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Neurological Complications in Sickle Cell Disease

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Abstract Sickle cell disease is a common inherited blood disorder that affects red blood cells. It is a hemoglobinopathy characterized by hemoglobin polymerization, erythrocyte stiffening, and subsequent vaso-occlusions. These changes can lead to microcirculation obstructions, tissue ischemia, infarction and acute stroke. In addition, chronic cerebral ischemia and cerebral vascular anomalies are considered among the most disabling problems in sickle cell disease. Neurological complications of sickle cell disease include, Ischaemic Stroke, hemorrhagic stroke, transient ischemic attack, silent cerebral infarction, headache, Moyamoya disease, neuropathic pain, and neurocognitive impairment. Early diagnosis and proper management of sickle cell disease neurological complications require specialised hematological and neurological experties. The newly used medications under ongoing research foster the hope to overcome this devastating disease and its complications.

Keywords: *sickle cell anemia, cerebral vascular accident, infarction, hemorrhage*

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1. Introduction

Sickle cell disease (SCD) is anautosomal recessive hemoglobin disorder [1]. This hemoglobinopathy arises from the substitution of the amino acid glutamine by the valine in the sixth position of beta globin chain [2]. SCD is characterized by hemoglobin polymerization, erythrocyte stiffening, and subsequent vaso-occlusion [3]. The pathophysiology in SCD is not completely understood; the increased red blood cells adhesion, coupled with increased shear stress due to anemia may initiate the injury of endothelial cells of the blood vessels including the cerebral arteries. This, in turn, initiates other processes including oxidative injury of the vessel wall, inflammation, abnormal vasomotor regulation, and increased coagulation [4]. The anemia associated with SCD results in hyperemia and vasodilation throughout the body,resulting in increase cerebral blood flow leads to a further perfusion to the brain during the period of hypoxic stress [5]. A key contributor tovaso-occlusion may be the increased tendency of the sickle red cells to adhere to the vascular endothelium [6]. As sickled red blood cells adhere to the vascular endothelium, blood flow is impeded and thereby increases the capillary transit time, it has been suggested that increased cell adherence can initiate and propagate vaso-occlusion [7]. The precipitating factors of sickling phenomenon include hypoxia, dehydration, and metabolic acidosis [8]. The sickled red blood cells are much less deformable, and, therefore, obstruct microcirculation, and cause tissue infarction. In many severe consequences of SCD, acute stroke, and chronic cerebral ischemia are among the most disabling vascular anomalies beside the neurocognitive impairment. [9,10]. This article reviews the neurological complications in SCD, its present investigations present and future trend treatments.

2. Neurological Complications in SCD

2.1. Headache

Headache is a frequent symptom in SCD [11]. It is unclear as to whether the headache is anemia-related, stress-related, or a consequence of as yet unknown factor that predisposes this population of patients to a headache [12]. In the presence of poor cerebral vessel autoregulationas seen in SCD patients, the cerebral vessels vasodilate but do not increase the blood flow [13]. Such cerebral vasodilatation is known to cause headaches. In addition, abnormalities in the cerebral perfusion, as measured by perfusion magnetic resonance studies, have been shown to be correlated with several neurologic symptoms [14]. Headaches were associated with steady lower state hemoglobin [15].

2.2. Neuropathic Pain

Pain related to SCD is unpredictable challenge, it could be due to involvement of the nociceptive and neuropathic pathways [16]. The nociceptive pain, is due to nociceptors sensory receptors activation by noxious stimuli [17]. Neuropathic pain is defined as persistent pain resulting from damage to the peripheral or central nervous system or abnormal communication within the nervous system

[18]. The neuropathic pain is usually described as the numb, tingling, lancinating, spontaneous, shooting, needles sensation, hyperalgesia, and allodynia pain [19]. The finding of neuropathic pain in SCD patients is contrary to common belief that this pain is only nociceptive, and this may have a profound impact on our understanding and treatment of SCD pain. Neuropathic pain in SCD may br the result of tissue damage after vaso-occlusion of blood vessels of nerves [20].

The mechanisms of underlying neuropathic pain in SCD may be relevant to signaling mechanisms involving protein kinases. [21] Some of these mechanisms may contribute to glial activation, pro-inflammatory or pro-nociceptive cytokines, chemokine receptors and transporter [22,23]. Changes in neuronal activity also have been observed in other chronic inflammatory pain models likely containing a neuropathic component such as SCD [24,25].

