

4. STROKE AND NEUROLOGICAL COMPLICATIONS

Introduction

Patients with sickle cell disease (SCD) may be affected by various disorders of the central nervous system, including ischemic and hemorrhagic stroke, transient ischemic attack, silent cerebral infarction, cerebral vasculopathy, and Moyamoya disease.¹ Prevention and early recognition of the neurological complications of sickle cell disease are necessary to reduce the long-term impact of these disorders.

A. Management of Stroke in Children with Sickle Cell Disease

Principles

- To identify children with SCD who are at an increased risk of stroke, and to implement measures to prevent stroke occurrence.
- To carry a high index of suspicion in patients with clinical signs and symptoms of stroke, and to urgently implement appropriate management to reduce stroke-associated morbidity and mortality.
- To prevent the recurrence of stroke among children with SCD who have already experienced a stroke event.

Recommendations

Education, Screening and Prevention of Ischemic Stroke in Children

- Parents and caregivers of children with SCD should be educated about the common presenting signs and symptoms of stroke, and advised to present emergently to the nearest hospital if any of these symptoms occur. Teaching should be reinforced at every follow-up visit.
- Annual TCD ultrasound screening should be performed in patients with SCD starting at 2 years of age. Available literature on this subject mainly comprises patients with HbSS and HbS-beta⁰-genotypes.
- Patients with abnormal TCD screening results (TAMM velocities ≥ 200 cm/s) should have repeat testing within 2 weeks, and should be counseled regarding the risk of stroke and the benefits of prophylactic blood-transfusion therapy. Referral to a hematologist with expertise in sickle cell disease is strongly recommended.
- Where long-term transfusions are not feasible (e.g., due to red cell alloimmunization and/or family refusal), physicians should consider hydroxyurea therapy and/or a referral for hematopoietic stem-cell transplantation.^{16,17,18}
- Patients with ≥ 1 conditional TCD velocity (170 to 199 cm/s) are at risk of conversion to abnormal TCD, and are at a higher risk of developing a first stroke than are patients with normal TCDs. Currently, no specific therapeutic intervention is recommended for these patients, and no randomized control trial has been performed to assess whether there is any benefit to treating these patients. More frequent TCD screening (every 3 to 6 months), however, has been recommended for these patients.¹⁹
- For secondary stroke prevention, chronic transfusions to maintain the HbS level $<30\%$ are also recommended.²⁰ The recently published results from the Stroke With Transfusions Changing to Hydroxyurea (SWITCH) trial have demonstrated that children with SCD who have already experienced a stroke are still at risk of stroke recurrence if they are switched from chronic transfusion therapy to hydroxyurea and phlebotomy.²¹
- For patients who receive chronic red cell transfusions, optimal chelation therapy is necessary ([see Part II, section 14 on Iron Overload](#)).

Management of Acute Ischemic Stroke in Children

- Admit to hospital.
- Administer high-flow oxygen to maintain an oxygen saturation of $\geq 95\%$.
- Identify and treat airway, breathing, and circulation issues.
- Maintain hydration with intravenous and oral intake to keep the total fluid intake at maintenance rate.

- Maintain normal body temperature, normal blood pressure, normoglycemia, and control seizures.
- If there is a high index of suspicion, and CT is negative, diffusion weighted magnetic resonance imaging/angiography (MRI/MRA) of the brain is more sensitive than CT for detecting early and small infarcts as well as hemorrhagic conversion of infarcts.¹⁹ MRI may be performed acutely if a CT scan is normal, but is usually deferred until after the initiation of acute therapy.
- Exchange red cell transfusion (erythrocytapheresis) to target an HbS <30% is recommended for the acute management of acute ischemic stroke, although there are no randomized control trials to support this recommendation.
- Other risk factors for acute ischemic stroke should be excluded, including infections, Moyamoya disease, cardiac disease, arterial dissection, and prothrombotic abnormalities. Also, consider computed tomography venography/magnetic resonance venography (CTV/MRV) (especially if MRA is normal) to investigate for cerebral sinovenous thrombosis (CSVT).
- Consultations with a pediatric hematologist and a pediatric neurologist are recommended.
- The use of thrombolytic therapy is not routinely recommended in children with ischemic stroke outside of a clinical trial.²²
- Once the patient is stable, consider investigations for other potential causes of acute ischemic stroke (e.g., echocardiography, ECG, MRI/A, carotid Doppler ultrasonography, fasting lipid profile, thrombophilia investigations).
- Consider the long-term use of anti-platelet and/or anti-thrombotic therapies.
- Long-term follow-up should be coordinated between multiple disciplines, including hematology, neurology, physical therapy, occupational therapy, and speech therapy.

