ABSTRACT

Sickle cell disease is the most common hereditary hemoglobinopathy, which results in abnormally shaped and rigid red blood cells. These sickle-shaped red blood cells cause vaso-occlusion and ischemic phenomena that can affect any organ in the body. As a common cause of disability, the neurological manifestations of sickle cell disease are particularly important. Neuroimaging has a crucial role in the diagnosis, management, and prevention of the complications of sickle cell disease. These complications can affect the brain parenchyma, vasculature, and skull and can be ascribed directly or indirectly to a vasculopathy of small and large vessels. Vaso-occlusion can cause ischemic stroke. Ischemic damage in the absence of an acute neurological deficit, and therefore only apparent on neuroimaging, is termed silent cerebral ischemia. Weakening of the arterial walls can cause aneurysms. In its most severe form, a vasculopathy of the terminal internal carotid arteries can progress to moyamoya syndrome, characterized by steno-occlusive disease and the formation of friable collateral arteries. Rupture of aneurysms or friable collateral arteries is a potential cause of intracranial hemorrhage. The skull and vertebrae may be affected by extra-medullary hematopoeisis, due to severe anemia, or iron deposition, due to chronic red blood cell transfusion. Impaired blood supply to bone is associated with osteomyelitis and osteonecrosis. Fat embolization syndrome is a rare complication of osteonecrosis, which may cause devastating neurological impairment. Awareness and early recognition of the diverse manifestations of sickle cell disease on neuroimaging is crucial to ensure optimal treatment in a complex patient cohort.

Keywords: Fat embolization syndrome, moyamoya syndrome, pediatric stroke, sickle cell disease, vasculopathy.

Introduction

Sickle cell disease (SCD) is the most common genetic hemoglobinopathy and is characterized by a chronic anemia and vasculopathy that causes vaso-occlusion and multiorgan ischemic damage.

The cerebral complications of sickle disease are particularly important as they are a common cause of disability, often at a young age. Imaging is central in the screening, diagnosis, and treatment optimization of patients with SCD. Awareness of the varied neurological complications of SCD, which have significant overlap in their clinical presentation, is vital.

In this review, the manifestations of SCD seen on imaging of the brain are discussed.

Pathophysiology of SCD

SCD is an autosomal recessive disorder caused by a mutation within the β-globin chain of the sickle hemoglobin molecule, HbS. Deoxygenated HbS is prone to polymerization resulting in insoluble crystals. HbS crystals deform the red blood cell (RBC) into a sickle shape, which are relatively rigid and adherent to vascular endothelium. Rigid RBCs are less able to flow through terminal arterioles and capillaries, causing congestion, intravascular sludging, and hemolysis. Adherence of RBCs to endothelium and circulating extracellular hemoglobin causes a vasculopathy due to a cascade of endothelial activation, vasoconstriction, intimal hyperplasia, and smooth muscle proliferation. RBC stasis in a proinflammatory and prothrombotic milieu brings about tissue ischemia and reperfusion injury.

Vaso-occlusion, the lower oxygen affinity of HbS, and physiological stress, such as sepsis, act together to promote further sickling. Consequently, a vicious cycle is instigated that culminates in an acute sickle crisis and ischemic damage that can affect any organ of the body.

Depending on various clinical, genetic, and rheologic factors, the endothelial damage may give rise to vascular stenosis, ectasia, or aneurysm formation. The clinical course of SCD is notoriously variable. This variability underlines the importance of neuroimaging to diagnose, or identify those at elevated risk, of suffering from the neurological complications of SCD.

Cerebral Manifestations of SCD

Ischemic Stroke

Ischemic stroke is a potentially devastating complication of SCD and is a major cause of cognitive impairment, disability, and death. SCD is the second most common cause of childhood stroke after congenital cardiac anomalies. The risk is highest in the first decade of life. Without intervention, 7.4%, 11%, and
A 28-year-old male patient with sickle cell disease presented with a right-sided visual field defect. On MRI, performed the day after presentation, there was hyperintensity on T2-weighted (A) and on B1000 DWI images (B) in the left occipital lobe due to an acute infarct (arrowheads).

Silent Cerebral Ischemia

Silent cerebral ischemia (SCI) refers to ischemic damage identified on imaging that does not have a clinical correlate. The lesion should be apparent in two planes and measure at least 3 mm in diameter on FLAIR imaging. SCI is associated with cognitive impairment and a 14-fold elevated risk of overt ischemic stroke.