2.3. Hemorrhagic Stroke

Haemorrhagic stroke is an acute neurologic injury resulting from bleeding in the brain. Approximately 70-80% of all strokes are ischemic and 20-30% is hemorrhagic in nature [26]. There are two distinct types of hemorrhagic strokes: intra cerebral haemorrhage in the brain, and subarachnoid hemorrhage, that cause bleeding in the area between the brain and the thin tissues that cover the brain. Other causes of hemorrhagic stroke include aneurysms, medications such as aspirin or the anticoagulants [27]. The CT scan of the brain is the most important test used to confirm a brain hemorrhage. MRI scan can be done later for better understanding to the cause of the bleeding. Conventional angiography may be done in some cases to identify the aneurysms or the arteriovenous malformation, although CT and MRI are more often use [28]. Hemorrhagic storks in sickle cell disease could be associated with advanced sickle cell hepatopathy, where the coagulation profile significantly impaired [29].

2.4. Ischemic Stroke

Stroke, defined as an acute or clinically apparent neurological event or dysfunction. It occurs in 8 to 11% of children with SCD [30]. Common presenting symptoms and signs include hemiparesis, monoparesis, aphasia or (dysphasia), seizures, severe headache, cranial nerve palsy, stupor, and coma [31]. Stroke occurs without warning as an isolated event or as a sequence of other complications in SCD [32] Ischemic stroke is a common brain injury. The most common intracranial vessels affected are the distal internal carotid, proximal middle cerebral, and anterior cerebral arteries. The vasculopathy of these large vessels is most often associated with cortical infarction [33]. SCD causes ischemia of small vessels by erythrocyte sickling in microcirculation, but most clinical strokes are due to large vessel occlusions. The endothelial damage in large vessels is believed to promote a stenotic and obliterative process. When a vessel is stenosed, the thrombosis can occur by a similar mechanism as known to occur in the microcirculation [34]. Several mechanisms predispose SCD patient to an increased risk of ischaemic stroke; these include sickling of large extracranial, and intracranial vessels which occur secondarily to fibrous intimal proliferation [35]. The large vessel, stenotic lesions can be identified by transcranial Doppler (TCD) ultrasound This technique is helpful in predicting patients that are at high risk of cerebral infarction, as in such patients, a program of exchange transfusion is beneficial. Prophylactic blood transfusion in SCD with abnormal TCD can reduce the incidence of stroke from10% per year to less than 1% per year [36].

2.5. Transient Ischemic Attack

A transient ischemic attack (TIA) is a focal neurologic deficit of acute onset lasting less than 24 hours (typically less than 1 hour), with no radiographic evidence of infarct [37]. The 24-hour threshold to distinguish an overt stroke from a transient ischemic attack has historical value. Cerebral infarcts also can be seen in individuals who have focal neurological deficits that last less than 24 hours [38]. The absence of the focal neurological deficit on examination 24 hours after presentation does not mean that the patient has not had a cerebral infarct [39]. The TIA symptoms may be mimicked by other neurological disorders such as migraine, seizure, and global hypo perfusion, that make the diagnosis sometimes difficult. There is often disagreement about TIA diagnosis, even among experienced neurologists [40]. The underlying cause of a TIA often is a buildup of cholesterol containing fatty deposits plaques (atherosclerosis) in an artery or one of its branches that supply oxygen and nutrients to the brain. Plaques can decrease the blood flow through an artery or lead to the development of a clot [41].

2.6. Silent Cerebral Infarction

Silent cerebral infarction (SCI) is a brain lesion that presumably a result of vascular occlusion found incidentally by MRI or CT in otherwise healthy subjects or during autopsy [42,43]. It is considered a precursor of symptomatic stroke and progressive brain damage [44] that may be associated with vascular dementia [45]. Individuals who have had silent strokes often have various neuropsychological deficits and have significant impairment in multiple areas of cognitive performance [46]. Despite not causing identifiable symptoms a silent stroke still causes damage to the brain, and places the patient at increased risk for both transient ischemic attack and major stroke in the future[47]. The risk of silent stroke increases with age but may also affect younger adults. Women appear to be at increased risk for silent stroke, with hypertension and current cigarette smoking being amongst the predisposing factors [48,49]. Diagnosis of a silent stroke is usually made as an incidental finding of various neuroimaging techniques. Silent strokes may be detected by (MRI) [50], Computerized axial tomography (CAT scan), [51] TCD, which measures cerebral blood flow velocity (CBFV) in the large intracranial arteries. The narrowing of these arteries which is a risk factor for cerebral infarction, is characterized by an increased velocity of blood flow. [52] Silent infarcts were seen by MRI in about 17% of those with SCD [53]. Patients with SCI are usually not managed as having had a stroke. [54]

