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Neurologic Complications of Sickle Cell Disease

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Abstract

Purpose of Review Sickle cell anemia is a multiorgan disease with acute and chronic complications. Involvement of the central nervous system (CNS) is associated with increased mortality and morbidity. This review highlights the broad spectrum of neurological complications seen in patients with sickle cell disease.

Recent Findings Increasing recognition of neurological complications has led to improved diagnostic and treatment options throughout the years. Neurologic complications in sickle cell disease include silent cerebral ischemia, ischemic/hemorrhagic stroke, moyamoya syndrome, posterior reversible encephalopathy syndrome, cerebral fat embolism, and cerebral venous sinus thrombosis. Treatment varies depending on the neurological complication.

Summary Sickle cell disease is the most common hereditary anemia with increasing global disease burden. Early recognition and treatment is imperative.

Keywords Sickle cell disease · SCD · Stroke · Silent cerebral ischemia · Transcranial Doppler ultrasound

Introduction

Sickle cell disease (SCD), the most common type of hereditary anemia and one of the most common genetic disorders worldwide, is an autosomal recessive hemoglobinopathy caused by a mutation of the HBB gene in chromosome 11 which encodes for the hemoglobin (Hb) subunit β. Sickle cell anemia is caused by the inheritance of two mutated HBB alleles and presents with chronic anemia, painful crisis, and multiorgan involvement. One of the most devastating complication of SCD is symptomatic stroke which affects 1 in 10 children and is associated with increased morbidity and mortality. In comparison, heterozygous individuals, called sickle cell trait, are typically asymptomatic but can develop generalized weakness, hematuria, and rhabdomyolysis under extreme conditions, such as strenuous physical activity, dehydration, or exposure to high altitude.

Worldwide, the prevalence of SCD is found to be highest in sub-Saharan Africa, Middle East, and India with migration patterns into Western Europe and America. Based on prediction models, it was estimated that the annual global number of newborns with homozygous and heterozygous HBB gene mutation for the year 2010 were > 300,000 and > 5,000,000, respectively [1, 2]. In several African countries, as many as 10–40% of the population carry the sickle cell gene. In the USA, about 100,000 individuals live with this condition. Among African Americans, 1 in 365 births suffers of SCD and 1 in 13 has sickle cell trait. The financial burden of SCD is significant. It was estimated that the annual costs associated with SCD for an average person ranges from > $10,000 for children to > $30,000 for adults [3]. This explains, at least in part, the global disparities in mortality. In the USA, approximately 90% of the people with this condition survive to adulthood. In comparison, in low-income countries, less than 10% of the children with SCD live into adulthood.

In this chapter, we review the pathophysiology, evaluation, and management of SCD complications of the CNS.

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Pathophysiology

There are different types of SCD with variable presentation and severity. The substitution of glutamic acid in the position 6 of the Hb subunit β by valine (Glu6Val, β^S) results in the production of HbS. The substitution of the same glutamic acid by lysine results in HbC. HbSS disease, that is the most common type of SCD, occurs when an individual inherits two HbS alleles. Other genotypes include HbS/β-thalassemia disease and hemoglobin SC disease (HbSC disease). HbSC disease tends to be a less severe form caused by the co-inheritance of HbS and HbC alleles [2].

In low oxygen tension, the HbS undergoes a conformational change that results in the formation of insoluble aggregates. Red blood cells (RBCs) adopt a sickle shape which is associated with increased fragility, augmented hemolysis, and shorter life span that lead to chronic anemia. Sickled cells also have increased propensity to adhere to the endothelial lining of blood vessels, particularly in the microvasculature, causing vaso-occlusion [4, 5]. Repeated sickling is associated with the upregulation of pro-inflammatory mediators, including interleukin (IL) IL-1, IL-6, and IL-8 as well as Tumor Necrosis Factor-α (TNF-α). In addition, there is an increased production of adhesion molecules, such as VCAM-1, ICAM-1, and selectins which facilitate the adhesion of circulating leukocytes to endothelial cells. The unrelenting intravascular hemolysis raises extracellular heme which is a potent oxidant and a damage-associated molecular pattern (DAMP) mediator that initiates and perpetuates non-infectious inflammation. In addition, owing its nitric oxide (NO) scavenger effect, the free Hb compromises the anti-inflammatory and vasoactive properties of NO on the endothelium. Several molecular mechanisms, including the increased release of iron and free Hb as well as the recurrent events of ischemia-reperfusion injury, upregulate the production of reactive oxygen and reactive nitrogen species which, along with the chronic inflammation, have a deleterious effect of the endothelium. This leads to the development of vaso-occlusive crisis and vasomotor dysregulation which manifests with microvascular constriction and occlusion. At the same time, vasoconstriction, cytokine release, activation of platelets, repeated cycles of sickling and unsickling, and the dysregulation of hemostatic and fibrinolytic pathways lead to a systemic prothrombotic state which can manifest with venous thrombosis. There is also evidence suggesting that platelet levels are elevated and chronically activated in SCD further adding to the hypercoagulable state [6].

