

# Magnetic resonance imaging in pediatric sickle cell anemia (Review)

XINXIAN ZHANG, CHENGLONG LI and QIANCHENG LI

Department of Radiology, Xuzhou Children's Hospital, Xuzhou, Jiangsu 221002, P.R. China

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**Abstract.** Sickle cell disease is the result of altered genetic make up due to hereditary encounter and its form as homozygous sickle cell anemia is the most common and severe. The disease is characterized by chronic anemia, recurrent pain crises and vascular occlusion. Neurologically, there is a high incidence of stroke in childhood, as well as cognitive dysfunction. Newborn screening programmes and preventative treatments have allowed a much longer lifespan. However, recently, neurological research has shifted to characterizing more subtle aspects of brain development and functioning that may be critically important to the individual's quality of life. The present review article examines the neurological and neurocognitive complications of sickle cell disease, and discusses the importance of magnetic resonance imaging scans in the management of the disease.

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## 1. Introduction

Hemoglobin is an iron-containing oxygen-transport protein in the red blood cells (RBCs) of humans (1). Normal hemoglobin transports oxygen to the tissues; however, inherited

sickle hemoglobin (HbS) gene has less affinity for oxygen as compared to normal haemoglobin (2). Furthermore, when oxygen is released in RBCs containing HbS, the hemoglobin molecules become polymerized into dense, elongated sickled cells. The process is irreversible even in the conditions of continued exposure to additional oxygen. The irreversible sickling cells (ISCs) form the essential underpinning of the major pathologies of the sickle cell disease (SCD) - notably hemolytic anemia, vaso-occlusion and recurrent pain crises (3).

Vaso-occlusion and chronically impaired blood flow constitute the basis for the most life-threatening clinical aspects of SCD, including overt and silent strokes, acute chest syndrome, pulmonary hypertension, kidney damage and the most frequent event, acute painful crises. Vasculopathy is a prominent feature in SCD, involving several organs (3). The most commonly affected areas are medium and large vessels of the spleen, umbilical vessels, pulmonary arterial tree and circle of Willis, resulting in serious complications, including autosplenectomy, growth restriction, pulmonary disease and ischaemic stroke.

## 2. Cerebral ischaemic events associated with SCD

*Overt stroke.* Clinical stroke is defined as a focal neurological event lasting over 24 h and is usually permanent, while transient ischaemic events are focal neurological events lasting less than 24 h (i.e., there is a full clinical recovery) (4). Reversible ischaemic neurological deficits last over 24 h, but recover fully. None of these clinical definitions require neuroimaging confirmation. Overt stroke is part of the natural history in children with SCD (5). Those with HbSS and HbS $\beta$ 0-thalassaemia genotypes are at highest risk, although stroke has been documented in children with HbSC and HbS $\beta$ <sup>+</sup>-thalassaemia genotypes (6). Stroke may occur as early as 6-12 months (7) when HbF decreases and HbS begins to be synthesized. The first decade of life, when the onset of stroke typically occurs, appears to constitute a 'critical period' for neurologic complications and subsequent neurocognitive morbidity (8). It has been reported that without prophylactic blood transfusions, approximately 5-11% of children would definitely experience a clinical stroke during childhood (9).

Strokes can be classified into infarction due to cerebral ischaemia from arterial or venous compromise, or haemorrhage. Ischaemic stroke accounts for 70-80% of all cerebrovascular episodes, and almost all the episodes in children younger than

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*Correspondence to:* Dr Chenglong Li, Department of Radiology, Xuzhou Children's Hospital, 18 Sudibei Road, Xuzhou, Jiangsu 221002, P.R. China  
E-mail: prk643@163.com

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15 years and adults older than 30 years. Intracranial haemorrhage typically occurs between 20 and 30 years of age (10). Death from a haemorrhagic event is more common than with ischaemic infarction, due to associated intracranial hypertension and cerebral herniation. Overt stroke is usually associated with large vessel arterial disease, with evidence of stenosis, or narrowing, of internal carotid arteries and anterior cerebral and middle cerebral arteries of the circle of Willis (11). Other abnormalities observed on arterial imaging, either contrast angiography or magnetic resonance angiography (MRA) included mainly moyamoya syndrome, occlusion and venous sinus thrombosis (12).