2.7. Moyamoya

Moyamoya, also known as Spontaneous Occlusion in the arteries of Circle of Willis. It is an uncommon cerebral vasculopathy, characterized by typical angiographic

changes associated with subsequent clinical features [55]. In Moyamoya, with other chronic steno-occlusive cerebrovascular diseases; steno-occlusive changes in the main cerebral arteries and decrease in the cerebral perfusion pressure, resulting in the formation of a fine network in neovascularization [56,57]. These collaterals show evidence of stress related to increased flow, including the combination of the fragmented elastic lamina, thinned media in the vessel wall, and the presence of microaneurysms; these findings help to explain why some patients present with hemorrhage [58]. Other Moyamoya related vessels are collapse, and their lumen thrombosis could cause ischemic symptoms [59]. It is expected that treatment with chronic transfusion may also prevent new cerebral infarction in patients with SCD who developed Moyamoya syndrome [60]. Moyamaya even found in sickle cell trait patients, but as a rare neurological complication, but it found in more prevalence in sickle cell disease patients [61]. The neurological status at the time of treatment predicts a long term outcome, suggesting that early diagnosis and treatment are important to avoid irreversible neurological deficits [62]. Patients with low stroke burden, or strokes limited to one hemisphere, may have a satisfactory long-term prognosis if further infarcts can be prevented [63]. The ability to identify the predictive factors for the development of Moyamoya in an at-risk population could lead to better outcomes for these patients through earlier diagnosis and treatment [64,65].

2.8. Brain Atrophy

Brain atrophy is shrinking of the brain caused by the loss of its neurons. Two types of brain atrophy can occur; generalized and focal. Generalized atrophy refers to neuron loss throughout the entire brain, and focal atrophy refers to neuron loss in a specific brain region [66]. Normal aging causes generalized atrophy [67]. Brain atrophy has several etiologies. Different mechanisms are involved including arterial occlusion, thrombosis, embolism [68]. Cerebral infarction and atrophy could be a serious complication in SCD patients, [69] caused secondary to occlusive vasculopathy developing in 5.5-17% of patients with SCD [70,71]. Clinical manifestation in brain atrophy includes dementia, seizures, loss of motor control, and difficulty with speaking, comprehension or reading. Dementia, which is marked by memory loss and an inability to perform daily activities, may be mild or severe and may worsen with increasing atrophy. Seizures can range from absence seizures (sudden loss of responsiveness) to convulsive seizures [66]. MRI is the procedure of choice for most brain disorders, as it creates images from multiple angles and provides a detailed view of many brain structures not visible by CT scan. [72] No cure for cerebral atrophy. Once brain cells have been lost, the damage is permanent. Treatment for cerebral atrophy focuses on treating the symptoms and complications [73].

