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Topical Review

Sickle Cell Disease and Stroke

Deborah Hirtz, MD [a], Fenella J. Kirkham, MD [b, *]

[a] University of Vermont School of Medicine, Burlington, Vermont
[b] Developmental Neurosciences Section and Biomedical Research Unit, Clinical and Experimental Sciences, University of Southampton, UCL Great Ormond Street Institute of Child Health, London, UK

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ABSTRACT

Cerebral infarction is a common complication of sickle cell disease and may manifest as overt stroke or cognitive impairment associated with "silent" cerebral infarction on magnetic resonance imaging. Vasculopathy may be diagnosed on transcranial Doppler or magnetic resonance angiography. The risk factors in sickle cell disease for cognitive impairment, overt ischemic stroke, silent cerebral infarction, overt hemorrhagic stroke, and vasculopathy defined by transcranial Doppler or magnetic resonance angiography overlap, with severe acute and chronic anemia, acute chest crisis, reticulocytosis, and low oxygen saturation reported with the majority. However, there are differences reported in different cohorts, which may reflect age, geographic location, or neuroimaging techniques, for example, magnetic resonance imaging field strength. Regular blood transfusion reduces, but does not abolish, the risk of neurological complications in children with sickle cell disease and either previous overt stroke or silent cerebral infarction or abnormal transcranial Doppler. There are relatively few data on the use of hydroxyurea or other management strategies. Early assessment of the risk of neurocognitive complications is likely to become increasingly important in the management of sickle cell disease.

Introduction

Sickle cell disease (SCD) is one of the most common hematologic disorders associated with neurological disease in children. Children with SCD have a high risk of developing cerebrovascular complications. Without treatment, clinically apparent arterial ischemic stroke or hemorrhagic stroke occurs in about 8% children with SCD by age 14 years.[1] Ischemic lesions of the brain that occur without clinical evidence of neurological deficits, termed *silent cerebral infarcts* (Fig 1), are also very common in children with SCD.[2]

Vasculopathy involving the large intracranial arteries, including the supraclinoid internal carotid artery (ICA), middle cerebral artery (MCA), and anterior cerebral artery (ACA), was originally demonstrated on conventional angiography in children with SCD and neurological complications in the 1970s; one patient also had vertebral occlusion, and two had prominent lenticulostriate collaterals.[3] In the 1980s, Adams et al. showed in young symptomatic patients with SCD that four transcranial Doppler (TCD) criteria—(1) time-averaged mean maximum velocity (TAMMV) ≥190 cm/second in any artery, (2) abnormally low velocity in the MCA defined as TAMMV less than 70 cm/second and an MCA ratio (lower/higher) of 0.5 or less, (3) an ACA/MCA ratio of greater than 1.2 on the same side, or (4) the inability to record an MCA in the presence of a demonstrated ultrasound window—predicted ≥50% lumen diameter reduction in intracranial arteries on conventional arteriography with a sensitivity of 90% and specificity of 100%.[4] In the 1990s, the same team showed that ICA/MCA TAMMV greater than 170 cm/second and greater than 200 cm/second predicted a 7% and 40% risk of stroke in asymptomatic patients with SCD over an average follow-up of 29 months[5]; other criteria were not included.

In isolation, a high TAMMV can be secondary to high cerebral blood flow (CBF) as well as arterial narrowing, and the risk of stroke may not be the same. In addition, TCD is highly operator dependent, and short segments of stenosis may be missed in incomplete studies. The technique requires adaptation in young children, who may embrace a parent or suck at the breast or bottle to allow a full examination along the length of the ICA/MCA. Magnetic resonance angiography (MRA) is a technique that also relies on the velocity of flowing blood, and conclusions drawn about the state of the vessel wall must be circumspect. There are relatively few large studies in

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* Communications should be addressed to: Dr. Kirkham; Developmental Neurosciences Section and Biomedical Research Unit; UCL Great Ormond Street Institute of Child Health; 30 Guilford Street; London, UK.
E-mail address: Fenella.Kirkham@ucl.ac.uk (F.J. Kirkham).

