Chapter 8

Neurological Complications and MRI

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Additional information is available at the end of the chapter

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Abstract

Cerebrovascular diseases (cerebral infarction, intracranial haemorrhage and vasculopathy) are common manifestations of sickle cell disease (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 a 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 (CBF) measurement, can provide 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, neuropsychology

1. Introduction

Sickle cell disease (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 and 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 magnetic resonance imaging (MRI) in patients with no focal neurological deficit, but is associated with

cognitive difficulties [8] that families often report. SCI can develop very early in life, with rates between 11 and 15% in children less than 2 years [9–11] and progressive accrual throughout childhood and adolescence [11, 12] and into adulthood.

2. Pathophysiology of cerebrovascular ischaemic events

Clinical stroke is defined as a focal neurological event lasting more than 24 hours and is usually permanent, whereas 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 HbSβ^0-thalassaemia genotypes are at highest risk, although stroke has been documented in children with HbSS 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 occurs, 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 (TCD) may be used to screen for high cerebral blood flow (CBF) 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], 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 [9, 30, 32, 33]. In children with evidence of SCI on MRI, there is a 14-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].

3. 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/s), conditional TCD velocities (170–200cm/s) and abnormal velocities (>200cm/s) [43]. The Stroke Prevention (STOP) trial randomised children with abnormal TCD velocities (>200 cm/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/s [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 the increased stroke risk, as TCD studies in adults with HbSS find lower velocities than in children and cannot accurately stratify the 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.

4. 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.

4.1. 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].

4.2. MRI findings

4.2.1. 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. SCI is described for the silent infarct transfusion (SIT) trial [37, 61] as an 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 an abnormal exam that could not be explained by the location of the brain lesion [62]. Many studies describe a localisation 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].

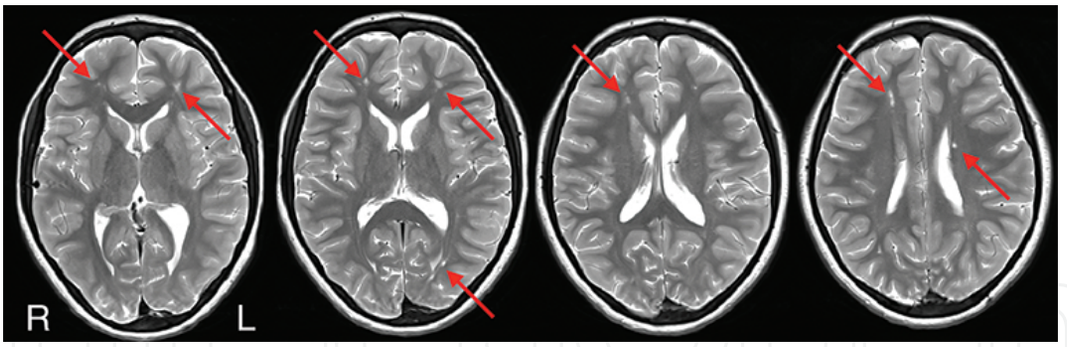

Figure 1. An example of SCI in a 12-year-old boy with HbSS.

4.2.2. Progression of SCI

Several longitudinal studies have shown the 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 and 48 months of age had SCI [9]; 3/23 children (13%) at an average age of

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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**).

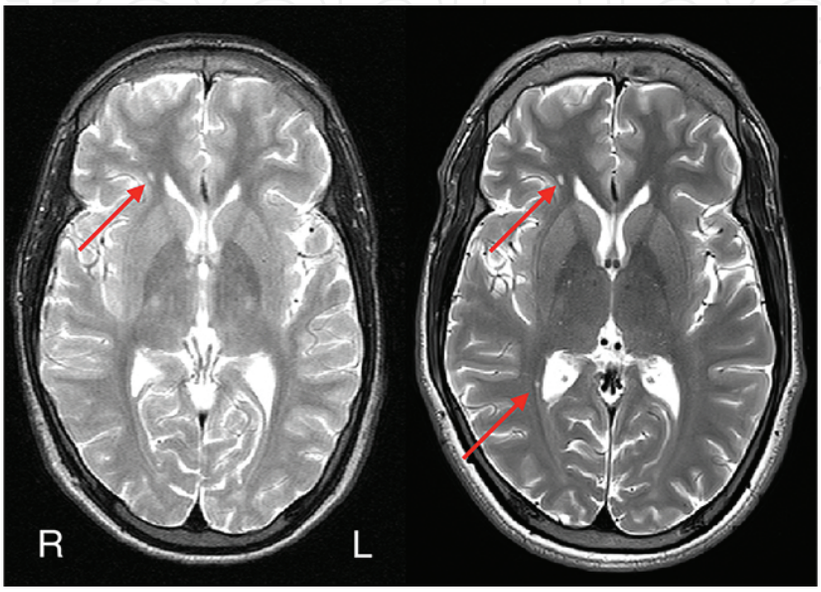

Figure 2. Serial imaging of a male with HbSS. Patient was 17 years old on T2-weighted image from 2001 (left)—showing a small right frontal SCI. Patient was 28 years old on T2-weighted image from 2013 (right)—showing no progression in size of original right frontal SCI but evidence of new SCI in the right peritrigonal region.

