Stroke Prevention and Treatment in Sickle Cell Disease

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While the problem of stroke in the patients with sickle cell disease (SCD) has been known for more than 75 years, adequate preventive and treatment strategies are just now being tested. Recent data on prevalence and incidence have been obtained from the Cooperative Study of Sickle Cell Disease of more than 4000 patients with SCD observed in 23 US clinical centers over a 10-year period. The overall age-specific incidence of first stroke in SCD (homozygous sickle cell anemia) is low (0.13%) at ages younger than 24 months, increasing to just over 1% at ages 2 to 5 years, with only a slight decrement to 0.79% at ages 6 to 9 years. The risk of brain infarction declines until a second peak is seen at ages older than 50 years, when the incidence again increases to nearly 1.3%. Although intracranial hemorrhage does occur in young children with SCD, the risk is low compared with older children and adults. The Cooperative Study of Sickle Cell Disease reported risk factors for infarction to be prior transient ischemic attack, low steady-state hemoglobin values, and rate and recency of episodes of acute chest syndrome, as well as elevated systolic blood pressure. Risk factors for intracranial hemorrhage included low steady-state hemoglobin values and a high leukocyte count. The burden of cerebrovascular disease is even higher if subclinical magnetic resonance imaging (MRI) lesions, presumed to be ischemic, are included. The prevalence of such lesions is more than 22% in patients with SCD, and most of these patients have not reported symptoms, although specialized neuropsychological testing shows lower scores in children with silent lesions on MRI scans. Patients with a history of clinical stroke typically have infarcts in the cortex and deep white matter, whereas silent infarcts tend to be more limited to deep white matter. Common infarction patterns are characterized by wedge-shaped lesions of large-vessel territories; border zone infarctions, particularly of the middle and cerebral artery watershed region; and small punctate lesions of the deep white matter. Fat embolism to the brain and venous thromboses are encountered rarely.

PATHOPHYSIOLOGY OF STROKE

Although vaso-occlusion in the microcirculation of other organs is an important cause of morbidity in SCD, the vascular disease of the brain is often associated with a large-vessel vasculopathy primarily localized to the distal supracholinoid internal carotid artery and the proximal portions of the middle and anterior cerebral arteries. Such lesions have been demonstrated in about 80% of angiograms of patients with sickle cell anemia and stroke. Also consistent with large-vessel disease as a prominent cause of stroke in SCD, MRI and computed tomographic studies of patients with SCD and stroke have shown 80% to have major distal vessel occlusion or distal insufficiency patterns. In the later stages of vasculopathy, there may be a striking similarity to the angiographic picture of moyamoya disease, with its abnormal network of subcortical vessels, giving the puff-of-smoke appearance in as
many as 30% of patients with SCD and vasculopathy.

Moyamoya disease and SCD show parallels in the risk of early infarction coupled with a later risk of hemorrhage possibly due to rupture of dilated weakened collateral vessels. Pathological examination of diseased vasculopathic segments reveals intimal proliferation with discontinuity of the internal elastic lamina. While endothelial cells may proliferate to resurface denuded areas, they remain a monolayer, while components of the hyperplastic intima include fibroblasts, fibrous tissue, and scattered smooth muscle cells. Concomitant thrombus formation in areas of endothelial damage may both perpetuate the vicious cycle of intimal changes and serve as the proximate source of artery-to-artery emboli responsible for some distal occlusions. The cause of intimal hyperplasia, and why it occurs at specific sites in the anterolateral vessels, is not known.

TREATMENTS USED FOR STROKE

Transfusion

There have been few studies of stroke in patients with SCD, and such patients are not often included in clinical trials, such as trials of antiplatelet drugs, that investigate stroke prevention and treatment. In the 1970s and 1980s, clinical series from several centers indicated that children with SCD and stroke had a very high early (3 years) recurrent stroke risk and that if they were given transfusion therapy this risk was drastically reduced. In most cases, the transfusion programs were sufficient to reduce total sickle cell hemoglobin values to less than 30% of the total hemoglobin values. Although not tested in a clinical trial, long-term transfusion therapy was associated with a reduced recurrence to as low as 10% and has become routine after stroke in children.

It has not been established when it is safe to discontinue long-term transfusion therapy after stroke. In practice, many adult hematologists discontinue this therapy in young adults when they take over their care owing to the maturation of children with stroke; alternatively, some patients tire of the program and fail to continue with regular transfusions, but the rate of stroke after discontinuation in these cases has not been systematically reported. One group found that discontinuation of transfusion therapy only 1 to 2 years after stroke led to recurrence within 1 year in 7 of 10 patients, however, another group observed no recurrences in 7 children who had received transfusions an average of 2 years before cessation. More recently, Rana et al reported that 9 patients of various ages who had undergone transfusions for an average of 6 years (minimum, 3 years) had no strokes over an observation period ranging from 3.0 to 18.5 years. At the time of cessation, 2 patients were approximately 10 years old, while the remainder were 17 to 25 years old. In opposition to these findings, Wang et al reported that discontinuation of transfusion therapy after an average of 9.5 years in 10 patients resulted in 5 recurrent cerebrovascular events in the ensuing 12-month period. Also, 1 death of unknown cause occurred. The ages of the patients with events at the time of discontinuation were 10, 13, 15, 16, and 17 years, while the ages of the 4 patients without complication were 7, 17, 20, and 21 years. Existing guidelines recommending that transfusion therapy after infarction continue for at least 5 years, or until the age of 18 years, are reasonable in the absence of better data.