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symptomatic or asymptomatic patients with SCD, and consensus has not yet been reached on the definition or grading of vasculopathy diagnosed on MRA (Fig 2).[6] Advantages of MRA include diagnosis of vasculopathy in the carotid and vertebral arteries in the neck (Fig 3) and the detection of aneurysms (Fig 4) as well as the possibility of over-reading to improve diagnostic reliability.

Silent cerebral infarcts (SCI) can readily be identified by neuroradiologists[7] and occur in children without any accompanying physical findings or abnormalities on neurological examination such as are associated with overt strokes. The pediatric neuroradiologic definition of SCI is a lesion of diameter ≥3 mm on T2-weighted imaging, which is not seen as hypointense on T1-weighted imaging. The definition of SCI for adults is a lesion ≥5 mm on T2-weighted imaging and hypointense on corresponding T1-weighted imaging.[8] These findings cannot be associated with specific deficits seen on neurological examination. At a magnetic resonance imaging (MRI) field strength of 1.5 T, SCI are detected in around a quarter of children with homozygous sickle cell disease (HbSS) aged less than six years of age, and in more than a third by the time they reach age 18 years.[9,10] In the Cooperative Study of Sickle Cell Disease, of 266 children with SCD aged six to 19 years, the baseline prevalence of SCI was 21.8% and the SCIs documented were smaller and less likely to be frontal or parietal than overt strokes.[11] More SCIs are detected at higher field strengths, for example, 3T or 7T.[12]

Although the average age of onset of overt stroke is 7.7 years, SCIs may occur in infants and preschoolers. Even in the absence of history of clinical stroke, very young children have a high rate of infarction and/or stenosis of the major cerebral arteries.[13–15] In a study of 36 children younger than 48 months, four (11%) had abnormalities including one with SCI and four with stenotic lesions of the MCA.[13] Of 23 children aged 10 to 18 months enrolled in the Pediatric Hydroxyurea Phase III Clinical Trial, three (13%) had SCI at baseline.[14] Children who have SCI are also at increased risk of overt stroke[11,16] and progressive silent infarction,[11] even when very young.[17] Associated morbidities include decrease in intellectual abilities[18] and academic achievement.[19]

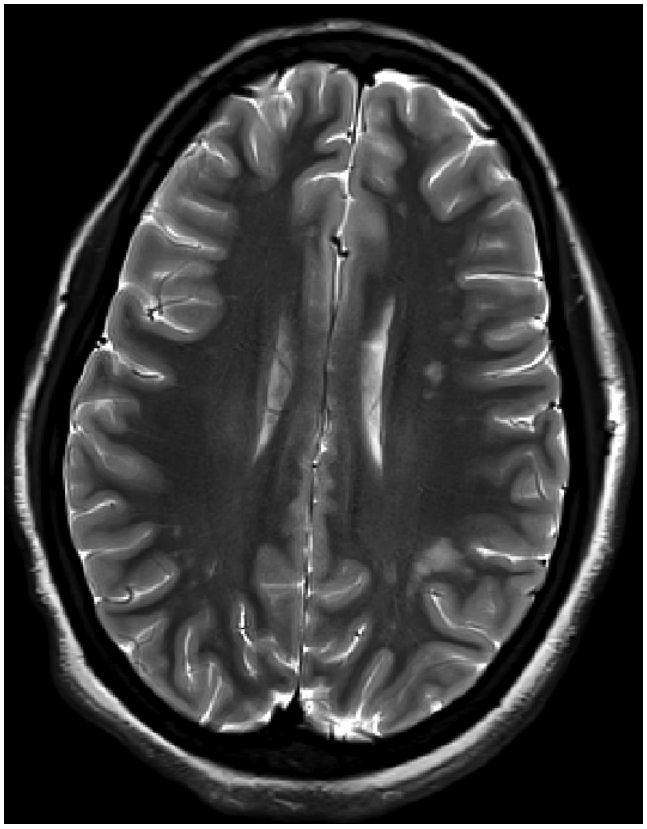

FIGURE 1. Typical distribution of silent cerebral infarctions in the white matter of the frontal and parietal lobes in a neurologically asymptomatic child with sickle cell disease.

