 Neurological complications and MRI

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**Abstract:** Cerebrovascular disease (cerebral infarction, intracranial haemorrhage, vasculopathy) are common manifestations of SCD associated with significant morbidity and mortality. These neurological complications and potential corresponding neuropsychological compromise may have devastating consequences for a child with SCD. This chapter aims to review the neurological complications in SCD using magnetic resonance imaging (MRI) as both a qualitative and quantitative tool for detecting abnormality. Advanced MRI pulse sequences, such as high-resolution 3D T1-weighted imaging for brain volumetrics, diffusion tensor imaging for white matter integrity and non-invasive perfusion MRI for cerebral blood flow measurement, can give additional information about the structure and function of brain tissue beyond the scope of conventional clinical imaging. These studies have set to establish quantitative biomarkers that relate to disease severity and neuropsychological sequelae.

Keywords: sickle cell anaemia, MRI, cerebrovascular disease, stroke

1. Introduction

SCD is the commonest cause of stroke in childhood [1,2]. Focal cerebral ischaemia due to arterial or venous compromise is rarely fatal but accounts for 70-80% of all strokes [3–5] and nearly all episodes in children younger than 15 and adults older than 30 years. Subarachnoid and intracerebral haemorrhage typically occurs between 20-30 years of age and has a high mortality [4,6,7]. Without preventative strategies, approximately 11% of patients with genotype HbSS will experience a clinically apparent stroke by age 20, and up to 24% by age 45 [6]. Silent cerebral infarction (SCI) is diagnosed only using MRI in patients with no focal neurological deficit, but is associated with cognitive difficulties [8] which families often report. SCI can develop very early in life, with rates between 11-15% in children less than 2 years [9–11] and progressive accrual throughout childhood and adolescence [11] [12] and into adulthood.

1. Pathophysiology of cerebrovascular ischaemic events

Clinical stroke is defined as a focal neurological event lasting more than 24 hours and is usually permanent, while transient ischaemic events are focal neurological events lasting less than 24 hours (*i.e.* there is a full clinical recovery) [13]. Reversible ischaemic neurological deficits last more than 24 hours, but recover fully. None of these clinical definitions require neuroimaging confirmation, although episodes lasting less than 24 hours but accompanied by an acute infarct in the corresponding territory should be considered as strokes. People with HbSS and HbSβ0-thalassaemia genotypes are at highest risk, although stroke has been documented in children with HbSC and HbSβ+-thalassaemia genotypes [6]. Stroke can occur as early as 6-12 months [14] when HbF decreases and HbS begins to be synthesised; the first decade of life, when the onset of strokes typically occur, appears to constitute a ‘critical period’ for neurologic complications and subsequent neurocognitive morbidity [6,15].

Overt stroke is usually associated with large vessel arterial disease, with evidence of stenosis in the internal carotid artery distribution [16], and pathologies are frequently seen in brain tissue within the anterior cerebral and middle cerebral artery territories [17–19]. Transcranial Doppler may be used to screen for high cerebral blood flow velocities consistent with stenosis or hyperaemia; although conventional angiography is rarely justified, magnetic resonance angiography may confirm focal stenosis but is not essential for management.

Risk factors for cerebral infarction include classical risk factors as in the general population: hypertension [6,20], presence of a prior cerebral infarct [3,21], acute low oxygen delivery associated with lower oxygen saturation [22,23], and acute drop in haemoglobin [24], and presence of cerebral vasculopathy [18,25] compromising cerebral blood flow (CBF). Increased CBF velocity, in response to anaemia, results in adaptive vasodilation of vessels to match metabolic demand, reducing cerebrovascular reserve [26] and causing injury to the endothelial cells lining the vascular wall [5,27]. Any further demand when metabolic rate is high (*e.g.* secondary to fever or seizures) or when there is an acute drop in oxygen delivery could cause large and small vessel injury/ischaemia [28], especially in “borderzones”, where blood flow may be lower [29] in the context of large vessel disease and relative hypotension [30].

More common than overt stroke, up to 35% of children will show evidence of SCI [31], diagnosed using MRI as a lesion seen in two planes of a scan with no history of stroke (focal neurological deficit lasting more than 24 hours) [9,30,32,33]. In children with evidence of SCI on MRI, there is a fourteen fold increase in the risk of clinical stroke [34] and further SCI [16]. Known risk factors for SCI are lower rate for pain crises, history of seizures, increased leukocyte count and Senegal beta-globin haplotype [35], but also low baseline haemoglobin [36], male sex and higher baseline systolic blood pressure [37]. The presence of acute silent cerebral infarction events (ASCIE) seen as lesions on imaging which may or may not progress to SCI, has been shown to be temporally associated with clinical events [38]. SCI by definition are clinically silent, so timing is unknown; however, it has been postulated that these lesions are the result of recurrent micro-infarctions and recurrent acute hypoxic damage [24,39,40] secondary to severe anaemia, diminished pulmonary function, splenic sequestration, aplastic crisis and acute chest syndrome [41,42].

1. Primary and Secondary Stroke Prevention

In children, transcranial Doppler (TCD) ultrasound screening to measure blood flow velocity in the intracranial vessels has become an established and effective method of primary stroke prevention. Three groups have been identified with increasing risk of stroke: normal TCD velocities (<170cm/sec), conditional TCD velocities (170-200cm/sec) and abnormal velocities (>200cm/sec) [43]. The Stroke Prevention (STOP) trial randomised children with abnormal TCD velocities (>200cm/s) to regular transfusion and was discontinued early as an interim analysis showed that there was a 92% reduction in the risk stroke in the transfused arm [44,45]. The US National Heart, Lung, and Blood Institute and UK National Health Service recommend all children should have TCD screening and be transfused if their velocities are greater than 200cm/sec [46]. Current guidelines state that those children should be transfused indefinitely [47], but the TCD with transfusions changing to hydroxyurea (TWiTCH) trial suggests that, for those with no MRA abnormality may be able to switch to hydroxyurea prophylaxis after a year of transfusion [48]. Hydroxyurea does appear to reduce TCD velocities even without prior blood transfusion [1] so in settings where TCD is available but blood transfusion is not possible or is considered hazardous, it is probably reasonable to start hydroxyurea while the results of controlled trials are awaited [49]. In adults with SCD, there are no validated methods to screen for increased stroke risk, as TCD studies in adults with HbSS find lower velocities than in children and cannot accurately stratify risk of stroke [50].

For secondary stroke prevention, it is important to know the nature of the primary event and any associated arterial or venous abnormality as well as the setting (*e.g.* ‘out-of-the-blue’ or in the context of acute chest or painful crisis), as estimating recurrence risk depends on these variables [21,51]. While chronic transfusion for secondary stroke prevention is common practice, it may not fully prevent recurrent stroke [21,51,52] and is associated with antibody development, iron overload and significant cost. Other treatments such as hydroxyurea for primary [53] and secondary stroke prevention [54,55] have been showing promise.

1. Sickle cell neuroradiology

In clinical settings after an acute event (*e.g.* hemiplegia, seizures or acute coma), MRI and MRA protocols usually consist of T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences in the axial and coronal planes, a coronal T1-weighted image, diffusion weighted images, and time-of-flight MR angiography protocols to show intravascular appearances.

