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Neurologic complications in children under five years with Sickle Cell Disease

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Abstract

Introduction: Sickle Cell Disease (SCD) is one of the most common genetic diseases in the world affecting every organ. The major challenge in the medical care of children with SCD is preventing end-organ dysfunction, particularly the brain. Major neurologic complications in children less than five years with SCD include, but are not limited to, Silent cerebral infarct, cerebral sinus thrombosis, epilepsy, reversible encephalopathy syndrome, and ischemic and hemorrhagic stroke. Recurrent headaches and migraine are not rare in children under five years with SCD. This review will focus on the neurologic complications and the description of the modifiable risk factors in children less than 5 years of age with emphasis on differences between high and low resource settings.

Areas covered: Neurologic complications of children under 5 years of age and the modifiable risk factors. The PUBMED database was searched using medical subject headings (MeSH) and keywords for articles regarding neurologic complications in children under 5 years of age.

Conclusion: Neurologic complications in children under five years of age with SCD may be more frequent than currently reported, among which Silent cerebral infarct and cognitive impairment are the most common.

Keywords

Sickle Cell Disease; Children under five years; Neurologic complications

Background

Sickle cell disease (SCD), an autosomal recessive hemoglobinopathy, is one of the most common genetic diseases in the world.^{1,2} In sub-Saharan Africa, the prevalence of SCD is high, and is associated with high morbidity and mortality.³

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Homozygous beta globin gene mutations (HbSS) are referred to as sickle cell anemia (SCA) and is the most severe form of SCD. Other compound SCD heterozygotes include mutations in the beta globin gene resulting in hemoglobin SC and hemoglobin S beta thalassemia. Every organ system is affected in individuals with this chronic debilitating condition, including the brain, lung, heart, and kidney in young children. The end result of this chronic disease is significant morbidity and shortened lifespan for children and adults in low-resource settings and adults in high-resource settings. In high-resource settings, at least 98% of children are now expected to reach adulthood^{4,5} because of improved medical care, parent anticipatory guidance for medical complications, conjugated vaccines for previously life-threatening infections, and penicillin prophylaxis.

The immediate next challenge in the medical care of children with SCD in high- resource settings is preventing end-organ dysfunction, particularly in the brain. Whereas in children in low-resource settings improving childhood survival, and prevention of end-organ dysfunction are both pressing needs. Regardless of the settings, children with SCD have a wide range of neurologic complications that include, but are not limited to, seizures, headaches, neurocognitive impairment, Silent cerebral infarcts, and ischemic and hemorrhagic strokes. The median age of an initial ischemic stroke in an unselected population of children with SCA that are not screened for abnormal Transcranial Doppler (TCD) is 6 years,⁶ with a prevalence of approximately 11% by 18 years of age.⁶ Risk factors for ischemic strokes in children with SCA include low hemoglobin, low hemoglobin oxygen saturation, presence of silent strokes, and abnormal TCD measurement in the terminal portion of the internal carotid or proximal portion of the middle cerebral artery.^{7,8}

The aims of this review are to document the range of neurologic complications of children under five years with SCD and to describe the modifiable risk factors for stroke in children less than five years of age.

Major neurologic complications in children less than five years with SCD

In children under five years with SCD, the most common permanent neurologic injury is a Silent cerebral infarct, referred to as a silent stroke.⁸ Detection of silent stroke in young children with SCD, as is the case in older children and adults, is based on a magnetic resonance image (MRI) of the brain. A silent infarct-like lesion is defined as an MRI signal abnormality that is at least 3 mm in one dimension and that is visible in two planes on fluid-attenuated inversion recovery (FLAIR) T₂-weighted images.⁹ The infarct like lesion cannot truly be considered a Silent cerebral infarct until after a neurologic examination is performed. The definition of Silent cerebral infarct includes two components, an MRI of the brain and thorough neurologic examination. Prior to their 6th birthday approximately 25% of children with SCA will have an infarct.¹⁰

Pediatric neurologists are preferred over a pediatric hematologist for evaluation of suspected Silent cerebral infarct. In the Silent Infarct Transfusion (SIT) Trial approximately 10% of the children, over five years, were initially classified as having Silent cerebral infarcts, but later reclassified as having strokes after a pediatric neurologist evaluation.¹¹ The discordance between a pediatric neurologist evaluation and a pediatric hematologist evaluation reflects the challenge of distinguishing a Silent cerebral infarct from an overt stroke, even in older

children. In children less than five years of age, the neurologic examination is difficult. Thus, for any young child with a Silent cerebral infarct like lesion detected on a MRI of the brain because computed tomography (CT) scans are not sensitive enough to identify the lesion, we would recommend a pediatric neurologist evaluation to distinguish a Silent cerebral infarct from an overt stroke. In the setting of no pediatric neurologist, we would suggest the pediatric provider learn how to perform the Pediatric National Institute of Health Stroke Scale assessment. (PedNIHSS).^{12,13}

