Magnetic resonance imaging in pediatric sickle cell anemia (Review)

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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.

Contents

1. Introduction
2. Cerebral ischaemic events associated with SCD
3. Screening programmes available
4. Neuroimaging in sickle cell anemia
5. MRI and neuroimaging findings
6. Radiological findings
7. Neurocognitive findings
8. Conclusion

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

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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 HbSβ0-thalassaemia genotypes are at highest risk, although stroke has been documented in children with HbSC and HbSβ+-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

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 β-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 improvise 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 dehydration136, 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 rated 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.

References

1. Vasseur C and Baudin-Creuza V: Role of alpha-hemoglobin molecular chaperone in the hemoglobin formation and clinical expression of some hemoglobinopathies. Transfus Clin Biol 22: 49-57, 2015 (In French).
2. Seakins M, Gibbs WN, Milner PF and Bertles JF: Erythrocyte Hb-S concentration. An important factor in the low oxygen affinity of blood in sickle cell anemia. J Clin Invest 52: 422-432, 1973.
3. Hebbel RP, Osarogiagbon R and Kaul D: The endothelial biology of sickle cell disease: inflammation and a chronic vasculopathy. Microcirculation 11: 129-151, 2004.
4. Lindsay P, Furie KL, Davis SM, Donnan GA and Norrving B: World Stroke Organization global stroke services guidelines and action plan. Int J Stroke 9 (Suppl A100): 4-13, 2014.
5. Pegelow CH, Macklin EA, Moser FG, Wang WC, Bello JA, Miller ST, Vichinsky EP, DeBaun MR, Guarini L, Zimmerman RA, *et al*: Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. Blood 99: 3014-3018, 2002.

6. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH and Gill FM: Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 91: 288-294, 1998.

7. Tarazi RA, Grant ML, Ely E and Barakat LP: Neuropsychological functioning in preschool-age children with sickle cell disease: the role of illness-related and psychosocial factors. Child Neuropsychol 13: 155-172, 2007.

8. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE and Serjeant GR: Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 120: 360-366, 1992.

9. Moser FG, Miller ST, Bello JA, Pegelow CH, Zimmerman RA, Wang WC, Ohene-Frempong K, Schwartz A, Vichinsky EP, Gallagher D, 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 17: 965-972, 1996.

10. Ohene-Frempong K: Stroke in sickle cell disease: demographic, clinical, and therapeutic considerations. Semin Hematol 28: 213-219, 1991.

11. McLaughlin JF and Ballas SK: High mortality among children with sickle cell anemia and overt stroke who discontinue blood transfusion after transition to an adult program. Transfusion: Nov 23, 2015 (Epub ahead of print).

12. Sébire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, Husson B, Williams AN, Wade A and Kirkham FJ: Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. Brain 128: 477-489, 2005.

13. Hess DC, Adams RJ and Nichols FT III: Sickle cell anemia and other hemoglobinopathies. Semin Neurol 11: 314-328, 1991.

14. Prohovnik I, Hurlet-Jensen A, Adams R, De Vivo D and Pavlakis SG: Hemodynamic etiology of elevated flow velocity and stroke in sickle-cell disease. J Cereb Blood Flow Metab 29: 803-810, 2009.

15. Kirkham FJ, Calamante F, Bynevelt M, Gadian DG, Evans JP, Cox TC and Connelly A: Perfusion magnetic resonance abnormalities in patients with sickle cell disease. Ann Neurol 49: 477-485, 2001.

16. Kirkham FJ, Hewes DK, Prengler M, Wade A, Lane R and Evans JP: Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet 357: 1656-1659, 2001.

17. Quinn CT and Ahmad N: Clinical correlates of steady-state oxyhaemoglobin desaturation in children who have sickle cell disease. Br J Haematol 131: 129-134, 2005.

18. Quinn CT, Variste J and Dowling MM: Haemoglobin oxygen saturation is a determinant of cerebral artery blood flow velocity in children with sickle cell anaemia. Br J Haematol 145: 500-505, 2009.

19. Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP and Martin-Rendon E: Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. Cochrane Database Syst Rev 4: CD007888, 2014.

20. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E and Kirkham FJ: Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood 119: 4587-4596, 2012.

21. Steen RG, Fineberg-Buchner C, Hankins G, Weiss L, Prifitera A and Mulhern RK: Cognitive deficits in children with sickle cell disease. J Child Neurol 20: 102-107, 2005.

22. Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, Bello J, Zimmerman RA, Adams RJ, Brambilla D, et al: Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. Arch Neurol 58: 2017-2021, 2001.

23. Quinn CT, McKinstry RC, Dowling MM, Ball WS, Kraut MA, Casella JF, Dlamini N, Ichord RN, Jordan LC, Kirkham FJ, et al: Acute silent cerebral ischemic events in children with sickle cell anemia. JAMA Neurol 70: 1-8, 2012.

24. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, Abboud M, Gallagher D, Kutlar A, Nichols FT, 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 339: 5-11, 1998.