* 1. MRA Findings

MRA studies confirm pattern of occlusion/stenosis from vessels of the internal carotid distribution with relative sparing of the posterior circulation [56]; stroke and SCI from vertebrobasilar artery circulation occlusion are less common, but have been reported [56,57]. Approximately 10% of children have cerebral vasculopathy [58,59] and/or moyamoya syndrome [25], which may be asymptomatic with SCI seen on MRI [59] but renders the child at significant risk of stroke [25].

* 1. MRI findings
		1. Definition of SCI

Although stroke is identified by abrupt onset of neurological deficit and does not require neuroimaging evidence, the term ‘covert stroke’ [60], or SCI, was first described in the Cooperative Study in Sickle Cell Disease (CSSCD) [32] and requires both a neuroimaging definition, described for the Silent Infarct Transfusion (SIT) trial [37,61] as a MRI lesion measuring at least 3 mm in greatest linear dimension, visible in two planes of T2-weighted images [axial and coronal]), and a neurology definition of a normal neurologic exam or abnormal exam that could not be explained by the location of the brain lesion [62]. Many studies describe a localization of SCI to deep white matter (Figure 1) , particularly in the arterial borderzones [11,42,57,63,64]. Infarcts in the subcortical grey matter structures (*i.e*. head of caudate, cerebellum) are less common [57,63].

1. An example of SCI in a 12-year-old boy with HbSS.
	* 1. Progression of SCI

Several longitudinal studies have shown presence of SCI as a risk factor for clinical stroke and further SCI. In the CSSCD study approximately 25% of the children with SCI, but only 2.5% of the children without SCI, had new and/or enlarging lesions on follow-up MRI scan [30], predicting a 14-fold higher risk for clinical stroke and further SCI [65].

SCI have been reported in very young children; 4/39 children (10%) with SCA and no history of stroke between 7-48 months of age had SCI [9]; 3/23 children (13%) at an average at of 13.7 months had SCI [10]; and 18/65 children (27.7%) with SCA who were asymptomatic had SCI [31]. A French study showed incidence of SCI as 28.2% by 8 years and 37.4% by 14 years [66]. Although it was thought that rates plateau in childhood, there is now evidence of new SCI in older adolescence and adulthood [1,67]. In the London cohort followed from the mid-1990s [68], 30% (3/10 patients) were found to have new SCI after the age of 14, 17 and 21 years, respectively (Figures 2 and 3).

The SIT trial showed that in children aged 5-14 years with SCI, regular blood transfusion reduced the risk of reinfarction, both overt (clinical stroke) and silent [62]. Preliminary observational data from the Hydroxyurea Study of Long-Term Effects (HUSTLE-NCT00305175) study suggest that progressive SCI are less likely to accumulate in children taking hydroxyurea to maximum tolerated dose [69], but no randomised controlled trials are available yet.

1. Serial imaging of a male with HbSS. Patient was 17 years old on T2-weighted image from 2001 (left) – showing a small right frontal SCI. Patient was 28 years old on T2-weighted image from 2013 (right) – showing no progression in size of original right frontal SCI but evidence of new SCI in the right peritrigonal region.
2. Serial imaging of a male with HbSS. Patient was 14 years old on T2-weighted image from 2002 (top panel) – showing a small left peritrigonal SCI. Patient was 26 years old on T2-weighted image from 2013 (bottom panel) – showing no progression in size of original SCI, but evidence of new SCI in both cerebellar hemispheres.
	* 1. Acute Silent Cerebral Ischemic Events (ASCIE)

It has been argued that categorically dividing ischaemic events between clinical stroke and SCI may be an oversimplification of the spectrum of brain injury in SCD [38]. ASCIE [38,40], following acute severe anaemia [24,35,70,71] can be detectable in the first few days after the clinical event using diffusion-weighted imaging (DWI), in which the ‘apparent’ diffusion coefficient (ADC) is measured within each voxel and representing an index of the mobility of water molecules inside biological tissues. In acute ischaemia, an area of oedema in the brain has a rapid decline in proton density and appears hyperintense on DWI and decreased on an ADC map, persisting for 10-14 days post-event [72], which can differentiate acute stroke from more remote events [24]. Not all children with evidence of ASCIE progress to SCI on MRI [1,62], which strongly suggests acute ischaemia may be reversible.

* + 1. Other acute pathologies on MRI

Imaging abnormality in the occipito-parietal or thalamic region suggests cerebral venous sinus thrombosis but there may be no parenchymal change and this diagnosis should always be excluded with a venogram in patients with SCD presenting in coma or with seizures or acute psychiatric symptoms as well as focal neurology [73]. Subarachnoid and intracerebral haemorrhage also occur [74], as a result of sinovenous thrombosis, rupture of aneurysms (usually located at the bifurcations of major vessels, particularly in the vertebrobasilar circulation) [75], or of fragile moyamoya vessels. Risk factors include recent trauma, transfusion in the past fortnight, corticosteroid or non-steroidal anti-inflammatory use and intermittent hypertension [76]. Posterior Reversible Encephalopathy Syndrome (Figure 4, left) has also been reported in the context of hypertension and cyclosporin use for nephrotic syndrome [77], as well as after acute chest syndrome [78,79]. Acute bilateral borderzone ischaemia may also occur secondary to inadequate global CBF to supply the tissue’s demand for oxygen (*e.g.* during acute chest crisis or seizures (Figure 4, middle, right). Management along the lines of the current guidelines for the diagnosed condition in the general paediatric population should be considered, e.g. acute anticoagulation with heparin for cerebral venous sinus thrombosis, neurosurgery for drainage of haematoma and surgery or interventional neuroradiology for removal of aneurysm after intracranial haemorrhage, and steady slow reduction of any associated high blood pressure associated with PRES [80,81].

1. Left. Signal change in the grey and white matter (arrows; posterior reversible encephalopathy syndrome) in a 9-year-old boy with HbSS and nephrotic syndrome who had seizures after cyclosporin therapy. Middle. Bilateral borderzone ischaemia in a 25-year-old woman with HbSS who collapsed with seizures soon after discharge after acute chest crisis. Right. Infarction in both anterior and posterior borderzones in an 8-year-old boy with previously uncomplicated sickle cell anaemia who developed seizures and coma after surgery to drain a painful swelling of his left cheek associated with fever.
2. Quantitative MRI findings: cross-sectional and longitudinal case control studies

Since the 1990s when MRI was used routinely in clinical practice, vast improvements in MRI hardware, software, sequence design and processing techniques have allowed for quantitative measurement of neurological abnormality in SCD. Beyond conventional MRI protocols for acute CNS event detection, only in the last 10-15 years have advanced MRI sequences for quantitative analyses been published, giving further insight into the pathophysiology and progression of neurological complications.

* 1. Morphometric studies using T1-weighted MRI

High-resolution T1-weighted data, with good contrast between grey and white matter, can give valuable insight into volumetrics of the brain. An earlier report showed significant reduction in total subcortical grey matter volume (*i.e.* basal ganglia volume) as compared to cortical grey matter volume [82]. Decreases in volume of specific subcortical structures (*e.g.* hippocampus, amygdala, globus pallidus, caudate, putamen) follows parallel to increasing burden of SCI: those with evidence of SCI in white matter have decreased volumes of deep grey matter structures compared to those without SCI and controls [83].