Risk factors for cerebrovascular complications

There are differences in risk factors for cognitive impairment, overt ischemic stroke, SCI, overt hemorrhagic stroke, and vasculopathy defined by TCD or MRA (Table 1). In the Cooperative Study of Sickle Cell Disease, the risk factors for ischemic and hemorrhagic stroke were different (Table 1), although low hemoglobin was a risk factor for both.[21] In Colombatti's study, coagulation activation was associated with SCI but not large vessel vasculopathy.[63] Defining cerebral risk as a combination of overt stroke, TCD abnormality, and MRI abnormality, Bernaudin found that the independent risk factors were reticulocytosis and high lactate dehydrogenase.[55] Using a similar definition, Joly et al. demonstrated a protective effect of α-thalassemia, whereas glucose-6-phosphate dehydrogenase deficiency was associated with increased risk of stroke, SCI, or abnormal TCD.[62] Many of the apparent predictors have not been reproduced in large well-conducted studies, and some may be important in one age group or geographical setting but not in another. There is a need for better predictors of central nervous system complications.[61]

Intracranial and extracranial vasculopathies

In children with SCD, intracranial and extracranial large vessel diseases are associated with both first and recurrent strokes and SCI.[6,64] In a study using a heatmap technique to determine SCI "hotspots," those with large vessel vasculopathy had larger SCI and were more likely to have parietal atrophy.[65] There is a correlation between daytime oxygen saturation and vasculopathy, as examined by TCD.[27,50,52,59,60] MRA studies have also demonstrated a relationship between mean overnight oxygen saturation and vasculopathy.[37]

Arterial ischemic stroke

Children with vasculopathy due to SCD have additional risk factors for infarction of brain tissue. Blood oxygen content is decreased as a result of anemia, and therefore baseline CBF is relatively high, which in turn reduces the ability of the cerebral vasculature to increase CBF.[66] A third additional problem in SCD is that HbSS leads to increased blood viscosity, further limiting tissue oxygen delivery.[67]

Silent cerebral infarction

Seizures; poor splenic function, diagnosed as an elevated pocked red cell count; low hemoglobin; and relatively high blood pressure are risk factors for SCI.[2,11,23] In the SIT trial of children aged five to 15 years, SCI were found in 30.8% (251 of 814), and were associated with lower baseline hemoglobin concentration, higher baseline systemic blood pressure, and male sex.[2]

Intracranial hemorrhage

Intracranial hemorrhage can occur in SCD in all locations: intracerebral, intraventricular, subdural, and extradural. This condition is more frequent in young adults, but it can be seen in children.[68] Risk factors include increased blood pressure due to use of