Neurologic Complications

SCD can cause severe pain and affect different organs as depicted in Table 1. Large artery intracranial occlusive disease constitutes one of the most devastating complications of SCD.

Table 1 Complications associated with sickle cell disease

Organ	Manifestation
Brain	Cerebral ischemia
	Cerebral hemorrhage
	Silent cerebral ischemia
	Neurocognitive decline
Blood	Aplastic crisis
	Hemolytic anemia
	Iron overload
	Procoagulability
Heart and Lung	Acute chest syndrome
	Pulmonary arterial hypertension
	Restrictive cardiomyopathy
	Heart failure
Eye	Retinopathy
	Retinal detachment
	Retinal hemorrhages
Liver, gallbladder, spleen	Hepatosplenomegaly
	Splenic sequestrations
	Splenic atrophy
	Gallstones
Kidney	Nephropathy
	End stage renal disease
	Hematuria
	Skin/leg ulcers
Bone	Avascular necrosis
Other	Painful crisis
	Infections
	Priapism
	Infertility

This is represented by stenosis and eventual occlusion of the distal internal carotid arteries (ICA), middle cerebral arteries (MCA), and/or anterior cerebral arteries (ACA). Interestingly, the vessels of the posterior circulation are seldom affected in SCD. The stenosis is thought to arise from endothelial hyperplasia and intraluminal thrombosis triggered by the repeated sickling episodes rather than atherosclerotic disease. Over time, patients will develop progressive narrowing with development of ill-defined and newly formed collateral vessels in a pattern resembling moyamoya vasculopathy. Moyamoya refers to the "puff of smoke" appearance of the cerebral vasculature on digital subtraction angiography. When moyamoya is a result of sickle cell disease it is known as moyamoya syndrome. This condition develops in 30–40% of the patients and manifests, particularly in children and young adults, with cognitive decline and/or intracranial hemodynamic failure leading to borderzone ischemia [7•, 8] (Fig. 1).

Silent cerebral infarction (SCI) is a common finding in SCD. SCI is characterized by radiographic findings