Morphometric studies give a quantitative approach to brain-tissue volumes. In a surface-based morphometric study, older children without SCI showed significant thinning of cortex compared to younger patients in the posterior medial surfaces of both hemispheres [84]. A whole-brain voxel-based morphometry (VBM) study found in children without evidence of SCI, decreased grey matter volume in bilateral frontal, temporal and parietal lobes was found to correlate with low IQ [85]. Also using VBM, Baldeweg and colleages [86] found that in a group with existing SCI, there were significant decreases in white matter density extending bilaterally from the anterior frontal lobes along the ventricles to parieto-occipital lobes, as well as along the corpus callosum. In those without evidence of SCI, smaller but similar significant decreases in white matter density were found, suggesting patients may have compromised white matter even with normal conventional imaging (Figure 5). The only longitudinal morphometric study to date has found different trajectories for brain tissue growth during childhood, with a significant decline in total grey matter volume distributed broadly across the brain compared to healthy controls [87].

1. Voxel-based morphometry study showing decreased white matter density extending bilaterally from the anterior frontal lobes along the ventricles to parieto-occipital lobes (Image from Baldeweg *et al*., 2006).
	1. Diffusion Tensor Imaging

Diffusion-tensor imaging (DTI) relies on the properties of the diffusion of water molecules to show directionality (anisotropy) of the underlying tissue. Anisotropy can be quantified by measuring at least 6 directions [88], unlike ADC maps from DWI data that only require 3 directions, by a diffusion tensor, a mathematical model usually visualized as an ellipsoid (Figure 6). From the diffusion tensor model, several quantitative metrics can be calculated: fractional anisotropy (FA), or the degree of anisotropy ranging from 0 to 1 representing the coherence, organization and/or density of the underlying tissue, and mean diffusivity (MD), or the average water molecular displacement which is equivalent to ADC. MD can also be divided into axial diffusivity (AD), the magnitude of diffusion along the principal direction of diffusion, and radial diffusivity (RD), or the average magnitude of diffusion along the two perpendicular directions of diffusion. These metrics may provide additional information related to demyelination [89] and axonal damage [90]. There are two main approaches to analyzing diffusion data: a voxel-based approach using regions-of-interest (ROIs) or whole-brain data, or tractography (Figure 6), where reconstruction of major white matter tracts can be performed by following the continuity and and direction of maximum diffusion from contiguous voxels [91].

1. Diffusion tensor imaging. 1) The diffusion tensor model showing ellipsoids representing voxel with isotropic diffusion (top) and anisotropic diffusion (bottom). 2) Diffusivity maps showing a) mean diffusivity b) axial diffusivity and c) radial diffusivity. 3) a) Fractional anisotropy maps with b) directions of principal diffusion overlaid (c) tractography of anterior corpus callosum overlaid.

A DWI study showed significant increases in mean regional ADC of patients relative to controls in six large ROIs (left and right frontal lobe, left and right cerebellum, pons, vermis), and in patients with no evidence of infarct, there was increased ADC in four regions (excluding pons and vermis) [92]. These widespread differences in diffusion have been confirmed by DTI studies. In a combined ROI and tractography study of 16 patients with SCD aged 16-45, reduced FA was found in the corpus callosum, centrum semiovale, periventricular areas and ROIs in the subcortical white matter. Tractography of the corpus callosum showed reduced fibre count (*i.e.* streamlines) and reduced FA in the anterior body [93]. Two studies have used a whole-brain analysis technique known as tract-based spatial statistics (TBSS) [94], in which a ‘skeleton’ of white matter is investigated to reduce partial volume effects. In a study of two groups of children with SCA, some of whom had mild gliosis although none had SCI, patients with mild gliosis had increased diffusivity and reduced FA in the body of the corpus callosum, while the no-SCI group had reduced FA in the centrum semiovale compared to controls [95]. Another TBSS study in 25 patients with no evidence of SCI showed FA significantly lower in cerebral peduncles and cerebellar white matter, while there were widespread increases in MD and RD across frontal and parietal lobes, corpus callosum and subcortical white matter. Furthermore, significant negative correlations were found between daytime peripheral oxygen saturation (SpO2) and haemoglobin and RD in the anterior corpus callosum [96] (Figure 7).

1. Results from a recent DTI-TBSS study [96], showing the white matter ‘skeleton’ (green) and significant correlations between RD and daytime peripheral oxygen saturation (blue) and haemoglobin (red).
	1. Perfusion MRI

Perfusion MRI, either through traditional imaging after injection of a paramagnetic contrast agent (e.g. Gadolinium) or non-invasive arterial-spin labelling (ASL) techniques, has the longest history in quantitative MRI in SCD. In patients with chronic cerebrovascular pathology and stroke, dynamic susceptibility contrast MRI (DSC-MRI) have shown *focal* areas of reduced CBF and prolonged mean transit time in the affected corresponding to stroke-like lesions [29,97]. Studies have consistently shown elevated *global* cerebral blood flow (CBF) [98–104], in association with the elevated cerebral blood flow velocity [28], which may be both a response to and a risk factor for cerebral hypoxia [98,99] and related to low haematocrit [98] and haemoglobin and haemoglobin F [103]. Strouse et al [99] found a strong inverse correlation with CBF and both full-scale IQ and performance IQ, which may be more sensitive than CBF velocity measured by TCD [105].

ASL protocols have become more popular as they do not require intravenous injection; however, they have widely differed in acquisition, CBF quantification and arterial territory segmentation techniques [103], leading to discrepancies in interpretation. CBF quantification depends on the T1 value of blood, which is assumed in some studies [99,101] but might be more accurate if it were corrected for haematocrit [100]. An ASL acquisition with multiple inflow times [106] does not require prior assumptions about the necessary delay for the fully-labelled bolus of blood to arrive and may characterize the full haemodynamic behaviour within a voxel.

* + 1. Combined diffusion and perfusion studies

Kirkham et al. [29] found perfusion/diffusion mismatch in areas seen as normal on T2-weighted images, suggesting CBF was reduced but not enough for cytotoxic oedema and tissue death. Similarly, a combined perfusion/diffusion study [102] found abnormal appearing white matter, described as leukoencephalopathy as well as SCI, had decreased CBF and also decreased FA.

1. Cognitive outcome and relationship to brain imaging findings

Chronic disease (*e.g.* conditions secondary to anaemia such as diminished pulmonary function and chronic hypoxic damage resulting in brain damage), potentially accumulating over time [107], could explain compromised cognitive functioning in children with SCD [41]. Recurrent micro-infarctions of the central nervous system, possibly undetected by screening measures, may affect general functioning [108].

* 1. General Intelligence

Full-scale intelligence quotient (IQ) is the most commonly reported and widely studied standardised measure of general cognitive ability in SCD. Chodokoff & Whitten (1963) published the first study investigating IQ between patients with SCD and controls – finding no differences; however from the 1980s/early 1990s there were many studies suggesting that patients have lowered global intelligence scores than matched controls, even when excluding those with history of stroke or abnormal neurological examination [109–114]. Results from studies at that time were mixed; some reported no differences in full-scale IQ (FSIQ) between patients and controls [115–117], others found patients had lowered intelligence scores than matched controls [109–112].

With the routine use of MRI added in the mid-1990s, patients were classed into groups based on history of stroke and presence or absence of SCI [42]; since then, several studies have confirmed that children with SCI generally have lower IQ scores than those without evidence of SCI [86,92,118–121]. Recent meta-analyses have found children with history of stroke perform significantly worse than those with SCI by 10 IQ points, children with SCI perform significantly worse than children with normal MRI by 5-6 IQ points [122] and children with normal MRI perform significantly worse than healthy controls by approximately 7 IQ points [8] (Figure 8).