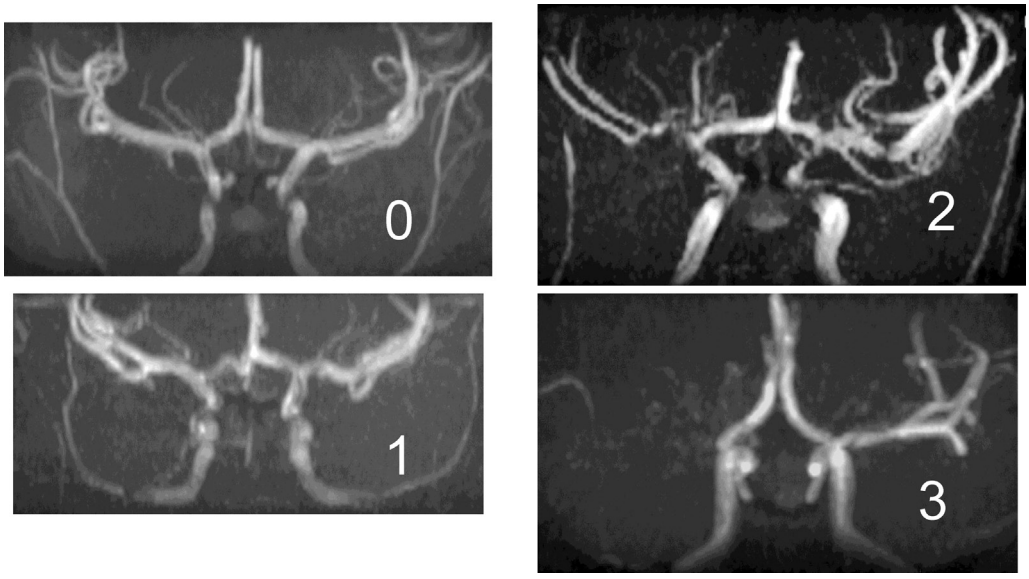

FIGURE 2. Vasculopathy on magnetic resonance angiography graded according to the severity of signal loss in neurologically asymptomatic children with sickle cell disease: Grade 0, normal; Grade 1, minor signal attenuation (turbulence) and normal appearing vessel on magnetic resonance imaging; Grade 2, obvious signal attenuation, but presence of distal flow (stenosis); Grade 3, signal loss and no distal flow (occlusion); Grade 4, occlusion with collaterals (moyamoya), not shown.

steroids, recent transfusion, splenic sequestration, and hyperviscosity post transfusion. Small saccular aneurysms developing at the bifurcations of major vessels may be diagnosed in asymptomatic children and are most subject to rupture.[69] Sinovenous thrombosis and moyamoya disease should also be considered.

Cerebral hemodynamics

In adults with atherosclerosis who have ischemic strokes, an immediate autoregulatory response to a decreasing perfusion pressure is vasodilatation of cerebral arterioles to preserve CBF. If perfusion pressure decreases more than can be compensated for by vasodilatation, oxygen extraction fraction (OEF) increases to maintain cerebral metabolic rate of oxygen consumption (CMRO2). CMRO2 is determined by the product of OEF and blood oxygen content (CaO2). If the perfusion pressure falls further, these compensatory mechanisms of autoregulation cannot maintain the oxygen delivery needed for tissue survival and infarction of brain tissue results.[70] Kawadler et al.[71] compared two age groups of children with SCD with and without SCI using a multiple-inflow time arterial spin labeling study. Overall, CBF was elevated in children with SCD compared with controls. Compared with the younger group with SCD, the older group had more of a difference from controls in the relationship between CBF and oxygen content

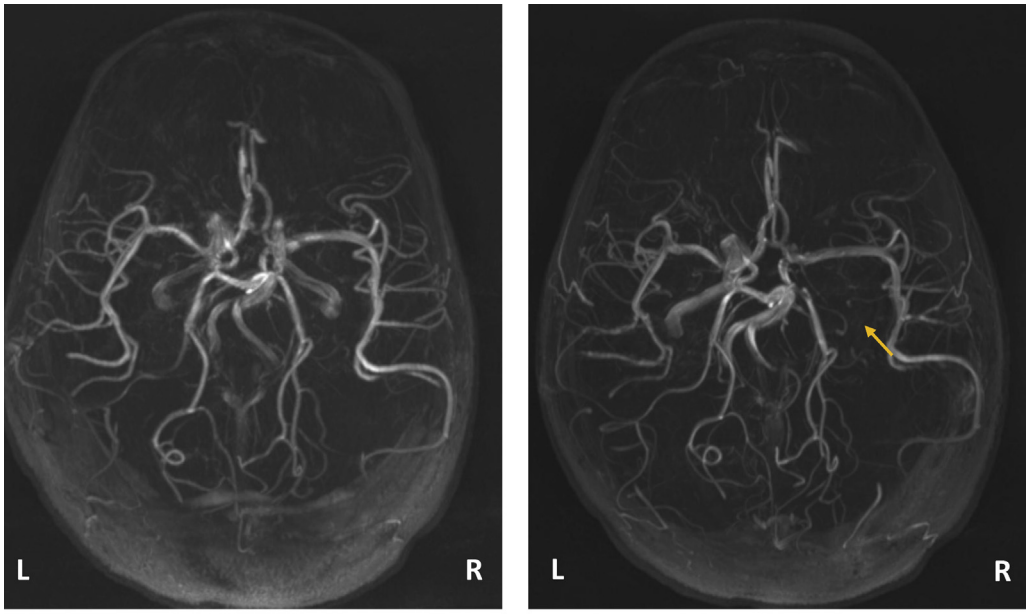

FIGURE 3. Right internal carotid is no longer visible (arrow) on repeat imaging after seven months in a neurologically asymptomatic teenager with sickle cell disease and a mean overnight oxygen saturation of 91.3%. The color version of this figure is available in the online edition.