Management of Hemorrhagic Stroke in Children

- For hemorrhagic stroke, there is no clear evidence on the role of exchange blood transfusion in the acute phase. Long-term transfusions are often considered for maintenance therapy.
- Supportive care is the same as with acute ischemic stroke ([see Recommendations above for Acute Ischemic Stroke](#)).
- Investigate for concurrent bleeding diathesis, and correct coagulopathy, if present. Consultation with a pediatric hematologist is recommended.
- Urgent neurology and neurosurgical consultations should be obtained to evaluate for the need for surgical intervention.
- Referral for hematopoietic stem-cell transplantation (HSCT) should be considered for children with SCD who have sustained a stroke event ([see Part I, section 2 on Transfusion](#)).¹⁵

Background

Stroke is a rare but significant cause of disability in children with SCD; neurologic deficits will occur in approximately two-thirds of survivors.² SCD is the most common cause of stroke in children. Overt stroke occurred in approximately 1 in 10 children with sickle cell anemia (HbSS) in the era prior to active screening by transcranial Doppler (TCD) and the use of transfusion prophylaxis in high-risk patients.¹ By 18 years of age, the cumulative risk of overt stroke is reduced to 1.9% (95% confidence interval [CI], 0.6% to 5.9%) with active screening by TCD and transfusion as primary stroke prophylaxis.³ Patients with HbSS disease have the highest risk of stroke, and have an 11% chance of developing a first stroke by the age of 20 years compared with a 2% risk for patients with hemoglobin⁵ SC disease (HbSC).¹ Children with SCD who are between the ages of 2 and 5 years have the highest incidence of first stroke followed by those between 6 and 9 years of age.⁴ Most strokes in children with SCD are ischemic, and commonly involve the large arteries supplying the brain such as the middle cerebral and internal carotid arteries.

Primary hemorrhagic stroke is less common than arterial ischemic stroke among children with SCD. Presenting signs and symptoms of hemorrhagic stroke may include severe headache, nausea and vomiting, nuchal rigidity,

focal neurologic deficits, seizures, and altered levels of consciousness. Some factors that have been reported to be associated with hemorrhagic stroke in children with SCD include hypertension, corticosteroid use, and a recent history of blood transfusion.⁵

Clinical features of ischemic stroke include focal weakness (usually hemiparesis), seizures, altered consciousness and mentation, confusion, visual, speech, and sensory disturbances. In children, these symptoms may be transient.

Recognized risk factors for ischemic or hemorrhagic stroke among patients with SCD include high blood-flow velocity on transcranial Doppler ultrasonography, low steady state hemoglobin levels, high white-cell count, hypertension, and a recent history of acute chest syndrome.³ Genetic factors (such as a family history of SCD and stroke, comcomitant alpha thalassemia, hemoglobin F levels) and nocturnal hypoxemia may also modify the risk of stroke.^{6,7}

TCD is used as a screening tool to evaluate stroke risk among children and adolescents with SCD. TCD is a non-invasive approach for measuring the time-averaged maximum mean (TAMM) velocity in the middle cerebral artery, distal internal carotid artery, anterior cerebral artery, posterior cerebral artery, and basilar artery. Patients with TAMM velocities ≥ 200 cm/second in any of the arterial segments are considered to have abnormal results, while velocities between 170 and 200 cm/second are termed conditional. Abnormal blood velocities reflect arterial narrowing, and predict a stroke risk of 40% over the subsequent 3 years.⁸