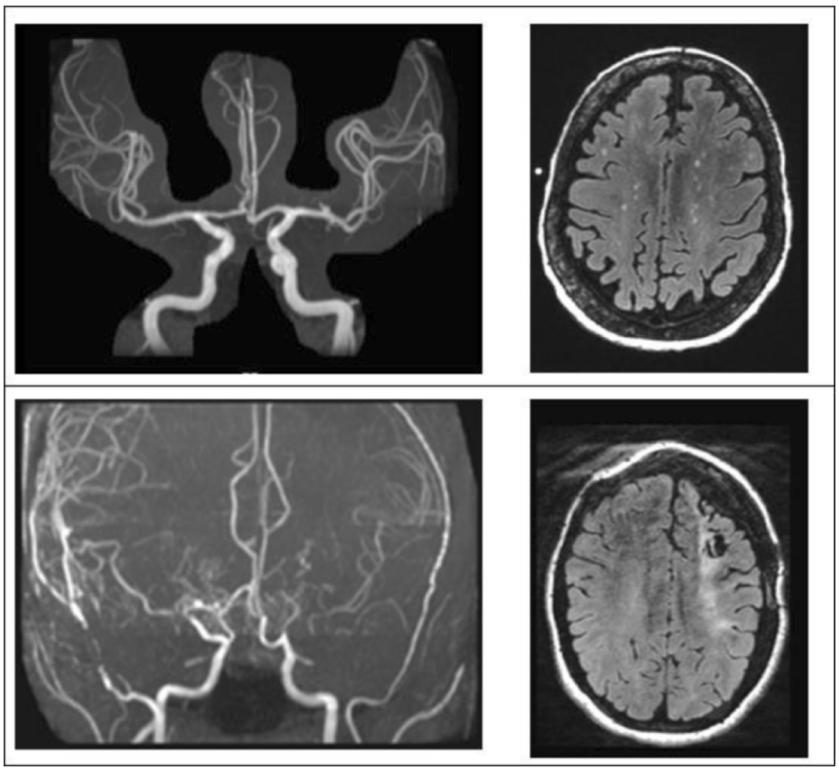

Fig. 1 The images in the upper panel belong to a patient presenting with bone crisis, confusion, and patent foramen ovale. The MRI/A show normal cerebral vasculature and multiple ischemic lesions in both hemispheres consistent with fat embolism. The lower panel shows a patient with severe intracranial occlusive disease with moyamoya vasculopathy and a chronic area of infarction in the left cerebral hemisphere

compatible with remote infarction on MRI brain in asymptomatic individuals. Imaging shows chronic ischemic changes that are at least 3 mm in length in one dimension [9, 10]. SCI occurs in approximately 27% of children before 6 years of age and 39% of children by 18 years of age [9, 11]. Risk factors for SCI include low pain event rate, seizure history, leukocytosis (white blood cell count greater than 11,800 cells per dL), low baseline hemoglobin level, and intracranial stenosis [11]. It is most common with HbSS disease but occurs from 3 to 38% of β-thalassemia patients and 5–31% of HbSC patients. Patients with SCI are at increased risk for neurocognitive deficits which is typically represented by executive dysfunction [1]. Children with worsening academic performance should be screened for SCI with MRI brain.

Stroke is a leading cause of morbidity and mortality in SCD and presents with focal neurological deficits such as hemiparesis, hemisensory loss, and/or aphasia. In some cases, it can manifest clinically with new onset of seizures and/or cognitive decline. The presentation depends on the location and size of lesion involved. Strokes are more commonly found in the anterior circulation affecting the ICA, MCA, and/or ACA distributions. The Cooperative Study of Sickle cell disease (CSSCD) is an observational study that monitored a cohort of 4082 adults and children with different SCD genotypes over a mean of 5 years. The overall prevalence of stroke was 3.75% and two prevalence peaks were seen at ages 2 to 5 years and 40 to 49 years. Ischemic strokes were most common in children between ages 2 and 5 years and over the age of 30 years. In comparison, hemorrhagic stroke was more frequently seen between ages 20 and 29 years and much less frequently seen in ages outside of that range. In addition, it was observed that the stroke incidence varies depending on sickle cell genotype. The chance of having a first stroke by 45 years of age was 24% for HbSS and 10% for HbSC disease [4].

Hemorrhagic strokes are associated with a mortality of 30–50% and most commonly present with severe headaches of acute onset along with focal neurologic deficits. In the CSSCD study, low hemoglobin levels and leukocytosis were risk factors for intracranial hemorrhage [4]. Based on selected case series, it has been estimated that almost 10% of the SCD patients harbor an intracranial aneurysm which predisposes to subarachnoid hemorrhage [12, 13]. In older adults, the rupture of the fragile collateral vessels formed in the context of moyamoya vasculopathy can manifest with subarachnoid hemorrhage or intraparenchymal hemorrhage.

Posterior reversible encephalopathy syndrome (PRES) clinically presents with headache, altered mental status, and seizures. Visual disturbance is commonly described in PRES patients but its occurrence is variable. PRES is typically seen in SCD patients with acute chest syndrome as well as those with post-hematopoietic stem cell transplant receiving calcineurin inhibitors. PRES is thought to be due to endothelial and cerebral autoregulatory dysfunction and vasoconstriction/vasospasm leading ischemia and disruption of the blood brain barrier causing vasogenic edema which is seen radiographically on MRI. In SCD individuals, in particular, PRES can also be triggered by

elevated blood pressures, underlying vasculopathy, endothelial damage, repeated infections, chronic red cell transfusions, and high cardiac output state. Treatment is supportive with aim to control hypertension, seizures, and removal of the offending agent [12, 14–16].