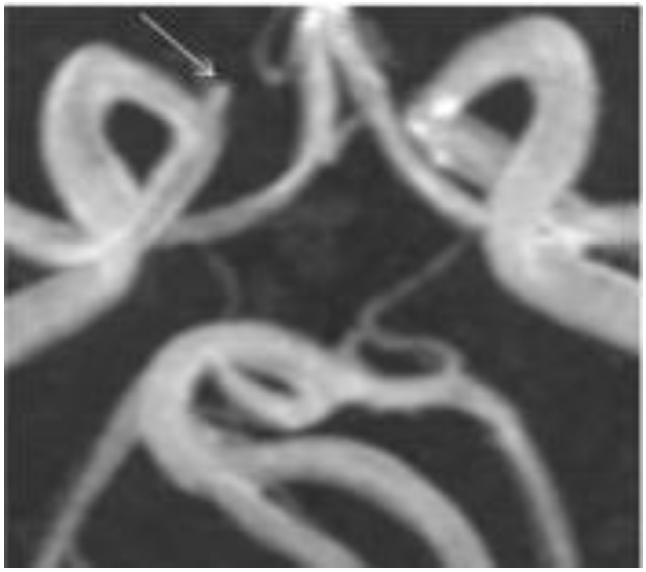

FIGURE 4. Small aneurysm (arrow) demonstrated on magnetic resonance angiography in a neurologically asymptomatic child with sickle cell disease.

in the cerebral circulation, which could increase the risk of acute or chronic compromise.

Right-to-left shunting at cardiac or pulmonary level

Intracardiac or intrapulmonary shunting could be a risk factor predisposing to thrombosis, and elevated right heart pressures may lead to embolization.[72] In one case-control study, there was an increased prevalence of right-to-left shunting in children with SCD and stroke, typically pretransfusion, compared with controls with conditions other than SCD with an intravenous line.[73] Obstructive sleep apnea may increase the risk of right-to-left shunting. There are as yet few data showing an association between intracardiac or intrapulmonary shunting and SCI.

Acute illness

Overt stroke and SCI may occur in the context of acute chest crisis.[21,31] In addition, acute anemic events associated with cerebrovascular accidents may be caused by splenic sequestration or infection, such as parvovirus B19.[74,75] Acute anemic events are also important risk factors for acute silent cerebral ischemic events (ASCIE).[76] Dowling et al. reported ASCIE in four of 22 (18%) children with SCD and in two of 30 (6.7%) children without SCD who had been hospitalized for an illness associated with acute anemia.[30] In four of the children with acute SCI, causes included acute chest syndrome and aplastic crises. All four had a nadir hemoglobin between 2.2 and 3.4 g/dL.[30]

Cognitive impairment

White et al. developed a model for distinguishing children with and without SCI. The cognitive battery to screen for SCI consisted of the California Verbal Learning Test, Children's Version, and the block design from the Wechsler Abbreviated Scales of Intelligence.[77] This model was derived from a population of 16 older children with and 49 children without SCI. The investigators suggested that this model could be used to screen for the presence of SCI.

In general, children with SCD and a history of stroke do significantly more poorly on most neuropsychological measures than children with either SCI or no abnormalities on MRI. A total of 240 children with SCD aged six to 12 years underwent MRI and neuropsychological evaluation. Of these 135 were HbSS; 22% had an abnormal MRI, of which 15.6% were silent infarcts; and 6.7% had a clinical history of stroke. Those with strokes had scores that were lower on full scale intelligence quotient (FSIQ), verbal IQ, performance IQ, and math achievement, and those with SCI did more poorly than those with no MRI abnormality on arithmetic, vocabulary, visual motor speed, and coordination. The effect of SCI on FSIQ was not as devastating as overt stroke: the average FSIQ in children with silent infarcts was 82.8, whereas it was 70.8 in children who experienced an overt stroke.[18] There is some evidence that SCI of larger size are associated with lower FSIQ[78] and other cognitive impairments, including slower processing speed.[38]

Wang et al. found that children with SCI had lower scores on math, reading, FSIQ, and both subscales compared with those with SCD and normal MRI.[79] However, in those with no MRI infarcts, verbal IQ scores declined 0.5 points per year, math scores declined 0.9 points per year, and coding subscales declined 0.2 points per year, with increasing age.

