Sickle Cell Disease and Stroke

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Acknowledgement: Dr Kirkham is funded by Action Medical Research (UK) GN2509

Abstract

Cerebral infarction is a common complication of sickle cell disease (SCD) and may manifest as overt stroke or cognitive impairment associated with ‘silent’ cerebral infarction (SCI) on magnetic resonance imaging (MRI). Vasculopathy may be diagnosed on transcranial Doppler (TCD) or MR angiography (MRA). The risk factors in SCD for cognitive impairment, overt ischemic stroke, SCI, overt hemorrhagic stroke and vasculopathy defined by TCD or MRA 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, e.g. MRI field strength. Regular blood transfusion reduces, but does not abolish, the risk of neurological complications in children with SCD and either previous overt stroke or SCI, or abnormal TCD. There are relatively few data on the use of hydroxyurea or other management strategies. Early assessment of the risk of neurological complications is likely to become increasingly important in the management of SCD.

**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 (AIS) or hemorrhagic stroke occurs in about 8% of children with SCD by the age of 14 years.(1) Ischemic lesions of the brain that occur without clinical evidence of neurological deficits, or silent cerebral infarcts (SCI) are among the most common forms of neurological disease in children with SCD.(2)

Vasculopathy involving the large intracranial arteries, including the supraclinoid internal carotid (ICA), middle cerebral and anterior cerebral (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/sec in any artery, 2) abnormally low velocity in the MCA defined as TAMMV<70 cm/sec and an MCA ratio (lower/higher) of 0.5 or less, 3) an ACA/ MCA ratio of > 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 >170 cm/sec and >200 cm/sec predicted a 7% and 40% risk of stroke in asymptomatic SCD patients 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 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 to allow a full examination along the length of the ICA/MCA. Magnetic resonance angiography (MRA) is a technique which also relies on velocity of flowing blood and conclusions drawn about the state of the vessel wall must be circumspect. There are relatively few large studies in symptomatic or asymptomatic SCD patients and consensus has not yet been reached on definition or grading of vasculopathy diagnosed on MRA,(6) but the possibility of over-reading to improve diagnostic reliability may be an advantage.

Silent cerebral infarcts can readily be identified by neuroradiologists (7)and occur in children without any accompanying physical findings or abnormalities on neurologic exam such as are associated with overt strokes. The pediatric neuroradiologic definition of SCI is a lesion of greater than or equal to 3 mm diameter on T2 weighted imaging, which is not seen as hypointense on T1 weighted imaging.  The definition of SCI for the adults is a lesion greater than or equal to 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 an MRI field strength of 1.5T, 27% of children <6 years and 37% by 14 years(9) and SCI occur in about 39% of children with homozygous sickle cell disease (SCD, HbSS) by the time they reach age 18 years.(10)  In the Cooperative Study of Sickle Cell Disease (CSSCD), of 266 children with SCD ages 6-19 years, the baseline prevalence of silent infarcts was 21.8%, and the silent infarcts that were seen were smaller and less likely to be frontal or parietal than overt strokes.(11) More lesions tend to be seen at higher field strengths e.g. 3T or 7T.(12)

Although the average age of onset of overt stroke is 7.7 years, silent cerebral infarcts 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 below the age of 48 months, 4 (11%) had abnormalities including one with SCI, and 4 with stenotic lesions of the MCA.(13) Of 23 children aged 10-18 months enrolled in the BabyHUG randomized trial of hydroxyurea, 3 (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)

**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 CSSCD, the risk factors for ischemic and hemorrhagic stroke were different (Table 1), although low hemoglobin was a risk factor for both.(20) In Colombatti’s study, coagulation activation was associated with SCI but not large vessel vasculopathy.(21) 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.(22) Using a similar definition, Joly et al demonstrated a protective effect of alpha thalassemia, while Glucose-6-phosphate dehydrogenase deficiency was associated with increased risk of stroke, SCI or abnormal TCD.(23) 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 CNS complications.(24)