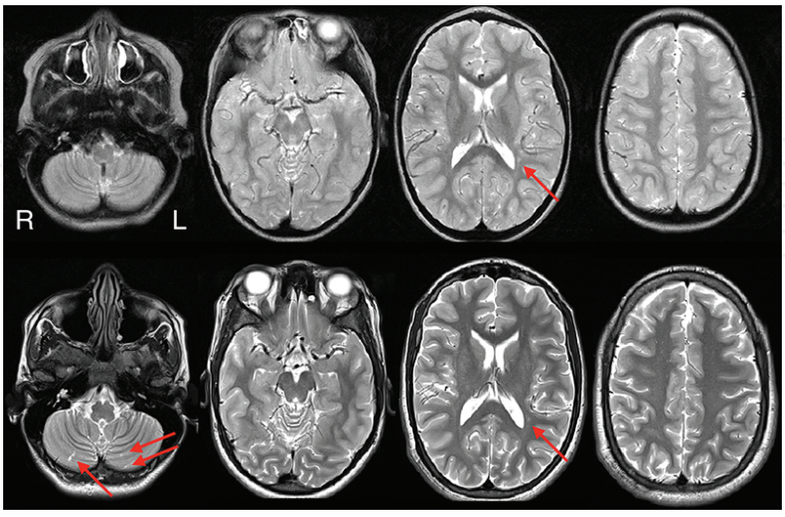

Figure 3. Serial imaging of a male with HbSS. Patient was 14 years old on T2-weighted image from 2002 (top panel)—showing a small left peritrigonal SCI. Patient was 26 years old on T2-weighted image from 2013 (bottom panel)—showing no progression in size of original SCI, but evidence of new SCI in both cerebellar hemispheres.

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.

4.2.3. 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.

4.2.4. 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 cyclosporine use for nephrotic syndrome [77], as well as after acute chest syndrome [78, 79]. Acute bilateral border-zone 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].

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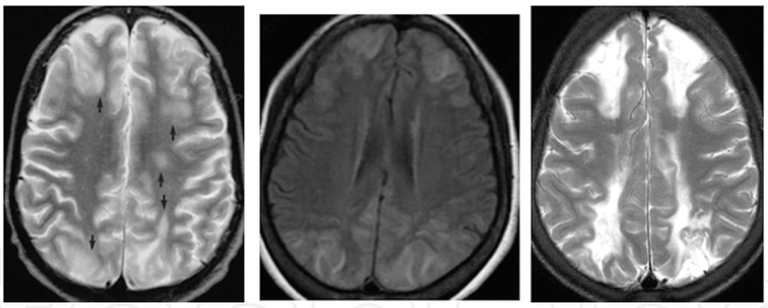

Figure 4. Left: Signal change in the grey and white matter (arrows; posterior reversible encephalopathy syndrome) in a 9-year-old boy with HbSS and nephrotic syndrome who had seizures after cyclosporin therapy. Middle: Bilateral borderzone ischaemia in a 25-year-old woman with HbSS who collapsed with 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.

5. 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 advanced MRI sequences for quantitative analyses have been published, providing further insight into the pathophysiology and progression of neurological complications.

5.1. 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]. Decrease in volume of specific subcortical structures (e.g. hippocampus, amygdala, globus pallidus, caudate and 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 et al. [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 (HC) [87].