2.9. Brain Infection

Infection is a significant contributor to morbidity and mortality in SCD. The sickle gene confers an increased susceptibility to infection, especially to certain bacterial pathogens, and at the same time infection provokes a cascade of SCD-specific pathophysiological changes [74]. Splenic atrophy or functional hyposplenism which occurs in sickle cell disease also render the patient with less immunity to infectious agent [75]. SCD increase the risk of meningitis and brain infection secondary to viral or bacterial infections mainly the encapsulated bacterial organisms [63,76]. Abscess is an accumulation of infectious material and offending microorganisms, and this can occur anywhere within the CNS [77]. Salmonella frequently reported causing brain abscess in SCD patients [78]. The majority of brain abscesses occur also in individuals who are compromised by underlying medical conditions other than SCD such as patients who are receiving immunosuppressive therapy [79,80]. In contrast, rhombencephalitis, a primary infection of the brain stem, is clearly different since it is found predominantly in noncompromised adults [81,82]. Brain abscess caused by inflammation and collection of infected material, coming from local sources as infections in ear, dental, paranasal sinuses, mastoid air cells of the temporal bone, or brain abscess could be from remote sources as lung, heart, kidney etc. Death occurs in about 10% of cases and people do well about 70% of the time. There is a large improvement from 1960s due to improved ability to image the head, better neurosurgery and better antibiotics [83]. Positive labeling in radionuclide imaging help in differentiating abscess from tumor [84,85]. On early phases the capsule will be difficult to visualize via conventional techniques, and double contrast CT often is helpful in defining encapsulation of abscess [86]. MRI features recognize pyogenic abscesses fairly accurately. Usually ‘triple high dose’ antibiotics intravenously for 2 weeks followed by four weeks of oral antibiotic therapy is recommended. Pyogenic intracranial abscess should be treated on an emergent basis. Abscess diameter more than 2 cm need surgical intervention and most of them show an excellent clinical and radiological response to single burr-hole aspiration. Craniotomy is required in selected cases and as a primary procedure in cerebellar [87]. The long term outcome is gratifying if prompt treatment is instituted in appropriate time period [88].

2.10. Neurocognitive Impairment

The majority of the studies to date have shown a higher frequency of impairments on executive functions in children with SCD when compared to the normal population [89,90]. Among the executive functions, working memory deficits appear to be more prominent [91,92]. Attention difficulties are commonly reported in children and adolescents with SCD, particularly sustained attention was suggested to be impaired in children with SCD [93,94]. The available literature on memory functions in SCD is relatively limited [95]. SCD may impair intellectual activity; 25% of the SCD patients have a significant cognitive deficit [96]. An incidence of mild mental deficiency was elevated at least 11-fold in a small sample of patients with SCD, and no clinical history of stroke. The full-scale intelligence quotient of these patients correlated with hematocrit. [97] Because SCD is a lifelong condition, age effects have also been examined. Cross-sectional studies have suggested that older children show greater neuropsychological impairment in reading achievement, spatial functioning, and sustained attention [98,99]. Hypoxemia has been described as a precipitating

factor for vaso-occlusive events at the microcirculatory level [100] and for "silent" ischemic cerebrovascular accident, which causes a number of neurocognitive deficits, such as learning problems, attention deficit and lack of executive functions, as well as short-term and long-term memory loss [101]. Several studies pointed out that children with SCD have impaired cerebral blood flow autoregulation compared with age matched healthy subjects, independently from their hemolysis rate [102]. It is suggested that cognitive impairment in children with SCD may be a function of chronic hypoxia of the brain [87]. SCD children with overt strokes usually have neuropsychological complications that have been shown to relate to the location and size of the lesion in the brain [103]. However, other areas of dysfunction include learning deficits in reading and mathematics; have also been identified [104]. Lesion size in relation to intellectual functioning has been documented in children with silent infarcts [105]. Studies on neuropsychological complications in adults with SCD are limited, although cognitive impairment including dementia has been demonstrated, irrespective of normal or abnormal MRI results [106]. Evidence from children with SCD suggests that lesion size and related neuropsychological complications tends to increase with age, [107]. and could suggest similar problems in adults. In addition, frontal lobe abnormal blood flow has been shown in adults with SCD [108]. This could indicate attention/concentration and executive function problems, and therefore should not be ignored by hematologists [92].

2.11. SCD Delirium

Delirium is an acute confusion state, characterised by disturbance of consciousness and change in cognition that develop over a short period. The disorder has a tendency to fluctuate during the course of the day, and there is evidences from the clinical history, examination and investigations that the delirium is a direct consequence of systemic infection as chest, renal, brain, liver, fever, medication side effect, dehydration, cessation of drug or opiods, alcohol use, major surgery, epilepsy, terminal illness [109]. Delirium is fairly common among hospitalized patients, with around 1 in 10 having a period of delirium [110]. It is more common among older people [111]. As collateral history should be taken from the care giver, the following information should be specifically sought: previous intellectual function, functional status, onset and course of confusion, previous episodes of acute or chronic confusion, sensory deficits hearing, sight, speech, symptoms suggestive of underlying cause, pre-admission social circumstances, full drug history including non-prescribed drugs, alcohol history. [95] In SCD it often exhibit tolerance to opioids due to repeated use of these agents. This results in the need for higher and higher doses of opioids to provide the same level of analgesia [112]. Clinical experience and previous studies demonstrate that delirium susceptibility varies among individuals [113].