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In high-resource settings where TCD screening is offered, coupled with regular blood transfusion therapy, the incidence of overt stroke has dropped approximately 10-fold,^{14,15} when compared to the era prior to TCD screening and blood transfusion therapy for those with abnormal levels. In young children with SCA, stroke can occur in children less than five years of age, with events occurring in children less than two years of age.^{16–18} However, detection of strokes in young children is particularly difficult and must be distinguished from other neurologic complications, including focal neurologic deficits following a seizure, or migraine. Given the challenges of differentiating seizure and headaches in older children, we would strongly recommend that all children less than five years of age presenting with focal neurologic deficit, acute seizures, or migraines be referred to a pediatric neurologist, or at the very least a pediatrician skilled in performing a neurologic examination in young children.

Recurrent headaches and migraines—Recurrent headaches and migraines are common in children under five years of age in the general population and are not rare in children with SCD. Unlike in the general population, in children with SCD, headaches can be confused with skull infarction.¹⁹ The prevalence of headaches among children in the general population increases with age ranging from 4 to 20% in preschool age, and from 38 to 50% in school-age children.²⁰ The prevalence of migraine in infancy and early childhood may be an underestimate because of the challenge in distinguishing a skull infarct from a headache, pseudotumor cerebri,²¹ or any combination of the before mentioned.

Several challenges occur in evaluating young children for headaches, including, but not limited to, an inability to describe symptomatology. Migraine onset in children usually occurs with symptoms including recurrent abdominal pain, cyclic vomiting, episodes of fever not apparently linked to the presence of an infectious disease process, joint pain, and other symptoms.^{22–24} Minna et al. reported fatigue and yawning as the most common symptoms of headache among children (82%), while nausea and vertigo were less common (53%, 34%).²⁵ The evaluation of a child with headache should include a thorough medical history followed by physical examination and measurement of vital signs, particularly blood pressure, and a complete neurologic examination including the optic fundus.^{26,27} Clues to the identification of secondary causes of headache are only found during the systematic process have a thorough history and physical examination.²²

Table 1 summarizes the clinical features of headache in 10 children with migraine without aura and in 16 children with episodic tension headache.²²

A detailed history and assessment of subtle clinical findings may be required to make a diagnosis of headaches in young children with SCD. For instance, bruxism and travel sickness are more common in very young children with headaches.²⁵ On physical exam minor clinical findings associated with headaches include increased clumsiness at the finger opposition test, tenderness in the occipital insertion areas and in temporomandibular joint areas. These are associated with higher prevalence of headaches.²⁵

In early childhood, migraine headache is often short-lived, having a frontal-median or bilateral distribution with a tightening-pressing quality.^{28–31} Diagnosis of primary headache disorders of children rests principally on clinical criteria as set forth by the International Headache Society.³²

Diagnostic studies for headaches should be limited. Evidence based studies have shown neuroimaging is not routinely indicated in children with chronic recurrent headache and normal neurologic examination.³³ Neuroimaging should primarily be considered in children with abnormal neurologic findings,³⁴ presence of thunder clap headache, atypical headaches, or a suspicion for pseudotumor cerebri. Given the challenges of electroencephalography (EEG) in very young children, is unlikely to provide an etiology or distinguish migraine from other types of headache. EEG is not recommended in the routine evaluation of a child with recurrent headache.³⁵

Epilepsy—Epilepsy is more common in children with SCD than in the general population, is associated with earlier death,³⁶ and may be related to cerebral infarcts. The prevalence of epilepsy in children in the general population ranges from 3.2–5.5/1,000 in high resource countries and 3.6–44/1,000 in low resource countries.³⁷

In Jamaica, the prevalence of epilepsy in the 2–9 year age group with SCD is 5.8/1000.³⁸ These epilepsy rates are similar to those documented in other low-resource settings like Kenya,³⁹ and in the North American population.⁴⁰

The most common cause of a seizure in young children with SCD is usually febrile convulsions, especially in malaria endemic zones. To distinguish the causes of seizure in very young children with SCD will thus require the expertise of a skilled pediatric neurologist. Causes of seizures in children under 5 years include meningitis, cerebral infarction, cerebral malaria, and congenital infections. *Chlamydia pneumonia* in young children with SCD may potentially be associated with cerebrovascular complications, though these findings have not been validated in other studies.⁴¹