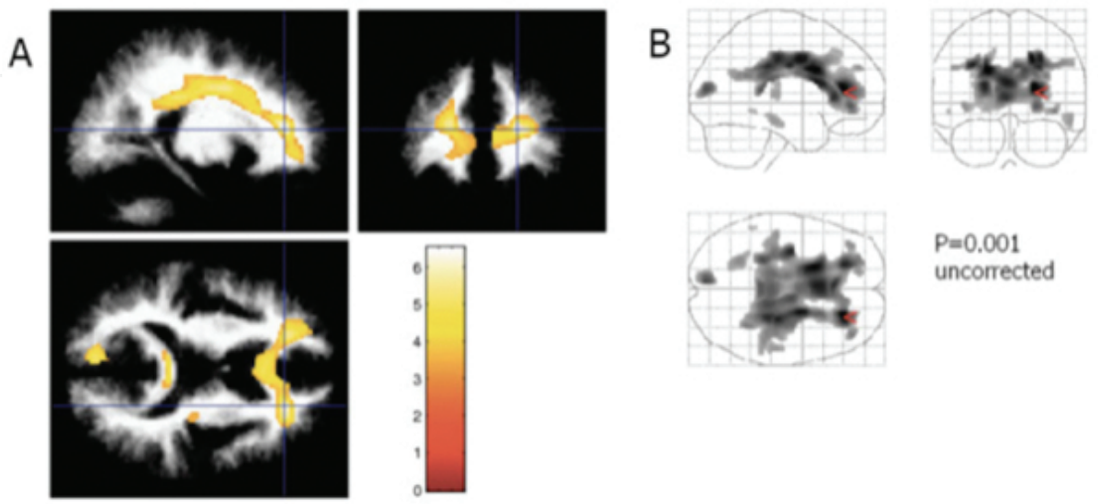

Figure 5. Voxel-based morphometry study showing decreased white matter density extending bilaterally from the anterior frontal lobes along the ventricles to parieto-occipital lobes (image taken with permission from Baldeweg et al. [86]).

5.2. 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 six directions [88], unlike ADC maps from DWI data that only require three directions, by a diffusion tensor, a mathematical model usually visualised 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, organisation 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 analyse 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 direction of maximum diffusion from contiguous voxels [91].

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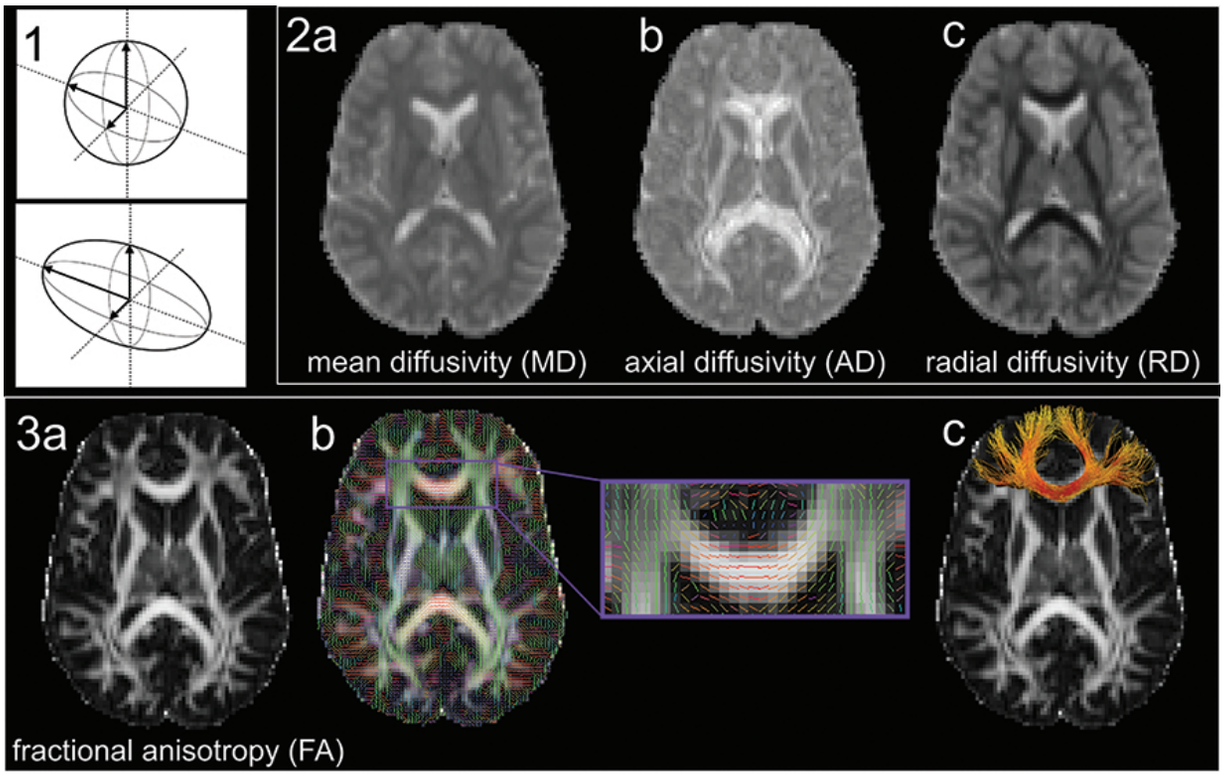

Figure 6. Diffusion tensor imaging. (1) The diffusion tensor model showing ellipsoids representing voxel with isotropic diffusion (top) and anisotropic diffusion (bottom). (2) Diffusivity maps showing (a) mean diffusivity (b) axial diffusivity and (c) radial diffusivity. (3) (a) Fractional anisotropy 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 and 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, whereas 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, whereas 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 (SpO_2) and haemoglobin and RD in the anterior corpus callosum [96] (**Figure 7**).