The pathophysiology of arterial vasculopathy is multifactorial. The body responds to anaemia by elevating cerebral blood flow velocity that can cause injury to the endothelial cells lining the vascular wall (13). Increased cerebral blood flow velocity results from adaptive vasodilation of vessels to match metabolic demand, causing a reduction in cerebrovascular reserve. Further demand when the metabolic rate is high (e.g., fever) or when there is a decrease in oxygen delivery (e.g., from worsening anaemia) may cause large and small vessel injury/ischaemia (14). Occlusion of small vessels by ISCs can produce microcirculatory ischaemia, especially in 'borderzones', where the blood flow may be lower in the context of large vessel disease and relative hypotension (15).

Low haemoglobin, high white blood cell count, previous transient ischaemic attack, hypertension, history of acute chest syndrome, high TCD velocities and low haemoglobin oxygen saturation are recognized risk factors for ischaemic stroke in SCD (16-18). Other precipitators for infarction include a painful or acute chest crisis, infection or systemic illness, short-term acute severe anaemia and obstructive sleep apnoea (sleep-disordered breathing). The most common neurological symptom following a cerebrovascular event is the onset of hemiparesis, along with dysphasia and difficulty in walking. Visual field deficits and ataxia may be detected after posterior circulation territory infarction. In 10-33% of cases, focal seizures are also evident with the onset of symptoms relating to ischaemic infarction (19). 'Soft neurological signs' may be detected by careful neurological examination in those with and without a history of previous clinical stroke or seizures.

Silent cerebral infarction (SCI) occurs more frequently than overt stroke, with up to 35% of children showing evidence of SCI. Diagnosis was made using magnetic resonance imaging (MRI) and a lesion was identified in two planes of a scan with no focal neurological deficit lasting over 24 h (20,21). In children with evidence of SCI on MRI, there is a 14-fold increase in the risk of clinical stroke and further lesions observed on MRI (22). Known risk factors for SCI are decreased rate for pain crises, history of seizures, increased leukocyte count and Senegal  $\beta$ -globin haplotype, but also low baseline haemoglobin, male gender and higher baseline systolic blood pressure. SCI by definition is clinically silent, thus timing is unknown; however, it has been postulated that brain damage is the result of recurrent micro-infarctions and recurrent acute hypoxic damage, secondary to severe anaemia, diminished pulmonary function, splenic sequestration, aplastic crisis and acute chest syndrome (23).

### 3. Screening programmes available

*RBC transfusions.* Transfusion is now widely used in the short-term management of acute complications of SCD and has a role in the prevention of chronic complications, specifically stroke (24). Transfusions improve the flow properties of the blood by lowering the fraction of HbS via dilution or 'replacing' HbS with HbA. Additionally, transfusions increase the oxygen-carrying capacity of the blood to prevent cerebrovascular events by minimising viscosity of the blood, increasing haematocrit and improving large vessel stenosis (25).

Although blood transfusions are standard in clinical practice in developed countries there are associated complications. Iron may become accumulated in the liver and heart, usually monitored using MRI (26). The possibility that there is an accumulation of iron in the brain is under investigation. Hyperviscosity of the blood may occur following over-transfusion (27). Transfusion reactions, possibility-contaminated blood with viruses such as HIV or hepatitis C, and allo-immunisation, where there is sensitization of RBC antigens, are also possible complications (28).

*Hydroxycarbamide.* Children with SCD who did not receive regular blood were treated with the drug known as hydroxycarbamide (also known as hydroxyurea). The drug acts to inhibit polymerisation of HbS, by increasing the percentage of HbF and decreasing cellular dehydration (29,30), both of which are useful in improving RBC survival. The risk of stroke is lowered by increased levels of HbF, and also by a reduction in white blood cell count and the expression of cell-adhesion molecules associated with vaso-occlusion (29,30). Controlled trials have shown hydroxycarbamide may ameliorate disease severity (i.e., decrease frequency of painful crises, acute chest syndrome and the need for blood transfusion), and is useful in reducing the risk of first stroke (31).

*Bone marrow transplantations.* The only successful treatment described in SCD thus far is bone marrow transplantation, which is a potential option for children with a matched sibling donor (32). This therapy is considered when there are severe complications (e.g., stroke) and there is urgent dependence on blood transfusions. Data suggested 92-94% survival, with 82-86% event-free rate post-transplantation (33). Induced pluripotent stem cells, as well as gene therapy, currently in pre-clinical research may offer promise for the future of SCD treatment (34,35).