*Intracranial and extracranial vasculopathy*

In children with SCD, intracranial and extracranial large vessel disease is a predictor for both first and recurrent strokes and for SCI.(25) 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.(25) There is a correlation between daytime oxygen saturation and vasculopathy, as examined by transcranial Doppler (TCD).(26-30) Magnetic Resonance Angiography (MRA) studies have also demonstrated a relationship between mean overnight oxygen saturation and vasculopathy.(31)

*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 cerebral blood flow (CBF) is relatively high. This in turn reduces the ability for the cerebral vasculature to increase CBF.(32) A third additional problem in SCD is that HbSS leads to increased blood viscosity, further limiting tissue oxygen delivery.(33)

*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;34). In the SIT trial of children ages 5-15 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. It is more frequent in young adults but can be seen in children.(35) Risk factors include increased blood pressure due to use of 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.(36) Sinovenous thrombosis 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 in order to maintain Cerebral Metabolic Rate of Oxygen Consumption (CMRO2). CMRO2 is determined by a product of OEF and blood oxygen content (CaO2). If perfusion pressure falls further, these compensatory mechanisms of autoregulation cannot maintain the oxygen delivery needed for tissue survival, and infarction of brain tissue results.(37) Kawadler et al compared 2 age groups of children with SCD with and without SCI using a multiple-inflow time arterial spin labeling study.(38) Overall CBF was elevated in children with SCD compared to controls. Compared to the younger group with SCD, the older group had more of a difference from controls in the relationship between CBF and oxygen content 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.(39) In the PFAST case-control study, there was an increased prevalence of right to left shunting in children with SCD and stroke, typically pre-transfusion, compared to controls with conditions other than SCD with an intravenous line.(40) Obstructive sleep apnea may increase the risk of right-to-left shunting. There are as yet few data in SCI.

*Acute illness*

Overt stroke and SCI may occur in the context of acute chest crisis.(20;41) In addition, acute anemic events associated with cerebrovascular accidents may be caused by splenic sequestration or infection such as Parvovirus B19.(42;43) Acute anemic events are also important risk factors for acute silent cerebral ischemic events (ASCIE).(44) Dowling et al reported ASCIE in 4 of 22 (18%) of children with SCD and in 2 of 30 (6.7%) of children with without SCD who had been hospitalized for an illness associated with acute anemia.(45) In 4 of the children with acute SCI, etiologies included acute chest syndrome and aplastic crises. All 4 had a nadir hemoglobin between 2.2 and 3.4 g/dl.(45)

**Cognitive impairment**

White et al (2006) developed a model for distinguishing children with and without SCI. Their 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.(46) This model was derived from a population of 16 older children with and 49 children without silent infarctions. They suggested 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. 240 children with SCD ages 6-12 years underwent MRI and neuropsychological evaluation. 135 were homozygous for HbSS; 22% had an abnormal MRI, of these, 15.6% were silent infarcts; and 6.7% has a clinical history of stroke. Those with strokes had scores that were lower on FS IQ, 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 silent stroke on full-scale IQ was not as devastating as overt stroke: the average full scale IQ 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 (47) and other cognitive impairments, including slower processing speed.(48)

Wang et al found that children with SCI had lower scores on math, reading, FSIQ and both subscales compared to those with SCD and normal MRI.(49) 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 (2016) involved a meta-analysis of 19 articles.(50) In 6 studies, IQ of children with overt strokes compared to that of children with SCI was lower by 10 points. 17 studies compared IQ of those with SCI vs those with no SCI, and found IQ was lower in the SCI group by 6 points. In children with SCD and no stroke, IQ was 7 points below that of control children.

