Neurologic and Head and Neck Manifestations of Sickle Cell Disease

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KEYWORDS

• Sickle cell disease • Sickle cell anemia • Sickle cell • Moyamoya • Stroke

KEY POINTS

- Clinical symptoms of sickle cell disease (SCD) occur primarily as a result of hemolytic anemia, vasocclusion, infection, or a combination thereof.
- Hemorrhagic and ischemic stroke is the leading cause of death and a major cause of morbidity in SCD patients.
- SCD results in diffuse gray and white matter abnormalities, which may account for accelerated neurocognitive deficits even in patients without focal lesions on conventional MRI.
- SCD-associated vasculopathy may result in vascular narrowing or aneurysm formation. Chronic progressive occlusion of the internal carotid artery with prominent lenticulostriate collaterals produces the stereotypical "moyamoya" angiographic pattern.
- Although less well-known, many patients suffer from head and neck manifestations of SCD, which may affect the inner ears, orbits, sinuses, lymphoid tissue, and bone.

BACKGROUND

Sickle cell disease (SCD) is an autosomal-recessive inherited disorder characterized by an abnormal oxygen-carrying hemoglobin molecule that results in deformed red blood cells (RBC). This widely studied entity was the first disease where the exact genetic and molecular defect was identified, attributable to a single nucleotide mutation of the β-globin gene located on the short arm of chromosome 11. The disease requires 2 defective genes for full disease penetrance and most patients are homozygotic HbS carriers. Although the term SCD refers to a somewhat varied population with clinically important compound heterozygous variants, including sickle D, sickle C, and sickle B thalassemia.[1]

Disclosure: The authors have nothing to disclose.
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Hematol Oncol Clin N Am 30 (2016) 779–798
http://dx.doi.org/10.1016/j.hoc.2016.03.004 **hemonc.theclinics.com**
0889-8588/16/$ – see front matter

SCD is common, with approximately 300,000 children born annually with the disease, predominating in sub-Saharan African and among African descendants around the world. The Centers for Disease Control and Prevention estimates that 90,000 to 100,000 Americans suffer from the disease. Despite recent advances in treatment, the high morbidity and mortality rates of SCD remain a major public health concern resulting in an average of 75,000 hospitalizations and US health care costs approaching $475 million annually.[2]

Low oxygen tension results in polymerization of the abnormal hemoglobin tetramer, which becomes relative insoluble when deoxygenated. Aggregates form long chains, disrupting the microstructural and macrostructural appearance of the cell. The normally plastic biconcave erythrocytes morph into crescentic or sickle-shaped cells that are more friable and easily hemolyzed. Preceding events may include infection, trauma, and other stressful conditions that may promote intracellular hypoxia and acidosis.

Acute and chronic clinical manifestations of SCD primarily occur as a result of hemolysis and vasoocclusion. Changes in membrane structure and function, loss of normal plasticity, disorganized cell volume control, increased sheer stress, and increased endothelial adherence are all thought to contribute to these phenomena. A typical RBC from a sickle cell patient has a life span on the order of just 10 to 20 days in comparison with the normal 90 to 120 days. Chronic anemia results in profound stresses on both the hematopoietic and cardiovascular systems.

After RBC sickling, vasoocclusion occurs through a cascade of events including endothelial adhesion and damage, arterial narrowing, and aggregation, ultimately leading to ischemia and/or infarction. Ischemic events may occur throughout the body, resulting in repeated acutely painful episodes known as crises. Hemolysis and vasoocclusion result in end organ damage affecting virtually every organ system to some degree. This review focuses on the central nervous system and the less recognized head and neck manifestations of the disease.

VASCULAR DISEASE

SCD vasculopathy results in large vessel arterial stenosis and occlusion with the distal internal carotid arteries, proximal anterior cerebral arteries, and middle cerebral arteries (MCA) most commonly affected (**Fig. 1**). Pathologic studies describe smooth muscle hyperplasia and intraluminal thrombus rather than inflammation or atherosclerosis as the underlying pathophysiology. This process occurs slowly over time as evidenced by extensive collateral vessel formation, particularly the lenticulostriate vessels coursing through the basal ganglia. The angiographic appearance of stenosis with an extensive network of ill-defined collateral vessels was likened to “a puff of smoke” by the original Japanese angiographers who coined the term “moyamoya” (**Fig. 2**). This moyamoya pattern has been described in several other disease entities including neurofibromatosis and postradiation vasculopathy.

Blood supply is tenuous, even in the setting of collateral vessel formation with regional perfusion abnormalities. These collateral vessels exhibit stress-related changes, including thinned walls and microaneurysm formation, predisposing them to both hemorrhage and thrombosis.[3]

In addition to stenosis, SCD may result in arterial dilatation. Reported rates of aneurysm formation in SCD patients appear much higher than that of the general population (>1% in children and 10% in adults), with a high prevalence of patients with multiple aneurysms. Chronic high-flow states, changes in circulatory patterns,