Silent cerebral ischemia is more common than overt strokes and is seen in approximately 25% and 39% of patients by the age of 6 and 18 years, respectively. RBC transfusions more than halved the risk of new SCI lesions and overt stroke over a 3-year period. This effect was observed in patients with a normal TCD, suggesting that SCI could be a more sensitive method of identifying children at elevated risk of stroke.

By virtue of being asymptomatic, silent ischemic lesions are not usually imaged in the acute phase and therefore appear...
A 17-year-old female patient with sickle cell disease underwent an MRI scan following consistently high peak velocities on transcranial Doppler. The patient was asymptomatic and no focal neurological deficits were evident on physical examination. T2-weighted (A) and fluid-attenuated inversion recovery (B) imaging revealed multiple foci of mature ischemic damage (arrowheads) within the deep watershed regions in the centrum semiovale bilaterally.

Parenchymal Volume Loss

Even in the absence of focal brain lesions, automated segmentation of volumetric MRI studies of patients with SCD has shown volume loss within the cortex, deep gray structures, and white matter, all of which correlate with reduced cognitive function. Diffusion tensor imaging has also shown reduced white matter tract density and integrity. Notably, the accelerated parenchymal volume loss observed in children with SCI when compared to healthy controls was not ameliorated by chronic RBC transfusion, unlike the risk of acute ischemic stroke. This suggests differences in the pathophysiology of ischemic stroke and atrophy.

As changes in volume, white matter tract integrity, as well as findings on quantitative MRI, such as gray matter T1 shortening, are observed in otherwise normal brains, focal lesions seen on conventional MRI may represent the “tip of the iceberg.” As such, future studies evaluating the association between these findings and the development of clinically significant disease, such as ischemic stroke, will be of great interest.

Moyamoya Syndrome

Endothelial damage and subsequent vasculopathy is a defining feature of SCD. The apex of the internal carotid artery (ICA) and middle cerebral artery (MCA) are particularly susceptible to a progressive steno-occlusive vasculopathy with the development of fragile collaterals. Collaterals arise from the thalamoperforate arteries, lenticulostriate arteries, as well as branches of the external carotid artery that supply the dura and skull base. On catheter angiogram, these collateral vessels appear as a “puff of smoke”—which translates to “moyamoya” in Japanese.

Among patients with SCD who had suffered at least one ischemic stroke, the prevalence of moyamoya syndrome was 43%, although 10.4% of asymptomatic children with SCD also had evidence of a large vessel vasculopathy on MRA. The presence of moyamoya collaterals was associated with 2.4-fold elevated risk of recurrent ischemic stroke.

Serpiginous collateral vessels should be sought on T2-weighted imaging, where they appear as threadflow-related signal voids. Dedicated angiography is required, such as CTA (Fig 3), to accurately evaluate the degree of stenosis and the extent of collateral vessels. The “ivy sign” is indirect evidence of a proximal stenosis and can be seen as hyperintensity on FLAIR and postgadolinium enhancement caused by slow flow and compensatory dilatation of pial vessels (Fig 4).

Treatment of moyamoya syndrome relies upon optimizing the treatment of underlying SCD. Surgical management can be considered in cases of recurrent stroke. There is a wide variety of surgical approaches to revascularization, which can be categorized as either direct or indirect. Both approaches have
different advantages and the choice of procedure depends on the surgical risk and the patient’s vascular anatomy. A direct bypass is possible if there is a suitably large branch of the MCA onto which a branch of the superior temporal artery can be anastomosed (Fig 4). The procedure provides immediate revascularization, which also brings the risk of hyperperfusion syndrome, characterized by headache, focal neurological deficits, and seizures. Indirect methods, such as an encephaloduroartherosynangiosis (EDAS), involves suturing of the galea associated with the posterior branch of the superficial temporal artery into a linear durotomy from which collateral supply to the cortex may develop (Fig 5). While this procedure is technically less demanding than a direct procedure, reperfusion only occurs when collaterals develop. Optionally, a pial synangiosis may be performed whereby the adventitia is sutured to the pia mater, hastening collateral vessel formation.