2.12. SCD Psychosis

Psychosis is a symptom of neuropsychiatric disorder [114]. It is experiencing things and believing them to be real when they are not; in other words, losing contact with reality. This happens in two broad forms: Hallucinations - hearing, seeing or feeling things that are not there, and Delusion - holding unusual beliefs not shared by other people [115,116]. Psychotic SCD patients could have complicating brain tissue silent infarct because of the red blood cell sickling patho-physiologic process. Isolated brain tissue in silent-infarcts could indicate this etiological factor of psychosis in SCD patients. That would obviously pose further treatment challenge in tackling this comorbidity [117]. Psychos treatment includes Rapid Tranquilization, as sometimes people suffering from psychosis can become agitated and be at risk of hurting themselves or others. Acute symptoms of psychosis can be controlled with antipsychotics. In many cases, patients only need to take antipsychotics for a short time to get their symptoms under control. The mental health counselor treatment approach has been shown to be effective in helping patients to made permanent changes and more effect in their illness management [118,119].

3. Investigations of Neurological Complications

3.1-Investigations to exclude other causes of neurocognitive impairment may need to be carried out e.g., liver and renal biochemistry profiles, vitamin B12, folate level, TSH, syphilis, hepatitis C, glucose and vitamin B1 as well as screening for dyslipidemia, sourse of infection in septic patients [120].

3.2-Electroencephalography (EEG) is an electrophysiological monitoring method used to record the electrical activity of the brain. It is non-invasive, with the electrodes placed on the scalp, although invasive electrodes are sometimes used in specific applications. EEG measures voltage fluctuations resulting from ionic current within the neurons of the brain.EEG refers to the recording of the brain's spontaneous electrical activity over a period of time to exclude non convulsive epilepticus [121].

3.3-TCD detects intracranial vessel abnormalities; it has been used to evaluate occlusions and stenosis in intracranial vessels. TCD accuracy is less than that of Computed Tomography Angiogram (CTA) and Magnetic Resonance Angiogram (MRA) in specificity and sensitivity 90% to 95%, which is in TCD 55% to 90 respectively for the steno-occlusive diseases. TCD is helpful in detecting microembolic signals, which are also seen with extracranial or cardiac sources of embolism [122].

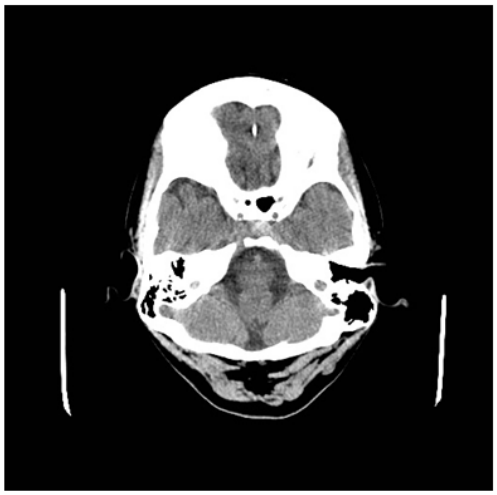
3.4-MRI: This may show lesions not visible on other imaging technique. It can detects cortical atrophy and reduced grey matter volume in the cortex and basal ganglia [123,120].

3.5-CSF cytology examination and culture may be required, especially when there are other signs of CNS infection [124].

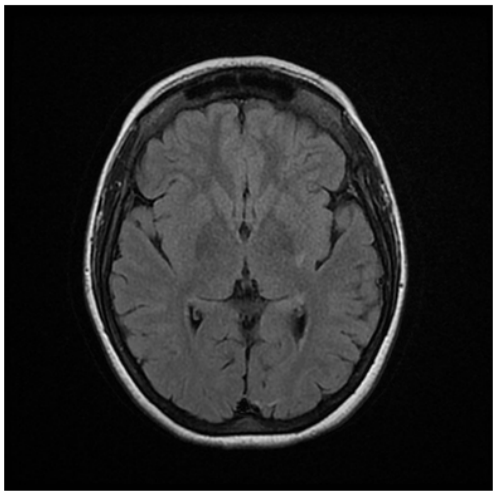
3.6-CT scan: The contrasts in general are not recommended in SCD, as the dye may damage the kidneys in the patients [125].