1. Forest plots of mean differences between SCD patients categorized by MRI status: stroke, silent cerebral infarct (SCI+), no evidence of SCI (SCI-) and healthy controls (HC). Mean differences (estimates) were significant between patients with history of stroke vs SCI+ (left panel), SCI+ vs SCI- (middle panel), and SCI- vs HC (right panel). CI=confidence interval.
	* 1. SCI and IQ

Although children with normal MRI have lowered IQ than healthy controls, these findings may link presence of SCI and size of SCI with IQ. Differences in T2-weighted/FLAIR protocols and lesion quantification methods have varied, and difficult to interpret. Results are mixed; where one study did not provide any correlation result with IQ [86], two studies found volume of SCI to be a significant predictor of IQ [123,124] and one study found only patients with larger lesions had lower IQ [125].

* 1. Executive Functioning

Due to the localization of SCI primarily in the frontal lobe white matter, much work has focused on deficits in executive functioning, an umbrella term for frontal lobe functions such as inhibition, planning, organisation, processing, decision-making, mental flexibility and working memory. A comprehensive systematic review published in 2007 [126] found that 11 out of 13 studies showed executive function and attention were impaired in children with SCD, in domains such as sustained attention [127–129], cognitive flexibility [68,130] and working memory [64,68,123,127,131–133]. Some executive function deficits have been linked specifically to presence of frontal lobe lesions [127,129,134], including one cognitive screening study finding the Test of Variables of Attention task was sensitive and specific in identifying 86% of children with SCI [135]. Patients with no evidence of SCI were found to have deficits in visuomotor functions compared to siblings [127,129], while other studies found no differences in sustained visual attention [92], working memory [123] or set-shifting [68]. A study of neurologically intact adults with SCD showed deficits in processing speed, working memory and other executive functions compared to controls [136].

* 1. Non-imaging biomarkers of function

Anaemia is a major mediator of cognitive function in neurologically intact children (*i.e.* without cerebrovascular abnormalities). Anaemia severity has shown moderate to large correlations with IQ [41,119,137,138]. Severely anaemic patients (i.e. haematocrit<20%) have shown poorer performance on both verbal and performance aspects of IQ [119], and have accounted for a significant proportion of variance in FSIQ [64,138] and executive functions [64]. Low nocturnal peripheral oxygen saturation was associated with reduced performance on the Tower of London test, which measures strategic planning and rule-learning [139]. In the baseline data from the Silent Infarct Trial, a 1% reduction in daytime oxygen saturation was associated with a reduction in 0.75 full scale IQ points [122].

Anaemia and hypoxia may also interact with social/environmental factors such as socioeconomic status [140]. Large cohort studies have found socioeconomic status and parent education as major predictors of cognitive function, rather than SCI [122,141].

1. Impact of therapeutic interventions

Although primary stroke prevention with prophylactic blood transfusions is effective [45], with post-RCT epidemiological evidence for reduction in the number of strokes in children with sickle cell disease [142,143], treatment is expensive [144], the number needed to treat to prevent one stroke is 7 and lifelong regular blood transfusion [145] is a heavy burden for the child and the family, with risk of allo-immunization and infection. Regular blood transfusion also prevents reinfarction in those with SCI but the number neeed to treat to prevent one reinfarction was even higher, the outcomes for the SIT trial included overt strokes and it is not clear whether this treatment can halt or reverse the progression of SCI while there was no benefit in terms of IQ [61,62]. Longer term clinical and imaging follow-up is required as blood transfusion does not prevent all recurrent infarcts, worsening vasculopathy [51] or progressive atrophy [146].

Hydroxyurea does appear to reduce TCD velocities and the TWiTCH trial supports its use for primary prevention in those with abnormal TCD velocities who have normal MRA and have been transfused for a year. There is now a little observational evidence suggesting prevention of progression of SCI [69] and intellectual decline [147] but RCTs are needed.

Daytime and nocturnal desaturation is associated with higher TCD velocities [39] as well as predicting increased stroke risk [22,23]. Hydroxyurea may reduce stroke risk by improving oxygen saturation [148] and other strategies, e.g. to prevent the development of or to treat obstructive sleep apnoea are under investigation. The SIT trial was the first to use MRI as an imaging endpoint; the new techniques such as volumetric analysis and DTI may be useful intermediate endpoints in RCTs of complex interventions, such as the Prevention of morbidity in Sickle Cell Disease (POMS) randomised trials of auto-adjusting continuous positive airways pressure [149,150].

1. Conclusion

In SCD, neurological complications secondary to chronic anaemia and hypoxia are prevalent from an early age. The research is mounting that stroke and SCI, as well as other pathologies, can have marked impact on neuropsychological outcome of the child. In clinical settings, MRI and MRA have been valuable tools for diagnosis and management of acute CNS events; but only relatively recently has the role of quantitative neuroimaging emerged for establishing potential biomarkers of SCD severity. Cross-sectional studies using high-resolution 3D T1-weighted images, diffusion tensor imaging and perfusion imaging have found pertinent tissue characteristics beyond the detection of conventional, clinical MRI/MRA. These studies open the way for use of quantitative MRI as endpoints in clinical trials.

1. References

1. DeBaun MR, Kirkham FJ. Central Nervous System Complications and Management in Sickle Cell Disease: A Review. Blood. 2016;127(7):1–39.

2. Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, et al. Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology. 1998 Jul;51(1):169–76.

3. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med. 1978 Sep;65(3):461–71.

4. Ohene-Frempong K. Stroke in sickle cell disease: demographic, clinical, and therapeutic considerations. Semin Hematol. 1991 Jul;28(3):213–9.

5. Pavlakis SG, Prohovnik I, Piomelli S, DeVivo DC. Neurologic complications of sickle cell disease. Adv Pediatr. 1989 Jan;36:247–76.

6. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998 Jan 1;91(1):288–94.

7. Powars DR, Schroeder WA. Progress in the natural history studies of the clinical severity of sickle cell disease: epidemiologic aspects. In: Caughey WA, editor. Biochemical and Clinical Aspects of Hemoglobin Abnormalities. New York: Academic Press; 1978. p. 151–64.

8. Kawadler JM, Clayden JD, Clark CA, Kirkham FJ. Intelligence Quotient in Paediatric Sickle Cell Disease: a Systematic Review and Meta-Analysis. Dev Med Child Neurol. 2016;

9. Wang WC, Langston JW, Steen RG, Wynn LW, Mulhern RK, Wilimas J a, et al. Abnormalities of the central nervous system in very young children with sickle cell anemia. J Pediatr. 1998 Jun;132(6):994–8.

10. Wang WC, Pavlakis SG, Helton KJ, Mckinstry RC, Casella JF, Adams RJ, et al. MRI Abnormalities of the Brain in One-Year-Old Children With Sickle Cell Anemia. Pediatr Blood Cancer. 2008;51:643–6.

11. Kwiatkowski JL, Zimmerman R a, Pollock AN, Seto W, Smith-Whitley K, Shults J, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol. 2009 Aug;146(3):300–5.

12. Bernaudin F, Verlhac S, Coïc L, Lesprit E, Brugières P, Reinert P. Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. Pediatr Radiol. 2005 Mar;35(3):242–8.