The MRA of the EDAS shown in Figure 5 highlights a pitfall in time-of-flight MRA. There are short segments where there is no flow-related vessel enhancement despite the presence of efferent flow indicating bypass patency. This loss of signal is usually a consequence of either slow (increasing saturation effects) or turbulent flow (increasing intravoxel dephasing). These artifacts can be reduced by minimizing the MRA echo time, ideally between 3 and 7 milliseconds, and performing 3D rather than 2D image acquisition. With the tendency of TOF MRA to overestimate stenosity, a CTA can be considered if more accurate assessment is required.

**Intracranial Aneurysms**

Aneurysm rupture is the most common cause of intracranial hemorrhage in SCD patients. Sustained endothelial injury causing vessel wall weakening is the presumed reason for increased prevalence of aneurysms in patients with SCD. While a similar pathophysiology is suggested for moyamoya vasculopathy, one study found little correlation between the two entities, which would suggest some differences in the underlying mechanisms.

Saccular aneurysms are found in routine imaging in approximately 6% of adults and 4% of children. Compared to the general population, SCD patients are more likely to have multiple aneurysms, which are more likely to be within the posterior circulation (5-14% vs. 30%). The ICA is the most commonly involved artery followed by the posterior cerebral artery. Similar to the general population, the vast majority of aneurysms are saccular.

Catheter angiography is the gold-standard for the detection of intracranial aneurysms; however, due to the practical advantages of noninvasive imaging techniques, TOF MRA and CTA are generally preferred (Fig 6). The accuracy of TOF MRA and CTA for unruptured intracranial aneurysms is comparable and generally reported at above 95%.
Fig 4. An MRI scan of a 14-year-old male sickle cell disease patient who suffered multiple infarcts in the right MCA territory revealed right precentral gyrus cortical infarcts (not shown) and small foci of white matter ischemic damage on T2-weighted imaging (A and C). Multiple serpiginous flow-related signal voids on T2-weighted imaging representing thalamoperforate and lenticulostriate collaterals due to a moyamoya vasculopathy were also present. (B) Sulcal hyperintensity due to pial vessel dilatation and collateralization representing the “Ivy sign” was seen on fluid-attenuated inversion recovery imaging. (D) A direct bypass was performed with anastomosis of a posterior branch of the superior temporal artery (open arrowhead) with a distal branch of the right MCA (arrowhead). (E) On a follow-up MRI scan performed 2 years later, T2-weighted imaging showed a reduction in the size and number of the lenticulostriate collaterals.

Fig 5. An 11-year-old female patient with sickle cell disease with severe bilateral terminal internal carotid artery stenoses (open arrowheads) underwent an indirect bypass with an encephaloduroarteriosynangiosis from which multiple small collateral vessels developed. The arrowheads show the diversion of a branch of the superior temporal artery below a craniotomy.

Close follow-up to identify large or enlarging aneurysms is particularly important in the context of SCD where aneurysms are more likely to rupture at smaller sizes when compared to the general population. Among patients with SCD, women between 30 and 39 years of age are at greatest risk of subarachnoid hemorrhage from a ruptured aneurysm.

Aside from discrete saccular aneurysm formation, dilatation of the vertebobasilar system is often seen in the context of SCD and the degree of dilatation was shown to be inversely proportional to hematocrit. Vessel dilatation and tortuosity is potentially a response to a hyperdynamic circulation due to chronic anemia. Intra or extracranial vessel tortuosity, but an otherwise normal brain on MR imaging, was associated with an increased risk of stroke.

Given the greater propensity to rupture at smaller sizes, aneurysm treatment has been suggested for aneurysms greater than 5 mm. Clipping after craniotomy has been the standard of care although endovascular coiling and stenting are becoming increasingly common. Treatment of aneurysms is complicated by their multiplicity, the risk of intraoperative sickling, and hypercoagulability increasing the risk of embolization after endovascular insertion of a permanent device. General measures, such as maintaining preoperative HbS below 30%, avoidance of hypoxia, and the use of nonionic contrast medium, are used to mitigate the risk of periprocedural complications.

**Intracranial Hemorrhage**

SCD patients are at risk of hemorrhage within the parenchymal, subarachnoid, subdural, and extradural compartments.
In a 35-year-old male with sickle cell disease, a surface rendered three-dimensional time-of-flight MR angiogram of the circle of Willis showed multiple incidental aneurysms (arrowheads) in the left terminal internal carotid artery, right MCA, and basilar artery tip.

Fig 6. In a 35-year-old male with sickle cell disease, a surface rendered three-dimensional time-of-flight MR angiogram of the circle of Willis showed multiple incidental aneurysms (arrowheads) in the left terminal internal carotid artery, right MCA, and basilar artery tip.