The only randomized clinical trial using any therapy in SCD-related stroke was performed as part of primary prevention strategy. The Stroke Prevention Trial in Sickle Cell Anemia tested whether long-term transfusion therapy can reduce the risk of first stroke by 92% in high-risk children aged 2 to 16 years selected by screening with transcranial Doppler ultrasonography (TCD). The children randomized in this study, none of whom had a history of stroke at entry, were identified by TCD showing time-averaged mean (as opposed to peak systolic) velocities of 200 cm/s or more in the internal or middle cerebral artery (normal mean±SD adult velocites, 62±12 cm/s). Children with SCD generally have TCD velocities in the range of 130 to 140 cm/s, and the 200-cm/s cutoff is about 2 SDs above normal for children of this age and degree of anemia. Children in the untreated arm had a stroke risk of 10% per year, which is about 10 to 20 times the baseline risk in children with SCD in this age group who are not selected by TCD. Eleven events occurred in the untreated group compared with only 1 in the group who underwent transfusion therapy (P<.001). These results led to early termination of the trial and the publication of a clinical alert by the National Heart, Lung, and Blood Institute that encouraged TCD screening and consideration of transfusion in cases of high risk based on the results of the Stroke Prevention Trial in Sickle Cell Anemia.

Exchange transfusions or simple transfusions are options; exchange transfusions have the advantage of causing less iron accumulation at the price of exposure to more units of blood and greater expense. In the acute setting, exchange transfusions avoid the potential adverse effect of bringing hemoglobin toward a more normal level and thus raising viscosity. In the long term iron loading is reduced but exchange transfusion requires more blood and exposes the patient to more units of blood.

Transfusion is also used in the acute setting of stroke in children immediately after stabilization, but there are no controlled data on the effect of transfusion on acute stroke itself. There are also no data supporting its use in adults, either for prevention or for treatment of stroke. In addition, it is unclear whether transfusion is helpful in preventing recurrent intracranial brain hemorrhage, although it is frequently administered in this setting in preparation for cerebral angiography. It may be able to reduce hemodynamic stress on a continuing basis, which may lower the risk of aneurysm rupture, but studies are needed to test the impact of transfusion on hemorrhage.

Transfusion has many drawbacks, including alloimmunization with long-term transfusion and iron overload, which becomes a problem after only a few years of therapy and has to be treated with chelation. Chelation therapy with the only available agent, desferoxamine, is usually recommended when serum ferritin levels reach 5618 pmol/L. The initial dose is 50 mg/kg administered by subcutaneous infusion over an 8-hour period daily for...
several days a week. Long-term compliance with chelation therapy is a problem as there is no oral chelator.

**Hydroxyurea**

Hydroxyurea therapy emerged from decades of unsuccessful efforts to find agents capable of elevating the percentage of fetal hemoglobin, since observations of populations and a study of natural history have shown that increased percentages of fetal hemoglobin correlate with reduced disease severity. Hydroxyurea is the only chemotherapeutic agent approved for the treatment of SCD. The double-blind, placebo-controlled study of hydroxyurea therapy in 299 adults with SCD for the reduction of painful episodes was terminated early when significant reductions in pain episode frequency, acute chest syndrome, need for hospitalization, and blood transfusions became evident. There were too few strokes in this study, however, to determine any effect of the drug on the risk of stroke. No study has addressed the issue of whether hydroxyurea therapy has efficacy in stroke prevention in a controlled fashion. Ware et al reported the outcomes of secondary stroke treatment with hydroxyurea and phlebotomy in 16 young patients in whom transfusion was no longer an option. Their results of a 19% recurrent event incidence are encouraging but need to be compared with an appropriate control. In this single report, the sample size was small and there were no controls or randomization.