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial showed a clear benefit for prophylactic blood transfusions in children with abnormal TCD, with a 92% reduction in stroke risk when compared with observation only.⁹ A decision-analysis model by Mazumdar *et al* suggests that the optimal stroke-prevention strategy using TCD is annual screening until age 10 years, with transfusions for children at high risk until age 18 years.¹⁰ This finding has not been evaluated within the parameters of a randomized controlled trial, however, and the optimal duration of transfusion therapy is unknown.^{11,12} During the STOP II trial, discontinuation of prophylactic red cell transfusions caused a high rate of reversion to abnormal TCD blood-flow velocities and strokes in high-risk children.¹³ A 2011 analysis of the STOP II data demonstrated that the cessation of prophylactic red cell transfusions is also associated with an increased risk of silent brain infarction in high-risk children with SCD.¹⁴

Patients with SCD who have already had a first stroke also benefit from regular blood transfusions. If left untreated, these patients have a 67% risk of a second stroke over the subsequent 9 years.¹⁵ Transfusions for primary and secondary prophylaxis of stroke are aimed at keeping the total sickle hemoglobin (HbS) level below 30%.¹¹

B. Management of Stroke in Adults with Sickle Cell Disease

Principles

- To carry a high index of suspicion in patients with clinical signs and symptoms of stroke.
- To urgently implement appropriate management to reduce stroke-associated morbidity and mortality.

Recommendations

Patient Education

- Patients and caregivers should be educated about the common presenting signs and symptoms of stroke, and advised to present emergently to the nearest hospital if any of these symptoms occur. Teaching should be reinforced at every follow-up visit.

Management of Acute Ischemic Stroke in Adults

- Admit to hospital.
- Administer high-flow oxygen to maintain an oxygen saturation of $\geq 95\%$.
- Identify and treat airway, breathing, and circulation issues.
- Maintain hydration with intravenous and oral intake to keep the total fluid intake at maintenance rate.

- Emergent imaging of the brain should be performed prior to initiating any specific therapy for treating acute ischemic stroke. Non-contrast CT is sufficient to provide this information in most cases.
- If there is a high index of suspicion and CT is negative, diffusion-weighted MRI/MRA is more sensitive than CT for detecting early and small infarcts as well as hemorrhagic conversion of infarcts.¹⁹ MRI may be performed acutely, if a CT scan is normal, but is usually deferred until after the initiation of acute therapy.
- As in the case of adult ischemic stroke in the absence of SCD, the use of a fibrinolytic agent (e.g., tissue plasminogen activator) may be considered within the first 3 hours of the acute phase.²³ Thrombolytic therapy may be pursued in consultation with a neurologist, with the caveat that its use in patients with SCD is associated with an increased risk of intracerebral hemorrhage.
- Consultations with both hematology and neurology subspecialists are recommended.

NOTE: The majority of the recommendations below are based on pediatric research literature. To date, there are insufficient data from high quality clinical trials to provide evidence-based recommendations.

- Exchange transfusion is recommended to reduce the HbS level below 30%. This recommendation is extrapolated from clinical literature, but there have been no randomized controlled trials to support this.
- Long-term simple or exchange red cell transfusion is recommended to maintain an HbS level $\leq 30\%$. Exchange transfusion, either manual or automated, is favored over simple transfusion in adults with SCD, to maintain iron balance or to assist in reducing iron overload.²⁴
- Consider hydroxyurea therapy if chronic transfusions are not feasible (e.g., due to severe alloimmunization or patient refusal).
- Once the patient is stable, consider investigations for other potential causes of acute ischemic stroke (e.g., echocardiography, ECG, MRI/A, carotid Doppler ultrasonography, fasting lipid profile, thrombophilia investigations).
- Consider the long-term use of anti-platelet and/or anti-thrombotic therapies.

Management of Hemorrhagic Stroke in Adults

- For hemorrhagic stroke, there is no clear evidence on the role of exchange blood transfusion in the acute phase. Long-term transfusions are often considered for maintenance therapy.
- Supportive care is the same as with acute ischemic stroke ([see Recommendations above for Acute Ischemic Stroke](#)).
- Investigate for concurrent bleeding diathesis, and correct coagulopathy if present. A consultation with a pediatric hematologist is recommended.
- Urgent neurology and neurosurgical consultations should be obtained to evaluate the need for surgical intervention.