Intracranial hemorrhage is less common than ischemic stroke; however, when it does occur, it is more likely to be fatal. While the incidence of ischemic stroke is highest in early childhood, the risk of hemorrhage is greatest in early adulthood, where a ruptured aneurysm is the most common cause. Parenchymal hemorrhage may be caused by shearing of friable and maximally dilated collateral vessels. Intra-axial hemorrhage is also seen following hemorrhagic transformation of an acute infarct. Subdural and extradural hemorrhages may complicate bone infarction, which is discussed in more detail in the Bone section.

Irrespective of the compartment, acute blood is hyperattenuating on CT, which decreases over time. MRI, specifically FLAIR, gradient echo imaging, and susceptibility weighted imaging (SWI), is at least as sensitive as CT in detecting acute blood. However, MRI is significantly more sensitive than CT at detecting subacute and chronic blood products. Local susceptibility-induced dephasing causes T2-weighted hypointensity within a parenchymal hematoma, except during the late subacute period when hemoglobin is extracellular. Development of methemoglobin, which causes T1 shortening, occurs in subacute blood. Interpretation of DWI is made difficult by the confounding effects of T2-shine through and T2-guscur in subacute blood. Interpretation of DWI is made difficult by the confounding effects of T2-shine through and T2-guscur in subacute blood. Interpretation of DWI is made difficult by the confounding effects of T2-shine through and T2- gadolinium enhancement. The posterior circulation is more commonly affected due to the reduced sympathetic innervation compared to the anterior circulation, which is important in CBF autoregulation. Much less frequently, cytotoxic edema can occur in PRES, perhaps due to mass effect from the vasogenic edema causing microcirculation compression, or due to severe reduced regional perfusion due to vasoconstriction or vasospasm, which may be partly immune mediated.

PRES is seen on CT as cortical swelling with mainly subcortical hypodensity. While there is a predilection for the parietal and occipital lobes, the watershed regions in the frontal lobes are also commonly involved. Rarely, there is involvement of the basal ganglia or the cerebellum. On MRI, vasogenic edema may give rise to T2-shine through, which is reversible. DWI hyperintensity with corresponding high values on the ADC map implies vasogenic edema. On the other hand, low ADC values imply cytotoxic edema, which implies irreversibility. PRES is seen on CT as cortical swelling with mainly subcortical hypodensity. While there is a predilection for the parietal and occipital lobes, the watershed regions in the frontal lobes are also commonly involved. Rarely, there is involvement of the basal ganglia or the cerebellum. On MRI, vasogenic edema may give rise to T2-shine through, which is reversible. DWI hyperintensity with corresponding high values on the ADC map implies vasogenic edema. On the other hand, low ADC values imply cytotoxic edema, which implies irreversibility.

Fat embolization syndrome (FES) is typically a complication of long-bone fractures caused by fat emboli entering the blood. In SCD, bone marrow infarction causes mobilization of fat globules into the systemic circulation via venous sinusoids within trabecular bone, which can cause microvascular occlusion in any organ. Furthermore, a high concentration of circulating diseases of the microvasculature, such as atherosclerosis and amyloid angiopathy.

Posterior Reversible Encephalopathic Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a radioclinical syndrome characterized by subcortical vasogenic edema that presents with headache, visual disturbance, seizures, and altered mental status. PRES is associated with many conditions, including SCD, where the majority of cases have been described in children in the context of acute chest syndrome, sepsis, and overtransfusion. The pathophysiology is multifaceted and not fully understood. Vasogenic edema may be due to increased perfusion pressure from systemic hypertension overwhelming cerebral autoregulation. This causes blood-brain barrier disruption and fluid extravasation. The posterior circulation is more commonly affected due to the reduced sympathetic innervation compared to the anterior circulation, which is important in CBF autoregulation. Much less frequently, cytotoxic edema can occur in PRES, perhaps due to mass effect from the vasogenic edema causing microcirculation compression, or due to severe reduced regional perfusion due to vasoconstriction or vasospasm, which may be partly immune mediated. PRES is seen on CT as cortical swelling with mainly subcortical hypodensity. While there is a predilection for the parietal and occipital lobes, the watershed regions in the frontal lobes are also commonly involved. Rarely, there is involvement of the basal ganglia or the cerebellum. On MRI, vasogenic edema may give rise to T2-shine through, which is reversible. DWI hyperintensity with corresponding high values on the ADC map implies vasogenic edema. On the other hand, low ADC values imply cytotoxic edema, which implies irreversibility. PRES is seen on CT as cortical swelling with mainly subcortical hypodensity. While there is a predilection for the parietal and occipital lobes, the watershed regions in the frontal lobes are also commonly involved. Rarely, there is involvement of the basal ganglia or the cerebellum. On MRI, vasogenic edema may give rise to T2-shine through, which is reversible. DWI hyperintensity with corresponding high values on the ADC map implies vasogenic edema. On the other hand, low ADC values imply cytotoxic edema, which implies irreversibility.