13. Lindsay P, Furie KL, Davis SM, Donnan GA, Norrving B. World stroke organization global stroke services guidelines and action plan. Int J Stroke. 2014 Oct;9 Suppl A1:4–13.

14. Tarazi R a, Grant ML, Ely E, Barakat LP. Neuropsychological functioning in preschool-age children with sickle cell disease: the role of illness-related and psychosocial factors. Child Neuropsychol. 2007 Mar;13(2):155–72.

15. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr. 1992 Mar;120(3):360–6.

16. Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, et al. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. Arch Neurol. 2001 Dec;58(12):2017–21.

17. Russell MO, Goldberg HI, Hodson A, Kim HC, Halus J, Reivich M, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood. 1984 Jan;63(1):162–9.

18. Stockman JA, Nigro MA, Mishkin MM, Oski FA. Occlusion of large cerebral vessels in sickle-cell anemia. N Engl J Med. 1972 Oct 26;287(17):846–9.

19. Gerald B, Sebes JI, Langston JW. Cerebral infarction secondary to sickle cell disease: arteriographic findings. AJR Am J Roentgenol. 1980 Jun;134(6):1209–12.

20. Strouse JJ, Lanzkron S, Urrutia V. The epidemiology, evaluation and treatment of stroke in adults with sickle cell disease. Expert Rev Hematol. 2011;4(6):597–606.

21. Scothorn DJ, Price C, Schwartz D, Terrill C, Buchanan GR, Shurney W, et al. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. J Pediatr. 2002 Mar;140(3):348–54.

22. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R, Evans JP. Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet. 2001 May 26;357(9269):1656–9.

23. Quinn CT, Sargent JW. Daytime steady-state haemoglobin desaturation is a risk factor for overt stroke in children with sickle cell anaemia. Br J Haematol. 2008 Feb;140(3):336–9.

24. Dowling MM, Quinn CT, Plumb P, Rogers ZR, Rollins NK, Koral K, et al. Acute silent cerebral ischemia and infarction during acute anemia in children with and without sickle cell disease. Blood. 2012 Nov 8;120(19):3891–7.

25. Dobson SR, Holden KR, Nietert PJ, Cure JK, Laver JH, Disco D, et al. Moyamoya syndrome in childhood sickle cell disease: a predictive factor for recurrent cerebrovascular events. Blood. 2002 May 1;99(9):3144–50.

26. Prohovnik I, Pavlakis SG, Piomelli S, Bello J, Mohr JP, Hilal S, et al. Cerebral hyperemia, stroke, and transfusion in sickle cell disease. Neurology. 1989;39:344–8.

27. Hess DC, Adams RJ, Nichols FT. Sickle cell anemia and other hemoglobinopathies. Semin Neurol. 1991 Dec;11(4):314–28.

28. Prohovnik I, Hurlet-Jensen A, Adams R, De Vivo D, Pavlakis SG. Hemodynamic etiology of elevated flow velocity and stroke in sickle-cell disease. J Cereb Blood Flow Metab. 2009 Apr;29(4):803–10.

29. Kirkham FJ, Calamante F, Bynevelt M, Gadian DG, Evans JP, Cox TC, et al. Perfusion magnetic resonance abnormalities in patients with sickle cell disease. Ann Neurol. 2001 Apr;49(4):477–85.

30. Pegelow CH. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood. 2002 Apr 15;99(8):3014–8.

31. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood. 2012 May 17;119(20):4587–96.

32. Moser FG, Miller ST, Bello J a, Pegelow CH, Zimmerman R a, Wang WC, et al. The spectrum of brain MR abnormalities in sickle-cell disease: a report from the Cooperative Study of Sickle Cell Disease. AJNR Am J Neuroradiol. 1996 May;17(5):965–72.

33. Steen RG, Fineberg-Buchner C, Hankins G, Weiss L, Prifitera A, Mulhern RK. Cognitive Deficits in Children With Sickle Cell Disease. J Child Neurol. 2005 Feb 1;20(2):102–7.

34. Miller ST, Wright E, Abboud M, Berman B, Files B, Scher CD, et al. Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. J Pediatr. 2001 Dec;139(6):785–9.

35. Kinney TR, Sleeper L a., Wang WC, Zimmerman R a., Pegelow CH, Ohene-Frempong K, et al. Silent cerebral infarcts in sickle cell anemia: a risk factor analysis. The Cooperative Study of Sickle Cell Disease. Pediatrics. 1999 Mar 1;103(3):640–5.

36. Quinn CT, Miller ST. Risk factors and prediction of outcomes in children and adolescents who have sickle cell anemia. Hematol Oncol Clin North Am. 2004 Dec;18(6):1339–54, ix.

37. DeBaun MR, Sarnaik S a, Rodeghier MJ, Minniti CP, Howard TH, Iyer R V, et al. Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, sex, and relative high systolic blood pressure. Blood. 2012 Apr 19;119(16):3684–90.

38. Dowling MM, Quinn CT, Rogers ZR, Buchanan GR. Acute Silent Cerebral Infarction in Children with Sickle Cell Anemia. Pediatr Blood Cancer. 2010;54:461–4.

39. Quinn CT, Variste J, Dowling MM. Haemoglobin oxygen saturation is a determinant of cerebral artery blood flow velocity in children with sickle cell anaemia. Br J Haematol. 2009 May;145(4):500–5.

40. Quinn CT, McKinstry RC, Dowling MM, Ball WS, Kraut MA, Casella JF, et al. Acute Silent Cerebral Ischemic Events in Children with Sickle Cell Anemia. JAMA Neurol. 2013 Oct 29;70(1):58–65.

41. Brown RT, Armstrong FD, Eckman JR. Neurocognitive Aspects of Pediatric Sickle Cell Disease. J Learn Disabil. 1993 Jan 1;26(1):33–45.

42. Armstrong FD, Thompson RJ, Wang W, Zimmerman R, Pegelow H, Miller S, et al. Cognitive Functioning and Brain Magnetic Resonance Imaging in Children With Sickle Cell Disease. Pediatrics. 1996;97(6):864–70.

43. Adams RJ, Nichols FT, Figueroa R, McKie V, Lott T. Transcranial Doppler correlation with cerebral angiography in sickle cell disease. Stroke. 1992 Aug 1;23(8):1073–7.

44. Adams RJ, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol. 1997 Nov;42(5):699–704.

45. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998 Jul 2;339(1):5–11.

46. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke. 2001 Jan;32(1):280–99.

47. Wang WC, Kovnar EH, Tonkin IL, Mulhern RK, Langston JW, Day SW, et al. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease. J Pediatr. 1991 Mar;118(3):377–82.

48. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. Lancet (London, England). 2016 Feb 13;387(10019):661–70.

49. Galadanci NA, Abdullahi SU, Tabari MA, Abubakar S, Belonwu R, Salihu A, et al. Primary stroke prevention in Nigerian children with sickle cell disease (SPIN): challenges of conducting a feasibility trial. Pediatr Blood Cancer. 2015 Mar;62(3):395–401.

50. Valadi N, Silva GS, Bowman LS, Ramsingh D, Vicari P, Filho AC, et al. Transcranial Doppler ultrasonography in adults with sickle cell disease. Neurology. 2006 Aug 22;67(4):572–4.

51. Hulbert ML, McKinstry RC, Lacey JL, Moran CJ, Panepinto JA, Thompson AA, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. Blood. 2011 Jan 20;117(3):772–9.

