilioretinal, or ophthalmic, depending on the location of the blockage.³ They are not the result of a single disease, but instead manifest a combination of chronic systemic abnormalities.^{2,3} As such, no definitive epidemiology for retinal artery occlusion has been determined. Rather, it falls under the epidemiology of systemic heart disease, cardiovascular disease, smoking, obesity and other chronic or episodic contributors including subacute bacterial endocarditis, tumors, leukemia, corticosteroid injection, polyarteritis nodosa, syphilis, blunt trauma, radiation exposure, optic nerve drusen, amniotic fluid embolism and cocaine abuse.^{3,4}

The majority of patients with retinal artery occlusion are older.³ Patients present with a chief complaint of sudden,



Central retinal artery occlusion.

painless vision loss.¹⁻⁴ In many instances, the loss is noticed upon waking. However, when a branch retinal artery is involved or a cilioretinal artery is present—preserving central vision—patients may complain of shadows in their visual field. Some may report that they have experienced episodes of transient visual loss before the current episode.³⁻⁵ Concurrent pain is more suggestive of underlying ocular ischemic syndrome (carotid circulation) rather than retinal artery occlusion.⁶ Although the etiology of retinal artery obstructions is primarily embolic, they are not always visible.²

As artery occlusions develop, the fundoscopic appearance will vary. Blood flow is impeded and retinal function becomes compromised immediately, although initially the retina may appear unaffected.¹⁻⁵ As the ischemia evolves, retinal arteries may visibly narrow, demonstrating segmented interrupted flow known as “box car vessels.” Over time, the retina may appear pale and swollen.¹⁻⁵ Nerve fiber layer hemorrhages may be present in the parapapillary area.³ The classic macular “cherry red spot” seen in central retinal artery occlusion occurs as a result of the absence of foveal photoreceptors and thinner anatomy in the macular region.³ The intact choroidal circulation is highlighted by the surrounding retinal pallor, making it stand out.¹⁻¹⁰

Following acute injury, the retinal appearance may resolve over the course of six weeks, but function rarely returns.¹⁻⁴ Rare instances however, have been reported in which visual function improves over time with or without treatment.^{2,7} The formation of neovascularization on the retina and iris is a possibility.^{1-3,11}

Pathophysiology

Calcific emboli are most likely to cause retinal artery occlusion and are often cardiac in origin. Emboli from various sources travel through the vascular system, becoming lodged inside a retinal vessel, partially or completely obstructing the flow of blood to distal tissues.^{2,4} Multiple reports in the literature cite etiologies related to malfunctioning clotting factors in blood, such as antiphospholipid disease, factor VIII abnormality, and with protein S and C alteration as an underlying source.⁷⁻⁹ Amniotic fluid embolism has also been recorded as an unusual but plausible source of retinal emboli.¹⁰

As the oxygen-sensitive retinal elements lose their source of sustenance, they quickly begin to fail, creating symptoms of variable visual phenomena or complete painless vision loss.¹⁻⁷ Retinal tissue is extremely sensitive to oxidative stress.¹² The inner layers of the retina succumb to ischemia, with intracellular

edema and necrosis present within minutes of the event.³

When partial or complete retinal arterial occlusion occurs, tissue ischemia begins. Retinal ischemia initiates the process of neovascularization in both the anterior and posterior segments.¹¹ Interestingly, neovascular complications



Image courtesy of Dr. Joe Overstreet

Cilio-retinal artery occlusion.

from retinal artery occlusion are infrequent when compared to other causes such as retinal vein occlusion and diabetes, because artery occlusion causes the retinal tissue to die rather than starve.

Hypertension is clearly a major risk factor for the development of microvasculopathy in general.¹³ As such, it increases the risk for retinal vascular events such as retinal vein occlusion, retinal artery occlusion and ischemic optic neuropathy.¹³ Sickle-cell disease has also been noted as an etiology of retinal artery occlusion.¹⁴ Although most cases are the result of cardiac, carotid, vascular, hemodynamic and autoimmune diseases, in rare instances retinal artery occlusions have occurred in healthy individuals with no attributable systemic etiology found.^{7,15} Additionally, some cases of central retinal artery occlusion are caused not by emboli but by thrombi from giant cell arteritis (GCA). This condition must be considered as a possible cause of retinal artery occlusion in older patients to prevent fellow eye vision loss.^{2,3}

Management

The key to visual recovery in any retinal arterial occlusion is timely interven-

tion. Anecdotally, the potential for achieving any restoration of vision is greatest when the blockage is dislodged within 100 minutes of the onset of the first symptoms.^{3,16} Although frequently unsuccessful, emergent treatments are designed to increase retinal perfusion by re-establishing retinal blood flow.^{1-4,16} The traditional mechanism of increasing intraocular pressure in the eye by aggressive digital palpation with sudden release is designed to stimulate retinal autoregulatory mechanisms. Here, as the retinal tissues sense the general hypoxia created by the digitally applied force, the retinal vasculature dilates to increase blood flow. When intraocular pressure drops as the force is removed, aqueous is forced from the eye, which decreases resistance to incoming blood. The hope is that the emboli will be dislodged and move farther down the retinal arterial system, permitting reperfusion of the critical retinal area.³ Other strategies for dislodging the embolus include decreasing the resistance to ocular blood flow by reducing intraocular pressure via topical and oral medication or paracentesis. An alternate strategy involves stimulating retinal vascular dilation by increasing blood carbon dioxide levels, either by having the patient breathe into a paper bag or by having him or her breathe a carbogen mixture (95% oxygen, 5% carbon dioxide) or with sublingual nitroglycerine.³ Unfortunately, such heroic measures rarely improve the final outcome.

Patients with artery occlusion must receive a complete systemic evaluation to uncover the underlying cause of the occlusion.^{4,15} Evaluation should include a complete blood count with differential and platelets, an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid panel, carotid artery evaluation using transcranial Doppler, prothrombin time, activated partial thromboplastin time, protein S, protein C, antiphospholipid antibody testing, antinuclear antibody and lupus anticoagulant testing, echocardiogram and transesophageal echocardiogram.^{8,9,15,17-20} In older patients with systemic symptoms

suggestive of GCA, obtaining ESR and CRP is emergently required.

In general, anticoagulation therapy is the staple of treating patients with artery occlusion secondary to coagulopathy, hyperviscosity, cardiac or carotid sources.^{15,17-20} In cases involving GCA, lupus or antiphospholipid antibody syndrome, immunosuppressants may be appropriate.¹⁸

Intra-arterial thrombolysis (IAT) represents an aggressive approach to treating retinal arterial occlusions, with the potential to produce superior visual outcomes compared with conventional treatments.²¹⁻²⁴ The use of intravenous and intra-arterial thrombolytic agents such as urokinase has been investigated for more than 20 years, but there remains insufficient evidence to support its routine use.²¹⁻²⁴ A potential side effect of the treatment is vitreous hemorrhage.²³ A prospective controlled clinical trial is ongoing in Europe, with the goal of providing reliable information and guidelines on this treatment.²²

Hyperbaric oxygen therapy is a primary or adjunctive therapeutic modality that is currently in off-label trials for eye diseases.²⁵ Increasing evidence has demonstrated safety and efficacy for use in retinal artery occlusion among other conditions.²⁵ A newly proposed technique using Nd:YAG laser to photodisrupt emboli within the central retinal artery and branch retinal arteries may help achieve rapid reperfusion of the retina.⁴ Transluminal Nd:YAG embolysis (TYL) or embolectomy (TYE) have been reported as potential procedures that can be deployed quickly in cases of retinal nonperfusion secondary to embolic blockage.⁴ In one study, following TYL, Snellen visual acuity improved by an average of 4.7 lines in 17 of 19 patients (89%), and 11 of the patients (58%) gained greater than 4 lines.⁴ Vitreous hemorrhage and subhyaloid hemorrhage are potential complications of this treatment, however.⁴

It should be noted that while retinal artery occlusion significantly deprives the retina of oxygen with tissue death rapidly ensuing, there still remains the

potential for spontaneous visual improvement, even without intervention. Over a 27 year period, Hayreh and Zimmerman noted spontaneous visual improvement in some patients with CRAO, dependent upon the classification and etiology of the occlusion.²⁶

Clinical Pearls

- Giant cell arteritis, optic neuritis, retinal vein occlusion, infectious neuroretinitis, vitreous hemorrhage secondary to proliferative retinopathy, retinal detachment and retinal vasculitis are all potential sources of monocular vision loss.

- Cilioretinal arteries take their blood supply from the choroid, often emerging from the temporal optic nerve and aiding in the supply of retinal tissues in the vicinity of the macula. In the event that a central retinal artery occlusion occurs in the presence of a cilioretinal artery, these vessels can partially preserve function over the area of their distribution, as long as the occlusion does not also affect the choroidal circulation.

- Patients with primary antiphospholipid antibody syndrome may develop retinal artery occlusions and may also exhibit episodes of amaurosis fugax, transient ischemic attack and anterior ischemic optic neuropathy, cilioretinal artery occlusion, central retinal artery occlusion and ophthalmic artery occlusion. Amaurosis fugax, retinal vascular thrombosis and optic neuropathy are considered the ocular hallmark signs of Hughes' syndrome. Testing for autoimmune factors and antiphospholipid antibody syndrome is especially important in younger patients with retinal artery occlusion.

- Heroic measures to restore retinal perfusion typically fail in the majority of these cases because many patients delay seeking treatment.

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DORSAL MIDBRAIN SYNDROME

Signs and Symptoms

Dorsal midbrain syndrome (DMS), also known as Parinaud's syndrome, pre-tectal syndrome, Sylvian aqueduct syndrome or Koerber-Salius-Elschnig syndrome, presents with findings that include a vertical gaze disturbance with paresis, spastic-paretic accommodation, convergence-retraction nystagmus and light-near dissociated (LND) pupils.¹⁻⁷ There may also be bilateral lid retraction without lid lag on down gaze (Collier's sign), as well as vertical diplopia due to unilateral or bilateral fourth cranial nerve palsies.⁸⁻¹⁰ Patients will present variably with these signs and symptoms, and not every symptom will be present in every patient.

Because of the inability to converge the eyes, coupled with the accommodative dysfunction, patients presenting with this condition most often complain of a newfound difficulty with reading or recent onset diplopia. Headache may be reported in cases that have associated intracranial hypertension.¹¹ Clinical testing reveals an inability to look upwards. Initially, only upward saccades are lost, but eventually upward pursuit movements fail as well. This finding may be vague, however, and is best elicited by using an optokinetic nystagmus drum or tape to test upgaze.¹⁻⁷ Downgaze paresis may occur as well, although it occurs less frequently. Accommodative difficulties range from intermittent spasms on attempted upgaze to complete accommodative paresis. Convergence-retraction nystagmus is easily elicited in these patients. Upon attempted upward saccades, the eyes demonstrate retro displacement into the orbit, with an associated nystagmus.^{1,5,7}

Bilateral LND pupils are a hallmark sign of DMS.¹² The pupils demonstrate no reactivity to light, but do react slowly to accommodative stimuli. Less commonly, skew deviations and downbeat nystagmus may be noted.