Treatment for PRES is generally supportive with the avoidance of any precipitating factors. Clinical outcome was poorer with increasing severity of edema on T2-weighted imaging and the presence of diffusion restriction. Like PRES, endothelial dysfunction has been implicated in reversible cerebral vasodilatation syndrome (RCVS). Two cases of RCVS in SCD patients have been reported in the literature. In one case report, RCVS occurred in an SCD patient immediately following RBC transfusion—a common precipitant of RCVS. In a second case, RCVS was diagnosed alongside PRES and large intracranial hemorrhage. Therefore, despite an overlap in the pathophysiology of PRES and RCVS, a clear association between RCVS and SCD has not been established.

Fat Embolization Syndrome

Fat embolization syndrome (FES) is typically a complication of long-bone fractures caused by fat emboli entering the blood. In SCD, bone marrow infarction causes mobilization of fat globules into the systemic circulation via venous sinusoids within trabecular bone, which can cause microvascular occlusion in any organ. Furthermore, a high concentration of circulating
free fatty acids, among other proinflammatory cytokines, causes endothelial damage, disruption of the blood-brain barrier, and ultimately microhemorrhages.\textsuperscript{92-94}

Clinical presentation is usually with respiratory distress, focal neurological deficits, altered mental status and, most specifically, a petechial rash.

While FES remains a very rare complication of SCD, it is becoming more commonly recognized due to the wider availability of more sensitive imaging techniques. A “starfield” pattern of diffuse hyperintensities on DWI may be observed due to small amounts of blood products or focal ischemic damage. Randomly scattered microhemorrhages are best appreciated as...
punctate hypointensities on T2* images or, ideally, dedicated SWI (Fig 8).92

In early studies, mortality has been reported to be as high as 64%.95,96 However, this is likely to be an overestimation due to recent improvements in FES diagnosis and medical management of acute sickling crises. In more recent reports, mortality with and without red cell transfusion were starkly different at 24% versus 92%.94 With improved survival, there has been an increase in the number of patients with ongoing neurological deficit; only one-fifth of patients return to baseline neurological function.94

Contrary to all other manifestations of SCD, the majority of FES occur in patients with milder forms of the disease, such as sickle cell trait and sickle cell β-thalassemia.97 Moreover, patients with sickle cell trait are only half as likely as patients with SCD to make a full recovery.94 The reason for this is unclear, but immune dysregulation in patients who have not undergone autologous stem cell transplantation (which is the most common in patients bearing the HbSβS genotype) has been proposed.96

**Bone**

The skull and the vertebrae are commonly affected by SCD through vaso-occlusive crises, chronic anemia, and infection. When these entities affect the skull or vertebrae, they are potential causes of headache or back pain.98,99

The physiological stress caused by increased red cell turnover, low oxygen saturation, and chronic anemia in SCD may cause bone marrow hyperplasia. Impaired blood flow caused by marrow hyperplasia predisposes to sickling, which causes loss of trabecular bone and cortical thinning, bone ischemia, and ultimately osteonecrosis. On radiography, marrow hyperplasia may manifest as widening of diploic space and hair-on-end appearance on skull radiograph. Osteonecrosis in the vertebral bodies may cause ill-defined radiolucency and eventually vertebral endplate collapse giving rise to H-shaped vertebra. MRI is significantly more sensitive than plain radiography and is able to detect marrow changes well before endplate collapse.99

On MRI, bone marrow hyperplasia is seen as vertebral body T1-weighted hypointensity relative to muscle.100 In more severe anemia, extramedullary hematopoiesis may occur, which is seen as soft tissue surrounding the bones and herniation of avidly enhancing medullary tissue into the paranasal sinuses.101