Cerebral fat embolism is a complication as a result of vaso-occlusive crisis causing bone marrow infarction and necrosis leading to non-traumatic fat embolism. Fat emboli may reach the brain by a patent foramen ovale (PFO). Patients typically present with altered level of consciousness, focal neurologic dysfunction, seizures, progressive respiratory failure, cutaneous petechiae, and lipemia retinalis [17]. The treatment is primarily supportive.

Cases of cerebral venous sinus thrombosis are relatively uncommon in SCD. Cerebral venous thrombosis in SCD has been associated with pro-coagulability, hyperviscosity, and blood stasis during sickling episodes. Patients present with mental status changes, headache, and/or focal neurological deficits. The venous congestion and the resultant cerebral edema can result in papilledema on fundoscopic examination. The diagnostic imaging of choice is MRV. Anticoagulation with heparin is the treatment of choice in the acute setting with transitioning to long-term oral anticoagulation with warfarin [18–20]. The use of direct oral anticoagulants (DOACs) in SCD-associated cerebral sinus venous thrombosis is limited. Endovascular recanalization can be considered in cases refractory to medical management.

Diagnosis and Evaluation

Laboratory Analysis

Sickle cell disease is diagnosed by hemoglobin electrophoresis. In selected cases, further laboratory tests can be done to evaluate coagulation profile such as PT, a PTT, INR, protein C and S, factor V Leiden mutation, anticardiolipin antibodies, antithrombin, and serum homocysteine [21].

Neuroimaging

Transcranial Doppler ultrasound (TCD) is a non-invasive and inexpensive imaging modality to measure mean blood flow velocities through large intracerebral arteries. Velocities are measured through bone windows including transtemporal, suboccipital, and transorbital. Narrowing due to stenosis of a vessel lumen results in increased flow velocities. Observational data have shown that time-averaged mean of maximum velocities (TAMMV) of the MCA of 170 cm/s or greater are a risk factor for stroke. This led to the STOP trial which showed that a TAMMV in either the terminal portion of the ICA or proximal portion of the MCA > 200 cm/s is a risk factor for stroke. Current guidelines recommend that patients ages 2 to 16 years with HbSS disease and HbS β-thalassemia should be screened annually if flow velocities < 170 cm/s, every 3 to 6 months for flow velocities between 170 and 185 cm/s, every 1 to 3 months for flow velocities between 185 and 200 cm/s, and every 1 to 2 weeks for flow velocities ≥ 200 cm/s [22, 23, 24••].

Computed tomography (CT) of the head is typically done in acute stroke cases to assess for cerebral hemorrhage [25]. MRI of the brain can provide additional information regarding acute and chronic areas of ischemia. Diffusion weighted imaging (DWI) detects acute ischemia within an hour after stroke onset. MRI brain can also help diagnose and monitor SCI and chronic infarction which appear as hyperintense lesions in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [9, 10, 21, 25].

Non-invasive intracranial vascular imaging using magnetic resonance angiography (MRA) or computed tomographic angiography of the head evaluates for cerebral vasculopathy. In some cases, they can also identify moyamoya vasculopathy, though addressing this possibility typically requires digital subtraction angiography [25].

Treatment

Management of Acute Ischemic Stroke in SCD Acute ischemic stroke management in SCD includes hydration and supplemental oxygenation to achieve a SpO2 greater than 95%. If febrile, the patient should be started on antipyretics and empiric antibiotics. Treatment goal is immediate exchange transfusion with the goal of decreasing the percentage of HbS to < 30% and increasing tissue oxygen delivery through non-sickle RBCs [7•, 26]. Erythrocytapheresis is the preferred transfusion method for initial treatment for acute stroke; however, a simple transfusion may be considered for immediate treatment in cases of severe anemia (defined as Hb < 8.5 g/dL) or when central line access, multiple cross-match pRBCs units, and apheresis team for erythrocytapheresis are being coordinated [24••, 27].

In a large observational study including 832 adults with stroke and SCD and 3328 matched controls, no statistically significant differences were observed in the rate of recombinant tissue plasminogen activator (tPA)-associated complications and outcome at hospital discharge [28]. Thus, acute stroke patients older than 18 years of age with sickle cell anemia who present within 4.5 h of onset of symptoms should be considered for treatment with tPA based on established inclusion and exclusion criteria [29]. Patients who are likely to benefit from tPA are older patients with atrial fibrillation, diabetes, hypertension, hyperlipidemia, and procoagulability. tPA administration should not delay simple or exchange transfusion, and it should not be given to patients less than 18 years of age [28]. The use of endovascular recanalization in cases of symptomatic acute large vessel occlusions is reasonable.