In Stotesbury’s study of 83 patients ages 8-37 years with SCD, compared with 32 sibling controls without SCD, those with SCD had lower mean processing speed index (PSI) compared to those without SCD. The trend for lower FSIQ disappeared when PSI was included as a covariate. The SCD group scores did not differ in those with and without SCI but lower PSI scores were associated with abnormalities on diffusion tensor MRI (DTI).(51)

The severity of anemia in 37 children with SCD age 6-18 years was associated with deceased verbal short term memory in a study by Hijmans et al.(52) There was no association of anemia with TCD velocity and cognitive function. This decrease was present regardless of 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 ages 4.3 to 17.9 years, those with HCT <27% had lower psychometric test scores and lower grey matter volume on T-1 weighted images than those with HCT >27%.(53)

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 associate 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.(54)

Cognitive changes have also been documented in a population of 120 adults with no history of neurologic dysfunction, compared to 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 (2006) developed a composite outcome of neurologic soft signs (NSS) consisting of sensory integration, motor coordination, sequencing of complex motor acts, and found those adults with SCD and with higher scores of NSS were more likely to have had silent cerebral infarcts.(55)

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 SCA.(56) 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 (BSID-II).(57) Impairment in growth also correlates with neurocognitive deficits in children with SCD.(58-60).

**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 as well as 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(61) 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.(62) 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 half- life of red cells can be prolonged with carbon monoxide, as well as the promotion of a left shift of the hemoglobin-oxygen dissociation curve.(61)

**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 that include higher global cerebral blood flow, and higher OEF and CMRO2 may be seen in children with SCA compared to their siblings. Regions of high SCI density corresponding to peak OEF in deep white matte also correlate with lower CBF and CMRO2 in these regions compared to all other white matter. It may be possible to detect acute silent cerebral infarcts using diffusion weighted imaging (DWI), which can allow for differentiation of acute insults (<14 days) from chronic insults.(63) Normal white matter may not be truly normal in some children with SCD; since some still develop cognitive decline.  Diffusion tensor imaging (DTI) might be a more sensitive biomarker for determining the extent, nature and etiology of any disruption to white matter integrity.(51;64)

Despite the association with overt stroke, as there are few pathological data confirming that SCI are definitively ischemic infarction, some authors have used the term ‘white matter hyperintensities’.(48) Some SCI might be called ‘lacunes’ in adult studies.(12) Since 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 where SCI was most common.(65) Regions of elevated OEF using asymmetric spin echo correspond with white matter lesions in children with SCD. (63) 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.(66)

**Treatment**

The STOP trial was a groundbreaking trial that established the role of transcranial Doppler (TCD) monitoring in children with SCD. It showed that an elevated cerebral arterial blood flow velocity, seen as flow of >200cm/sec, was associated with an increased risk of stroke, and that risk could be mitigated by transfusion therapy resulting in Hgb S remaining at 30% or below. Furthermore, if transfusion therapy was stopped, the risk of stroke returned to baseline.(67;68)

The SIT trial was a multicenter clinical trial using 29 sites in the US, Canada, the UK 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 silent cerebral infarct measured by MRI of the brain. It enrolled 1880 children with SCD who received an MRI of the brain. 102 eligible children without elevated TCD over 200 cm/sec were assigned to each arm, blood transfusion versus observation. Followed over three years, the transfusion group had fewer events- 6%, consisting of 1 stroke and 5 new or enlarged silent strokes.  This compared to 14% in the observation group, who had 7 stokes and 7 new or enlarged SCIs.(69) However, there was no effect of transfusion therapy on full scale IQ.(69)

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.(70) However, there was little evidence for a reduction in new SCI in children with SCI and normal TCD.(70)

One study of 21 children with SCD who received chronic transfusion therapy showed that the treatment increased 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 reduced CBF from 88 to 82 ml/100g/min, and OEF decreased from 43% to 31%.(71) This suggests 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 SWITCH trial (stroke with transfusions changing to hydroxyurea) was a multicenter randomized trial of children with SCD comparing hydroxyurea and serial phlebotomy in 67 children to transfusion and chelation in 66 children, with the primary aim of preventing strokes and reducing iron overload.(72) The study was terminated early because of futility of reaching the primary endpoint.