Identifying osteonecrosis may be made difficult by persistent T1-weighted and T2-weighted hypointensity caused by persistent red marrow or iron overload from chronic RBC transfusion (Fig 9).102 Areas of bone marrow infarction cause edema and, potentially, fluid collections appearing as T2-weighted and DWI hyperintensity (Fig 8).103 Vertebral body osteonecrosis is also associated with intravertebral air, appearing as hypointensity on all MRI sequences.104 Chronically, areas of infarcted bone become hypointense on both T1-weighted and T2-weighted imaging due to sclerosis and fibrosis.105 An important complication of bone infarction is the development of subperiosteal hematomas, which can cause raised intracranial or intraorbital pressure.104,106 A subperiosteal hematoma within the orbit can cause pain, loss of vision, and proptosis. Large hematomas may require surgical decompression or evacuation due to the risk of orbital compartment syndrome.

The loss of normal blood supply to the bone marrow that can cause osteonecrosis also confers an elevated risk of osteomyelitis, where *Salmonella* species are the most likely causative organism.107 The mandible is more susceptible to osteomyelitis than the skull due to a relatively poor blood supply.108 Distinguishing osteomyelitis from osteonecrosis on imaging can be challenging, particularly in the early stages of disease where both processes can cause bone marrow edema and subperiosteal fluid collections. Acute vaso-occlusive crises are significantly more common than osteomyelitis. The presence of T1 shortening, due to the presence of sequestered RBCs, may favor bone marrow infarction.98,109 Second, a fluid collection associated with a bone infarct is more likely to cause susceptibility artifact due to the presence of blood products, while a fluid collection associated with osteomyelitis is more likely to cause diffusion restriction.110 Vertebral body infarction typically causes a thin rim of enhancement, while osteomyelitis is more likely to display an irregular, geographic, enhancement pattern.111 Within the spine, involvement of the disk is more suggestive of infection than osteonecrosis. Chronically, osteomyelitis is more likely than osteonecrosis to cause cortical destruction.100

**Conclusion**

There are wide-ranging neuroimaging manifestations of SCD in the early and late stages of disease affecting the vessels, parenchyma, and bone. The cerebral complications are associated with significant neurological and cognitive deficit.