Pathophysiology

The dorsal mesencephalon (mid-

brain) contains many structures that can be compromised, resulting in the numerous clinical signs seen in the syndrome. DMS represents a supranuclear palsy that primarily affects conjugate vertical eye movements. It results from damage to the medial longitudinal fasciculus (MLF), mainly at the level of the superior colliculus. The rostral interstitial nucleus of the MLF (riMLF) controls vertical gaze; the superior colliculus controls vertical saccades and houses the intercalated neurons, which are associated with pupillomotor function. Downgaze paralysis results from bilateral lesions involving the regions located just caudal, medial and dorsal to the upper poles of the red nuclei, while upgaze paralysis results from unilateral lesions in or near the posterior commissure. Combined downgaze and upgaze paralysis results from bilateral lesions involving the region related to the whole riMLF on both sides.¹³ Probable destruction of the olivary pretectal nucleus and the nucleus of the optic tract likely abolishes the pupillary light reflex.¹¹ Occasionally, damage will involve the midbrain at the level of the inferior colliculus. The trochlear nuclei (cranial nerve IV) are located in this area, ventral to the cerebral aqueduct. Their motor fibers leave the nuclei and decussate within the anterior medullary vellum. Involvement in this area gives rise to unilateral and bilateral cranial nerve palsies.⁸⁻¹⁰

Most often, DMS is associated with pinealoma, a compressive lesion of the pineal gland that impinges on the structures of the dorsal midbrain in the pre-tectal area.^{2,6} Midbrain infarction and closed head trauma are common etiologies.^{4,9-11} Other reported causes include obstructive hydrocephalus, congenital aqueductal stenosis, metastatic cancer, mesencephalic hemorrhage, multiple sclerosis, A-V malformations, infective endocarditis, posterior fossa aneurysm, neurosarcoidosis and neurosyphilis.^{1,4,8,14-19}

Management

Once DMS is diagnosed, neuroimaging of the midbrain must be obtained (preferably MRI with contrast medium) to ascertain the cause. The most critical

element of managing patients with DMS is determining the underlying etiology. Treatment options are dictated by the specific condition. Today, pinealomas are most commonly managed by surgical excision with radiation. Chemotherapy is an alternative or adjuvant therapy, depending upon the nature of the tumor. All cases of DMS warrant prompt referral to a qualified neurologist and/or neurosurgeon.

Clinical Pearls

- The initial presentation of DMS may involve loss of upward saccades in isolation of other findings. Pupillomotor dysfunction is another early sign. All of the abovementioned signs need not be present to implicate damage to the dorsal midbrain.
- Hydrocephalus often ensues in cases of DMS because of aqueductal stenosis. In these cases, patients may present with associated symptoms of headache, nausea and vomiting, transient visual obscurations, tinnitus, alterations of mental status and gait disturbance. Papilledema is typically observed in these patients.
- DMS is often confused with myasthenia gravis in its early stages because of its variable presentation. Pupil involvement is never associated with myasthenia gravis, however, and ocular motility dysfunctions improve following rest. Also, ptosis is a common early finding in myasthenia gravis that is not encountered in DMS.
- When patients present with pupils that do not react to light, near function must be assessed. If the pupils react properly to near, vertical saccades must be examined. When vertical saccades are abnormal, DMS should be ruled out.

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PITUITARY ADENOMA

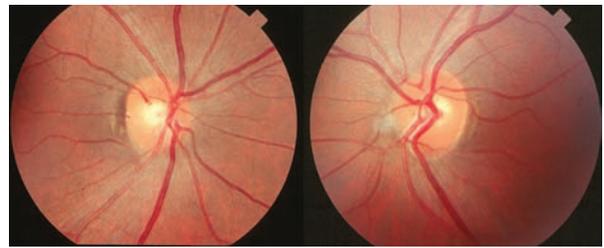
Signs and Symptoms

Pituitary adenomas are a common type of intracranial tumor. The prevalence in the general population, based upon meta-analysis of the prevailing literature, is about 17%.¹ Pituitary tumors demonstrate a peak incidence between the ages of 30 and 60 years and are considered rare in individuals younger than age 20.² There is no substantial gender difference in overall incidence, although on average, women seem to be affected at a substantially earlier age than men.^{2,3} There are no reported geographic or race differences; however, pituitary adenomas account for a greater percentage of intracranial tumors in African Americans.⁴

Clinical presentations can vary

widely. From an ophthalmic standpoint, patients may present with an array of visual symptoms, including diminished acuity, color desaturation, field loss and even diplopia (if the cavernous sinus is involved).⁵ The classic visual field defect is a bi-temporal hemianopia that is more dense from superior to inferior, although a variety of field defects can occur, including such non-localizing entities as peripheral constriction and arcuate scotomas.⁵⁻⁷ Less common ocular manifestations include nystagmus and photophobia.^{7,8} Funduscopically, patients with pituitary adenoma may display a completely normal optic nerve, though longstanding chiasmal compression may lead to primary optic atrophy and the development of disc pallor.⁵ Optic disc edema is not a characteristic finding of this disease state.

A variety of systemic signs and symptoms can accompany pituitary adenomas. Mass effects of the expanding neoplasm include headache, seizures or cerebrospinal fluid rhinorrhea (i.e., dripping of CSF from the nose).⁹ Depending on the location and severity of the tumor, numerous hormonal changes may occur. Prolactinomas—tumors that produce excessive levels of prolactin—are the most common form of pituitary adenoma, and cause *amenorrhea* (the loss of menstruation), *galactorrhea* (the spontaneous flow of milk from the breast) and infertility in females; in males, prolactinomas cause *hypogonadism*, decreased libido and impotence.⁹ Tumors that secrete excess growth hormone cause gigantism in children and acromegaly in adults.^{4,9} Adrenocorticotrophic hormone (ACTH)-secreting adenomas

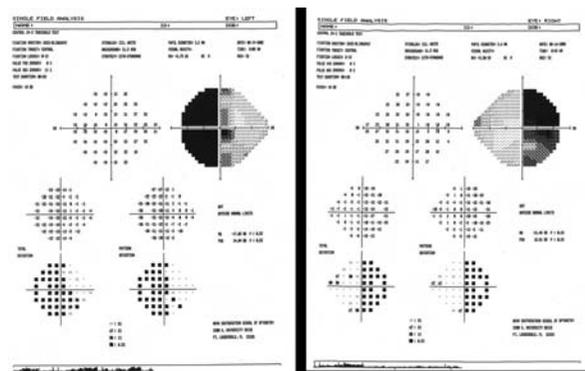


Patient diagnosed with pituitary macroadenoma. The only visible finding is subtle blurring of the disc margin.

produce Cushing's disease (hyperadrenalism).⁴ Rarely, tumors can secrete thyroid stimulating hormone (TSH), producing signs and symptoms of thyrotoxicosis, including heat intolerance, sweating, tachycardia, fine tremor and weight loss.⁹ Despite this vast array of potential signs and symptoms, a significant proportion of pituitary adenomas are silent and discovered only by chance during unrelated brain imaging; the term *incidentaloma* has been proposed for such non-functioning, asymptomatic pituitary adenomas.^{9,10}

Pathophysiology

The pituitary gland is situated within the sella turcica of the sphenoid bone, at the base of the skull. The anterior lobe of the pituitary gland secretes six hormones: thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicle stimulating hormone (FSH), leutenizing hormone, growth hormone (GH) and prolactin.² The posterior pituitary gland secretes vasopressin and oxytocin. The cavernous sinuses, which contain cranial nerves III and IV, the ophthalmic and maxillary divisions of cranial nerve V, cranial nerve VI and



Bitemporal visual field loss is pathognomonic for chiasmal disease.

the internal carotid artery are located lateral to the pituitary gland.

Pituitary adenomas are typically benign, slow-growing neoplasms of epithelial origin.¹¹ In most cases, they arise from the adenohypophysis (the anterior lobe of the pituitary gland) and are capable of producing both systemic and visual signs. The optic chiasm is situated approximately 8–13mm above the pituitary gland. The nasal retinal fibers of each eye (representing temporal visual field) cross, proceeding into the contralateral optic tract, while temporal retinal fibers (representing nasal visual field) continue posteriorly uncrossed. Inferior nasal fibers (representing superior temporal field) decussate within the chiasm anteriorly and superior nasal fibers (representing inferior temporal field) decussate posteriorly.

Upwardly growing pituitary tumors that reach appropriate sizes can impinge on the anterior notch of the chiasm at its lowest lying aspect, producing the classic bitemporal hemianopsia, with increased density superiorly. Since tumor growth is usually asymmetrical, the field loss between two eyes is also typically asymmetrical.

Pituitary adenomas are differentiated clinically by size and by the presence or absence of hormonal hypersecretion. Microadenomas, defined as 10mm or less in diameter without sellar enlargement, have little impact on the visual system or gland function. Macroadenomas, which by definition are 10mm or larger, have the capacity to expand beyond the sella turcica and induce mass effect symptoms, such as headache and visual disturbances.⁹ Macroadenomas include (in order of most common to least common): non-secreting adenomas, prolactin secreting (chromophobe) adenomas, growth hormone secreting (acidophil) adenomas, ACTH secreting (basophil) adenomas and FSH or TSH secreting adenomas.^{2,9} Secreting tumors are usually diagnosed by internists and endocrinologists. Non-secreting tumors are often diagnosed by eyecare practitioners because they produce visual symptoms in the absence of systemic signs.

Management

Patients who present with signs or symptoms indicative of chiasmal pathology, such as pituitary adenoma, warrant prompt neuroimaging and medical consultation. The preferred radiologic technique is high-resolution dynamic magnetic resonance imaging (MRI). Contrast enhancement with gadolinium helps to further delineate pituitary irregularities, and is crucial in diagnosing microadenomas.¹² Computed tomography (CT) scanning can also be used to delineate pituitary abnormalities and may actually be superior in demonstrating calcification within the tumor mass; however, MRI is substantially better than CT at depicting the complex anatomy and delicate structures surrounding the sella.⁹ Patients with any indication of hormonal abnormalities should undergo pituitary function testing, preferably by a pituitary endocrinologist. A neurology consultation may be required in cases of substantial neurologic symptoms, such as seizure, nystagmus, memory disturbance or impairment of the senses.

Therapeutic intervention is aimed at reducing the tumor mass and normalizing hormonal secretion. The three treatment modalities that are employed with regularity include surgery, radiation and medical (i.e., pharmacologic) therapy. The preferred treatment in any given case depends upon the age and health of the patient, the size and invasiveness of the tumor, and the degree of hormone production by the tumor.

Surgical intervention for pituitary adenomas is indicated when there is evidence of tumor enlargement, especially when growth is accompanied by compression of the optic chiasm, cavernous sinus invasion or the development of pituitary hormone deficiencies. A transphenoidal or subfrontal transcranial approach may be used, though the transphenoidal technique is preferred by the vast majority of skilled pituitary neurosurgeons.⁹ Visual improvement following treatment is often dramatic, with the greatest degree of improvement occurring within the first few months.

Complications of transphenoidal resection include cerebrospinal fluid rhinorrhea (discharge from nasal mucous membranes), diabetes insipidus and sinusitis.¹³

As an alternative (or adjunctive treatment) to surgery, fractionated radiotherapy offers a non-invasive option to arrest tumor growth in pituitary tumors. The usual dose is 50 Gy \pm 5 Gy and may be delivered via several techniques, including external proton beam, cobalt gamma-knife or linear accelerator focal stereotactic technology.⁹ Potential complications associated with this form of therapy include radiation-induced hypopituitarism, cerebrovascular accident, optic nerve damage and non-specific neurological dysfunction.¹⁴

Medical therapy is primarily limited to prolactinomas and somatotrophic tumors, although in such cases tremendous efficacy has been noted, to the point of excluding other, more invasive treatment options. Key medical therapies include dopamine agonists (e.g., bromocriptine, cabergoline and quinagolide) for hyperprolactinemia, and somatostatin analogues (e.g., octreotide and lanreotide) and GH antagonists (e.g., pegvisomant) for acromegaly. The dopamine agonists have particularly impressive outcomes in 85–90% of patients, but, unfortunately they are plagued by substantial adverse side effects, including nausea and vomiting, postural hypotension and dizziness, headache, constipation and depressive reactions.² Thus, despite their efficacy, these drugs are often intolerable to patients. Also, the practitioner must realize that the effects of these agents persist only as long as therapy is continued; hence, these medications must be continued for life, unless other forms of therapy are used.

