

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Prevention and Treatment of Stroke in Patients With Sickle Cell Disease



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H&O What types of stroke occur in people with sickle cell anemia (SCA)?

AK Overt strokes occur in approximately 5% to 10% of children with sickle cell disease (SCD) and are most common in patients with SCA (genotype SS or S β^0 thalassemia). Ischemic stroke has a bimodal distribution, being more common in children and older adults and less common in adults aged 20 to 29 years. Among individuals with SCA, hemorrhagic stroke has been shown to be most frequent in the 20- to 29-year age group.¹ Silent cerebral infarcts, the most commonly recognized cause of neurologic injury, are ischemic lesions that are detected with magnetic resonance imaging (MRI). Silent strokes are cerebral infarcts that have a signal abnormality measured at a minimum of 3 mm (visible on fluid-attenuated inversion recovery MRI in both axial and coronal views), do not cause abnormalities that are revealed on neurologic examination, and are associated with cognitive difficulties.²

H&O How common is stroke in patients with SCD?

AK Among adults with SCA, the reported risk for overt stroke is 11% by 20 years of age and 24% by 45 years of age.¹ For younger patients with SCA, the cumulative risk for stroke is 11.5% by 18 years of age³ and 12.8% by 20 years of age.⁴ Silent cerebral infarcts are estimated to occur in 20% to 40% of children with SCD and are most common in SCA. Although the prevalence of silent cerebral infarct has not been well studied in adults, the rate of silent ischemic stroke was estimated to be 53% in an unselected group of adults with SCA.⁵

H&O How does sickle cell phenotype affect the risk for stroke?

AK Patients with the hemoglobin SS phenotype of SCA are at the highest risk for stroke, both overt and silent, and the risk continues to increase with age. There is also an age-dependent increase in stroke risk in other phenotypes, which is complicated by other known risk factors for stroke, such as hypertension, renal disease, diabetes mellitus, atrial fibrillation, and hyperlipidemia.

H&O How do physicians predict which patients are most likely to have a stroke?

AK In children with SCA, transcranial Doppler ultrasonography (TCD) can detect patients with a high stroke risk months to years before the stroke occurs. TCD measures blood flow velocity in the large arteries of the circle of Willis. Velocity in these patients with SCA generally is increased by the severe anemia, and becomes elevated in a focal manner when stenosis reduces the arterial diameter.⁶ Children with a velocity of 200 cm/s or more have the highest risk for stroke, which is approximately 0.5% to 1.0% per year in children who have SCD. There are no effective ways to predict stroke risk in adults with SCD at this time.

H&O What strategies are used for the primary prevention of stroke in patients at high risk?

AK In children with SCA who are at high risk for stroke, indefinite chronic blood transfusion therapy has been

shown to reduce the annual risk for stroke from 10% to less than 1%.⁶ In STOP (Stroke Prevention Trial in Sickle Cell Anemia), the TCD velocities of many patients undergoing transfusion reverted from high risk to apparently low risk (<170 cm/s, approximately 53%) or intermediate risk (170-199 cm/s, approximately 17%), especially if the velocity at the initiation of treatment was in the low abnormal range (200-230 cm/s) and the findings on magnetic resonance angiography (MRA) were relatively normal.⁷

However, TWiTCH (Transcranial Doppler With Transfusions Changing to Hydroxyurea), a study conducted by Ware and colleagues, showed that in high-risk children with SCA and abnormal TCD velocities who have received transfusions for at least 1 year and have no MRA-defined severe vasculopathy, hydroxycarbamide treatment can be substituted for chronic transfusions to maintain TCD velocities and reduce the risk for primary stroke.⁸ In this study, children and adolescents aged 4 to 16 years with SCA who were considered to be at elevated risk for stroke based on TCD velocity and who had received transfusions for at least 1 year were randomly assigned to 24 weeks of either continued transfusions or hydroxyurea. The researchers found that hydroxyurea worked as well as blood transfusion, validating hydroxycarbamide as a possible substitute for indefinite blood transfusion therapy in children at elevated risk for stroke. In areas of the world where chronic transfusion therapy is not feasible, hydroxycarbamide therapy may be a reasonable alternative. There is presently no optimal stroke prevention strategy for adults, but if a number of associated comorbid conditions in adults that are known risk factors for stroke, such as hypertension, hyperlipidemia, renal disease, atrial fibrillation, and coagulopathy, are addressed, the risk for stroke may be reduced.⁹

H&O How do physicians diagnose stroke in patients with SCD?

AK The best diagnostic modality for patients with SCD who present with acute neurologic symptoms is MRI with diffusion-weighted imaging (DWI) performed within the first hour after development of the neurologic deficit. This allows differentiation between an ischemic and a hemorrhagic stroke and helps to determine whether the ischemic event occurred within the previous 10 days. In addition, magnetic resonance venography (MRV) to look at the veins in the brain helps to rule out cavernous sinus thrombosis. In the rare case that MRI is not available, computed tomography also may be used for stroke detection.

H&O What is the treatment for acute stroke in patients with SCD?

AK After a diagnosis of acute stroke, emergency exchange blood transfusion therapy is preferred. Initially, a simple blood transfusion is preferred if the hemoglobin level is less than 10 g/dL, followed by an exchange blood transfusion as soon as possible. Simple transfusion or exchange blood transfusion may not be indicated if the hemoglobin level at admission is greater than 10 g/dL or less than 50% of the baseline level, respectively. Other supportive care measures should be used, such as the administration of oxygen to keep the oxygen saturation above 95%, and blood culture, antipyretics, and antibiotics in patients who are febrile.

H&O What follow-up care is required?

AK Within the next 30 days, the patient should undergo MRA to evaluate the blood vessels of the brain for vasculopathy, areas of severe stenosis, or moyamoya disease. The results of these tests determine the subsequent risk for stroke. The long-term strategy should include the following steps:

1. Discuss MRI results with the patient and family face to face in the clinic.
2. Refer the patient to a neurologist to confirm a new baseline for any focal neurologic deficit and determine the presence or absence of silent cerebral infarcts.
3. Refer the patient to a psychologist for testing to identify cognitive strengths and weaknesses and to determine the need for school or workplace accommodations.
4. Meet with the patient and family to discuss treatment recommendations when appropriate. These are based on the patient's cognitive test scores and school or work performance, and on the patient's or parents' wishes. Treatment will consist of blood transfusion therapy or hydroxyurea in special circumstances. The physician also may need to advocate for a written individualized education program (IEP) or workplace accommodations and refer adult patients to vocational and/or neurologic rehabilitation programs.
5. Perform MRI and MRA annually to evaluate for new infarcts or progressive vasculopathy. If signs of progression are seen, discuss the use of alternative therapy, such as hematopoietic stem cell transplant (HSCT), if the patient has already started regular blood transfusion therapy.

However, Hulbert and colleagues in 2011 showed that a second stroke or silent cerebral infarct occurs in 45% of children with SCD despite chronic blood transfusion therapy,¹⁰ showing that blood transfusion was palliative for secondary stroke prevention. As a result, researchers

are investigating whether HSCT can reduce the risk for a second stroke in children with SCD. Studies by Walters and colleagues¹¹ and Hsieh and colleagues¹² appear to support this approach.

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Suggested Readings

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