Primary hemorrhagic stroke—Primary hemorrhagic stroke is an uncommon complication of SCD in children under five years, with reported mortality rates of 24 to 65%.⁶ The definition of hemorrhagic stroke is quite broad and includes intraparenchymal, subarachnoid (SAH), and intraventricular hemorrhage and is responsible for almost all of the mortality from stroke in SCD.⁶ In children with SCD, subarachnoid and intraventricular hemorrhages are responsible for more than half of the hemorrhagic strokes compared with about a third in the general pediatric population.⁴²

Subarachnoid hemorrhage—Subarachnoid hemorrhage in SCD tends to occur with smaller aneurysms than in the general population.⁴³ Typical presenting symptoms and signs include severe headache, nuchal rigidity, coma, and focal neurologic deficits. Management strategies for acute hemorrhagic stroke should follow the evidence based guidelines for children of similar age in the general population.^{44,45} However, SAH is rare in young children with SCD, and if present, causes other than SCD should be considered and systematically evaluated with a neurosurgery team.

Cerebral sinovenous thrombosis (CSVT)—Cerebral sinovenous thrombosis (CSVT) is a rare, but serious cerebrovascular disorder which can start from early infancy and continue to and through adulthood.⁴⁶ Risk factors include, but are not limited to, acute systemic infection.⁴⁶ The most common manifestation in newborn are seizures and altered mental states, while in children and adolescents headache, vomiting, and lethargy are the most common symptoms.⁴⁶ Neonates have a greater risk of poor outcome including motor, cognitive impairment and notably, epilepsy.^{46,47} A definitive diagnosis often requires a CT venogram. (Table 2)

Posterior reversible encephalopathy syndrome (PRES)—Posterior reversible encephalopathy syndrome (PRES) has been described in young children with SCD, with acute neurologic symptoms; although, stroke is the reasonable first diagnosis to be excluded. A high index of clinical suspicion of PRES is required when faced with neurologic symptoms in SCD patients.⁴⁸ PRES is characterized by reversible radiographic signs of posterior leukoencephalopathy in the presence of headache, altered level of consciousness and seizures with or without disturbance.⁴⁹ There has been at least one report of PRES mimicking focal stroke syndrome (Wernicke's aphasia) without hemiparesis;⁵⁰ although, features are different from classic stroke presentation. PRES is likely an under-recognized complication in children with SCD,⁴⁸ particularly if prompt neuroimaging is not completed. In the management of PRES, MR images can better rule out hemorrhagic stroke; however, in low-resource settings, neuroimaging may not be easily accessible which necessitates distinguishing PRES from stroke in SCD based on history, systolic blood pressure, and neurologic examination, a difficult task.⁴⁸

Modifiable risk factors for neurologic complications in children less than five years of age with SCD

Risk factors for neurologic complications in SCD differ in the adult and pediatric population especially in children under five years of age and can affect the early behavioral effects of very young children with SCD.

Prevention of life threatening and serious infections in children with SCD is a major modifiable risk factor for decreasing strokes in young children with SCD. In both high and low-resource settings, conjugated vaccines including, *Streptococcus pneumoniae* *Haemophilus Influenza type B* and *Neisseria meningitis* have dramatically decreased the incidence of these infections and associated strokes. Serious systemic illnesses such as meningitis are well known risk factors of stroke in this age group.⁵¹ Infection provokes a

cascade of SCD-specific pathophysiological changes⁵² including, but not limited to, vaso-occlusive process.

Malaria—Malaria is a leading cause of morbidity and mortality among 50–80% of children with SCA in sub-Saharan Africa.^{53,54} The term cerebral malaria has been used loosely in the medical literature to describe any disturbance of the CNS during a malaria infection.⁵⁵ Typical manifestations of malaria may be seen in infants and children less than 5 years of age with SCD in sub-Saharan Africa.⁵⁶ In children living in endemic malaria areas, severe falciparum malaria usually manifests as seizures, impaired consciousness, metabolic acidosis presenting as respiratory distress, and signs of severe anemia. The pathogenesis of cerebral malaria is heterogeneous and the neurologic complications are often part of a multisystem dysfunction.⁵⁷ Seizures are seen in 20 to 50% of patients with cerebral malaria. Electroencephalography (EEG) studies, especially in children, may sometimes demonstrate underlying status epilepticus even when it is not clinically apparent.⁵⁸ Changes in behavior may occur in the early stages and are usually followed by convulsion, delirium, and coma.⁵⁷ The terminal event in cerebral malaria is death.⁵⁹ Increased malaria attacks and deaths have been reported in SCD patients who are not on malaria chemoprophylaxis.^{60–62} In malaria endemic areas, lifelong malaria chemoprophylaxis is used to decrease its sequelae such as cerebral infarcts, other morbidities, and death associated with malaria. In the recently completed NOHARM study, Opoka et al reported no difference in incidence of malaria between those children who were prescribed hydroxyurea (0.05 episodes per child per year; 95% confidence interval [0.02, 0.13]) Vs. those on placebo (0.07 episodes per child per year [0.03, 0.16]). The incidence of malaria in this cohort was low, suggesting effective protection by insecticide-treated bed nets and monthly oral malaria prophylaxis provided to all study participants.