Clinical Pearls

- Although pituitary adenomas are considered benign, they have the capacity to cause significant morbidity in vision and other organ systems. In a small percentage of patients, pituitary tumors may be malignant. By definition, these are

referred to as pituitary carcinomas and represent pituitary tumors with evidence of subarachnoid, brain, or systemic metastasis.¹²

- The differential diagnosis of pituitary tumor includes craniopharyngioma (a slow-growing tumor arising from vestigial remnants of Rathke's pouch), meningiomas and gliomas; all of these can impinge on the chiasm and present with a similar ophthalmic picture. Clinical masqueraders can include chronic retrobulbar optic neuritis, toxic/nutritional optic neuropathy, uncorrected refractive error, normal tension glaucoma and age-related maculopathy. Misdiagnosis is often attributable to an inadequate history, failure to correlate systemic signs and visual symptoms, or failure to perform adequate testing or follow up.

- Bilateral tilted disc syndrome can result in a superior bi-temporal field defect similar to that seen in pituitary adenoma. Careful ophthalmoscopic evaluation should be performed before more invasive testing (such as MRI or pituitary function testing) is ordered. However, bitemporal field loss respecting the vertical meridian warrants neuroradiologic investigation even in the presence of tilted disc syndrome.

- In pregnant women, bi-temporal visual field loss and headache may signal pituitary apoplexy (rapid degeneration with hemorrhagic necrosis of the pituitary gland). Pituitary apoplexy is a potentially life-threatening condition and warrants prompt referral for an MRI with or without lumbar puncture to rule out subarachnoid hemorrhage from this type of tumor.

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AMAUROSIS FUGAX AND TRANSIENT ISCHEMIC ATTACK

Signs and Symptoms

The word amaurosis originates from the Greek meaning "darkness."¹ The word fugax originates from the Latin meaning "fleeting." Hippocrates was the first to use the term amaurosis fugax to connote blindness in the absence of any apparent lesion of the eye.¹ Today, the term is used to describe an event of monocular vision loss lasting from seconds to minutes.¹⁻⁴

Amaurosis fugax (AF) almost always presents as sudden, painless vision loss, lasting seconds to minutes, without evidence of headache, secondary to an embolic event or hemodynamic insufficiency, frequently leaving some permanent remnant.¹⁻⁹ AF may forecast impending retinal hemorrhages, cotton wool spots, central retinal vein occlusion, anterior ischemic optic neuropathy, retinal artery occlusion, ophthalmic artery occlusion or cerebrovascular accident (CVA).^{6,10} It is a sign of beginning, impending or worsening vascular disease.¹¹ As such, its epidemiology is non-specific and is associated with the systemic illnesses that induce it, along with smoking, hyperlipidemia and age older than 64 years.¹⁻¹²

Transient ischemic attack (TIA) may be characterized by monocular or binocular vision loss lasting minutes to hours, may induce other noticeable visual phe-

nomena without affecting acuity, and typically includes other neurologic symptoms. In some cases, TIA presents with no visual involvement, and these patients typically present to a neurologist or hospital emergency room. The pattern demonstrated is often diagnostic for location.³ Scotomas may be monocular or binocular, idiopathic, altitudinal, sectoral or homonymous.³ Monocular, sectoral episodes indicate involvement in the carotid/ocular circulation.³ Binocular, homonymous events signify a retrochiasmal effect and posterior or vertebral circulatory issue. Like AF, TIA is a sign of vascular disease, making its epidemiology similar to that of AF.¹⁻¹¹

TIA is on a continuum with AF but is considered its own entity because of the length of time the events last and because it reflects influence on more than one neurologic area. AF is strictly a local ocular event; TIA represents the beginning of a territorial issue. As the name implies, TIA affects a sector of neurologic tissue momentarily and temporarily, secondary to an event or process that interrupts circulation.¹⁻¹¹ When the effects of an episode remain permanently, they cross the line into the category of cerebrovascular accident or stroke.

Pathophysiology

AF and TIA share the common etiology of interrupted blood flow either to the eye or areas of the brain which subserve vision.⁴⁻⁸ Patients with common carotid artery stenosis may be susceptible to transient hemodynamic insufficiency of the retina as a result of simultaneous reductions in blood supplies from both the external carotid artery and the internal carotid artery.^{2,3}

TIA may be caused by papilledema, epilepsy, hypertension, diabetes, cardiac disease, pregnancy, seizures, blood coagulopathy and hyperviscosity syndromes, the toxic effects of medications, hyperlipidemia, as well as thrombosis and emboli.¹¹⁻²⁰ Disorders of clotting, hypercoagulopathy and hyperviscosity, such as antiphospholipid antibody syndrome, should be considered in young people experiencing either phenomenon.^{6,14}

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Spontaneous dissection of the cervical internal carotid artery causes territory ischemia and symptoms on the side of dissection. Local signs and symptoms include head, facial or neck pain, Horner's syndrome, pulsatile tinnitus, cranial nerve palsy (III, IV, V and VI), headache, ischemic stroke in 80–84%, transient ischemic attack in 15–16%, amaurosis fugax in 3%, ischemic optic neuropathy in 4% and retinal infarct in 1%.¹⁵ Optic disc drusen have also been reported to induce episodes of transient visual interruption via the mechanism of intermittent compression.⁹

Retinal migraine is characterized by its vasospastic etiology.^{3,5-8} Although the International Headache Society diagnostic criteria for retinal migraine requires reversible visual loss, irreversible visual loss may be part of the retinal migraine spectrum, representing an ocular form infarction.⁸

Light-induced amaurosis fugax is a manifestation of ocular ischemic syndrome (carotid occlusive syndrome) occurring when significant, bilateral, carotid artery disease has developed.⁴ The frequency of amaurotic episodes seems to be significantly higher in cases involving common carotid artery stenosis compared against internal carotid artery stenosis and indicates advanced disease.²

Giant cell arteritis (GCA) is a possible cause of TIA and AF in the elderly.²¹ In a classic report on the subject, examining biopsy-proven GCA in a prospective study of 170 patients over a 12-year period, amaurosis fugax occurred in 30.6% of patients. This underscores the need to consider GCA in all patients experiencing transient vision loss. Uncovering GCA as the cause of TIA or AF may save patients from certain catastrophic vision loss from central retinal artery occlusion (CRAO), anterior ischemic optic neuropathy (AION) or cerebrovascular accident.^{21,22}

Management

AF and TIA are symptoms of an underlying vasculopathic process.¹⁻⁸ The

management will vary with ultimate cause.¹⁻²⁵ Obviously, work must be done in the area of the modifiable risk factors: stopping smoking, reducing cholesterol, lowering blood pressure, managing diabetes and maintaining a proper weight. The medical evaluation should include a complete blood count with differential and platelets, an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lipid panel, carotid artery evaluation using transcranial Doppler, prothrombin time, activated partial thromboplastin time, protein S, protein C, antiphospholipid antibody testing, antinuclear antibody and lupus anticoagulant testing, echocardiogram and transesophageal echocardiogram.¹⁶⁻¹⁹ Older patients, especially those demonstrating systemic symptoms suggestive of giant cell arteritis (jaw claudication, pain upon palpation of the temporal forehead, anorexia, loss of appetite), should undergo ESR and CRP immediately.²³

Ocular management should include detailed, dilated inspection of the posterior pole to rule out the presence of emboli and perimetry to determine any visual field loss. Neuroimaging, such as magnetic resonance imaging and magnetic resonance angiography, may be indicated to ascertain a cause.

The systemic management for TIA and AF resulting from vascular disease is oral anticoagulant therapy. Management for systemic autoimmune disease is oral anti-inflammatory therapy with or without immune modulation.⁶ Surgical management of carotid artery disease can be accomplished via percutaneous angioplasty with stenting or endarterectomy.^{9,24} Patients experiencing AF will need consultation from an internist or cardiologist to determine the underlying cause. Patients experiencing TIA are best managed by a neurologist.

AF must be differentiated from monocular visual loss labeled retinal migraine.^{5,6} A true retinal migraine is a diagnosis of exclusion that produces a fully reversible monocular visual disturbance (classic aura vs. other episodic phenomena) in concert with a headache in

the setting of a normal neuro-ophthalmic examination.⁵⁻⁷

Clinical Pearls

- Important clinical questions for patients presenting with the chief complaint of an episode of sudden painless vision loss include:

- What activities preceded the episode?
- Was it one eye or both?
- Was vision completely lost during the episode?
- Was vision blacked out or blurry?
- How long did the episode last?
- When vision returned, did it come back suddenly or gradually?
- Did the episode leave any permanent loss?
- Has this happened before, and if so, how many times?
- If the episodes are new, what is their frequency, and is the frequency changing?
- Did a headache occur after the episode?

- Retinal migraine is classically seen in women of childbearing age and includes classic, cluster or complicated headache with aura.⁶ It typically is characterized by monocular visual phenomena lasting less than one hour.

- Acephalic retinal migraine can produce variable visual symptoms in the absence of headache, further complicating the diagnosis.

- Light-induced AF from ocular ischemic syndrome is often an indication that timely carotid surgical intervention is indicated because of the major risk for stroke.

- Amaurosis fugax is a significant symptom with a much higher association to extracranial CVA than either Hollenhorst plaque or artery occlusion. It warrants immediate investigation.

- Recurrent bouts of AF in elderly patients may indicate the presence of GCA and impending permanent vision loss from retinal artery occlusion or ischemic optic neuropathy.

- AF and TIA are straws that tell us which way the intracranial wind is blowing.

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CRANIAL NERVE III PALSY

Signs and Symptoms

A patient with acute cranial nerve (CN) III palsy will usually present with a sudden onset of unilateral ptosis (or rarely, a bilateral ptosis if the damage occurs to the third nerve nucleus) and ophthalmop-



Left cranial nerve III palsy.

plegia, frequently accompanied by significant eye or head pain dependent upon the cause.¹⁻⁴ The patient often complains of double vision, though in some cases the diplopia may be masked by the ptosis which obscures the vision in the affected eye; however, if the lid is manually elevated, the patient will experience diplopia. Acuity is typically unaffected unless the provoking lesion occurs in the superior orbital fissure causing simultaneous cranial nerve II involvement.

CN III palsy produces a noncomitant exotropic, hypotropic eye position (down and out). There is limitation of elevation, depression and adduction. There is an underaction of the superior, inferior, and medial recti muscles and inferior oblique muscle.¹⁻³ The underaction of these muscles may be complete or incomplete.⁵⁻⁷ Total involvement of the levator palpebrae superioris and all extraocular muscles subserved by CN III is termed a complete CN III palsy. Patients with some degree (but not total paralysis) of the extraocular muscles are said to have an incomplete CN III palsy.³ In any case of CN III palsy, the pupil may be dilated and minimally reactive to light (pupillary involvement), totally reactive and normal (pupillary non-involvement) or may be sluggishly responsive (partial pupillary involvement).^{3,4,7-10}

Various neurological signs may present concomitantly with the development of

CN III palsy. Patients may additionally have contralateral intention tremor, cerebellar ataxia or contralateral hemiplegia, depending upon the cause and location of damage to CN III.³

Patients developing acute CN III palsy tend to be older; CN III palsy is uncommon in children, though it does occur.⁷ There is often concurrent diabetes and/or hypertension.^{3,6,7,11} Occasionally, there will be head trauma associated with the development of CN III palsy.¹²

Pathophysiology

The third cranial nerve arises in the dorsal mesencephalon with distinct paired subnuclei that give rise to fibers that pass through the brainstem, subarachnoid space, cavernous sinus and orbit to ultimately innervate the levator palpebrae superioris, superior rectus, inferior rectus, medial rectus and inferior oblique muscles. All subnuclei innervate ipsilateral structures with the exception of the superior rectus (innervating the contralateral eye) and the levator palpebrae superioris, which has a single subnuclei innervating both eye lid muscles.^{3,13} In concert with the third cranial nerve nucleus is the Edinger-Westphal nucleus, which controls the pupil sphincter and ciliary body muscles. Pupillary fibers travel the course with CN III.