*Psychosocial interventions.* Another advantage of newborn screening is the involvement of parents at an early stage as care partners with clinicians managing complications of SCD. Parents and children occasionally have considerable on-going fear of hospital visits and painful crises, and post-traumatic stress disorder in children with SCD often mirrors parents' worries, and has been reported to adversely affect recovery. Early family education of the aspects of the disease (e.g., learning how to palpate the spleen to feel for enlargement) and identifying lifestyle factors (e.g., reduced fluid intake) that increase the risks of vaso-occlusive episodes, is critical to achieve the best

possible comprehensive care. It is also of crucial importance to educate adolescents concerning the potential severity of their disease and how to manage their chronic illness as they start living independently from relatives. The transition from paediatric to adult care has been under scrutiny, requiring 'uninterrupted, coordinated, appropriate care' and for healthcare providers to establish multidisciplinary teams offering education, psychosocial support and vocational training (36).

#### 4. Neuroimaging in sickle cell anemia

Successful medical interventions have allowed the childhood mortality rate of SCD to decrease and life expectancy to increase. However, cerebrovascular events in childhood are relatively common and can significantly limit the full potential of a developing child, adolescent or adult. MRI is a safe, non-invasive, useful technique for the diagnosis and management of SCD-related cerebral infarction, cerebrovascular disease and other neurological abnormalities. Conventional structural MRI sequences are routinely used in hospital settings, while more advanced MRI sequences are becoming more commonplace in research institutes.

#### 5. MRI and neuroimaging findings

MRI studies have showed that the majority of overt stroke and SCI occur from a distribution of the internal carotid artery, and pathologies are frequently observed in tissue within the anterior cerebral and middle cerebral arterial distribution. MRA studies confirmed this pattern, as publications have reported stenosis (narrowing) or occlusion of these vessels with relative sparing of the posterior circulation, other than tortuosity. Stroke and SCI from vertebrobasilar artery circulation occlusion are less common, but have been reported. Cerebral infarction is rarely fatal, however approximately 11% of patients with genotype HbSS may experience a clinically apparent stroke by age 20, and up to 24% by age 45. SCI may develop very early in life, with rates between 11 and 15% in children younger than 2 years of age (37). By 6 years of age, at least 25% of children are likely to have shown evidence of SCI, and up to 37% by 14 years of age (38,39).

#### 6. Radiological findings

Although stroke is identified by the abrupt onset of neurological deficit, the term 'covert stroke', or SCI was first described in the Cooperative Study in Sickle Cell Disease (CSSCD) to radiologically define an abnormal MRI resulting in the absence of overt neurological symptoms (40). SCI may be concurrent with neurological symptoms lasting under 24 h, but must occur in the absence of a focal neurological deficit compatible with the anatomic location of the MRI lesion. A previous study described localization of SCI to be deep white matter, particularly in the arterial border zones, where flow is more vulnerable (41). Brain injury in children with SCD also extends to concurrent vasculopathy and moyamoya syndrome observed on MRA, as well as generalised and focal cortical atrophy (42).

#### 7. Neurocognitive findings

Brown *et al* suggested some factors that accumulate over time, and elucidated the compromised intellectual functioning in children with SCD (43). Recurrent micro-infarctions of the central nervous system, possibly undetected by screening measures, may affect general functioning. Additionally, conditions secondary to anaemia, such as diminished pulmonary function and chronic hypoxic damage can cause brain damage. Although the exact mechanisms underpinning cognitive dysfunction in SCD remain unknown, there is substantial literature characterizing the effect of SCD on cognition, particularly effects on general intelligence (44,45), and associated executive functions are also hampered during SCD (46,47). Furthermore, a study of neurologically intact adults with SCD showed deficits in processing speed, working memory and other executive functions compared to controls (48).

*Neurocognitive biomarkers.* Some indices of disease severity may be exploited as biomarkers of cognitive functioning. The most commonly reported marker is anaemia, usually measured by haematocrit or haemoglobin levels. Low daytime oxygen saturation may reflect state of chronic hypoxia, and haemoglobin levels are likely to act as a surrogate marker for reduced oxygen delivery to the brain (49). In neurologically intact children (i.e., without cerebrovascular abnormalities), anaemia severity has shown moderate to large correlations with intelligence, and may even be related to verbal short-term memory and severity of cognitive impairments in children with SCI.

#### 8. Conclusion

Neurological and neurocognitive complications associated with SCD were reviewed. Research has shown that ischaemic events significantly affect brain development and function. However, in children with no imaging evidence of ischaemic stroke or SCI, the chronic disease-specific effects, such as anaemia and hypoxia, have on the brain remains to be identified. The above studies indicate that MRI imaging is important in the use of quantitative MRI analysis as well as neurological differences between patients and their siblings in order to underpin the effect of chronic illness.

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