How hydroxyurea therapy works in SCD is debatable, but it elevates the percentage of fetal hemoglobin, improves red blood cell deformability, reduces the irreversibly sickled cell fraction, and is associated with improvements in rheology and red blood cell survival. Abnormal adhesion of blood cells may also be modified. Hydroxyurea therapy has been shown to reduce granulocytes, reticulocytes, and platelets, but it is not clear if it has a beneficial effect on pain crises. Hydroxyurea therapy is initiated at a dosage of 15 mg/kg per day, and the dosage is typically escalated by 5 mg/kg per day every 8 to 12 weeks, with monitoring of the levels of platelets, reticulocytes, and neutrophils and interruption of treatment temporarily or permanently if toxic effects are evident. Few patients can tolerate a dosage higher than 30 mg/kg. It is not clear how important it is to increase the dosage to the maximal tolerated dose as opposed to lower doses for the control of pain crises. In any case, the role of hydroxyurea therapy in stroke prevention needs to be established.

**Bone Marrow Transplantation (BMT)**

Bone marrow transplantation may be curative in SCD and is potentially an option for stroke prevention. Data are available on 120 patients that show that HLA-identical sibling stem cell allografts can successfully replace sickle cells with normal donor-derived red blood cells and that stable mixed chimerism, even with a relatively low proportion of donor cells, can ameliorate the symptoms and complications of SCD, although an effect on stroke specifically is not clear. Survival has been in the 90% range, and event-free survival about 85%. The cumulative incidence of graft rejection or return of SCD is 11%. Although most patients who have undergone BMT have survived without developing SCD, approximately 8% have died, and about half of these deaths occurred in the setting of graft-vs-host disease. In addition to acute and chronic graft-vs-host disease, seizures and intracerebral hemorrhage have been reported in patients with stroke who undergo BMT, and there are other transient but benign complications of the procedure.

The impact of BMT on central nervous system disease in 22 patients with stable donor engraftment who were followed up for at least 2 years was reported by Walters et al. Ten patients had history of stroke, 4 had silent infarcts on MRI scans, one had a transient ischemic attack, and 1 had positive results on TCD screening prior to BMT. Conclusions based on clinical and MRI follow-up were that no significant central nervous system events had occurred and that most of the patients had shown "stabilization" of underlying cerebral vasculopathy. Bernaudin reports from France that a history of stroke has become the main indication for BMT and argues that it should be considered in patients with silent cerebral infarcts associated with cognitive impairment or TCD evidence of stroke risk. The paucity of available HLA-identical sibling donors is a major obstacle to transplantation, and there is no clear consensus on the indications for its use in SCD, but it remains an option for some patients, especially for those who are at highest risk of significant adverse events, including stroke.

**Other Treatments**

Intravenous tissue plasminogen activator therapy should be considered in adults with acute ischemic stroke, if the therapy can be delivered within 3 hours of symptom onset and there are no contraindications according to existing guidelines. There is no clear justification to exclude the adult patient with SCD from thrombolytic therapy. Adequate hydration, normothermia, and euglycemia should be maintained, and hypotension should be avoided in the setting of acute stroke.

In terms of stroke prevention, in adults with stroke, or in children who cannot undergo long-term transfusion therapy, warfarin therapy is an unproven alternative and may be reasonable if there is evidence of intracranial arterial stenosis. There is no systematic experience with either anticoagulation or antiplatelet agents in this setting, but given the support for use of these agents in adults generally, it is reasonable to use them in adults with SCD when no other specific stroke prevention strategy is available on the basis of existing guidelines for their use. In cases of treatment failure and recurrent strokes despite medical therapy, and in the setting of severe vascular disease, surgery is an option. There have been a few reports of the successful establishment of a collateral supply using a procedure called *encephaloduroarteriosynangiosis*, in which a superficial scalp artery with galea is mobilized and passed through the dura to lie on the arachnoid surface of the brain. Modification of other factors unrelated to SCD may contribute to stroke prevention, and patients with SCD should receive a workup for the cause of stroke. Al-
though the prevalence of SCD-related vasculopathy is high, other mechanisms and risk factors for stroke should be considered, especially in adults with SCD and stroke. Drug abuse, the presence of anticardiolipin antibodies and other hypercoagulable states, vasculitides, arterial dissection, cardioembolic or paradoxical emboli, and elevated homocysteine levels should all be considered. Also, other modifiable stroke risks, such as smoking, diabetes, hypertension, and obesity, should be addressed in cases of SCD.

CURRENT STATE OF KNOWLEDGE

Stroke remains one of the important complications of SCD and is especially critical in the care of children with this disorder. The epidemiology of stroke and primary and secondary prevention strategies based on transfusion have recently been established in large multicenter studies, but treatment of acute stroke and a basic understanding of what causes cerebrovascular disease in this hemoglobinopathy have progressed very little in recent years. Two newer treatments for SCD, hydroxyurea therapy and BMT, need to be applied specifically to stroke prevention in randomized trials. The growing armamentarium for prevention and treatment of stroke in general (e.g., antiplatelet agents, anticoagulation, thrombolytic approaches, endovascular treatment, and neuroprotection) need to be considered, and the most promising of these should be applied in well-designed studies to add to the available choices for clinicians and patients seeking to protect the brain of the patient with SCD.

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