Third nerve palsy results from damage to the oculomotor nerve anywhere along its route from the nucleus in the dorsal mesencephalon, its fascicles in the brainstem parenchyma, the nerve root in subarachnoid space, the cavernous sinus or the posterior orbit.^{3,13} Damage to the third nerve nucleus results in an ipsilateral third nerve palsy with contralateral superior rectus underaction and bilateral ptosis. Damage to the third nerve fascicles emerging from the CN III subnuclear complex and passing through the parenchyma of the mesencephalon can result in an ipsilateral third nerve palsy with contralateral hemiparesis (Weber's syndrome), contralateral intention tremor (Benedikt's syndrome) or ipsilateral cerebellar ataxia (Nothnagel's syndrome). Vascular infarct, metastatic disease and demyelination are the common causes

of brainstem involvement.^{7,13}

Once the CN III fascicles emerge from the brainstem, they form the nerve proper and travel through the subarachnoid space parallel to the posterior communicating artery. Damage to the third nerve within the subarachnoid space produces an isolated third nerve palsy. The main concern in an isolated CN III palsy occurring within the subarachnoid space is compression of the nerve by an expanding aneurysm of the posterior communicating artery. Additionally aneurysmal compression can occur from the internal carotid, basilar, anterior communicating or temporal arteries, though to a lesser extent than from the posterior communicating artery.^{8,9,14-16} Approximately 15% of isolated CN III palsies occurring secondary to damage within the subarachnoid area are the result of aneurysms.¹¹ Vasculopathic infarct, often associated with concurrent diabetes or hypertension, accounts for 35% of cases of isolated CN III palsy.¹¹

Aneurysmal compression is marked by head or retro-orbital pain and anisocoria with ipsilateral pupil dilation as the



Right cranial nerve III palsy.

expanding aneurysm compresses the pupillomotor fibers within CN III as well as pain-sensitive dura and other such structures. Approximately one-third of patients with CN III palsy from vascular infarct manifest a small degree of anisocoria of typically less than 1mm. In contradistinction, aneurysmal compression typically causes more than 2mm of anisocoria.¹¹ Additionally, patients developing CN III palsy from aneurysmal compression initially may not present with anisocoria or pupil involvement.^{5,8-10} These patients typically present initially with an incomplete palsy that evolves and develops pupil dilation over several days.^{3,7,11}

Damage to the third nerve in the cavernous sinus, superior orbital fissure or posterior orbit is unlikely to present as an isolated palsy due to the confluence of other structures within these areas. Cavernous sinus involvement will also include possible concurrent pareses of cranial nerve IV, VI and V1, as well as an ipsilateral Horner's syndrome. The most common causes of damage in these areas include metastatic disease, inflammation, herpes zoster, carotid artery aneurysm, pituitary adenoma, pituitary apoplexy and sphenoid wing meningioma.^{2,3,7}

Management

Management of third nerve palsy in the adult depends upon the associated findings and etiology. In complicated third nerve palsies in which other neural structures are involved, the patient should undergo MRI scanning to ascertain the etiology. The scan should be directed to the anatomical location as dictated by the associated findings described above.³

In cases of isolated, complete third nerve palsies with no pupillary involvement and in which the patient is older than 50 years, the main cause is predominantly ischemic vascular infarct. Giant cell arteritis is also a potential etiology. Tumor and aneurysm also can produce isolated lesions without pupillary involvement, although this is rare.³ Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), erythrocyte sedimentation rate, C-reactive protein, blood pressure measurement, complete blood count with differential, blood glucose testing, antinuclear antibody testing and syphilis serology are indicated. Close pupil observation is required, as pupil involvement may be delayed by five to seven days. This is especially true for patients with incomplete CN III palsy with pupil sparing, because these patients are more likely to have an incipient aneurysm developing.⁵ In ischemic vascular CN III palsy, the pupil will not evolve, aberrant regeneration will not occur and the palsy will spontaneously improve or resolve over the course of three to six months.^{3,11} If the palsy shows no improvement over six to eight weeks or if aberrant

regeneration develops, MRI/MRA is required to rule out the presence of a mass in the subarachnoid space.³

Children younger than 14 years rarely have aneurysms, and the majority of third nerve palsies in this age group are traumatic or congenital.⁷ If the patient is younger than 50 years and has a non-pupillary-involved, isolated third nerve palsy, intracranial angiography is indicated, since ischemic vasculopathy is less likely than aneurysm to occur in this age group. If an adult patient of any age presents with complete or incomplete isolated third nerve palsy with pupillary involvement, it should be considered a medical emergency and the patient should undergo immediate MRA/MRI or intracranial angiography. In these cases, the cause is likely an aneurysm at the junction of the internal carotid and posterior communicating arteries or at the tip of the basilar artery. If the aneurysm ruptures, the patient may die from subarachnoid hemorrhage and brainstem herniation through the foramen magnum.

In cases of CN III palsy caused by subarachnoid aneurysm, immediate neurosurgical intervention is necessary. Common endovascular treatment involves direct clipping of the aneurysm or embolization with detachable coils.¹⁶⁻¹⁷

Clinical Pearls

- Isolated third nerve palsy resulting from ischemic vasculopathy will spontaneously resolve and recover over a period of three to six months. If the palsy fails to resolve in this time, then neuroradiologic studies must be undertaken once again to determine the true etiology.
- Complete and total CN III palsy in an adult older than age 50 without pupil involvement is rarely ever caused by an aneurysm.
- Patients manifesting an incomplete CN III palsy should be suspected of having a developing aneurysm.
- Myasthenia gravis can mimic virtually any cranial neuropathy, including isolated non-pupillary involved third nerve palsies. It must remain a possible diagnosis when encountering a third nerve palsy, especially when the course is

variable or atypical.

- There will always be pain in aneurysmal compression. In ischemic vascular CN III palsies, however, pain is frequent but may be absent, and it is typically less severe than with aneurysmal compression.

- Consider GCA as a cause of CN III palsy in older patients.

- Ischemic vascular CN III palsy does not progress to develop aberrant regeneration.

- Anisocoria in ischemic infarction CN III palsy is nominal, typically less than 1mm between the eyes. In contradistinction, the anisocoria from aneurysmal compression typically exceeds 2mm.

- Pupil-involved CN III palsy in adults is one of the few true medical emergencies seen in eye care. These patients must be sent to the hospital immediately for neurosurgical consult.

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CRANIAL NERVE IV PALSY

Signs and Symptoms

A patient with cranial nerve (CN) IV palsy will typically present with complaints of vertical diplopia, which worsens if the patient tries to read. There may be an inability to look down and in. There may also be a component of horizontal diplopia as a lateral phoria becomes manifest due to the vertical dissociation.¹⁻⁴ The chin is often tucked downwards (moved into the field of the dysfunctional muscle) as well. The patient may note greater diplopia or visual discomfort when head tilting toward the side of the palsy. Commonly, the patient develops a compensatory head tilt opposite to the affected superior oblique muscle.

Visual acuity is unaffected and there is very rarely any concurrent pain. Ocular motility testing with the alternate cover test will reveal a hyperphoric or hypertropic deviation that will increase in contralateral gaze, reduce in ipsilateral gaze, increase on ipsilateral head tilt and decrease on contralateral head tilt. In bilateral cranial nerve IV palsy, the patient will manifest a hyperdeviation which reverses in opposite gaze. The hyperdeviation increases on ipsilateral head tilt.⁵⁻⁸

Frequently there is concurrent hypertension and/or diabetes.⁹⁻¹¹ Often, there will be a history of head trauma immedi-

ately preceding development of the CN IV palsy. The trauma need not be major; relatively minor injuries can precipitate CN IV palsy.^{2,3,12-14} In cases of longstanding decompensated CN IV palsy, the inciting trauma may have been many years antecedent.

Pathophysiology

The fourth cranial nerve nucleus is located in the dorsal mesencephalon. Nerve fibers decussate and exit the brain stem dorsally into the subarachnoid space. The nerve then courses around the brain to enter the cavernous sinus, superior orbital fissure and orbit to innervate the superior oblique muscle. Damage to the fourth nerve nucleus or its fascicles within the brain stem produces a contralateral fourth nerve palsy, along with the possible associated signs of light-near dissociated pupils, retraction nystagmus, upgaze palsy, Horner's syndrome and/or internuclear ophthalmoplegia. Bilateral fourth nerve palsies are possible as well. The main causes of damage to the fourth nerve in this area are hemorrhage, infarction, trauma, hydrocephalus and demyelination.^{9,14}

The fourth nerve is especially prone to trauma as it exits the brain stem and courses through the subarachnoid space. In contrast to third nerve palsies with an etiology in subarachnoid space, fourth nerve palsies are rarely the result of aneurysmal compression. The most common causes of damage to the fourth nerve in this region are trauma and ischemic vasculopathy.³

Due to the large number of other neural structures that accompany the fourth nerve as it travels through the cavernous sinus and superior orbital fissure, it is unlikely that patients will exhibit isolated fourth nerve palsy from damage within these areas. More likely, there will be a concomitant palsy of cranial nerves III and VI. Common causes of damage to the fourth nerve in these areas are herpes zoster, inflammation of the cavernous sinus or posterior orbit, meningioma, metastatic disease, pituitary adenoma and carotid cavernous fistula.¹⁵ Trauma to the head or orbit can cause damage to the

trochlea with resultant superior oblique muscle dysfunction.

Trauma and vascular disease are considered the main causes of acquired CN IV palsy.^{14,15} However, there have been numerous reports of other potential causes of isolated CN IV palsy, including multiple sclerosis, polycythemia vera, cat-scratch disease and, rarely, metastatic disease.¹⁵⁻²¹

Management

A fourth nerve palsy often presents suddenly but may additionally result from decompensation of a longstanding or congenital palsy. To differentiate these two types of palsies, old photographs of the patient (such as a driver's license) should be examined. A patient with a decompensated longstanding palsy will present with a compensatory head tilt. Further, patients with decompensated longstanding fourth nerve palsies will have an exaggerated vertical fusional ability. Longstanding fourth nerve palsies typically have a benign course and no further management is necessary.

In the case of complicated fourth nerve palsies—those that present with other concurrent neurological dysfunction—the patient should undergo neuro-radiological studies dictated by the accompanying signs and symptoms. In the case of isolated fourth nerve palsies caused by recent trauma, the patient should undergo neuroradiological studies of the head to dismiss the possibility of a concurrent subarachnoid hemorrhage. If the fourth nerve palsy is not associated with recent trauma, a history of past trauma should be investigated. If the fourth nerve palsy is the result of previous trauma and has recently decompensated, the diplopia can be managed by the placement of vertical prisms in spectacles. If the patient is elderly and has a fourth nerve palsy of recent origin, an ischemic vascular evaluation should be undertaken to determine whether he or she has diabetes and hypertension. Giant cell arteritis should also be considered and appropriate history and testing should then occur. If the palsy is caused by vascular infarct, then it will spontaneously resolve over three to six months and no further

management beyond periodic observation and either occlusion or press-on prism therapy is required.^{2,3} In some cases, recovery does not occur.^{2,3} In these cases, permanent prism (ground into the spectacle lenses), muscle surgery or botulinum injections may be considered.²²

Clinical Pearls

- Cases of true vertical diplopia can be considered a fourth nerve palsy until proven otherwise.
- If the presenting motility of a patient is a hyperdeviation in one eye that increases on opposite gaze and ipsilateral head tilt, the cause is nearly always CN IV palsy.
- Myasthenia gravis can mimic CN IV palsy and must always be considered.
- Bilateral CN IV palsy localizes damage to the dorsal mesencephalon.
- In children, nearly all cases of isolated fourth nerve palsy are either congenital or traumatic. In adults, nearly all isolated acquired fourth nerve palsies can be ascribed to trauma or vascular disease. Rarely is tumor or aneurysm a cause. The majority of fourth nerve palsies follow a benign course.
- When encountering isolated fourth nerve palsy, delay prescribing permanent prisms for at least three months to allow for the palsy to recover. Otherwise, glasses with permanent prism correction can induce vertical diplopia should the palsy recover.