In 50 children ages 1-17 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 O2 saturation at baseline were more likely to have a SCI at 3 and 6 years.(73) 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.(74) A smaller study of adults who were heterozygous for hemoglobin SβThalassemia also found no effect of hydroxyurea.(75)

Although all of 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.(76) 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 therpy can reduce cerebrovascular complications in children with SCD (77) (78) 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. (79)In children with elevated TCD velocities, hematopoetic stem cell transplantation was effective in lowering TCD values at one year post transplantation, (80), and may also be an effective therapy in those with moyamoya syndrome. (81)

**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 most risk with overt stroke, then next level of risk silent stroke, with some risk even with no proven strokes. 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 permit decreasing the impact of lowered oxygen content and may allow prevention of strokes in SCA through 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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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 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 | (82) |  |  |  |  |  |  |  |  |  |  |  |
| Male gender |  |  |  |  | (2) |  |  |  |  |  |  |  |
| High BP |  |  | (20) |  | (2;83) | (34) |  |  |  |  |  |  |
| Height | (58-60) |  |  |  |  | (30) |  |  |  |  |  |  |
| Weight |  |  |  |  |  | (30) |  |  |  |  |  |  |
| High BMI |  |  |  |  |  | (30) |  |  |  |  |  |  |
| Parent education | (82;84) |  |  |  |  |  |  |  |  |  |  |  |
| Income | (82) |  |  |  |  |  |  |  |  |  |  |  |
| TIA |  |  | (20) |  |  |  |  |  |  |  |  |  |
| Seizures |  |  |  |  | (34) |  |  |  |  |  |  |  |
| Headache |  |  |  |  |  | (85) |  |  |  |  |  |  |
| Acute anemia |  |  |  |  | (10;34;45) |  |  |  |  |  |  |  |
| ACS |  |  | (20) |  | (41) |  |  |  |  |  |  |  |
| Frequent pain |  |  |  |  |  | (34;75;86) |  |  |  |  |  |  |
| TCD not normal | (87;88) | (89) | A, B |  | (14) | (15) |  |  |  |  |  |  |
| Abnormal MRI | (17;48;82;90-94) | (89) | (16) |  | (11) |  |  |  |  |  |  |  |
| Intracranial MRA |  |  | (95) |  | (86;95-97) |  |  |  |  |  |  |  |
| Extracranial MRA |  |  |  |  |  |  |  |  |  |  |  |  |
| Low CBF |  |  |  |  | (65) |  |  |  |  |  |  |  |
| CBF asymmetry |  | (89) |  |  |  |  |  |  |  |  |  |  |
| Low hemoglobin | (89) | (84) | (20) |  | (2;10;10;34;73;86) | (14;98) | (20) |  | (28;30) |  |  |  |
| Low hematocrit | (87;92;99) |  |  |  |  |  |  |  | (28) |  |  |  |
| High MCV |  |  |  |  |  |  |  |  | (29;30) |  |  |  |
| High MCH |  |  |  |  |  |  |  |  | |  | | --- | | (17) | |  |  |  |
| Low HbF |  |  |  |  | (14;73;83;100;101) | (34;98) |  |  |  |  |  |  |
| High reticulocytes |  |  | B |  |  | (34) |  |  |  |  | (31) |  |
| High WBC |  |  |  |  | (34) |  |  |  | (29) |  |  |  |
| High platelets | (92) |  |  |  | (102) | (34) |  |  |  |  |  |  |
| High pocked RBC |  |  |  |  | (34) |  |  |  |  |  |  |  |
| Low O2 saturation | (54;82) |  | (103) |  | (73) |  |  |  | (26-30) |  | (31) |  |
| Alpha thal |  |  | (24) |  |  | (24;34) |  |  | (24) |  |  |  |
| SEN haplotype |  |  |  |  | (34) |  |  |  |  |  |  |  |
| G-6-PD |  |  |  |  |  |  |  |  |  |  | (97) |  |
| High LDH |  |  |  |  |  |  |  |  | (29) |  |  |  |

Table 1 Literature on risk factors for cerebral complications of sickle cell disease

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