Primary and Secondary Stroke Prevention in Children With Sickle Cell Disease

A. Kyle Mack, MD, & Alexis A. Thompson, MD, MPH

ABSTRACT

Children with sickle cell disease (SCD) have numerous acute and chronic complications, including central nervous system (CNS) disease, which can be debilitating over their life span. Recognition of risk factors for CNS disease and overt CNS disease should be properly identified by primary care providers, including physicians, physician assistants, and nurse practitioners. Here, we discuss an emerging and important early indicator of CNS disease in the form of silent cerebral infarcts and review overt stroke in patients with SCD. We also discuss transcranial Doppler ultrasonography, when and how often transcranial Doppler ultrasounds should be performed, and management of abnormal results. Lastly, we review the clinical data for the management and prevention of silent cerebral infarcts and overt stroke in children with SCD. J Pediatr Health Care. (2016)

KEY WORDS

Cerebral infarct, sickle cell disease, stroke, transcranial Doppler ultrasonography

Sickle cell disease (SCD) is a common autosomal recessively inherited red blood cell (RBC) disease that affects persons of African, Mediterranean, and occasionally Asian and Hispanic descent (Serjeant, 2013). Globally, it is estimated that about 300,000 children are born with SCD annually (Piel et al., 2013). Each year in the United States, approximately 2,000 babies are born with SCD (Buchanan, Vichinsky, Krishnamurti, & Shenoy, 2010). Prevalence studies are scarce; however, available data show that the estimated prevalence of SCD in the United States is approximately 100,000 individuals (Brousseau, Panepinto, Nimmer, Hoffmann, 2010; Hassell, 2010).

SCD shows considerable phenotypic heterogeneity as a result of genetic and environmental factors,
such as infection, climate, nutrition, socioeconomic status, and access to medical care. In the United States, the most common genotypes associated with SCD are homozygous hemoglobin SS (HbSS), hemoglobin SC (HbSC disease), and sickle-beta thalassemia syndromes (HbSβ+, HbSβ0). Persons with HbSS and HbSβ0 tend to have the most severe form of disease, with marked anemia and frequent painful episodes, although patients with alternate genotypes also can have painful episodes requiring hospital admission.

Recognition of persons at risk for stroke and silent cerebral infarct (SCI), two debilitating and serious conditions associated with SCD, is critical to the successful treatment and management of patients of all ages. The incidence of overt stroke in children with SCD with the HbSS genotype by the age of 20 years is 11% (Ohene-Frempong et al., 1998). The rate of stroke increases with age in persons with SCD: 310/100,000 person-years in children (younger than 18 years), 360/100,000 person-years in young adults (aged 18 to 34 years), 1160/100,000 person-years in middle-aged adults (aged 35 to 64 years), and 4700/100,000 person-years in elderly adults (65 years or older; Strouse, Jordan, Lanzkron, & Casella, 2009). SCI is perhaps even more frequent, with reported prevalence rates of 21% at baseline (DeBaun, Armstrong, et al., 2012). Furthermore, patients with SCI are at increased risk for both progressive infarcts and overt strokes (Hulbert et al., 2011). With the expectant changes in health care access, a larger proportion of primary practitioners will be treating patients with SCD and are therefore likely to interface with patients who have SCD-related neurologic complications.

The objectives of this article are to (a) provide the general practitioner with a background on SCD and abnormal transcranial Doppler ultrasounds (TCDs), overt stroke, and SCIs; (b) discuss clinical assessment and screening for these patients; and (c) discuss future directions in stroke prevention management in patients with SCD.

**CEREBROVASCULAR ACCIDENTS AND SCD**

**Pathophysiology of Cerebrovascular Accidents**

In persons with SCD, cerebrovascular accidents (CVAs) result from impaired cerebral vascular hemodynamics caused by sickling and chronic hemolysis. Patients with resulting chronic anemia have a compensatory increase in cerebral blood flow as a way to maintain a constant perfusion pressure and increase oxygen delivery to the brain. In these patients, vessel stenosis and vessel occlusion also can develop (Figure 1). Factors that appear to be seminal in the development of vessel occlusion include inflammation, excessive adhesion of RBCs to activated endothelium, ischemia-reperfusion injury, a hypercoagulable state, and dysregulation of vascular tone. Therefore, acute sickling may be the ultimate event that causes stroke in the setting of an underlying chronic vasculopathy. The critical vessels, which become narrowed and stenotic, include the distal internal carotid artery (dICA), the anterior cerebral artery (ACA), and the middle cerebral artery (MCA). In patients with SCD, cerebral vasculopathy and Moyamoya disease can then develop, possibly resulting in increased fragility of newly formed blood vessels that can rupture and cause hemorrhagic strokes.

**Ischemic Stroke**

Ischemic stroke in persons with SCD occurs as a result of vessel occlusion in one of the seminal arteries in the brain, typically the dICA, ACA, or MCA distributions. Ischemic stroke is common in young children with SCD, with increased incidence during the first decade of life and after the age of 30 years (Ohene-Frempong et al., 1998). Because ischemic strokes primarily occur in young patients aged younger than 10 years, it is imperative that the general practitioner or pediatrician be well versed in the presentation and identification of such strokes.

The risk factors for ischemic stroke include the HbSS genotype, increasing age, recent or recurrent acute chest syndrome, elevated systolic blood pressure, low hemoglobin level, recent infection, nocturnal hypoxemia, prior transient ischemic attacks (TIAs), and abnormal elevated velocities on TCD screening (Table 1; Redding-Lallinger & Knoll, 2006). TIAs are defined as a completed infarctive stroke with acute neurologic deficit lasting less than 24 hours. One of the most common secondary diagnoses for pediatric patients with TIA in the United States is SCD (Adil, Qureshi, Beslow, & Jordan, 2009).

**Hemorrhagic Stroke**

In contrast, hemorrhagic strokes occur most commonly in young adults during the second decade of life and are often associated with a high mortality rate (Ohene-Frempong et al., 1998; Strouse, Lanzkron, & Urrutia, 2011; Verduzco & Nathan, 2009). The most typical cause of these types of strokes is a rupture in weakened cerebral blood vessels, which can result in vascular changes, including formation of aneurysms. Moyamoya disease is a secondary event associated with rupture of tortuous collateral blood vessels that develops as a result of stenosis. The risk factors for
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