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CRANIAL NERVE VI PALSYP

Signs and Symptoms

A patient with isolated, unilateral, acute onset cranial nerve (CN) VI palsy will present with horizontal uncrossed diplopia that worsens at distance in either right or left gaze depending upon the involved eye. The patient will have an abduction deficit in the involved eye and either a non-comitant esophoric or esotropic posture.^{1,2} If the palsy is isolated, there will be neither visual acuity nor visual field loss. There may be some degree of head or retro-orbital pain present, dependent upon the cause.

There are three distinct demographic groups that develop CN VI palsy. Most patients developing acute CN VI palsy are older. This group often has a concurrent history of hypertension and/or diabetes.³⁻⁵ The peak incidence occurs in the seventh decade of life.⁶ Children are also prone to develop CN VI palsy. The cause may range from benign, such as viral illness or trauma, to malignant.⁷⁻¹¹ The third group consists of adults aged 20–50 years. This group is more likely to have neurologically complicated CN VI palsies involving other cranial nerves.^{12,13} In contrast to older adults, vascular disease such as diabetes and hypertension are uncommon in this group, which typically exhibits more serious conditions such as central nervous system (CNS) mass lesions and multiple sclerosis.¹³⁻¹⁵

Because various cancers have been associated with CN VI palsy, patients may present with a pre-existing history of malignant disease. However, CN VI palsy may be the premonitory sign of cancer in some patients. Carcinoma in particular has been associated with the development of CN VI palsy, either through direct invasion from the nasopharynx or metastasis from the prostate or other sites.¹⁶⁻²¹ Other less common associations with CN VI palsy include herpes zoster, temporal arteritis, Lyme disease, sarcoidosis, pituitary tumor, aneurysm, inflammation and ophthalmoplegic migraine.²²⁻²⁸

Pathophysiology

CN VI arises in the pons in close association with the facial nerve and paramedian pontine reticular formation (PPRF). Because of this arrangement, damage to the sixth nerve within the brain stem can produce a sixth nerve palsy along with a facial nerve palsy or internuclear ophthalmoplegia. Associated findings may also include leg paralysis with sixth nerve palsy (Raymond's syndrome) or leg paralysis, facial paralysis and sixth nerve palsy (Millard-Gubler syndrome). These additional findings identify the location of damage as the pons, in which ischemic infarct, tumor and demyelination are the common causes.^{3,4}

CN VI travels through the subarach-

noid space, ascends the clivus and enters the cavernous sinus. Within the subarachnoid space, the sixth nerve may be stretched against the clivus if the brain stem herniates through the foramen magnum due to increased intracranial pressure. This may induce a bilateral sixth nerve palsy (which is often intermittent) and papilledema.¹³ The sixth nerve passes over the petrous apex of the temporal bone; damage here can result in a sixth nerve palsy, facial pain, and hearing loss. This is the result of inflammation of the temporal bone (Gradenigo's syndrome) or nasopharyngeal carcinoma.^{16,21} Within the cavernous sinus, the sixth nerve is joined by the oculosympathetic nerves, as well as CN III, IV and VI. Damage here



Cranial nerve VI palsy with resultant abduction deficit.

will yield a sixth nerve palsy and Horner's syndrome, as well as possibly concurrent CN III and IV palsy.^{19,20,29} The etiology may be aneurysm, meningioma, pituitary adenoma, inflammation or fistula.³⁰⁻³³ The sixth nerve is also vulnerable to ischemic infarct from diabetes and hypertension; this remains a prime cause of isolated sixth nerve palsy.

Although CN VI can be affected in many areas through its course from the pons to the orbit, a significant number of cases will have no conclusive etiology, despite extensive medical evaluation.^{2-4,6,13} As many as one-third of CN VI palsies will remain idiopathic.⁶

Management

The most important consideration in the management of patients with acute onset CN VI palsy involves identifying the causative factor efficiently and cost-effectively. Doing so involves understanding common causes for each

patient profile and palsy. In one large population-based study, the four most common causes were idiopathic, hypertension alone, coexistent diabetes and hypertension and trauma.⁶

Detailed presenting and medical history must be obtained as well as a neurologic examination upon presentation. Each case of CN VI palsy should be classified as traumatic or non-traumatic. Non-traumatic cases should be subdivided as neurologically isolated or non-neurologically isolated.⁶ Additionally, patients should be ascribed to one of three groups: children, young adults, and older adults.⁶

A non-neurologically isolated sixth nerve palsy involving any of the above-mentioned neurological signs indicates the need for an MRI of the suspect area as well as a cerebrospinal fluid analysis. Non-neurologically isolated CN VI palsies are commonly caused by cerebrovascular accidents involving the pons, aneurysm (typically within the cavernous sinus) or neoplasm.⁶ While neurologically complicated CN VI palsy has a high likelihood of a serious cause such as neoplasm, isolated CN VI palsy actually has a very low risk (2% in one series) of being caused by a neoplasm.⁶

In children, sixth nerve palsy can occur from a presumed viral cause and has an excellent prognosis.^{9,10} However, nearly one-half of all CN VI palsies in children result from neoplastic disease, notably pontine glioma.^{8,11} Thus, neurologic evaluation and consultation is urgent in this group, and the cause of the palsy should not be presumed benign.¹¹

In younger adults, CN VI palsy is likely to be caused by serious underlying disease. In this group, CNS mass lesions and multiple sclerosis account for 33% and 24% of CN VI palsies, respectively.¹³ Idiopathic CN VI palsies account for 13% of cases and vascular disease only 4%.¹³ It should be noted that CN VI palsy caused by CNS mass lesions in young adults involve other cranial neuropathies and are not isolated. Thus, neuroimaging is highly recommended in this group.

In adults older than 50 years with an

isolated sixth nerve palsy, an evaluation for ischemic vascular diseases such as diabetes and hypertension should be undertaken, since these are the most likely causes.²⁻⁶ If the patient is older than 60 years, an erythrocyte sedimentation rate (ESR) should be ordered to rule out giant cell arteritis. In cases of isolated CN VI palsy in older adults with a history of diabetes or hypertension, neuroimaging and other extensive evaluation can be deferred, unless the palsy progresses, fails to improve over three months, or other neurologic complications develop. Ischemic vascular palsies typically progress over several days, but progression over two weeks warrants neuroimaging.⁶

Spontaneous recovery of CN VI palsy is common, especially if the etiology is idiopathic, traumatic or microvascular.^{3,4,6,13,34} Resolution of CN VI palsy is typically complete by three to six months, although some cases may take longer to resolve. CN VI palsies associated with CNS mass lesions tend to have a worse prognosis for spontaneous recovery.^{6,13} In cases where complete recovery does not occur, Fresnel prism correction may alleviate diplopia and visual discomfort. More aggressive therapy in non-remitting cases includes strabismus surgery or medial rectus injection with *botulinum* toxin (Botox).³⁵⁻³⁷

Clinical Pearls

- The etiology of isolated CN VI palsy in the adult is undetermined in a significant number of cases, despite full diagnostic evaluation.
- Vasculogenic CN VI palsies can be expected to progress over several days, but they will not worsen over two or more weeks. Such a clinical course suggests alternate etiologies.
- Myasthenia gravis may mimic a sixth nerve palsy and should always be considered in the differential diagnosis, especially if the palsy takes on a variable course with exacerbations and remissions. However, routine diagnostic testing is not indicated unless the patient's history suggests myasthenia gravis.
- A patient with horizontal diplopia

and lateral rectus underaction can be said only to have an abduction deficit. A negative forced duction test ascribes the motility to CN VI palsy.

- There is a very low risk of acute isolated CN VI palsy being caused by a neoplasm in an older adult.
- Acute CN VI palsies in children are often harbingers of serious disease such as cancer, and they must be promptly investigated.
- Non-neurologically isolated CN VI palsies are often associated with CNS mass lesions and should be promptly evaluated.
- Acute CN VI palsy in a young adult is not commonly caused by microvascular infarct but by more serious disease such as multiple sclerosis and CNS mass lesions; therefore, it should be promptly investigated.

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MYASTHENIA GRAVIS

Signs and Symptoms

Myasthenia gravis (MG) takes its meaning from the Greek words *myo*, meaning muscle, and *asthenia*, meaning weakness.¹ The condition is characterized as a chronic autoimmune disease of the neuromuscular junction which leads to varying degrees of weakness and fatigability in the skeletal muscles.^{2,3} It affects men and women equally, though mostly older men and women in their second or third decade.^{3,4} It is not known to be genetically transmitted.^{3,5} Prevalence rates for MG approach 1 in 5,000 individuals.⁶ The disease may affect any muscle of the body, including the muscles of the eye. MG may involve just the muscles of the body without affecting the muscles of the eye (generalized myasthenia) or just the muscles of the eye without affecting the muscles of the body (ocular myasthenia).²⁻⁸ Some of the classic systemic symptoms of the disorder include difficulty in swallowing (dysphagia) and slurred speech.²⁻⁷ Ocular signs and symptoms include intermittent pupil sparing ophthalmoparesis and diplopia, ptosis of the eyelid, and the pathognomonic Cogan's lid twitch (overshooting of the affected eyelid on upgaze with a final ptotic resting position after prolonged fixation in down gaze).²⁻⁹

Generalized myasthenia gravis will develop in more than 50% of patients presenting with ocular myasthenia, typically within two years.^{2,7} The conversion rate to the generalized form is as high as 90% within three years of the onset of ocular symptoms.^{2,7,10} If MG affects only the eye for four years, it rarely will progress to systemic involvement.

Late-onset MG is a phenomenon of elderly men that is often misdiagnosed.³ While the involvement of oropharyngeal musculature has been well described as symptoms of dyspha-

gia and slurred speech, the presence of fluctuating dysphonia (changing of the voice tone) is an under-recognized sign.³ "Dropped head sign" or weakness in the neck muscles creating an inability to raise the head has also been recognized as a potential sign of impending MG.⁹ Myasthenic crisis is the catastrophic failure of the skeletal muscles involved in respiration.¹⁰ Patients in myasthenic crisis develop acute respiratory failure and require prompt airway protection in the form of ventilation support.¹²

Pathophysiology

MG results from an antibody-mediated, T-cell-dependent immunologic attack on the endplate region of the postsynaptic membrane.⁶ As the receptors which receive the neurotransmitter acetylcholine become degraded, the signal intended to invoke a muscle movement cannot be propagated or maintained, and acetylcholine is blocked from reaching the post-synaptic receptors.¹³ Subsequently, an enzyme, acetylcholinesterase, degrades acetylcholine and the component parts are sequestered into the presynaptic membrane to formulate new acetylcholine for the next action potential. This leads to an inability to move muscles, rapid fatiguing and loss of stamina.¹³

A subset of myasthenia gravis patients are seronegative for anti-acetylcholine receptor (anti-AChR) antibodies.¹² They are referred to as seronegative myasthenics.¹² These patients are instead seropositive for antibodies against the muscle-specific kinase (anti-MuSK-positive).¹² Just because an individual is seronegative after one test does not mean they will remain so.¹² In one study, 15.2% of patients initially determined to be seronegative became seropositive 12 months later, yielding an ultimate seronegativity rate of 8.2%.¹⁴ The classification of seronegative MG is

reserved for immunocompetent patients with generalized MG who lack muscle AChR binding, AChR modulating or MuSK antibodies at presentation and again at a follow-up 12 months later.¹⁴

The predilection of myasthenia to attack ocular muscles may be related to differences between limb muscle and extraocular muscle physiology, function or antigenicity.¹⁵ In simpler terms, the autoantibodies involved in the pathophysiology, for reasons that remain unclear, prefer the receptors of the eye muscles to the skeletal muscles of the body.¹⁵

MG has a well-established association with thymus gland pathology and the paraneoplastic syndrome thymoma.¹³ Thymoma (tumorous infiltration of the gland by nonmalignant or malignant cells) is found in approximately 10–15% of patients with myasthenia gravis.^{15,16}

Management

There are four easy clinical tests for MG that can be performed in the office. In the sleep test, the patient is asked to rest with eyes closed for 20 minutes. As the acetylcholine builds up in the presynaptic membranes, pre-existing weaknesses will improve for a short time. In another test, the patient is asked to look up (for ocular MG) or to keep the arms up (for general MG). As patients fatigue, they become unable to continue and the eyelid or arms will drift down. Additionally for ocular MG, the patient can be asked to squeeze eyes closed, or, for systemic MG, to squeeze the examiner's finger. If they lack strength or they fatigue quickly, it becomes apparent that MG may be involved. For patients with ptosis or ophthalmoplegia, the ice-pack test can be employed. In this situation, a bag of crushed ice covered in a towel is placed over the affected eye, with eyelid closed, for two minutes. Lowering the temperature slows the

action of acetylcholinesterase, allowing acetylcholine a longer duration in the synaptic cleft and a greater opportunity to interact with post-synaptic receptors with a subsequent improvement in function.