52. Hulbert ML, Scothorn DJ, Panepinto JA, Scott JP, Buchanan GR, Sarnaik S, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr. 2006 Nov;149(5):710–2.

53. DeBaun MR, Kirkham FJ. New option for primary stroke prevention in sickle cell anaemia. Lancet (London, England). Elsevier Ltd; 2015;387(10019):626–7.

54. Ware RE, Zimmerman S a, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. Blood. 1999 Nov 1;94(9):3022–6.

55. Lagunju IA, Brown BJ, Sodeinde OO. Stroke recurrence in Nigerian children with sickle cell disease treated with hydroxyurea. Niger Postgrad Med J. 2013 Sep;20(3):181–7.

56. Pavlakis SG, Bello J, Prohovnik I, Sutton M, Ince C, Mohr JP, et al. Brain infarction in sickle cell anemia: Magnetic resonance imaging correlates. Ann Neurol. 1988 Mar;23(2):125–30.

57. Adams RJ, Nichols FT, McKie V, McKie K, Milner P, Gammal TE. Cerebral infarction in sickle cell anemia: Mechanism based on CT and MRI. Neurology. 1988 Jul 1;38(7):1012 – .

58. Abboud MR, Cure J, Granger S, Gallagher D, Hsu L, Wang W, et al. Magnetic resonance angiography in children with sickle cell disease and abnormal transcranial Doppler ultrasonography findings enrolled in the STOP study. Blood. 2004 Apr 1;103(7):2822–6.

59. Thangarajh M, Yang G, Fuchs D, Ponisio MR, McKinstry RC, Jaju A, et al. Magnetic resonance angiography-defined intracranial vasculopathy is associated with silent cerebral infarcts and glucose-6-phosphate dehydrogenase mutation in children with sickle cell anaemia. Br J Haematol. 2012 Nov;159(3):352–9.

60. Hindmarsh PC, Brozovic M, Brook CG, Davies SC. Incidence of overt and covert neurological damage in children with sickle cell disease. Postgrad Med J. 1987 Sep;63(743):751–3.

61. Casella JF, King A a, Barton B, White D a, Noetzel MJ, Ichord RN, et al. Design of the silent cerebral infarct transfusion (SIT) trial. Pediatr Hematol Oncol. 2010 Mar;27(2):69–89.

62. DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White D a, Sarnaik S a, et al. Controlled Trial of Transfusions for Silent Cerebral Infarcts in Sickle Cell Anemia. N Engl J Med. 2014 Aug 21;371(8):699–710.

63. Pavlakis SG, Bello J, Prohovnik I, Sutton M, Ince C, Mohr JP, et al. Brain infarction in sickle cell anemia: Magnetic resonance imaging correlates. Ann Neurol. 1988 Mar;23(2):125–30.

64. Kral MC, Brown RT, Connelly M, Curé JK, Besenski N, Jackson SM, et al. Radiographic Predictors of Neurocognitive Functioning in Pediatric Sickle Cell Disease. J Child Neurol. 2006;21(1):37–44.

65. Miller ST, Macklin EA, Pegelow CH, Kinney TR, Sleeper LA, Bello JA, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr. 2001 Sep;139(3):385–90.

66. Bernaudin F, Verlhac S, Arnaud C, Kamdem A, Chevret S, Hau I, et al. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood. 2011 Jan 27;117(4):1130–40; quiz 1436.

67. Kassim AA, Pruthi S, Day M, Rodeghier M, Gindville MC, Brodsky MA, et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell disease. Blood. 2016;

68. Watkins KE, Hewes DK, Connelly A, Kendall BE, Kingsley DP, Evans JE, et al. Cognitive deficits associated with frontal-lobe infarction in children with sickle cell disease. Dev Med Child Neurol. 1998 Aug;40(8):536–43.

69. Nottage KA. Hydroxyurea Treatment and Brain MRI/MRA Findings in Children with Sickle Cell Anaemia. Br J Haematol. 2016;

70. Steen RG, Emudianughe T, Hankins GM, Wynn LW, Wang WC, Xiong X, et al. Brain Imaging Findings in Pediatric Patients with Sickle Cell Disease. Radiology. 2003;228:216–25.

71. Enninful-Eghan H, Moore RH, Ichord R, Smith-Whitley K, Kwiatkowski JL. Transcranial Doppler ultrasonography and prophylactic transfusion program is effective in preventing overt stroke in children with sickle cell disease. J Pediatr. 2010 Sep;157(3):479–84.

72. Muir KW, Buchan A, von Kummer R, Rother J, Baron J-C. Imaging of acute stroke. Lancet Neurol. 2006 Sep;5(9):755–68.

73. Sébire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. Brain. 2005 Mar;128(Pt 3):477–89.

74. Kossorotoff M, Brousse V, Grevent D, Naggara O, Brunelle F, Blauwblomme T, et al. Cerebral haemorrhagic risk in children with sickle-cell disease. Dev Med Child Neurol. 2015 Feb;57(2):187–93.

75. Nabavizadeh SA, Vossough A, Ichord RN, Kwiatkowski J, Pukenas BA, Smith MJ, et al. Intracranial aneurysms in sickle cell anemia: clinical and imaging findings. J Neurointerv Surg. 2016 Apr;8(4):434–40.

76. Strouse JJ, Hulbert ML, DeBaun MR, Jordan LC, Casella JF. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. Pediatrics. 2006 Nov;118(5):1916–24.

77. Coley SC, Porter DA, Calamante F, Chong WK, Connelly A. Quantitative MR diffusion mapping and cyclosporine-induced neurotoxicity. AJNR Am J Neuroradiol. 1999 Sep;20(8):1507–10.

78. Solh Z, Taccone MS, Marin S, Athale U, Breakey VR. Neurological PRESentations in Sickle Cell Patients Are Not Always Stroke: A Review of Posterior Reversible Encephalopathy Syndrome in Sickle Cell Disease. Pediatr Blood Cancer. 2016 Feb 12;

79. Henderson JN, Noetzel MJ, McKinstry RC, White DA, Armstrong M, DeBaun MR. Reversible posterior leukoencephalopathy syndrome and silent cerebral infarcts are associated with severe acute chest syndrome in children with sickle cell disease. Blood. 2003 Jan 15;101(2):415–9.

80. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke. 2008 Sep;39(9):2644–91.

81. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic Therapy in Neonates and Children. CHEST J. 2012 Feb 1;141(2\_suppl):e737S.

82. Steen RG, Emudianughe T, Hunte M, Glass J, Wu S, Xiong X, et al. Brain volume in pediatric patients with sickle cell disease: Evidence of volumetric growth delay? AJNR Am J Neuroradiol. 2005 Mar;26(3):455–62.

83. Kawadler JM, Clayden JD, Kirkham FJ, Cox TC, Saunders DE, Clark CA. Subcortical and cerebellar volumetric deficits in paediatric sickle cell anaemia. Br J Haematol. 2013 Nov;163(3):373–6.

84. Kirk GR, Haynes MR, Palasis S, Brown C, Burns TG, McCormick M, et al. Regionally specific cortical thinning in children with sickle cell disease. Cereb Cortex. 2009 Jul;19(7):1549–56.

85. Chen R, Pawlak M a, Flynn TB, Krejza J, Herskovits EH, Melhem ER. Brain morphometry and intelligence quotient measurements in children with sickle cell disease. J Dev Behav Pediatr. 2009 Dec;30(6):509–17.

