Sickle Cell Disease and Stroke

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The increased risk of stroke in sickle cell disease has been recognized for over 50 years. Recent reports have increased our understanding by better describing the clinical characteristics and presentation of sickle cell disease patients with stroke and provided relatively consistent estimates of prevalence applicable to younger cohorts. The experience from established clinics in Los Angeles, Philadelphia, and Kingston, Jamaica, indicate that clinically evident cerebrovascular disease has a prevalence of about 7% to 8% in cohorts followed for the first 2 decades of life. Less is known about stroke in older patients, but the Cooperative Study of Sickle Cell Disease is developing estimates of stroke incidence and prevalence data from adults as well as children with sickle cell disease.

Studies using magnetic resonance imaging (MRI) or computed tomography (CT) have shown that the prevalence of cerebral infarction is higher than that of stroke. This is consistent with the definition that stroke is a clinical syndrome, and cerebral infarction is a pathologic entity detected with high sensitivity and specificity by MRI and, to a lesser extent, CT. The study by Glauser and colleagues supports prior observations that not all sickle cell disease patients with abnormal MRIs have a history or neurologic findings that go with the lesion(s). Their systematic study provides an estimate of silent infarction from their sample of 30 patients of 24% based on history and examination alone. This is higher than the 11% reported from a 55-patient series from Columbia-Presbyterian Hospital and from the Cooperative Study of Sickle Cell Disease, in which 16% of 172 patients had abnormal MRI without a stroke history. This suggests that only about half of the sickle cell disease patients with brain infarction report or develop symptoms sufficient to prompt recognition, at least early in life. Clinical surveillance alone misses a sizable number of patients with brain lesions.

The rate of silent infarction in sickle cell disease is comparable to that reported in other groups at high risk for cerebrovascular disease. The Asymptomatic Carotid Atherosclerosis Study, which compared carotid endarterectomy with medical treatment in patients with 60% or greater cervical carotid stenosis, reported that 126 (15%) of 848 patients with no history of transient ischemic attacks or stroke had one or more CT lesions, primarily small, deep infarcts, at entry into the study. Ten percent of Framingham patients presenting with first-time stroke already had CT-evident lesions. In the presence of chronic atrial fibrillation, the reported prevalence of silent cerebral infarction has ranged from 11% to 48%.

The more pressing issue is the significance of silent infarction. Although the notion that silent lesions predispose to subsequent clinical stroke is intuitively appealing, the evidence from adult studies to date has not been compelling. Patients whose clinical syndrome is a transient ischemic attack but who have an infarct on CT have shown a higher risk of recurrence than those with negative CT, but this has not been supported by studies of patients presenting with stroke. In adult cerebrovascular disease, as in sickle cell disease, prospective long-term data relating neuroimaging to outcome in completely asymptomatic patients are lacking. The only study to examine this question in sickle cell disease found that three of eight neurologically asymptomatic patients with abnormal MRIs had subsequent stroke, compared to none of eight without MRI lesions. Larger studies, however, are needed to secure this finding. How often silent infarcts cause cognitive deficits is unknown, but the study by Kugler and colleagues found no correlation between cognitive deficits and MRI appearance or stroke outcome. Some of the Cooperative Study of Sickle Cell Disease patients have received neuropsychological testing as well as repeat MRI studies, and these data should provide answers to these questions.

The vascular distribution of the MRI lesions may also be important. So called "watershed" lesions, either between the major named artery territories or between superficial and deep arterial circulations, have predominated in both the MRI reports, such as the report of Glauser and colleagues, and in pathologic studies of the brain in sickle cell disease. Cortical watershed lesions have been taken by some as inferential evidence of the presence of proximal, flow-restricting lesions of the large brain arteries feeding that hemisphere, but alternative explanations have also been proposed, and it is possible that several mechanisms may be in play.

Although there has been intense recent interest in large artery disease in sickle cell disease, both macrocir-
culatory and microcirculatory derangements are evident from autopsy and can be present alone or in tandem in any given patient. An intriguing possibility is that the severe anemia that characterizes sickle cell disease may represent a third type of lesion, which causes relative hypoperfusion by reducing oxygen-carrying capacity beyond the point that can be compensated by hyperemia, resulting in an "anemic infarction." The observation that some children first present with focal neurologic symptoms at a time of profound anemia suggests that this mechanism may be important in some patients. It is important to emphasize that the best clinical response to the discovery of silent brain infarction is unknown. Regular blood transfusion has become the standard of care for the prevention of recurrent stroke in sickle cell disease. However, the published experience that established the recurrent stroke risk and beneficial effect of transfusion was entirely based on patients selected because they reported or manifested neurologic symptoms. Glauser and colleagues suggest that future studies of cerebral infarction in sickle cell disease should not limit the case definition to those with clinical markers of cerebrovascular disease. This is good advice, provided the reader is aware that studies based on selection by MRI will not relate directly to the sizable body of literature on stroke in sickle cell disease that now exists.

The extent to which surrogate measures of risk, such as abnormal transcranial ultrasonography and probably MRI, or putative markers of disease, such as abnormal magnetic resonance imaging, asymmetric cerebral blood flow, or focal cognitive deficits, can be used to select patients for a therapy with significant risks such as transfusion remains to be established. What is clear is that careful studies using multicenter designs are needed so that adequate statistical power can be achieved, and answers to these important questions can be obtained.

References