The abovementioned in-office tests greatly increase the index of suspicion for MG. Definitive testing is necessary to make a conclusive diagnosis. This involves pharmacologic testing with edrophonium chloride (Tensilon™, ICN, Costa Mesa, CA) that elicits unequivocal improvement in strength and function, electrophysiological testing with repetitive nerve stimulation and/or single-fiber electromyography (SFEMG) that demonstrates a primary postsynaptic neuromuscular junctional disorder and serologic assay of acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) antibodies.^{5,12}

Once MG has been confirmed, additional laboratory work should include a computed tomography scan (CT) of the chest, antinuclear antibody testing (ANA), a rheumatoid factor test (RF) and a thyroid panel (T3, T4, TSH), since it has been associated with other autoimmune diseases.¹⁷

Treatment must be individualized for each patient, and may include cholinesterase inhibitors (Mestinon™, pyridostigmine, Valeant, Aliso Viejo, CA) and immune modulation with corticosteroids, azathioprine, cyclosporine and mycophenolate mofetil.^{6,18} Rapid, temporary improvement may be achieved for myasthenic crises and episodic exacerbations with either steroids, plasma exchange (PEX) or intravenous immunoglobulin (IVIg).⁶ One report demonstrated that prednisone significantly lowered the conversion rate from pure ocular MG to systemic MG.⁷ The benefit of 50–60 mg of daily prednisone followed by tapered doses to 10mg or less has also demonstrated stabilizing/resolving power for ptosis and diplopia for peri-

ods lasting at least two years in approximately 70% of patients.¹⁹ Thymectomy may be required in selected cases.²⁰ Age, gender, onset of symptoms, the duration of the disease, the response to medicinal preparations and the presence of thymoma help to determine whether thymectomy is appropriate.²¹ Owing to improved diagnostic testing and immunotherapy, the prognosis for MG is favorable with less than 5% mortality and a nearly normal life expectancy.⁶

Clinical Pearls

- Myasthenia gravis never affects the pupil. If there is ptosis and ophthalmoplegia, and the pupil is affected, MG is not the cause.

- Eaton-Lambert myasthenic syndrome resembles late-onset MG; however, its pathophysiology occurs in the presynaptic endplate, not the post synaptic. Although it produces systemic signs similar to those of MG, Eaton-Lambert patients do not fatigue upon working, rarely exhibit eye signs and have a pathology linked to paraneoplastic (small-cell lung carcinoma and others) or autoimmune systemic disease, making this element an essential component of the laboratory work in suspicious cases.

- MG becomes unpredictable in pregnant women, with life-threatening sequelae possible. These patients require frequent and regular progress evaluations.

- The ice-pack test works exceptionally well with ptosis as the presenting weakness, but it is less effective and diagnostic when ophthalmoparesis is the presenting sign.

- The late great Dr. Larry Gray used to remind us of the testing for MG by saying, “Sleep ’em, tease ’em, squeeze ’em and freeze ’em.”

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MULTIPLE SCLEROSIS

Signs and Symptoms

Multiple sclerosis (MS) is the most

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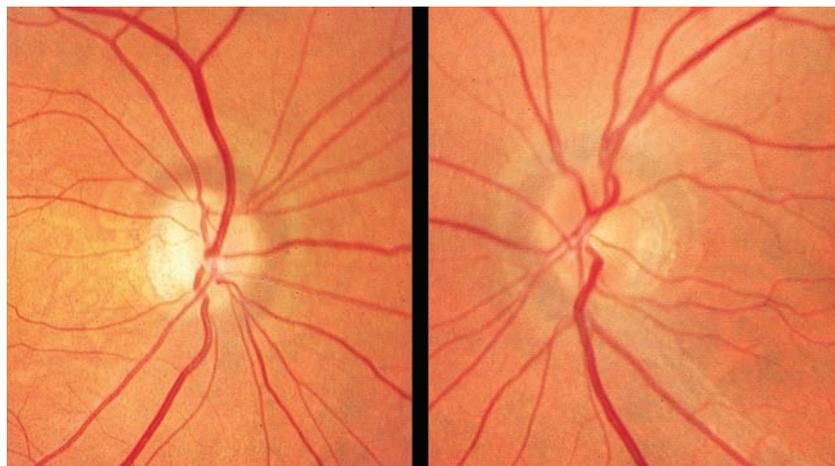
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common cause of immunologic inflammation that initiates the process of *demyelination*, the loss of insulating

Romberg's sign is a disequilibrium associated with cerebellar dysfunction; it causes patients to be unable to main-

precisely certain of the etiology of MS. The disease seems to develop in patients who demonstrate genetic susceptibility, although there are likely several environmental triggers that play a role in its pathogenesis. Based upon animal models of experimental autoimmune encephalomyelitis, MS appears to involve autoantigens within the CNS that recruit microglial cells and macrophages; in turn, these cells activate cytokines (e.g., interferon-gamma and tumor necrosis factor alpha), complement and other immunomodulatory regulators to spur an inflammatory reaction.² This response specifically targets oligodendrocytes and results in myelin disruption. When the myelin sheath becomes damaged, saltatory nerve conduction is disturbed, resulting in motor impairment. There is also evidence that a smaller subset of MS patients may have a primary disorder within the oligodendrocytes that is reminiscent of virus or toxin-induced demyelination.¹¹

The characteristic pathology of MS involves multicentric, multiphasic CNS inflammation and demyelination.² There is a predilection for specific areas of the nervous system including the optic nerve and periventricular white matter of the cerebellum, brain stem, basal ganglia and spinal cord. On average, patients experience clinical relapses every one to two years during the so-called relapsing-remitting phase of the disease, although studies using serial magnetic resonance imaging (MRI) suggest that inflammatory lesions are practically continuous throughout this period.¹² In later stages of MS, active inflammation appears to diminish, although disability often continues to advance, suggestive of a more chronic, degenerative process.^{12,13} Speculation exists that consecutive tissue injury in MS ultimately exceeds a critical threshold beyond which the nervous system can no longer compensate. At this point the disease becomes primarily degener-



This MS patient had a history of optic neuritis in his right eye several years before being diagnosed.

myelin sheath about the body's nerve axons.^{1,2} MS affects approximately 400,000 Americans and nearly 2 million people worldwide.² The classic MS patient is a white female in her child-bearing years; women between the ages of 20 and 40 have a twofold greater incidence than men, and white individuals (particularly those of northern European descent) are especially vulnerable.²

MS tends to present insidiously and produces a wide variety of neurological complaints, but the most common initial symptoms appear to be weakness in one or more limbs, paresthesias, optic neuritis (demyelinating optic neuropathy), diplopia and vertigo.² Patients may also experience classic dysfunctions associated with demyelinating disease, including Uhthoff's phenomenon, L'Hermitte's phenomenon and Romberg's sign. Uhthoff's phenomenon is characterized by impairment of vision with increased body temperature. It is often encountered when taking a hot shower or during vigorous exercise.³ L'hermitte's phenomenon is noted as a radiating neck pain (sometimes described as an electric shock wave) upon flexure of the cervical vertebrae.⁴

tain balance when their eyes are closed.⁵

From an ophthalmic perspective, the most frequently encountered ocular manifestation of MS is optic neuritis (ON). ON is often the initial presenting sign of MS as well.⁶⁻⁸ Internuclear ophthalmoplegia (INO) has a well documented association with MS. In fact, a higher percentage of young female patients experiencing INO eventually develop MS than those who have suffered an episode of optic neuritis.^{9,10} Other ocular manifestations associated with MS include acquired pendular nystagmus, central vestibular nystagmus (i.e., downbeat and upbeat), periodic alternating nystagmus, supranuclear gaze palsies (i.e., dorsal midbrain syndrome) and isolated ocular motor abnormalities (i.e., abducens palsy).⁹ Pars planitis also demonstrates a relatively high association with MS.¹⁰

Pathophysiology

MS is defined by recurrent bouts of central nervous system (CNS) inflammation that results in damage to both the myelin sheath surrounding axons and the axons themselves.¹⁻¹⁰ As with most autoimmune disorders, no one is

ative in nature and is referred to as secondary progressive MS.²

Management

Four decades ago, Schumacher and associates suggested that the core diagnosis of MS involved CNS lesions disseminated in space and time, as well as the elimination of alternative diagnoses.¹⁴ Despite the numerous procedures that have been added to our diagnostic armamentarium since that time, there exists today no single, absolute pathognomonic criterion for MS. The diagnosis ultimately must be a clinical decision, based upon the presenting signs and symptoms, as well as the supporting laboratory and radiographic findings.

Serologic testing of the cerebral spinal fluid is often helpful in a diagnosis of MS. Oligoclonal IgG bands have been found to be prevalent in patients suffering from MS.¹⁵ Moreover, MRI is perhaps the single greatest diagnostic and prognostic tool in the management of MS today. Clinically definite MS demonstrates multiple periventricular and discrete cerebral hemisphere white matter lesions known as plaques; these are sometimes referred to as “unidentified bright objects” or “UBOs” because of their appearance on MRI.

In 2001, new recommendations regarding diagnostic criteria for MS were published by an international panel of experts.¹⁶⁻¹⁸ The “McDonald criteria” allowed for MRI evidence in the diagnosis of MS in patients who experienced a single acute clinical episode.¹⁶ Subsequent revisions of these McDonald criteria were published in 2005, and updated further by Swanton and associates in 2006.^{17,18} Today, most clinicians rely on the following to make a diagnosis of MS:

- At least two attacks with objective clinical evidence of at least two lesions;
- At least two attacks with objective clinical evidence of one lesion plus dissemination in space shown on MRI or

two or more MRI lesions consistent with MS plus positive CSF finding or second clinical attack;

- One attack with objective clinical evidence of at least two lesions plus dissemination in time on MRI or second clinical attack;

- One attack with objective clinical evidence of one lesion, plus dissemination in space shown on MRI or two or more MRI lesions consistent with MS plus positive CSF finding and dissemination in time shown on MRI or second clinical attack;

- Insidious neurologic progression suggestive of MS plus one year of disease progression determined retrospectively or prospectively and two of the following: positive brain MRI result (nine T2 lesions or at least four T2 lesions with positive Visual Evoked Potential), positive spinal cord MRI result with two focal T2 lesions, and positive CSF findings.