86. Baldeweg T, Hogan AM, Saunders DE, Telfer P, Gadian DG, Vargha-Khadem F, et al. Detecting white matter injury in sickle cell disease using voxel-based morphometry. Ann Neurol. 2006 Apr;59(4):662–72.

87. Chen R, Arkuszewski M, Krejza J, Zimmerman RA, Herskovits EH, Melhem ER. A Prospective Longitudinal Brain Morphometry Study of Children with Sickle Cell Disease. Am J Neuroradiol. 2015;36:403–10.

88. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994 Jan;66(1):259–67.

89. Ciccarelli O, Catani M, Johansen-Berg H. Diffusion-based tractography in neurological disorders: concepts , applications, and future developments. Lancet Neurol. 2008;7(August):715–27.

90. Song S-K, Sun S-W, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage. 2002 Nov;17(3):1429–36.

91. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magn Reson Med. 2000 Oct;44(4):625–32.

92. Scantlebury N, Mabbott D, Janzen L, Rockel C, Widjaja E, Jones G, et al. White matter integrity and core cognitive function in children diagnosed with sickle cell disease. J Pediatr Hematol Oncol. 2011 Apr;33(3):163–71.

93. Balci A, Karazincir S, Beyoglu Y, Cingiz C, Davran R, Gali E, et al. Quantitative brain diffusion-tensor MRI findings in patients with sickle cell disease. AJR Am J Roentgenol. 2012 May;198(5):1167–74.

94. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006 Jul 15;31(4):1487–505.

95. Sun B, Brown R, Hayes L, Burns T, Huamani J, Bearden D, et al. White Matter Damage in Asymptomatic Patients with Sickle Cell Anemia: Screening with DIffusion Tensor Imaging. AJNR Am J Neuroradiol. 2012;33(11):2043–9.

96. Kawadler JM, Kirkham FJ, Clayden JD, Hollocks MJ, Seymour EL, Edey R, et al. White Matter Damage Relates to Oxygen Saturation in Children With Sickle Cell Anemia Without Silent Cerebral Infarcts. Stroke. 2015;1793–800.

97. Tzika AA, Massoth RJ, Ball WS, Majumdar S, Dunn RS, Kirks DR. Cerebral perfusion in children: detection with dynamic contrast-enhanced T2\*-weighted MR images. Radiology. 1993 May;187(2):449–58.

98. Oguz KK, Golay X, Pizzini FB, Freer CA, Winrow N, Ichord R, et al. Sickle cell disease: continuous arterial spin-labeling perfusion MR imaging in children. Radiology. 2003 May;227(2):567–74.

99. Strouse JJ, Cox CS, Melhem ER, Lu H, Kraut M a, Razumovsky A, et al. Inverse correlation between cerebral blood flow measured by continuous arterial spin-labeling (CASL) MRI and neurocognitive function in children with sickle cell anemia (SCA). Blood. 2006 Jul 1;108(1):379–81.

100. Gevers S, Nederveen AJ, Fijnvandraat K, van den Berg SM, van Ooij P, Heijtel DF, et al. Arterial spin labeling measurement of cerebral perfusion in children with sickle cell disease. J Magn Reson Imaging. 2012 Nov 16;35(4):779–87.

101. van den Tweel XW, Nederveen AJ, Majoie CBLM, van der Lee JH, Wagener-Schimmel L, Van Walderveen M a a, et al. Cerebral blood flow measurement in children with sickle cell disease using continuous arterial spin labeling at 3.0-Tesla MRI. Stroke. 2009 Mar;40(3):795–800.

102. Helton KJ, Paydar A, Glass J, Weirich EM, Hankins J, Li C, et al. Arterial Spin-Labeled Perfusion Combined With Segmentation Techniques to Evaluate Cerebral Blood Flow in White and Gray Matter of Children With Sickle Cell Anemia. Pediatr Blood Cancer. 2009;52:85–91.

103. Helton KJ, Glass JO, Reddick WE, Paydar A, Zandieh AR, Dave R, et al. Comparing segmented ASL perfusion of vascular territories using manual versus semiautomated techniques in children with sickle cell anemia. J Magn Reson Imaging. 2014 Jan 8;41(2):439–46.

104. Hales PW, Kawadler JM, Aylett SE, Kirkham FJ, Clark CA. Arterial spin labeling characterization of cerebral perfusion during normal maturation from late childhood into adulthood: normal “reference range” values and their use in clinical studies. J Cereb blood flow Metab. Nature Publishing Group; 2014 Feb 5;34(5):776–84.

105. Kral MC, Brown RT, Nietert PJ, Abboud MR, Jackson SM, Hynd GW. Transcranial Doppler ultrasonography and neurocognitive functioning in children with sickle cell disease. Pediatrics. Am Acad Pediatrics; 2003;112(2):324–31.

106. Buxton RB, Frank LR, Wong EC, Siewert B, Warach S, Edelman RR. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. Magn Reson Med. 1998 Sep;40(3):383–96.

107. Logothetis J, Haritos-Fatouros M, Constantoulakis M, Economidou J, Augoustaki O, Loewenson RB. Intelligence and behavioral patterns in patients with Cooley’s anemia (homozygous beta-thalassemia); a study based on 138 consecutive cases. Pediatrics. 1971 Nov;48(5):740–4.

108. Chapar GN. Chronic diseases of children and neuropsychologic dysfunction. J Dev Behav Pediatr. 1988 Aug;9(4):221–2.

109. Swift A V, Cohen MJ, Hynd GW, Wisenbaker JM, McKie KM, Makari G, et al. Neuropsychologic impairment in children with sickle cell anemia. Pediatrics. 1989 Dec;84(6):1077–85.

110. Hariman LM, Griffith ER, Hurtig AL, Keehn MT. Functional outcomes of children with sickle-cell disease affected by stroke. Arch Phys Med Rehabil. 1991 Jun;72(7):498–502.

111. Wasserman ALL, Wilimas JAA, Fairclough DLL, Mulhern RKK, Wang W. Subtle neuropsychological deficits in children with sickle cell disease. Am J Pediatr Hematol Oncol. 1991;13(1):14–20.

112. Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. Arch Dis Child. 1995;73(4):316–20.

113. Noll RB, Stith L, Gartstein M a, Ris MD, Grueneich R, Vannatta K, et al. Neuropsychological functioning of youths with sickle cell disease: comparison with non-chronically ill peers. J Pediatr Psychol. 2001 Mar;26(2):69–78.

114. Hijmans CT, Fijnvandraat K, Grootenhuis MA, van Geloven N, Heijboer H, Peters M, et al. Neurocognitive deficits in children with sickle cell disease: a comprehensive profile. Pediatr Blood Cancer. 2011 May;56(5):783–8.

115. Fowler M, Whitt J, Lallinger R, Nash K, Atkinson S, Wells R, et al. Neuropsychologic and Academic Functioning of Children with Sickle Cell Anemia. Dev Behav Pediatr. 1988;9(4):213–20.

116. Goonan BT, Goonan LJ, Brown RT, Buchanan I, Eckman JR. Sustained attention and inhibitory control in children with sickle cell syndrome. Arch Clin Neuropsychol. 1994 Jan;9(1):89–104.

117. Midence K, McManus C, Fuggle P, Davies S. Psychological adjustment and family functioning in a group of British children with sickle cell disease: preliminary empirical findings and a meta-analysis. Br J Clin Psychol. 1996 Sep;35:439–50.