Particularly, as the life expectancy of patients with SCD continues to increase, it is hoped that this review will remind the radiologist of the importance of the early identification of the complications of SCD to enable treatment optimization and minimization of the risk of further neurological impairment in this complex multiorgan disease.
References
1. Stotesbury H, Kawadler JM, Hales PW, et al. Vascular instability and neurological morbidity in sickle cell disease: an integrative framework. Front Neurol 2019;10:1-21.
2. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J Clin Invest 2017;127:750-60.
3. Connes P, Verlhac S, Bernaudin F. Advances in understanding the pathogenesis of cerebrovascular vasculopathy in sickle cell anemia. Br J Haematol 2013;161:484-98.
4. Kossmoroff M, Brouse V, Grevent D, et al. Cerebral haemorrhagic risk in children with sickle-cell disease. Dev Med Child Neurol 2015;57:187-93.
5. Driss A, Asare KO, Hibbert JM, et al. Sickle cell disease in the post genomic era: a monogenic disease with a polygenic phenotype. Genomics Insights 2009;2009:23-48.
6. Webb J, Kwiatkowski JL. Stroke in patients with sickle cell disease. Expert Rev Hematol 2013;6:301-16.
7. Mittal SO, Thatianganna S, Kuhns B, et al. Acute ischemic stroke in pediatric patients. Stroke 2015;46:e32-4.
8. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288-94.
9. Balkaran B, Char G, Morris JS, et al. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992;120:360-6.
10. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood 2004;103:4023-7.
11. Tise DS, Valente JH. Pediatric stroke: a review. Emerg Med Int 2011;2011:1-10.
12. Dowling MM, Lee N, Quinn CT, et al. Prevalence of intracardiac shunting in children with sickle cell disease and stroke. J Pediatr 2010;156:645-50.
13. Bigi S, Fischer U, Wehrli E, et al. Acute ischemic stroke in children versus young adults. Ann Neurol 2011;70:245-54.
14. Goeggel Simonetti B, Cavelti A, Arnold M, et al. Long-term outcome after arterial ischemic stroke in children and young adults. Neurology 2015;84:1941-7.
15. Pavlakis SG, Bello J, Prohovnik I, et al. Brain infarction in sickle cell anemia: magnetic resonance imaging correlates. Ann Neurol 1988;23:125-30.
16. Moritani T, Numaguchi Y, Lemer NB, et al. Sickle cell cerebrovascular disease: usual and unusual findings on MR imaging and MR angiography. Clin Imaging 28:173-86.
17. Lansberg MG, Thijs VN, O'Brien MW, et al. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. AJNR Am J Neuroradiol 2001;22:637-44.
18. Silva GS, Vicari P, Figueiredo MS, et al. Brain magnetic resonance imaging abnormalities in adult patients with sickle cell disease correlation with transcranial Doppler findings. Stroke 2009;40:2408-12.
19. Hubert ML, McKinstry RC, Lacey JI, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. Blood 2011;117:772-9.
20. Deane CR, Goss D, Bartram J, et al. Extracranial internal carotid arterial disease in children with sickle cell anemia. Haematologica 2010;95:1287-92.
21. Telfer PT, Evanson J, Butler P, et al. Cervical carotid artery disease in sickle cell anemia: clinical and radiological features. Blood 2011;118:6929-9.
22. Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann Neurol 1997;42:699-704.
23. Buchanan JD, James-Herry A, Osumkwo I. The other side of abnormal: a case series of low transcranial Doppler velocities associated with stroke in children with sickle cell disease. J Pediatr Hematol Oncol 2013;35:543-6.
24. Mazzeucco S, Diomedi M, Qureshi A, et al. Transcranial Doppler screening for stroke risk in children with sickle cell disease: a systematic review. Int J Stroke 2017;12:580-8.  
25. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease. JAMA 2014;312:1033.
26. Strourse JJ, Lanzkron S, Urrutia V. The epidemiology, evaluation and treatment of stroke in adults with sickle cell disease. Expert Rev Hematol 2011;4:597-606.
27. Choudhury NA, DeBaun MR, Ponsio MR, et al. Extracranial vasculopathy and infarct recurrence in children with sickle cell anemia, silent cerebral infarcts and normal transcranial Doppler velocities. Br J Haematol 2018;183:324-6.
28. Platt OS. Prevention and management of stroke in sickle cell anemia. Hematol Am Soc Hematol Educ Program 2006;2006:54-7.
29. Ware RE, Davis BR, Schultz WH, et al. Hydroxy carbamide versus chronic transfusion for maintenance of transcranial Doppler flow velocities in children with sickle cell anemia – TCD with Transfusions Changing to Hydroxyurea (TWHY): a multicentre, open-label, phase 3, non-inferiority trial. Lancet 2016;387:661-70.
30. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710.
31. Vichinsky EP, Neumayr LD, Gold JJ, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA 2010;303:1823-31.
32. Cancio MI, Helton KJ, Schreiber JE, et al. Silent cerebral infarcts in very young children with sickle cell anemia are associated with a higher risk of stroke. Br J Haematol 2015;171:120-9.
33. King AA, Strourse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. Am J Hematol 2014;89:162-7.