A systematic review by Kawadler et al. involved a meta-analysis of 19 articles.[80] In six studies, the IQ of children with overt strokes compared with that of children with SCI was lower by 10 points; 17 studies compared the IQ of those with SCI with those with no SCI and found that the IQ was lower in the SCI group by six points. In children with SCD and no stroke, IQ was seven points below that of control children.

In Stotesbury's study of 83 patients aged eight to 37 years with SCD, compared with 32 sibling controls without SCD, those with SCD had lower mean processing speed index (PSI). Importantly, the trend for lower FSIQ disappeared when PSI was included as a covariate. The SCD group scores did not differ between those with and without SCI, but lower PSI scores were associated with abnormalities on diffusion tensor MRI.[81]

The severity of anemia in 37 children with SCD aged six to 18 years was associated with deceased verbal short-term memory in a study by Hijmans et al.[36] There was no association of anemia with TCD velocity and cognitive function. This decrease was present regardless of the presence or absence of SCI. Steen et al. (1999) also saw an association of cognitive deficits that correlated with anemia severity. In 27 children with SCD aged 4.3 to 17.9 years, those with a hematocrit of less than 27% had lower psychometric test scores and lower gray matter volume on T1-weighted images than those with a hematocrit that is greater than 27%.[82]

A study of 30 adolescents with SCD, mean age 17 years, and controls found that decreases in brain oxygen saturation were associated with increases in blood velocity, which in turn was associated with lower IQ scores, relative to controls. It was hypothesized that this may be due to chronic decreased oxygen delivery to the brain. Differences were significant for verbal but not performance IQ.[57]

Cognitive changes have also been documented in a population of 120 adults with no history of neurological dysfunction, compared with 33 control subjects. A decrease in the volume of basal ganglia and thalamus was associated with a decrease in performance IQ and perceptual organization. Although the frontal lobe cortex was thinner, this was not significantly associated with cognitive measures. Melek et al.[83] developed a composite outcome of

TABLE 1.
Literature on Risk Factors for Cerebral Complications of Sickle Cell Disease

	Cognitive Impairment		Overt Ischemic Stroke		Silent (Covert) Infarction		Overt Hemorrhage		TCD Abnormality		Vasculopathy on MRA	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Age	20											
Male gender					2							
High BP			21		2,22	23						
Height	24–26					27						
Weight						27						
High BMI						27						
Parent education	20,28											
Income	20											
TIA			21									
Seizures					23							
Headache						29						
Acute anemia					10,23,30							
ACS			21		31							
Frequent pain						23,32,33						
TCD abnormal	34,35	36	5,37		14	15						
Abnormal MRI	17,20,38-43	36	16		11							
Intracranial MRA			44		33,44-46							
Extracranial MRA					10							
Low CBF					47							
CBF asymmetry		36										
Low hemoglobin	36	28	21		2,10,23,33,48	14,49	21		27,50			
Low hematocrit	34,41,51								50			
High MCV									27,52			
High MCH									17			
Low HbF					14,22,48,53,54	23,49						
High reticulocytes			37,55		55	23			55		37	
High leukocytes					23				52			
High platelets	41				56	23						
High pocked RBC					23							
Low O_2 saturation	20,57		58		48				27,50,52,59,60		37	
α-Thalassemia			61			23,61			61			
SEN haplotype					23							
G-6-PD			62		62				62		46	
High LDH			55		55				52			
Coagulation activation					55							

Abbreviations:
ACS = Acute chest syndrome
BMI = Body mass index
BP = Blood pressure
CBF = Cerebral blood flow
G-6-PD = Glucose-6-phoshate dehydrogenase
HbF = Hemoglobin F
LDH = Lactate dehydrogenase
MCV = Mean corpuscular volume
MCH = Mean corpuscular hemoglobin
MRA = Magnetic resonance angiography
MRI = Magnetic resonance imaging
RBC = Red blood cells
TCD = Transcranial Doppler
TIA = Transient ischemic attack

neurological soft signs consisting of sensory integration, motor coordination, and sequencing of complex motor acts and found that adults with SCD and with higher scores of neurological soft signs were more likely to have experienced SCI.