25. Wayne AS, Kevy SV and Nathan DG: Transfusion management of sickle cell disease. Blood 81: 1109-1123, 1993.

26. Ballas SK: Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. Semin Hematol 38 (Suppl 1): 30-36, 2001.

27. Wang W and Dwan K: Blood transfusion for preventing primary and secondary stroke in people with sickle cell disease. Cochrane Database Syst Rev 11: CD003146, 2013.

28. Smith-Whitley K and Thompson AA: Indications and complications of transfusions in sickle cell disease. Pediatr Blood Cancer 59: 358-364, 2012.

29. Adekile AD, Yacoub F, Gupta R, Sinan T, Haider MZ, Habeeb Y, Al-Bloushi M and Moosa A: Silent brain infarcts are rare in Kuwaiti children with sickle cell disease and high Hb F. Am J Hematol 70: 228-231, 2002.

30. Benkerrou M, Delarche C, Brahimi L, Fay M, Vilmer E, Elion J, Gougerot-Pocidalo MA and Elbim C: Hydroxyurea corrects the dysregulated L-selectin expression and increased H(2)O(2) production of polymorphonuclear neutrophils from patients with sickle cell anemia. Blood 99: 2297-2303, 2002.

31. Lagunju IA, Brown BJ and Sodeinde OO: Stroke recurrence in Nigerian children with sickle cell disease treated with hydroxyurea. Niger Postgrad Med J 20: 181-187, 2013.

32. Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC, Davies SC, Ohene-Frempong K, Bernaudin F, Matthews DC, et al: Bone marrow transplantation for sickle cell disease. N Engl J Med 335: 369-376, 1996.

33. Bhatia M and Walters MC: Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. Bone Marrow Transplant 41: 109-117, 2008.

34. Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, Beard C, Brambrink T, Wu LC, Townes TM, et al: Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science 318: 1920-1923, 2007.

35. Rees DC, Williams TN and Gladwin MT: Sickle-cell disease. Lancet 376: 2018-2031, 2010.

36. Jordan L, Swerdlow P and Coates TD: Systematic review of transition from adolescent to adult care in patients with sickle cell disease. J Pediatr Hematol Oncol 35: 165-169, 2013.

37. Wang WC, Pavlakis SG, Helton KJ, McKinstry RC, Casella JF, Adams RJ and Rees RC; BABY HUG Investigators: MRI abnormalities of the brain in one-year-old children with sickle cell anemia. Pediatr Blood Cancer 51: 643-646, 2008.

38. Kwiatkowski JL, Zimmerman RA, Pollock AN, Seto W, Smith-Whitley K, Shults J, Blackwood-Chirchir A and Ohene-Frempong K: Silent infarcts in young children with sickle cell disease. Br J Haematol 146: 300-305, 2009.

39. Bernaudin F, Verlhac S, Coïc L, Lesprit E, Brugières P and Reinert P: Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler. Pediatr Radiol 35: 242-248, 2005.

40. Casella JF, King AA, Barton B, White DA, Noetzel MJ, Ichord RN, Terrill C, Hirtz D, McKinstry RC, Strouse JJ, et al: Design of the silent cerebral infarct transfusion (SIT) trial. Pediatr Hematol Oncol 27: 69-89, 2010.

41. Kral MC, Brown RT, Connelly M, Curé JK, Besenski N, Jackson SM and Abboud MR: Radiographic predictors of neurocognitive functioning in pediatric Sickle Cell disease. J Child Neurol 21: 37-44, 2006.

42. Emam AT, Ali AM and Babikr MA: Magnetic resonance spectroscopy of the brain in children with sickle cell disease. Neurosciences (Riyadh) 14: 364-367, 2009.

43. Brown RT, Armstrong FD and Eckman JR: Neurocognitive aspects of pediatric sickle cell disease. J Learn Disabil 26: 33-45, 1993.

44. Gold JI, Johnson CB, Treadwell MJ, Hans N and Vichinsky E: Detection and assessment of stroke in patients with sickle cell disease: neuropsychological functioning and magnetic resonance imaging. Pediatr Hematol Oncol 25: 409-421, 2008.

45. van der Land V, Hijmans CT, de Ruiter M, Mutsaerts HJ, Cnossen MH, Engelen M, Majoie CB, Nederveen AJ, Grootenhuis MA and Fijnvandraat K: Volume of white matter hyperintensities is an independent predictor of intelligence quotient and processing speed in children with sickle cell disease. Br J Haematol 168: 553-556, 2014.

46. Schatz J, Brown RT, Pascual JM, Hsu L and DeBaun MR: Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. Neurology 56: 1109-1111, 2001.

47. Berg C, Edwards DF and King A: Executive function performance on the children's kitchen task assessment with children with sickle cell disease and matched controls. Child Neuropsychol 18: 432-448, 2012.

48. Vichinsky EP, Neumayr LD, Gold JI, Weiner MW, Rule RR, Truran D, Kasten J, Eggleston B, Kesler K, McMahon L, et al; Neuropsychological Dysfunction and Neuroimaging Adult Sickle Cell Anemia Study Group: Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA 303: 1823-1831, 2010.

49. Thompson RJ Jr, Gustafson KE, Bonner MJ and Ware RE: Neurocognitive development of young children with sickle cell disease through three years of age. J Pediatr Psychol 27: 235-244, 2002.