Background

Although ischemic strokes are more common among individuals with HbSS who are younger than 20 years of age, patients with HbSS who are aged 30 years and older (especially those ≥ 50 years of age) are also at risk of ischemic stroke. Within the adult population of individuals with HbSS, the rate of ischemic stroke is lowest in the 20- to 29-year-old age group. Interestingly, this group of patients also had the highest incidence of hemorrhagic stroke.³

To date, there have been no clinical trials to evaluate approaches for primary stroke prevention for adult patients with sickle cell disease (SCD). The use of TCD ultrasound is not generally recommended as screening tool for the prevention of stroke among adults with SCD.²¹

C. Silent Cerebral Infarction

Principles

- To identify children and adults with SCD who have silent cerebral infarcts.
- To implement close neuroradiological and neurocognitive follow-up in children and adults with SCD.

Recommendations

- A screening MRI/MRA at least once during childhood is recommended.³⁰ The need for sedation or general anesthesia and the presence of neurocognitive abnormalities may depend upon the age at initial screening.
- Follow up MRI/MRA may be indicated if abnormal radiographic findings are found, and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.
- In the multicentre Silent cerebral Infarct Transfusion (SIT) trial, therapy with regular red cell transfusions to keep HbS<30% led to a significant reduction in the incidence of recurrent cerebral infarction in children with SCD.²⁹

Background

Silent cerebral infarcts (SCI) are more frequent than overt strokes among individuals with SCD. Upon MRI, these SCI present as abnormalities not associated with overt symptoms or focal neurological abnormalities. Silent infarcts commonly occur in the frontal and parietal lobes, and may be seen in 20% to 35% of children with SCD.²⁵ Silent infarcts are associated with impaired cognitive function and an increased risk of stroke.¹ SCI may also progress over time.²⁶ Risk factors for SCI include positive history of seizures, presence of the SEN beta-S globin gene haplotype, white blood cell (WBC) count $\geq 11.8 \times 10^9/L$ and less than one painful event per year.²⁷ In the Silent Cerebral Infarct Multi-Center Clinical Trial, lower baseline hemoglobin concentration, higher baseline systolic blood pressure, and male sex were identified as risk factors associated with SCI.²⁸ In this trial, therapy with regular red cell transfusions led to a significant reduction in the incidence of recurrent cerebral infarction in children with SCD, at the expense of increased rates of iron overload.²⁹

D. Cerebral Vasculopathy

Principles

- To identify children and adults with SCD with Moyamoya disease.
- To implement close neurological and/or neurosurgical follow-up in children and adults with SCD and Moyamoya disease.

Recommendations

Investigation

- A screening MRI/MRA at least once during childhood is recommended.³⁵ The age at initial screening may depend on the need for sedation/general anesthesia and the presence of neurocognitive abnormalities.
- Follow-up MRI/MRA may be indicated if abnormal radiographic findings are found and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.

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- Follow-up MRI/MRA may be indicated if abnormal radiographic findings are found and/or if neurocognitive difficulties occur.
- Children with SCD who are found to have cognitive/learning difficulties should also have follow-up MRI/MRA studies.
- Regular neuropsychological testing and review of school performance is recommended for school-aged children with SCD.

Management

- Moyamoya disease usually requires a referral to a neurosurgeon for possible surgical intervention with or without prophylaxis with antiplatelet agents.
- Under the direction of a neurologist, medical therapy (such as antiplatelet therapy and/or calcium channel blockers) may be used in individuals who are poor surgical candidates or those with mild disease. Short- and long-term efficacy data are very limited, however.³⁶
- Consultation with a neurology and/or stroke subspecialist is recommended for guidance on acute management and follow-up.

Background

Moyamoya disease results from progressive occlusion of the circle of Willis arteries and particularly the distal internal carotid artery (ICA) (less often the proximal anterior cerebral artery by [ACA], the middle cerebral artery [MCA], the basilar artery, and the posterior cerebral arteries [PCAs]). This progressive occlusion causes the development of characteristic collateral, the appearance of which on angiographic imaging may be described as a “hazy puff of smoke,” which is the direct Japanese translation. Children with Moyamoya disease typically develop acute ischemic stroke or transient ischemic attacks, while adults may have ischemic or hemorrhagic events.³¹ The highest known prevalence of the disease is in the Japanese population.³² Moyamoya is associated with a higher risk of cerebrovascular events among affected individuals with SCD, and more children tend to progress to occlusion than adults.³³

Diagnosis is made by MRI/MRA/cerebral angiography; diagnostic criteria using these neuro-imaging techniques have been described.³⁴

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