School performance correlates with many factors besides IQ, and when other factors that contribute to school performance were examined as part of the SIT trial, it was found that household income, parental education, age, and decrease in hemoglobin oxygen saturation as measured by pulse oximetry, and not silent cerebral infarction, correlated most with grade retention in students with SCD.[84] In a single-center study of young children with SCD, the home environment, which was correlated with socioeconomic status, also correlated with the cognitive subscale of the Bayley Scales of Infant Development-II.[85] Impairment in growth also correlates with neurocognitive deficits in children with SCD.[24–26]

Environmental factors and cerebrovascular morbidity

The effect of environmental factors in cerebrovascular disease of children with SCD is not well understood and can be contradictory. However, clearly there is a difference in outcomes between higher- and lower-income countries, and increase in poverty is associated with worse overall health including cerebrovascular complications. Possible environmental factors include climate, air pollution, prevalence of infections, and socioeconomic status. Extremes of weather can precipitate complications, and peripheral vasoconstriction with reduced blood flow in cold weather produces more rigid, sickled red cells. However, the effects of temperature on complications of SCD are complex[86] and may vary with other environmental factors, including increased risk of infection. Air pollution exposure is likewise complex, as particulate matter exposure may increase blood velocity in the carotid artery and

hence the risk of vasculopathy.[87] In contrast, nitric oxide and carbon monoxide, which are components of air pollution, may possibly be beneficial in that rates of hemolysis can be lower with nitric oxide and the half-life of red cells can be prolonged with carbon monoxide, in addition to the promotion of a left shift of the hemoglobin-oxygen dissociation curve.[86]

Quantitative neuroimaging for understanding of pathology

Abnormalities on neuroimaging have been related to specific neurocognitive deficits. Use of imaging biomarkers from quantitative MRI techniques that are sensitive to local areas of vascular compromise may enable noninvasive assessment of cerebral hemodynamics. Patterns that demonstrate a vulnerability to ischemia, including higher global CBF and higher OEF and CMRO2, may be seen in children with SCD compared with their siblings. Regions of high SCI density corresponding to peak OEF in deep white matter also correlate with lower CBF and CMRO2 in these regions compared with all other white matter. It may be possible to detect acute SCI using diffusion-weighted imaging, which can allow for differentiation of acute insults (less than 14 days) from chronic insults.[88] Normal white matter may not be truly normal in some children with SCD, because some still develop cognitive decline. Diffusion tensor imaging might be a more sensitive biomarker for determining the extent, nature, and cause of any disruption to white matter integrity.[81,89]

Despite the association with overt stroke, as there are few pathological data confirming that SCI definitively represent ischemic infarction, some authors have used the term *white matter hyperintensities*.[38] Some SCI might be called *lacunes* in adult studies.[12] As no hypointensity is seen on the T1-weighted image, the SCI may not represent an old infarct, but rather could be a local mismatch of SCD-associated perfusion and oxygen delivery and may be an active process. Regions of lower CBF were shown to correspond to areas wherein SCI was most common.[47] Regions of elevated OEF using asymmetric spin echo correspond with white matter lesions in children with SCD.[88] It is possible that any abnormalities seen in the border zones could be white matter injuries, but not full infarcts, similar to what is seen in typical lacunes in adults.[90]

Treatment

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial was a groundbreaking trial that established the role of TCD monitoring in children with SCD. This trial showed that an elevated cerebral arterial blood flow velocity, defined as flow of greater than 200 cm/second, was associated with an increased risk of stroke and that risk could be mitigated by transfusion therapy, resulting in hemoglobin S remaining at 30% or below. Furthermore, if transfusion therapy was stopped, the risk of stroke returned to baseline.[91,92]