Sleep apnea—Children with sleep apnea and or upper-airway obstruction have a higher risk of nocturnal hypoxemia,⁶³ which are associated with a greater risk of neurologic complications.⁶³ Upper-airway obstruction and bronchial obstruction were strongly associated with the occurrence of cerebrovascular accident (CVA) in children with SCD.⁶⁴ However, the aforementioned studies were completed in high-resource settings before the routine use of TCD screening and blood transfusion or hydroxyurea treatment for primary stroke prevention.

Congenital infections are associated with neurologic complications in very young children with SCD

Little data exist to determine whether children with SCD are more susceptible to neurologic injury than the general population after in-utero infection with Toxoplasmosis, Rubella, cytomegalovirus, herpes simplex, and syphilis. Prenatal exposure has been well documented to cause microcephaly, hydrocephalus, seizures, cognitive impairment and blindness due to chorioretinitis.⁶⁵

Cognitive function in children less than five years of age

The physical effects of SCD begin in infancy or early childhood.⁶⁶ Cerebral infarction can occur at or before seven months of age.⁶⁷ Children with SCD and severe complications have

greater autonomic nervous system reactivity to physical or mental stress than those with mild disease.⁶⁸ The findings of Thompson et al. showed a decline in mental development index scores between one and two years of age compared with children in the general population.⁶⁹

Executive Function deficits are commonly reported in children with SCA.⁷⁰ Executive function is a term for a collection of skills that is used to control everyday behavior.⁷¹ Basic executive function skills such as attention control tend to emerge first and later progress into more complex skills such as cognitive flexibility.⁷² Findings of Downes et al revealed that children with SCA perform poorer than their matched peers on multistep assessment.⁷³

Infants with SCA tested at 9 and 12 months ($n = 14$) showed preliminary evidence for a delay in the development of early markers of executive function on classical “A not B” object retrieval tasks.⁷⁴ Potentially children with SCA require more support to complete the task and show specific difficulties in organization and initiating and completing the task. Executive dysfunction is widely reported in children with SCD;⁷⁵ however, the lack of appropriate measures has been a barrier in the characterization of executive development in children under five. More research is required to better characterize neuro developmental effects of SCA and once identified, such children may be amendable to remedial services and strategies to improve their academic skills at school and at home.

Primary and secondary stroke prevention

In high-resource settings the single greatest advancement for children with SCD is primary stroke prevention. Standard care in high resource settings include screening for abnormal TCD in the terminal portion of the internal carotid and proximal portion of Middle Cerebral Artery starting at two years of age. In randomized controlled trial where children with SCA were randomly allocated to observation or regular blood transfusion, the intervention was associated with a 92% relative risk reduction compared to observation.⁷⁶ More recently, based on the results of the TCD with Transfusions Changing to Hydroxyurea (TWiTCH) Trial (NCT01425307),⁷⁷ the new standard of care involve regular monthly transfusion for at least one year followed by either hydroxyurea or chronic transfusion therapy. In low resource settings, no strategy has been established for primary stroke prevention, but randomized controlled trials are under way (Sickle cell disease Stroke PREvention In NiGeria (SPRING) TRIAL, NCT02560935).⁷⁸ For children with abnormal TCD two different doses of hydroxyurea are used to test its efficacy. Based on the promising early results of the feasibility trial in Kano, Nigeria TCD screening has been initiated for primary stroke prevention and blood transfusion therapy is not routinely used.

