Sickle Cell Trait Is a Risk Factor for Early Stroke

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SICKLE CELL ANEMIA IS A well-known risk factor for stroke. In conditions of mild hypoxemia, red blood cells sickle and sludge in arteries and veins, leading to thrombosis and infarction at a young age. Children with sickle cell anemia have approximately 285 strokes per 100,000 children per year. The viscosity of SCT that are exposed to a combination of dehydration precipitates sickling in vitro and in patients with sickle cell anemia, and it has been associated with episodes of infarction in people with SCT. Red blood cells with SCT that are exposed to a combination of dehydration and low pH sickle more easily. The viscosity of SCT blood may increase during anesthesia. There is a small but statistically significant increase in viscosity with partial deoxygenation (P<.01), and this viscosity increases further after 75 minutes of exposure to halothane.

It is possible that SCT may lead to other anatomical differences that predispose persons to stroke. I am aware of 1 study with prospective radiographic imaging of children with SCT. Children with SCT were more likely to have cerebrovascular tortuosity than normal controls were. Vascular abnormalities in children with sickle cell anemia are thought to be owing in part to pathological thrombosis, endothelial activation, and platelet activation; it is unclear whether the same mechanisms influence vasculopathy related to SCT.

Admittedly, there are fewer descriptions of stroke in people with SCT than we might expect based on the frequency of the gene in the population. Both arterial ischemic stroke and sinovenous thrombosis have been described in children and adults with SCT, documented by hemoglobin electrophoresis in the patient or, in 1 case, a first-degree relative. In the patients who came to autopsy, pathological examination demonstrated thrombi of sickled cells in nearby vessels. While sickling is known to occur after death in people with SCT, the locations of the thrombi suggest that the thrombi played a role in the ultimately fatal infarctions. One study suggests that SCT actually reduces the risk of ischemic stroke and increases the risk of hemorrhagic stroke. However, patients in this study were examined with computed tomography, which may not effectively distinguish primary hemorrhages from hemorrhagic infarctions.

The literature on infarction in other organs with SCT is much broader. Sickle cell trait has been associated with infarction in the spleen, heart, kidney, bone, liver, and lungs. One study describes a premature neonate who developed renal and splenic infarctions following a transfusion with SCT blood; autopsy results demonstrated sickle cell thromboses in the vessels of those organs. Military recruits with SCT are at a significantly higher risk of sudden explained death than recruits without SCT (P<.001), with death rates of 32.2 deaths per 100,000 recruits with SCT, compared with 1.2 deaths per 100,000 African American recruits without SCT and 0.7 deaths per 100,000 non–African American recruits without SCT. Many of these cases were cardiac deaths. With clearly documented infarction in so many organs, it is reasonable to believe that SCT is also a risk factor for infarction in the brain.

Two major weaknesses of previous descriptions of organ infarction are that SCT is not always documented by hemoglobin electrophoresis and that many of the studied individuals have not undergone a prothrombotic workup. Many of these descriptions appeared before levels of protein C, protein S, antithrombin III, and other risk factors such as the factor V Leiden and prothrombin 20210 mutations were known and routinely studied.

It may be that SCT is only a significant risk factor in the setting of other risk factors. Sickling increases in people with SCT during periods of exercise without fluid intake and US military policies on hydration and exercise monitoring during basic training appear to have decreased the death rate in military recruits with SCT. African and African American patients with both type 2 diabetes mellitus and SCT have a higher rate of microvascular
complications than African and African American patients with type 2 diabetes mellitus and normal hemoglobin.46 An individual’s genetic background may be important. Several authors41-43 have suggested that white carriers of SCT may be more susceptible to splenic infarction at high altitude than are black carriers. As I learned from my past clinical experience, non–African American patients with stroke are rarely, if ever, screened for SCT, so it is difficult to tell whether SCT is a risk factor for stroke in white patients. Sickle polymorphisms have been associated with variations in disease severity of sickle cell anemia,44-45 although this relationship is less clear in African Americans.46 It is possible that sickle polymorphisms might affect risk associated with SCT. Human leukocyte antigen type has been associated with risk for stroke in sickle cell anemia,47 and it might influence risk in people with SCT. Other as-yet-undefined genes may play a role in modifying the risk of infarction.48

The literature suggests that SCT is a risk factor for stroke. It is possible that additional concurrent risk factors need to be present for infarction to occur in people with SCT. Accepted for Publication: June 14, 2005.

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