3.7- Radionuclide imaging with III-Indium labeled leukocytes, scintigraphy help in differentiating abscess from tumor [84,85].

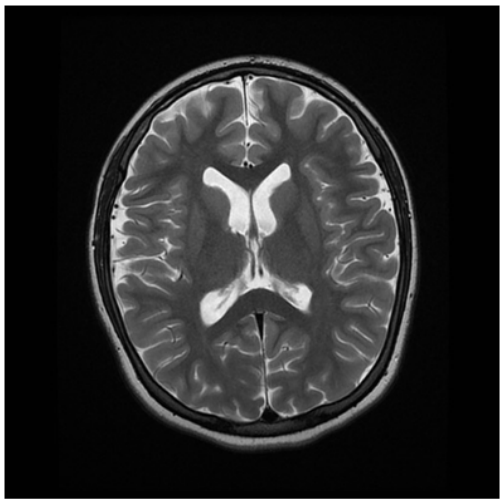
3.8-Depression, anxiety and the effects of alcohol and drugs may all need to be excluded by the apropriet invistigations methods [126].



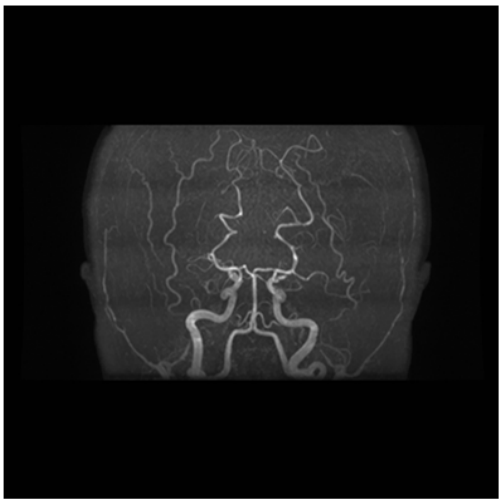
A- Axial non-enhanced brain CT show an enlarged and dense pituitary fossa structure consistent with pituitary hemorrhage in 28 years old female with SCD



B-Axial T2 FLAIR image show a focus of increased signal in the left lentiform nucleus impressive of cerebral infarction in 29 years old female with SCD



C-Axial T2WI show prominence of cortical sulci and blunted anterior horns of lateral ventricle consistent with atrophy in of 14 years old female SCD



D-Axial T2 flair show multiple parietal white matter foci of hyper intensities in SCD 12 years old female with Moyamoya disease

Brain complications in sickle cell disease

4. General Treatment Approach for SCD Neurological Complications:

In SCD patients, both hematology and neurology specialists should be consulted in addition to ICU team by the attending physician. If an acute ischemic stroke is confirmed, exchange transfusion with a goal of Hb 10g/dl, and % HbS < 30 % is recommended [127]. Elevated intracranial pressure is considered an emergency in the setting of acute change of neurological status, especially in the stroke or infections such as meningitis. Antiepileptic medications may be used in case of overt seizures or in the setting of non-convulsive status epilepticus which may occur in critically ill patients with hypoxia in SCD [128,129,130,131]. MRI/MRA should be carried out after exchange transfusion if not previously done [132].

4.1. Hydroxyurea

Hydroxyurea was first approved by the FDA in 1967 for the treatment of neoplastic diseases. In February 1998, Hydroxyurea received a new indication, for the treatment of SCD. It was approved for use in reducing the frequency of painful crises and the need for blood transfusions in adult patients with recurrent moderate to severe painful crises [133].Hydroxyurea is the only disease modifying therapy approved for SCD [134].

4.2. RBC Transfusions

RBC transfusions remain essential components of the medical management in patients with SCD. Transfusions decrease the morbidity of acute complications, reduce the recurrence of SCD associated complications, and prevent neurologic events in patients with high-risk features [135]. As the indications for transfusion expand for this population, the incidence of RBC alloimmunization also increases [136]. Regular transfusions may be appropriate in this group if there is evidence of established or progressive cerebral-vasculopathy or other neurocognitive concerns. The course of action in these cases should be decided by the clinicians responsible for the clinical care, taking into account individual circumstances and the

diagnostic facilities available**.**Transfusions are often used to increase the oxygen-carrying capacity of the blood and to decrease the concentration of cells with abnormal hemoglobin [137].