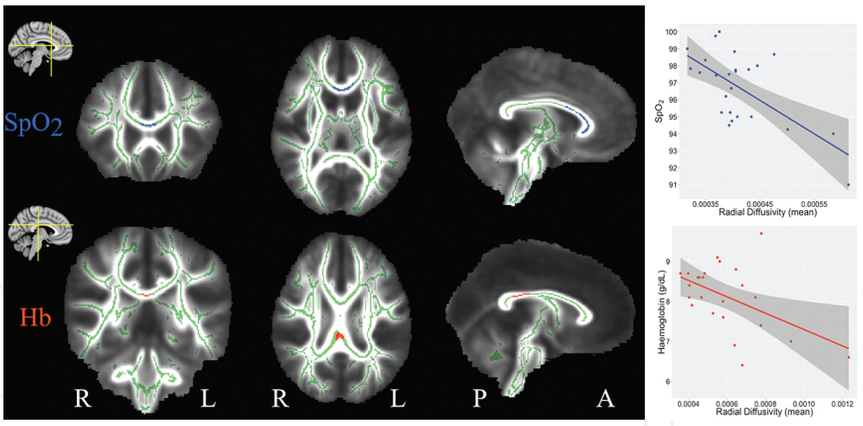

Figure 7. Results from a recent DTI-TBSS study [96], showing the white matter 'skeleton' (green) and significant correlations between RD and daytime peripheral oxygen saturation (blue) and haemoglobin (red).

5.3. 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) has 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 characterise the full haemodynamic behaviour within a voxel. Unpublished data from a London cohort (n=39 patients) with multiple inflow time data confirms global elevated CBF compared to a previously published reference range for healthy children [1]. This study also shows significant correlations with oxygen saturation and haematocrit with CBF in the anterior, middle and posterior cerebral arteries.

5.3.1. 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.

6. 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 neuropsychological function [108].

6.1. General intelligence

Full-scale intelligence quotient (IQ) is the most commonly reported and widely studied standardised measure of general cognitive ability in SCD. Chodorkoff and Whitten [2] (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], whereas others found patients had lowered intelligence scores than matched controls [109–112].

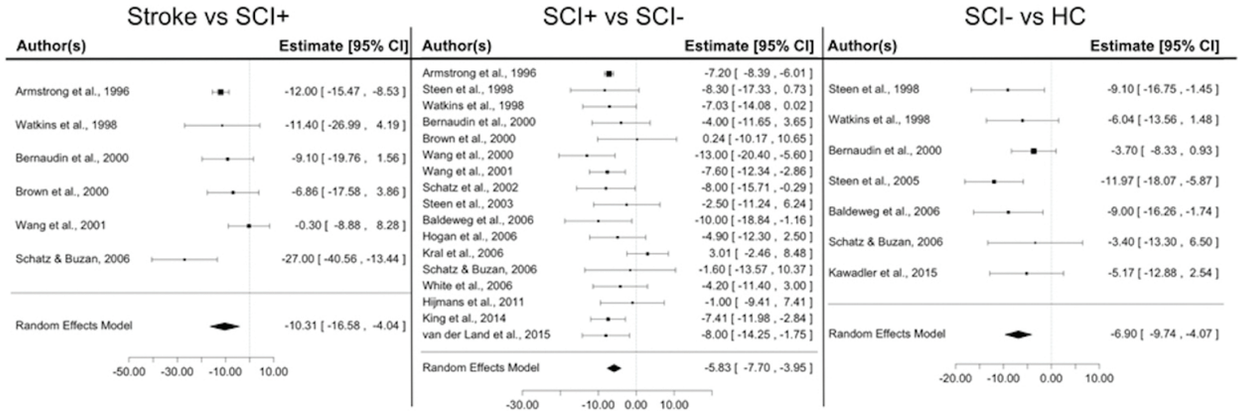

Figure 8. Forest plots of mean differences between SCD patients categorised by MRI status: stroke, silent cerebral infarct (SCI+), no evidence of SCI (SCI−) and healthy controls. Mean differences (estimates) were significant between patients with history of stroke vs. SCI+ (left panel), SCI+ vs. SCI− (middle panel) and SCI− vs. HC (right panel). CI: confidence interval [3].

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 evi-

dence 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**).

6.1.1. 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 are 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].

6.2. Executive functioning

Due to the localisation 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 the 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], whereas 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].

6.3. 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].

7. 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-immunisation and infection. Regular blood transfusion also prevents reinfarction in those with SCI, but the number needed 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].

8. 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 considered valuable tools for diagnosis and management of acute CNS events, but only relatively recently the role of quantitative neuroimaging has 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.

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