Treatment for patients with MS involves management of acute attacks and symptoms and prevention of relapses and progression. In this regard, it is crucial to initiate disease-modifying therapy as soon as possible. Current therapies are aimed at eliminating the immune dysfunction and resultant neural damage with the goal of preventing the long-term risk of clinically significant disability.

Acute attacks (and those resulting in ON) are usually treated with intravenous methylprednisolone 1000 mg daily for three days, followed by a tapering dose of oral prednisone over several weeks. Although protocols vary, this is the most widely used regimen according to current sources.^{19,20} In addition, 4-aminopyridine and 3,4-diaminopyridine may prove useful for the symptomatic treatment of some multiple sclerosis patients. Pemoline may be an alternative to amantadine for the control of fatigue, and acetazolamide may be an alternative to carbamazepine and phenytoin for the treatment of painful

tonic spasms.²¹

Ongoing disease-modifying therapy consists primarily of immunomodulatory agents. The major drugs used in the United States include interferon beta-1b (Betaseron[®] subcutaneous; Schering, Berlin) and interferon beta-1a (Avonex[®] intramuscular; Biogen, Cambridge, MA; Rebif[®] subcutaneous; Serono, Geneva). Also widely used is glatiramer acetate (Copaxone[®] subcutaneous; Teva; Petach Tikva, Israel). In randomized, placebo-controlled trials, all of these medications were shown to decrease the rate of clinical relapses by about 30–40%, and they also reduced the number of new lesions appearing on magnetic resonance imaging.²²⁻²⁵

Mitoxantrone (Novantrone[®] intravenous infusion; Serono USA, Rockland, MA) is a newer immunosuppressant medication that has demonstrated efficacy in progressive MS. It is typically administered every three months, although it may be given monthly for the first few doses to patients with very active disease. Unfortunately, side effects and potential toxicities, including cardiac toxicity, limit the use of Novantrone[®] to patients with secondary progressive MS or very active relapsing-remitting MS.²⁶

Clinical Pearls

- Certain clinical and/or demographic risk factors such as age of onset, gender, CNS involvement, course of disease and attack frequency can aid clinicians in determining the prognosis for a patient with MS. Individuals with a favorable prognosis fit the following profile: age of onset younger than 40 years, female, optic neuritis or other sensory symptoms at onset, relapsing/remitting disease course and a low attack frequency. Individuals with an unfavorable prognosis are those whose age of onset is older than 40 years, male, have motor or cerebellar symptoms, neurologic findings at onset, a progressive course of the disease and a high

number of attacks.

• The association between optic neuritis and MS has been previously demonstrated and is well documented. However, a number of other types of demyelinating disorders have been associated with optic neuritis. These include acute transverse myelitis, Gullain-Barré syndrome, Devic's neuromyelitis optica, Charcot-Marie-Tooth syndrome, multifocal demyelinating neuropathy and acute disseminated encephalomyelitis.

• At one time, when a patient presented with an acute optic neuropathy or INO suggestive of demyelinating disease, there was no great hurry to confirm a diagnosis of MS because no effective treatments were available. Today there are a number of medications that reduce the incidence and recurrence of neurological deficits and impairment and delay the onset of clinical MS. Hence, if MS is suspected, testing should be conducted immediately to confirm the diagnosis.

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THYROID OPHTHALMOPATHY

Signs and Symptoms

Graves' disease, Graves orbitopathy, dysthyroid orbitopathy, thyroid eye disease and thyroid ophthalmopathy (TO) are all synonymous terms connoting an autoimmune disorder characterized by multiple systemic manifestations.^{1,2}

Thyroid ophthalmopathy manifests in approximately 50% of patients with systemic thyroid dysfunction with advanced effects in 3–5%.³ The fifth

and seventh decades of life represent age peaks of incidence, with a slight preponderance for women.³ The natural history of the disease remains poorly defined.¹⁻⁴ In fact, the ocular aspects of the disease may remit or improve spontaneously.³ The ocular conditions characteristic of the disease may exist in the



Graves' Disease is evident in this patient with thyroid ophthalmopathy.

absence of clinical or biochemical evidence of thyroid dysfunction.^{2,3} When the systemic and ocular condition exist together, they may follow completely different clinical courses.²⁻⁶

The hallmark sign of TO is bilateral, non-pulsatile proptosis secondary to tendon sparing extraocular muscle enlargement.¹⁻⁴ Other important findings include impaired ocular motility and ophthalmoplegia with resultant diplopia, firm resistance to globe retropulsion, eyelid retraction, poor upper eyelid tracking upon downgaze (Von Graefe's sign), variable diplopia, possibly impaired visual acuity and visual field defects, sight loss secondary to corneal exposure-related keratopathy or compressive optic neuropathy.^{7,8}

Thyroid-associated dermopathy with fluid infiltration in the lower extremities, particularly the pretibial area of the leg (pretibial myxedema), the dorsum of the foot, rarely the hand, elbow, upper arm and forearm, and acropachy (clubbing of the fingers and toes) almost always occurs in advanced stages of systemic thyroid disease.^{5,6} These two indicators often occur in the

presence of progressing ophthalmopathy.⁵ The curiosity of thyroid disease is its often unpredictable nature. As an example, dermatopathy has been observed in many cases without any clinical ophthalmopathy.⁵

Pathophysiology

The etiology of the disorder is multifactorial and secondary to newly discovered heritable abnormalities that interfere with immune regulation.¹ Not all of the mechanisms responsible for the systemic and/or ocular manifestations are understood.² Research regarding the clinical manifestations of thyroid ophthalmopathy traditionally point to a combination of increased orbital fat and extraocular muscle volume within the orbital space.^{1,2,9-12} TO is a slowly progressive disease in which a malfunctioning immune system activates thyrotropin receptor-specific T-cells and B cells.¹¹ This activation produces autoantibodies.¹⁰ Orbital fibroblasts residing within orbital tissues succumb to autoimmune attack when these antibodies bind both to their thyrotropin receptors (TSHr) and insulin-like growth factor-1 (IGF-1) receptors.⁹⁻¹² It appears that orbital fibroblasts act as sentinel cells, initiating lymphocyte recruitment and tissue remodeling.⁶ Evidence suggests that when the autoantibodies bind to the thyrotropin receptor sites, they stimulate a subset of these cells to undergo adipogenesis, thus increasing orbital adipose tissue volume.^{9,10} Autoantibodies that bind to the insulin-like growth factor-1 receptors appear to impact pathogenesis through recruitment and activation of additional T-cells and by upregulating the production of hyaluronan (hyaluronic acid), a cytokine that plays a key role in the development of inflammation and increased orbital tissue swelling.^{9,10} Simultaneously, the process stimulates an overproduction of thyroid hormones.⁹⁻¹²

Activated T-cells continue to infil-

trate orbital tissues, further kindling the cascade of inflammation.^{9,10} Finally, although originally thought to represent a separate pathway for inflammation, antibodies that develop against the extraocular muscles are now considered a secondary consequence of global extraocular muscle inflammation.⁹ Thyroglobulin (Tg) may also be involved in the pathogenesis of TO.^{13,14} Following its release from the cytokine stimulated thyroid, Tg may have the ability to elicit autoimmune aggression in orbital tissues and extraocular muscles by becoming complexed with glycosaminoglycans, infiltrating the tissues and then serving as a binding site for the other previously mentioned cytokines.^{13,14} Previously viewed as the main mechanism of pathogenesis, Tg has recently been confirmed by research as playing a secondary role.¹³

Environmental triggers, such as smoking, can also induce or hasten ophthalmopathy.^{3,15} Because smoking is a modifiable risk factor, it must be included in the historical questioning and then approached in management.

Hashimoto's autoimmune thyroiditis (HAT) is the most common cause of thyroid diseases in children and adolescents.¹⁶ It is also the most common cause of acquired hypothyroidism with or without goiter.¹⁶ It is capable of inducing the orbital changes consistent with thyroid orbitopathy.¹⁶

Management

Thyroid cancer should be considered when examining patients with suspected TO.¹⁰ Prognosis for the disease, when diagnosed promptly, is excellent in the long term, with low rates of mortality.¹² Unlike other cancers of the head and neck, it tends toward delayed metastasis to regional lymph nodes.¹⁷

Since the hallmark sign of TO is a bilateral, symmetrical, proptotic appearance, laboratory testing and imaging is indicated to understand the potential etiology in suspicious cases.¹⁸ However,

because ophthalmopathy can develop in the setting of an underactive, hyperactive or normally functioning thyroid gland, contingencies for treating glandular malfunction and eye signs and symptoms must be developed separately.^{1-4,7,17-25}

Laboratory testing should include assays for the levels of triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), thyroid peroxidase antibodies, thyroglobin antibodies, thyrotropin receptor antibodies and thyroid stimulating immunoglobulins.^{2,3} Ultrasonography can be used to assess the condition of the extraocular muscles, and computed tomography (CT) is generally considered the accepted modality. Magnetic resonance imaging (MRI) may be used for those requiring a detailed view of the soft tissues of the entire orbit.¹⁸ Monitoring of proptosis should be done either with an exophthalmometer or photographs.

Resultant proptosis may require monitoring only. Any signs and symptoms associated with ocular surface compromise can be managed with efficient hydration.^{25,26} Artificial tear solutions and ointments may remedy most symptoms.^{25,26} Punctal occlusion can be used to retard drainage as well. Patients with increased symptoms upon waking may have lagophthalmos. In these instances, they should be counseled to use a blindfold to create an enclosed, moist environment and prevent exposure-based corneal abrasion. In the most severe cases, moisture chambers can be created for waking hours by affixing face-conforming plastic barriers to the temples of the patient's spectacles. Affixed Fresnel or ground-in prisms may improve fusion in patients with ophthalmoparesis and diplopia.²⁶ In rare instances, congestion of the orbit can lead to raised intraocular pressure. Here, topical hypotensives may be appropriate.

Clinical trials with oral antihistamine and anti-leukotriene preparations, traditionally used in treating

nasal itching, rhinorrhea and congestion, have demonstrated some effectiveness for patients with mild-to-moderate thyroid eye disease and orbital congestion.¹⁹ A six-week course of oral cetirizine (10mg q.a.m.) and oral montelukast (10mg q.p.m.) in a series of patients with significant ophthalmopathy yielded subjective improvement in tearing, dryness and itching in 50% of subjects compared to controls, although it was less effective for diplopia and proptosis.¹⁹

Oral and intravenous steroids have been demonstrated as successful therapies for cases of moderate-to-severe ophthalmopathy.^{20,21,26} Work has shown that blocking the CD-20 receptor on B lymphocytes has significantly affected the clinical course of TO, resulting in rapid reduction of inflammation and proptosis.²⁰

Experimental use of infliximab (anti-tumor necrosis factor alpha) has also been investigated in TO patients secondary to its ability to decrease inflammation.²² Although the option is a reasonable alternative to surgical approaches, the data on this new strategy is currently limited with respect to thyroid eye disease and orbital inflammatory conditions.²²

In cases in which TO is associated with an overactive thyroid gland, various antithyroid medications can be employed, with or without the possibility of radioiodine treatment.^{25,26} Some indications suggest that the use of radioiodine treatment may worsen ophthalmopathy.^{3,23,26} A concomitant course of oral steroids is frequently used to mitigate this effect.^{3,23,26} The combination of corticosteroid treatment and external beam radiation to the thyroid gland is another effective modality in which multiple mechanisms can be placated.²¹

Orbital radiation is a controversial local treatment modality for patients with severe thyroid ophthalmopathy.^{24,27} The literature demonstrates a lack of

consensus and standardization, with a varying quality of published reports.^{24,27} At best, radiation therapy offers an option for patients with extraocular motility impairment; however, mixed results have been presented in clinical trials, indicating that proptosis, eyelid retraction and soft tissue changes may not improve with radiation treatment.^{5,24,27} Given the risk of radiation retinopathy vs. the controversial gains against symptoms, patients should be appropriately educated before considering this solution.²⁴

Orbital decompression by transpalpebral fat removal is a proven, reliable, effective and safe method of relieving the compressive complications of TO. The results were first described in 1988, and the procedure has developed a track record for lasting results, improvement in visual function and development of patient well-being, with benefits outweighing risk.⁷

Clinical Pearls

- Thyroid eye disease can occur in the presence of hyperthyroid, hypothyroid or euthyroid states. Hyperthyroid is marked by unexplained weight loss, nervousness and tachycardia; hypothyroidism is marked by intolerance to cold, premature fatigue and depression.