34. Miller ST, Macklin EA, Pegelow CH, 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;139:385-90.
35. Quinn CT, McKinstry RC, Dowling MM, et al. Acute silent cerebral ischemic events in children with sickle cell anemia. JAMA Neurology 2013;70:58.
36. Bernaudin F, Verlhac S, Arnaud C, et al. Chronic acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. Blood 2015;125:1653-61.
37. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol 2009;146:300-5.
38. Ford AL, Ragan DK, Fellah S, et al. Silent infarcts in sickle cell disease occur in the border zone region and are associated with low cerebral blood flow. Blood 2018;132:1714-23.
39. Qin Q, Li W, Liu D, et al. Simultaneous measurement of cerebral blood flow and arterial transit time for sickle cell disease. Blood 2016;128:1298.
40. Strouse JJ, Cox CS, Melhem ER, 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;108:379-81.
41. Kirk GR, Haynes MR, Palasis S, et al. Regionally specific cortical thinning in children with sickle cell disease. Cereb Cortex 2009;19:1549-56.
42. Chen R, Arkuszewski M, Kreja J, et al. A prospective longitudinal brain morphometry study of children with sickle cell disease. Am J Neuroradiol 2015;36:403-10.
43. Mackin RS, Insel P, Truran D, et al. Neuroimaging abnormalities in adults with sickle cell anemia: associations with cognition. Neurology 2014;82:835-41.
44. Baldeweg T, Hogan AM, Saunders DE, et al. Detecting white matter injury in sickle cell disease using voxel-based morphometry. Ann Neurol 2006;59:662-72.
45. Stotesbury H, Kirkham FJ, Köbel M, et al. White matter integrity and processing speed in sickle cell anemia. Neurology 2018;90:E2042-50.
46. Kawadler JM, Kirkham FJ, Clayden JD, et al. White matter damage relates to oxygen saturation in children with sickle cell anemia without silent cerebral infaracts. Stroke 2015;46:1793-9.
91. Regling K, Pomerantz D, Narayanans S, et al. Reversible cerebral vasoconstriction syndrome and sickle cell disease: a case report. J Pediatr Hematol Oncol 2019 [Epub ahead of print]:https://pubmed.ncbi.nlm.nih.gov/31789782/
92. Mossa-Basha M, Izbudak I, Gurda GTT, et al. Cerebral fat embolism syndrome in sickle cell anaemia/β-thalassemia: importance of susceptibility-weighted MRI. Clin Radiol 2012;67:1023-6.
93. Gibbs WN, Opatowsky MJ, Burton EC. AIRP best cases in radiologic-pathologic correlation: cerebral fat embolism syndrome in sickle cell β-thalassemia. RadioGraphics 2012;32:1301-5.
94. Tsitsikas DA, May JE, Gangaraju R, et al. Revisiting fat embolism in sickle syndromes: diagnostic and emergency therapeutic measures. Br J Haematol 2019;186:e112-5.
95. Dang NC, Johnson C, Eslami-Farsani M, et al. Bone marrow embolism in sickle cell disease: a review. Am J Hematol 2005;79:61-7.
96. Tsitsikas DA, Gallinella G, Patel S, et al. Bone marrow necrosis and fat embolism syndrome in sickle cell disease: increased susceptibility of patients with non-SS genotypes and a possible association with human parvovirus B19 infection. Blood Rev 2014;28:23-30.
97. Scheifer C, Lionnet F, Bachmeyer C, et al. Cerebral fat embolism in hemoglobin SC disease. Am J Med 2017;130:e187-9.
98. Watanabe M, Saito N, Nadgir RN, et al. Craniofacial bone infarcts in sickle cell disease. J Comput Assist Tomogr 2013;37:91-7.
99. Ejindu VC, Hine AL, Mashayekhi M, et al. Musculoskeletal manifestations of sickle cell disease. Radiographics 2016;27:1005-21.
100. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol 2005;129:482-90.
101. Saito N, Nadgir RN, Flower EN, et al. Clinical and radiologic manifestations of sickle cell disease in the head and neck. Radiographics 2010;30:1021-35.
102. De Sanctis V, Soliman AT, Elsefy H, et al. Bone disease in β-thalassemia patients: past, present and future perspectives. Metabolism 2018;80:66-79.
103. Mallon D, Dixon L, Campion T, et al. Beyond the brain: extra-axial pathology on diffusion weighted imaging in neuroimaging. J Neurol Sci 2020;415:116900.
104. Yu CW, Hsu CY, Shih TTF, et al. Vertebral osteonecrosis: MR imaging findings and related changes on adjacent levels. Am J Neuroradiol 2007;28:42-7.
105. Martinoli C, Bacigalupo L, Forni G, et al. Musculoskeletal manifestations of chronic anemias. Semin Musculoskelet Radiol 2011;15:269-80.
106. Procianoy F, Brandão Filho M, Cruz AAVE, et al. Subperiosteal hematoma and orbital compression syndrome following minor frontal trauma in sickle cell anemia: case report. Arq Bras Oftalmol 2008;71:262-4.
107. Burnett MW, Cook BA. Etiology of osteomyelitis complicating sickle cell disease. Pediatrics 1998;101:296-7.
108. Olaitan AA, Amuda JT, Adekeye EO. Osteomyelitis of the mandible in sickle cell disease. Br J Oral Maxillofac Surg 1997;35:190-2.
109. Jain R, Sawhney S, Rizvi SG. Acute bone crises in sickle cell disease: the T1 fat-saturated sequence in differentiation of acute bone infarcts from acute osteomyelitis. Clin Radiol 2008;63:59-70.
110. Umans H, Haramati N, Flusser G. The diagnostic role of gadolinium enhanced MRI in distinguishing between acute medullary bone infarct and osteomyelitis. Magn Reson Imaging 2000;18:255-62.