However, the beneficial effect of this treatment in patients with SCD has not been investigated.

Prevention of Stroke in SCD Specific recommendations have been developed for primary and secondary stroke prevention in SCD. TCD and MRI have been used for stroke risk stratification in pediatric patients. Three trials (STOP, STOP 2, and SIT) compared RBC transfusion to standard care for primary stroke prevention (Table 2).

In the Stroke Prevention Study in Sickle Cell Anemia (STOP) trial, TAMMVs measured by transcranial ultrasonography were used to screen SCD children with no history of stroke. Individuals considered as high risks for stroke, defined as TAMMV of the ICA or MCA ≥ 200 cm/s, were randomized to standard of care or prophylactic red cell transfusions with the goal of reducing the HbS levels to less than 30%. This study was halted prematurely after an interim analysis showed a 92% stroke risk reduction associated with exchange transfusion [30]. Participants with initial TAMMVs ≥ 200 cm/s treated with regular transfusion for at least 30 months and reduction of the velocities to < 170 cm/s were eligible to participate of the STOP 2 trial. In this study, 79 subjects were randomly assigned to continued transfusion or discontinued transfusion. The primary outcome of this study was a composite of stroke or reversal of TAMMVs to the high risk range. This study was terminated early after 16 end point events, all of them occurring in the discontinuation group, developed [31, 32]. More recently, the Silent Infarct Transfusion (SIT) trial compared red cell transfusions to standard of care for the prevention of clinical or radiologic cerebral infarction in SCD children with SCI and normal TCD velocities but no history of stroke. The rate of clinical or radiologic (silent) cerebral infarction was 6% in the transfusion group and 14% in the standard of care group [6].

Chronic red cell transfusions are associated with risks such as antibody formation to donor RBCs (alloimmunization), iron overload, and increased risk of infections. Therefore, other treatment options, such has hydroxyurea, were explored. Hydroxyurea (hydroxycarbamide) is an antineoplastic drug which increases HgF (fetal hemoglobin) concentration. Hydroxyurea also decreases the interaction between RBCs and the endothelium, and decreases erythrocyte density. The BABY HUG trial was the first randomized, double-blind trial of hydroxyurea in children with sickle cell anemia. This study showed similar results as adults in which there was decrease in pain episodes, acute chest syndrome, dactylitis, overall less hospital admission, and requirement for transfusions. As a secondary outcome, it was noted that TCD velocities were on average lower in the hydroxyurea group than the placebo group suggesting hydroxyurea potential to reduce stroke risk [36]. Two trials were then done to compare hydroxyurea and chronic red cell transfusions. The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial was a non-inferiority study that compared hydroxyurea with phlebotomy to chronic red cell transfusions as a means of reducing iron overload without increasing risk of strokes in SCD individuals with prior history of stroke and iron overload. This trial was terminated early due to futility. Acute stroke occurred in 7 patients out of 67 subjects in the hydroxyurea/phlebotomy arm; 6 were ischemic and 1 was fatal hemorrhagic stroke. No acute strokes were seen in the 66 patients in the chronic red cell transfusion arm [33]. Though the rate of stroke was within the margins of non-inferiority, the numerical excess of stroke cases in the group treated with hydroxyurea and phlebotomy raised safety concerns about discontinuation of transfusions.

The TCDs with Transfusions Changing to Hydroxyurea (TWiTCH) trial randomly assigned children with SCD at high risk of stroke—defined as TCD flow velocities ≥ 200 cm/s but no severe vasculopathy—who had already received chronic transfusions for one or more years to receive continued transfusions (standard group) or to transition to hydroxyurea (alternative group). A total of 121 children were randomly assigned to gradually transition (over months) from chronic transfusion to hydroxyurea or to continue with chronic transfusions. Iron overload was managed by serial phlebotomy in hydroxyurea arm once transfusions were discontinued and by iron chelation in the chronic transfusion arm. The trial ended early after first interim analysis revealed non-inferiority primary end point in maintaining low TCD velocities with hydroxyurea concluding that hydroxyurea has similar efficacy than blood transfusion in maintenance of TCD velocities. Significantly, there were no strokes in either arm [34]. The trial demonstrated that hydroxyurea can be used as an alternative to transfusions in patients when high economic costs, availability of chronic transfusions, or burden of chronic transfusion (e.g., iron overload, transfusion reactions, chelation therapy) is an issue.