4.3. Aspirin

Aspirin might prevent stroke, silent infarcts and cognitive impairment by mechanisms that include the reduction of inflammation and the antiplatelet effect [138]. The antithrombotic effect of aspirin results largely from irreversible inhibition of the cyclooxygenase-1 enzyme in platelets, leading to impaired platelet aggregation and activation [139,140]. Aspirin therapy could reduce recurrent ischemic events, but also could put the patient at risk of an intracranial hemorrhage [141]. Due to bleeding risk, aspirin is not recommended to be given within 24 hours of any thrombolytic therapy [35]. International Stroke Trial (IST), a randomized trial, demonstrated that patients allocated to aspirin therapy had significantly fewer recurrent events measured 14 days later compared to "avoid aspirin" group, with no significant increase in intracranial bleeds [142]. Aspirin is often empirically given to children with idiopathic stroke, TIAs, recurrent strokes, and TIAs not previously treated with aspirin and who are not candidates for warfarin therapy [143,144,145]. One risk of aspirin therapy is the possible development of Rey'e syndrome although Roach et al. have treated three dozen children with aspirin without complications [146].

5. Future Trend for SCD treatment

Promising agents are in the clinical pharmaceutical research trials to reduce or prevent the neurological complications of SCD.

5.1-Increase hemoglobin F agents to prevents polymerization by hypomethylating agents as 5-azacytidine, decitabine [147].

5.2-Increase hemoglobin-oxygen affinity agents which subsequently decrease RBC deformity in SCD as Aes - 103 (5-HMF) showed in vitro. It is safe and well tolerated in adults with SCA at doses up to 4,000 mg as an asingle dose or divided doses every 6 months. Although this study was not statistically powered for pharmacodynamics or efficacy measures, there are several interesting preliminary findings in patients treated with Aes-103 compared with placebo [148].

5.3- GBT 440 (GTx 011) it is an oral agent, used once daily. It is a direct-acting hemoglobin modifier to prevent sickling of RBC. GBT 440 increases hemoglobin affinity for oxygen, inhibits polymerization of sickle hemoglobin, [149] restores normal RBC function and decreased reticulocyte counts in preclinical SCD models. Phase I/II trial of GBT440 in SCD started in December 2014 [150].

5.4-GMI-1070 (rivipansel, Pfizer) pan selection inhibitor, Phase 2 trial completed in 76 adults treated for VOC, an intravenous dosing twice daily in the hospital until resolution in the duration of vaso-occlusive crises [151].

5.5-Pentosanpoly sulfate sodium, oral phase 1 study with a single dose improved macrovascular blood flow and shortened the duration of hyperaemia, as measured by laser Doppler velocimetry. [152]

5.6-Low molecular weight heparin: Heparin and heparin sulfate binding selection. An initial trial of tinzaparin (Innohep) showed efficacy in painful crises [153].

5.7-Sulfated non-anticoagulant heparins have been shown to inhibit adhesion of sickled RBC to endothelium; it has no effect on coagulation [154]. Sevuparin (Dilaforette) anticoagulant activity removed through chemical depolymerization removes antithrombin binding domain [155].

5.8-Platelets inhibitors: Prasugrel Platelet P2Y 12 ADP receptors antagonist [156]. It blocks adhesion to hydrophobic domains on the damaged membrane, and restores surface hydration [157]. Reduce RBC aggregation, adhesion, viscosity [158].

5.9- SCD neurological pain and headache reduction by SelG1 anti–P-selection humanized monoclonal antibody, as it prevents VOC [159].

5.10- Gene therapy for SCD aiming to correct the sickle phenotype via gene therapy [160].

6. Conclusion

Neurological complications are known in sickle cell disease. The treating hematologist should be aware of the neurological signs and symptoms. Early neurological consultation is necessary to avoid major complications. The general practitioner, family and the patient should be educated on the available prophylactic measures for sickle cell patients. The future is promising with more agents which could work better than Hydroxyurea. Many studies are ongoing or planned to evaluate potential agents. The combination therapy may be more effective than single agents.

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