The standard treatment for secondary stroke prevention in high-resource settings is chronic regular blood transfusion therapy; however, preliminary evidence strongly suggests that Hematopoietic Stem Cell Transplant (HSCT) decreases the rate of stroke recurrence.⁸ Unfortunately, the challenge with HSCT is most children and adults do not have a viable donor.⁸ Based on the SWiTCH trial results, transfusion and chelation remain the better way to manage children with SCA, stroke, and iron overload.⁷⁹ Based on the challenges of blood transfusion therapy in low- and middle-income countries, SCD secondary stroke prevention in Nigeria (SPRINT) trial (NCT01801423) is now funded in Nigeria to determine the

efficacy of preventing stroke recurrence comparing 20 versus 10mg/kg per day of hydroxyurea therapy.⁸

Conclusion

Neurologic complications in children fewer than five years of age with SCD may be more frequent than currently reported. The difficulty in diagnosis of neurologic complications, most likely results in underdiagnoses of significant neurologic impairment in young children with SCD. The most commonly reported neurologic complication in children under five with SCD is Silent cerebral infarct, with a prevalence of 26% before their 6th birthday. Unlike TCD screening, which has led to significant decrease of overt strokes, no strategy has been developed for primary prevention of Silent cerebral infarct. Detection of overt stroke in very young children is challenging and must be distinguished from other neurologic complications including focal neurologic deficits following a seizure or migraine. Whenever possible, children less than five years of age presenting with focal neurologic deficit, migraine, or acute seizures should be referred to a pediatric neurologist. Research is needed to prevent Silent cerebral infarct and its sequelae including cognitive impairment in young children with SCD.

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Highlights

- Neurologic complications in children under five years of age with SCD are common
- Diagnosis of neurologic complications is difficult in young children with SCD
- Silent cerebral infarct and cognitive impairment are the most common neurologic complications
- Detection of overt stroke in very young children is challenging

Table 1

Clinical features of headache in children less than 6 years

	site	Type	Intensity	Exercise	Duration	Photo/phonophobia	Nausea/vomitting	IHS diagnosis
Patients with migraine without aura								
1	-	-	+	+	+	+	-	1.1
2	-	+	+	+	+	+	+	1.1
3	-	-	+	+	-	-	+	1.7
4	+	+	-	-	-	+	-	1.7
5	-	-	+	+	-	+	+	1.7
6	-	+	+	-	-	-	+	1.7
7	+	+	+	+	-	+	+	1.7
8	±	+	+	+	-	+	+	1.7
9	+	-	+	+	-	-	-	13
10	-	-	+	+	-	-	-	13
Patients with episodic tension headache								
11	+	+	+	-	+	+	+	2.1
12	+	-	+	+	+	+	+	2.1
13	+	+	-	-	+	+	+	2.1
14	+	+	+	-	+	+	+	2.1
15	+	+	+	+	-	+	+	2.1
16	+	-	-	+	+	+	-	2.3
17	+	-	+	+	-	+	+	2.3
18	+	-	+	+	-	+	+	2.3
19	+	+	+	+	+	+	-	2.3
20	+	-	-	-	-	+	+	2.3
21	+	+	+	+	+	-	-	13
22	+	+	+	+	+	-	+	2.3
23	+	-	-	+	-	+	+	2.3
24	+	-	+	-	-	+	+	2.3
25	+	+	-	-	-	+	+	2.3
26	-	+	+	+	-	+	+	2.3

Code IHS 1.1, Migraine without aura; HIS 1.7; Migranous disorder not fulfilling above criteria; IHS 2.1, Episodic tension headache; HIS 2.3, Headache of the tension type not fulfilling above criteria; IHS 13, Headache not classifiable; +, HIS criterion fulfilled; and - IHS criterion not fulfilled.

Table 2

Differential Diagnosis of Focal Neurological Deficits in Children less than five years with SCD

Differentials of focal neurological deficits	Diagnosis
1 SCI	<ul style="list-style-type: none"> • Magnetic Resonance Imaging of the brain • A silent infarct-like lesion is defined as an MRI signal abnormality that is atleast 3mm in one dimension and that is visible in two planes on fluid attenuated inversion recovery (FLAIR) T2 weighted images
2 Headaches and Migraine	<ul style="list-style-type: none"> • Diagnosis of primary headache disorders of children rests principally on clinical criteria as set forth by the International Headache Society • Evidence based studies have shown that neuroimaging is not routinely indicated in children with chronic headache and normal neurologic examination
3 Seizure	<ul style="list-style-type: none"> • To distinguish the causes of seizures (cerebral malaria, meningitis and TORCHES) in very young children with SCD will require the expertise of a skilled pediatric neurologist • Electroencephalography
4 Primary hemorrhagic stroke (Subarachnoid Hemorrhage, Intraventricular hemorrhage)	<ul style="list-style-type: none"> • Computed Tomography Angioraphy • Magnetic Resonance Angiography
5 Cerebral Sinovenous Thrombosis Posterior Reversible Encephalopathy Syndrome	<ul style="list-style-type: none"> • Computed Tomography Venogram