Bone Marrow Transplant (BMT) Even with chronic transfusions, 20% of individuals will have recurrent strokes [5]. Curative treatment for SCD is allogeneic hematopoietic stem cell transplant (HSCT). Myeloablative HLA-identical sibling transplant in children has shown overall and event-free survival rates of 95% and 92%. The use of bone marrow transplant is limited due to high risk of graft versus host disease, infections, and long-term transplant complications [7•, 37, 38]. There is limited information about the effect of bone marrow transplant on stroke or cerebral vasculopathy. In the multicenter study of bone marrow transplantation for sickle cell disease, 59 patients < 16 years of age with symptomatic SCD underwent BMT; 29 of them had history of stroke and 10 had SCI. Individuals with successful BMT were protected from recurrent stroke and experienced stabilization of their cerebral vasculopathy (mean follow-up of 7 years) [39]. Another study reported the outcome of 87 patients aged 2–22 with severe SCD who underwent HSCT for different indications, including previous stroke/TIA ($n = 36$). In the median

Table 2 Landmark stroke studies in sickle cell disease

Study	Type and population	Primary outcome	Results	Conclusions
CSSCD (Cooperative study of sickle cell disease) [4]	Observational study which monitored a cohort of 4082 SCD children and adults over mean of 5 years.			Overall prevalence of ischemic stroke was 3.75% with two prevalence peaks, 2–5 years of age and 40–49 years of age.
STOP (Stroke Prevention Study in Sickle Cell Anemia) [30]	Prospective randomized controlled, multicenter trial. SCD children with ICA or MCA velocities ≥ 200 cm/s randomized to chronic transfusions with goal of HbS < 30% or standard of care.	Cerebral infarction and intracranial hemorrhage	Early termination. Medial follow up of 1.75 years. 11 strokes in the standard of care group ($n = 67$) versus 1 stroke in the transfusion group ($n = 63$).	There was 92% stroke risk reduction in children assigned to the transfusion group compared to standard of care group.
STOP 2 (Stroke Prevention Study in Sickle Cell anemia 2) [31]	Prospective randomized controlled, multicenter trial. SCD children from STOP study who had received transfusions for > 30 months with normalized TCD velocities randomized to continuing red cell transfusions or discontinuing red cell transfusions.	Stroke or reversion of TCD velocities to high risk range of stroke	Early termination. Among the 41 children in the transfusion-halted group, high-risk TCD results developed in 14 and stroke in 2 others. Neither of these events occurred in the 38 children who continued to receive transfusions.	Discontinuation of prophylactic red cell transfusions results in TCD velocities to revert back to abnormal with increase rates of SCI and overt acute ischemic strokes.
SIT (Silent Infarct Transfusion) Trial [32]	Randomized, single blind clinical trial. SCD children between ages 5–15 with 1 or more SCI on MRI were randomly assigned to standard care group or transfusion group. Primary end point was recurrence of an infarct or new or enlarged SCI	Recurrence cerebral infarction, defined as a clinical stroke or a new or enlarged silent cerebral infarct	Median follow up of 3 years. 6 events in transfusion group ($n = 99$) versus 14% in the control group ($n = 97$).	Compared to standard of care, red cell transfusions decrease the incidence of recurrent infarcts in children with SCI and normal TCD velocities (2.0 vs. 4.8 per 100 person-years; $p = 0.04$).
SWiTCH (Stroke With Transfusions Changing to Hydroxyurea) trial [33]	Multicenter, randomized, non-inferiority trial comparing transfusion/chelation (standard of care) to hydroxyurea/phlebotomy in SCD children with stroke and iron overload.	Composite of quantitative liver iron content and stroke recurrence rate	Early termination due to futility. No strokes in the transfusion/chelation group ($n = 66$) versus 7 strokes ($n = 67$; 10%) in the hydroxyurea/phlebotomy group	Though within the non-inferiority margin, a trend for increased stroke risk was noted with hydroxyurea/phlebotomy
TWiTCH (Transfusions Changing to Hydroxyurea) Trial [34]	Multicenter, randomized, open label, non-inferiority trial. SCD children with TCD velocities ≥ 200 cm/s and without severe vasculopathy were randomized to continue standard of care (transfusions with HbS goal < 30%) or hydroxyurea for primary stroke prevention in high risk children	24-month TCD velocity	Mean TCD velocities were comparable in the chronic transfusions and hydroxyurea arms (143 ± 1.6 cm/s vs. 138 ± 1.6 cm/s, $p < 0.001$ for non-inferiority). No child in either treatment arm suffered stroke or reverted from normal to abnormal TCD velocities.	Hydroxyurea is non-inferior to chronic transfusion for maintaining TCD velocities.
DREPAGREFFE (Allogeneic Genoidentical Stem Cell Transplantation in Children With Sickle-cell Anemia and Cerebral Vasculopathy) [35]	Multicenter, non-randomized, open-label, prospective study. SCD children ≤ 15 years with TCD ≥ 200 cm/s were assigned to matched sibling donor hematopoietic stem cell transplantation or standard care defined as transfusion for at least 1 year	Highest TCD velocity in 8 cerebral arteries at 12 months	Highest time-averaged mean of maximum TCD velocities were 129 cm/s in the transplantation group and 170 cm/s in the standard of care group ($p < 0.001$). These findings were sustained at 3 years. In secondary analysis, transplant improved quality of life, reduced iron toxicity, and was well tolerated.	Among high risk SCD children, transplant is associated with reduced TCD velocities compared with standard of care