The SIT trial was a multicenter clinical trial involving 29 sites in the United States, Canada, the United Kingdom, and France. The primary aim was to determine the effectiveness of blood transfusion therapy to prevent new ischemic brain injury in the form of either overt stroke or SCI detected on MRI of the brain. The trial enrolled 1880 children with SCD who underwent MRI of the brain; 102 eligible children without elevated TCD over 200 cm/second were assigned to each arm, blood transfusion versus observation. Followed up over three years, the transfusion group had fewer events—6%, consisting of one stroke and five new or enlarged silent strokes. This compared with 14% in the observation group, which had seven strokes and seven new or enlarged SCIs.[93] However, there was no effect of transfusion therapy on full-scale IQ.[93]

A review of Cochrane reviews found that regular transfusions were probably beneficial in preventing stroke in children and adolescents at high risk of stroke (abnormal TCDs or SCI) with some evidence for a decrease in the risk of SCI in children with abnormal TCD velocities.[94] However, there was little evidence for a reduction in new SCI in children with SCI and normal TCD.[94]

One study of 21 children with SCD who received chronic transfusion therapy showed that the treatment increased the hemoglobin from 9.1 to 10.3 and decreased hemoglobin S from 40% to 24%. There was a reduced volume of peak OEF in deep white matter and a reduction in CBF from 88 to 82 mL/100 g/min, whereas the OEF decreased from 43% to 31%.[95] These data suggest that it might be possible to lower the risk of SCI by relieving the metabolic stress on cerebral tissue.

Hydroxyurea has been explored as an alternative therapy to transfusion for stroke prevention, because of the burden on children and families of regular transfusions and because of the risk of iron overload with chronic transfusions. The Stroke With Transfusions Changing to Hydroxyurea trial was a multicenter randomized trial of children with SCD comparing hydroxyurea and serial phlebotomy in 67 children with transfusion and chelation in 66 children, with the primary aim of preventing strokes and reducing iron overload.[96] The study was terminated early because of futility of reaching the primary end point.

In 50 children aged one to 17 years who were treated with hydroxyurea or placebo, there was a decreased rate of new or worsening strokes. Not surprisingly, those with lower hemoglobin and fetal hemoglobin and lower O_2 saturation at baseline were more likely to have an SCI at three and six years.[48] However, a study of 652 Italian children and adults with SCD found that SCI continued to occur despite hydroxyurea treatment, but overt stroke was rare.[97] A smaller study of adults who were heterozygous for hemoglobin S β-thalassemia also found no effect of hydroxyurea.[32]

Although all these treatment trials have made major contributions to the prevention of overt and silent strokes in children with SCD, there are still some children who continue to have new overt strokes or SCI even with transfusion.[98] Long-term sequelae in stroke survivors include aphasias, speech impairment, intellectual disability, and motor disability, including hemi- or quadriparesis.

Other potential new therapies include antiplatelet therapy, revascularization therapy, and stem cell transplantation. There is no convincing evidence that antiplatelet or anticoagulant therapy reduces cerebrovascular complications in children with SCD.[99,100] In children who had SCD and severe vasculopathy identified as moyamoya syndrome, indirect cerebral revascularization therapy was successful in reducing the rate of overt and silent cerebral infarcts.[101] In children with elevated TCD velocities, hematopoetic stem cell transplantation was effective in lowering TCD values[102] and CBF[103] and may also be an effective therapy in those with moyamoya syndrome.[104]

Conclusion

Children with SCD are at high risk of all types of stroke syndromes and are especially prone to silent cerebral infarcts. There is some level of cognitive compromise in children with SCD, with the highest risk in those with overt stroke, with intermediate risk in those with silent stroke, and, importantly, some risk even in those no evidence of cerebral infarction. Stroke risk and cerebrovascular disease in SCD are related to oxygen delivery to the brain. The more novel brain imaging techniques can detect brain damage, and investigation of stroke etiology should include available neuroimaging techniques. Increasing knowledge through studies of

imaging biomarkers may eventually reduce the impact of lowered oxygen content and may allow prevention of strokes in SCD by addressing anemia and decreased oxygen delivery to regional white matter. Prevention through reducing exposure to risk factors is still possible, such as avoidance of cold, dehydration, trauma, and blood loss. In addition, interventions directed at early diagnosis and remedial plans to address school problems are important to minimize the consequences of stroke in children with SCD.

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