118. Steen RG, Reddick WE, Mulhern RK, Langston JW, Ogg RJ, Bieberich AA, et al. Quantitative MRI of the brain in children with sickle cell disease reveals abnormalities unseen by conventional MRI. J Magn Reson Imaging. 1998;8(3):535–43.

119. Bernaudin F, Verlhac S, Freard F, Roudot-Thoraval F, Benkerrou M, Thuret I, et al. Multicenter Prospective Study of Children With Sickle Cell Disease: Radiographic and Psychometric Correlation. J Child Neurol. 2000 May 1;15(5):333–43.

120. Wang W, Enos L, Gallagher D, Thompson R, Guarini L, Vichinsky E, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. J Pediatr. 2001 Sep;139(3):391–7.

121. Steen RG, Miles M a, Helton KJ, Strawn S, Wang W, Xiong X, et al. Cognitive impairment in children with hemoglobin SS sickle cell disease: relationship to MR imaging findings and hematocrit. AJNR Am J Neuroradiol. 2003 Mar;24(3):382–9.

122. King AA, Strouse JJ, Rodeghier MJ, Compas BE, Casella JF, McKinstry RC, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. Am J Hematol. 2014 Feb;89(2):162–7.

123. Schatz J, Buzan R. Decreased corpus callosum size in sickle cell disease: relationship with cerebral infarcts and cognitive functioning. J Int Neuropsychol Soc. 2006 Jan;12(1):24–33.

124. van der Land V, Hijmans CT, de Ruiter M, Mutsaerts HJMM, Cnossen MH, Engelen M, et al. Volume of white matter hyperintensities is an independent predictor of intelligence quotient and processing speed in children with sickle cell disease. Br J Haematol. 2015 Oct 10;168:553–6.

125. Schatz J, White DA, Moinuddin A, Armstrong M, DeBaun MR. Lesion burden and cognitive morbidity in children with sickle cell disease. J Child Neurol. 2002 Dec;17(12):891–5.

126. Berkelhammer LD, Williamson AL, Sanford SD, Dirksen CL, Sharp WG, Margulies AS, et al. Neurocognitive sequelae of pediatric sickle cell disease: a review of the literature. Child Neuropsychol. 2007 Mar;13(2):120–31.

127. Craft S, Schatz J, Glauser T a, Lee B, DeBaun MR. Neuropsychologic effects of stroke in children with sickle cell anemia. J Pediatr. 1993 Nov;123(5):712–7.

128. Brown RT, Davis PC, Lambert R, Hsu L, Hopkins K, Eckman J. Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. J Pediatr Psychol. 2000;25(7):503–13.

129. Schatz J, Brown RT, Pascual JM, Hsu L, Debaun MR. Poor school performance and cognitive functioning with silent cerebral infarcts and sickle cell disease. Neurology. 2001;56:1109–11.

130. Berg C, Edwards DF, King A. Executive function performance on the children’s kitchen task assessment with children with sickle cell disease and matched controls. Child Neuropsychol. 2012 Sep 3;18(5):432–48.

131. White DA, Salorio CF, Schatz J, Debaun M. Preliminary Study of Working Memory in Children with Stroke Related to Sickle Cell Disease. J Clin Exp Neuropsychol. 2000;22(2):257–64.

132. Brandling-Bennett EM, White DA, Armstrong MM, Christ SE. Developmental Neuropsychology Patterns of Verbal Long- Term and Working Memory Performance Reveal Deficits in Strategic Processing in Children With Frontal Infarcts Related to Sickle Cell Disease. Dev Neuropsychol. 2003;24(1):423–34.

133. Hijmans CT, Grootenhuis MA, Oosterlaan J, Peters M, Fijnvandraat K. Neurocognitive Deficits in Children With Sickle Cell Disease Are Associated With the Severity of Anemia. Pediatr Blood Cancer. 2011;(July 2010):297–302.

134. Christ SE, Moinuddin A, McKinstry RC, DeBaun M, White DA. Inhibitory control in children with frontal infarcts related to sickle cell disease. Child Neuropsychol. 2007 Mar;13(2):132–41.

135. DeBaun MR, Schatz J, Siegel MJ, Koby M, Craft S, Resar L, et al. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. Neurology. 1998 Jun;50(6):1678–82.

136. Vichinsky E, Neumayr L, Gold J. Neuropsychological Dysfunction and Neuroimaging Abnormalities in Neurologically Intact Adults With Sickle Cell Anemia. JAMA. 2010;303(18):1823–31.

137. Thompson RJ, Gustafson KE, Bonner MJ, Ware RE. Neurocognitive development of young children with sickle cell disease through three years of age. J Pediatr Psychol. 2002;27(3):235–44.

138. Steen RG, Xiong X, Mulhern RK, Langston JW, Wang WC. Subtle brain abnormalities in children with sickle cell disease: relationship to blood hematocrit. Ann Neurol. 1999 Mar;45(3):279–86.

139. Hollocks MJ, Kok TB, Kirkham FJ, Gavlak J, Inusa BP, DeBaun MR, et al. Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia. J Int Neuropsychol Soc. 2012 Jan;18(1):168–73.

140. Schatz J, Finke R, Roberts CW. Interactions of biomedical and environmental risk factors for cognitive development: a preliminary study of sickle cell disease. J Dev Behav Pediatr. 2004 Oct;25(5):303–10.

141. King A, Rodeghier M, Panepinto J, Strouse J, Casella J, Quinn C, et al. Silent Cerebral Infarction, Income and Grade Retention among Students with Sickle Cell. Am J Hematol. 2014;2–28.

142. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. Blood. 2004 Jul 15;104(2):336–9.

143. Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica. 2007 Jul;92(7):905–12.

144. Cherry MG, Greenhalgh J, Osipenko L, Venkatachalam M, Boland A, Dundar Y, et al. The clinical effectiveness and cost-effectiveness of primary stroke prevention in children with sickle cell disease: a systematic review and economic evaluation. Health Technol Assess. 2012 Jan;16(43):1–129.

145. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med. 2005 Dec 29;353(26):2769–78.

146. Kawadler JM, Clark CA, McKinstry RC, Kirkham FJ. Brain atrophy in paediatric sickle cell anaemia: findings from the silent infarct transfusion (SIT) trial. Br J Haematol. 2016;

147. Puffer E, Schatz J, Roberts CW. The association of oral hydroxyurea therapy with improved cognitive functioning in sickle cell disease. Child Neuropsychol. 2007 Mar;13(2):142–54.

148. Pashankar FD, Manwani D, Lee MT, Green NS. Hydroxyurea Improves Oxygen Saturation in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2015 Apr;37(3):242–3.

149. Marshall MJ, Bucks RS, Hogan AM, Hambleton IR, Height SE, Dick MC, et al. Auto-adjusting positive airway pressure in children with sickle cell anemia: results of a phase I randomized controlled trial. Haematologica. 2009;94(7):4–8.

150. Howard J, Inusa B, Liossi C, Jacob E, Murphy PB, Hart N, et al. Prevention of Morbidity in sickle cell disease - qualitative outcomes, pain and quality of life in a randomised cross-over pilot trial of overnight supplementary oxygen and auto-adjusting continuous positive airways pressure (POMS2a): study protocol for a. Trials. Trials; 2015;16(1):376.