- The classic "NOSPECS" mnemonic permits an easy-to-recall system of staging: N=no signs or symptoms, O=only signs such as the "stare" or Von Graefe's sign but no symptoms, S=soft tissue involvement (resistance to retropulsion, conjunctival edema, fullness of the eyelids, injection of the horizontal recti insertions), P=proptosis, E=extraocular muscle involvement, C=corneal involvement, S=sight loss.

- The classic Dalrymple's sign is characterized by eye lid retraction and "stare," Moebius, sign is marked by an inability to converge, and Gifford's sign is marked by difficulty in everting the eyelids.

- Many patients have shallow

orbits, making them appear proptotic. Checking old photographs of patients to chronicle their habitual appearance is a helpful tool for determining baseline appearance.

- Thyroid ophthalmopathy is generally symmetric and bilateral. A measurement difference of 6mm or more between the eyes is ominous and not consistent with TO.

- Cases involving thyroid dysfunction should be referred to an endocrinologist.

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ALBINISM

Signs and Symptoms

Albinism is a genetic condition associated with defects in melanin production or storage, causing maldevelopment of the visual system and fovea, reduced retinal cell numbers and abnormal routing of ganglion cell nerve fibers within the optic chiasm and visual pathway.¹ The prevalence of all forms of albinism varies with estimates at approximately one in 17,000 persons.² This suggests that one in 70 people carry a gene for albinism in one form or another.²

Oculocutaneous albinism (OCA), also known as oculodermal albinism, is a group of inherited defects of melanin biosynthesis characterized by reduction in pigmentation of the hair, skin and eyes.² The clinical spectrum of OCA ranges from OCA1A, the most severe type, which demonstrates a complete lack of melanin production throughout life, to milder forms such as OCA1B, OCA2, OCA3 and OCA4, each of which shows some pigment accumulation over time.² The clinical manifestations of OCA include congenital nystagmus, iris hypopigmentation and translucency, varying degrees of strabismus, reduced stereoscopic vision, reduced pigmentation of the retinal pigment epithelium (RPE), foveal hypoplasia, reduced visual acuity (20/60 to 20/400), varying refractive errors, color vision impairment and debilitating photophobia.² Patients with OCA have a normal lifespan with normal development and fertility.²

Some forms of OCA have systemic associations.³⁻⁵ Hermansky-Pudlak syndrome (HPS), for example, is an autosomal-recessive disorder characterized by oculocutaneous albinism, platelet dysfunction and multisystem tissue lysosomal ceroid deposition.^{3,4} It is most common in the Puerto Rican population.³ Chediak-Higashi syndrome is a rare autosomal recessive disorder in which patients show hypopigmentation, recurrent infections, mild coagulation defects and varying neurologic problems.⁵

Ocular albinism (OA) is characterized as a group of genetic disorders presenting with reduced pigmentation only of the eye in association with decreased visual acuity, nys-

tagmus, strabismus and photophobia, in the setting in which pigmentation of skin and hair is relatively normal.⁶ Incomplete albinism or albinoidism is characterized by variable manifestations of the albino condition, owing to a genetic variation.⁷

Pathophysiology

All types of OCA have been established as inherited autosomal recessive disorders.² The four genes determined to be responsible for the different types of the disease are TYR, OCA2, TYRP1 and MATP.² Because of the clinical overlap in forms of albinism, molecular techniques must be employed to establish a specific subtype.² Studies have shown that ocular albinism may constitute a clinically mild presentation of oculocutaneous albinism resulting from mutations either in the TYR (OCA1) or OCA2 (P) genes.⁶ The genetic mutation responsible for HPS remains unknown.⁴ The CHS1/LYST gene has been associated with Chediak-Higashi syndrome.⁵ Mutations in the OA1 gene on the short arm of the X chromosome are known to cause X-linked ocular albinism known as the Nettleship-Falls variant.⁸

The common denominator of decreased vision in patients with albinism is decreased foveal volume and macular hypoplasia.^{1,9-11} This finding is compatible with a reduction or loss of ganglion cell numbers.^{1,2} This is a different process than the one that merely produces an anatomical lack of foveal pit, which is not a requirement for foveal cone specialization.^{9,10} New research suggests that the observation of no foveal pit be known by the specif-



External view of ocular albinism.



Ocular albinism - fundus.

ic term as fovea plana.^{9,10} Patients may be fovea plana without the effects of foveal hypoplasia, as seen in albinotic maculopathy.^{9,10}

Since the foveal region contains the highest cell density in the human retina, a large area of the visual cortex is dedicated to its representation.^{10,11} In cases of both aniridia and albinism, the fovea does not properly develop, causing its corresponding cortical representations to be reduced.^{1,11} Analysis reveals that regionally specific decreases in grey matter at the occipital poles in patients with albinism corresponds to the cortical representation of the central visual field and correlates to most of the compromises in visual function.¹ Patients with albinism have additional chiasmal irregularities and alterations in the hemispheric projections.^{1,11} Misrouting of the fibers at the optic chiasm, where the majority of fibers cross to the contralateral side, produces an abnormal decussating pattern.⁹⁻¹¹ This reflects the disturbance within the retina controlled in part by the dysfunction of melanin metabolism.¹² It also is the predominant reason most of these patients lack true binocularity and often present with some strabismus.

Foveal hypoplasia is related to poor fundus pigmentation in the region.¹³ Melanocytes are pigment-producing cells residing primarily in hair follicles, the skin and the eyes.¹³ Pigmentation is achieved inside melanocytes when melanin is produced from the amino acid tyrosine and sequestered within specialized organelles known as melanosomes.¹³ Normal foveal development requires a proper underlying substrate; that is, a normally pigmented RPE. The enzyme tyrosinase, a type I membrane glycoprotein, plays a key role in the initiation of the melanogenesis process in humans.¹⁴⁻¹⁶ Mutations in the human tyrosinase gene cause the tyrosinase negative form of oculocutaneous albinism.¹⁵ In tyrosi-

nase positive OCA, there is activity of the enzyme, but melanin that is produced cannot be sequestered into melanosomes. In tyrosinase-negative OCA, inactivity of the enzyme prevents melanin formation.^{17,18}

Management

When a patient with fair skin and minimal fundus pigmentation presents with or without the presence of compromised visual acuity, the possibility of albinism should be considered.^{1-11,19} A complete family history, including investigation of family photographs, may help uncover a genetic link previously not realized. Since albinism has linkage to systemic syndromes, its exist-



Ocular albinism - fundus.

tence cannot be dismissed simply because the patient reports no clinical symptoms. In cases of high suspicion, referral for genetic counseling/testing (tyrosinase hair bulb assay) may be indicated, both for the welfare of the patient and to understand the risk to potential future generations of the patient's family.^{2,16}

Ocular management for all forms of albinism begins with appropriate spectacle correction. Consideration includes refractive error and protection from the harmful rays of the sun. Spectacle corrections should be designed considering either sun specific lenses, photochromic lenses (Transitions, Pinnel Park, FL, Transitions Optical Inc.; Photogray™, Corning Optical via

Winchester optical, Scranton, PA) or the option for protective UV shields™ (Fieldale, VA, CP films) or NOIR shields™ (South Lion, MI, NOIR medical technologies). Prescribing the maximum correction, especially in younger patients, will maximize visual acuity and minimize the amblyogenic effects of large astigmatic or asymmetric corrections. In cases of strabismus (with or without an accommodative or refractive component) or where visual acuity cannot be corrected to the values obtained via laser interferometry, amblyopia must be considered, with an appropriate surgical referral or referral for binocular evaluation and training. Surgical results are variable, and unfortunately, because a facet of this disease induces axons to aberrantly cross in the chiasm, visual training may not be effective.^{20,21} The literature confirms evidence that surgery on the extraocular muscles in patients with albinism exhibits independent neurologic and visual results.²⁰ A positive angle kappa seems to be another clinical feature of the disorder. Surgeons must consider this when planning extraocular muscle surgery, particularly when preoperative testing indicates the potential for a binocular outcome.²¹

In cases in which traditional spectacles do not alleviate visual disabilities, low vision rehabilitation along with orientation and mobility rehabilitation services may provide magnifying devices (full-field full-diameter microscopes, prism half-eye microscopes, stand magnifiers, handheld microscopes, telemicroscopes, telescopes and closed circuit televisions) as well as supportive aides (acetate filters to increase the contrast of printed materials, large print books, enlarged clocks). Prescribing practitioners and rehabilitation specialists each have a role in the management of these patients.

The nystagmus in patients with albinism is often termed "searching nystagmus."^{22,23} Research supports that

acuity development in these cases is directly related to the visual sensory defects and not the nystagmus.^{20,22,23} The nystagmus develops secondary to the poor ability to stabilize fixation as a result of the compromised fovea. The characteristics of searching nystagmus include bilaterality, conjugate horizontal uniplanar movements and an accelerating slow phase. Unfortunately, no single ocular motor characteristic can differentiate a benign form of infantile/searching nystagmus from one with an alternate neurological etiology. Clinicians must therefore consider the host of clinical features and rule out the need for neurologic consultation.^{22,23}

Patients with OCA are especially vulnerable to the harmful rays of the sun because they lack protective melanin.^{1,11,24} This puts them at risk for developing skin lesions that have both cosmetic and systemic health implications and that increase their risk for developing skin cancers.⁵ Patients with any form of albinism must have regular skin evaluations and must be informed about the need for strict and consistent sun protection strategies.^{1,24}

Work is underway to develop a foveal hypoplasia grading system using optical coherence tomography (OCT).²⁵ The same group is undertaking the task of attempting to correlate visual acuity to iris transillumination, macular transparency and foveal hypoplasia in young albinism patients.²⁵ This could provide patients and guardians with valuable prognostic information.

The traditional treatment for Chediak-Higashi syndrome is a bone marrow transplant to remedy the hematologic and immune defects.⁵ Unfortunately, nothing is currently available to alter the neurologic problems.⁵ The treatment for Hermansky Pudlak syndrome ranges from transfusion of platelets to medicating with antifibrinolytics to clotting factor replacement therapy and stem-cell transplantation.^{3,26}

Clinical Pearls

- The differential diagnosis for albinism in general includes ocular albinism, albinoidism, the Hermansky-Pudlak variant (albinism + bleeding disorder), the Chediak-Higashi variant (Albinism + susceptibility to infection), Griscelli syndrome (albinism + immunodeficiency) and Waardenburg syndrome type II (facial anomalies, heterochromia of the iris, fundus pigmentation variation and congenital sensorineural deafness).

- Genetic detection in carriers and obtaining a prenatal diagnosis is plausible when a history of the disease is identified in the family line.

- Albinoidism or ocular albinism may be present in patients with normal visual acuity who possess the complaint of photophobia. In these cases, the patient should be questioned regarding the pigmentation and tanning status of family members.

- Strabismus cases undergoing surgical correction have a poor prognosis because of the dysfunctional hardwiring (mal-decussating fibers).

- Medications with antiplatelet properties can produce significant ill effects on HPS patients and should be avoided.

- Patients with extremely blond fundus may be misdiagnosed with albinism. Patients with albinism will have reduced acuity and nystagmus.

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