follow-up period of 6 years, no recurrent strokes or silent ischemic lesions were observed in patients with successful engraftment [40].

More recently, the multicenter, non-randomized, open-label study DREPAGREFFE compared the effect of matched sibling donor hematopoietic stem cell transplantation and standard of care in children with SCD and abnormal TCD velocities. The standard of care group was treated with regular transfusions to keep HbS levels below 30% and total Hb between 9 and 11 g/dL, with the option to switch to hydroxyurea after 1 year of transfusion therapy if TCD velocities normalized and intracranial vasculopathy was not present. In the 3-year follow-up, TCD velocities in the HSCT group were consistently lower than in the standard of care group. In addition, transplanted patients were more likely to report improved quality of life and had reduced ferritin levels. Although there were no strokes or deaths in either group, three children in the standard of care group developed new silent infarcts and two developed stenosis [35]. These studies support the notion that BMT may halt the progression of cerebrovascular pathology and play an important role in stroke prevention. However, the effect of this approach in adult SCD patients with stroke and/or cerebral vasculopathy has not been addressed.

Antithrombotic Treatment in SCD There is limited data or evidence to recommend antiplatelet or anticoagulant therapy in sickle cell disease as prevention of thrombotic events rather consider using it in conjecture with chronic transfusions [12]. Aspirin has also shown to reduce risk of intracranial hemorrhage in patients with known cerebral aneurysms which may be due to anti-inflammatory and antithrombotic properties of aspirin [7•, 23]. Currently, antiplatelets are used as adjuvant therapy to chronic exchange transfusion for adults with sickle cell disease and history of stroke. However, antiplatelet agents are seldom used as monotherapy. Also, in children, Reye's syndrome is a potential concerning side effect, although rare [23].

Management of Cerebral Vasculopathy Current evidence suggest consideration for direct or indirect revascularization surgery known as encephaloduroarteriosynangiosis (EDAS), encephaloduroarteriosynangiosis (EMAS), or by plial synangiosis in addition to standard chronic red cell transfusions. [8, 41]. Both revascularization and chronic transfusion therapy have led to a reduction in both first time and recurrent strokes in moyamoya syndrome patients [7•].

Conclusion

SCD patients are at risk for neurological complications throughout their lifetime, especially those with HbSS and HbS/β-thalassemia. Patients should undergo early screening with TCD for stroke risk stratification. High-risk patients based on TCD velocities and those with neurocognitive deficits should have further MR imaging studies and be considered for chronic red cell transfusion therapy with the goal of keeping the HbS below 30%. Later, they may be transitioned to hydroxyurea after TCD velocities have been normalized. Allogeneic hematopoietic stem cell transplant is curative and there is evidence suggesting that it may be effective for the prevention of stroke and neurocognitive decline in children. However, its effects in SCD adults with cerebral vasculopathy are largely unknown. As the global disease burden of SCD increases, continued improvement of prevention modalities as well as curative treatments like stem cell treatments will be imperative in the years to come.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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