Acute Ischemic Stroke in Pediatric Patients

Shivam Om Mittal, MD; Sreenath ThatiGanganna, MD; Benjamin Kuhns, MS; Daniel Strbian, MD, PhD; Sophia Sundararajan, MD, PhD

A 17-year-old boy with Down’s syndrome was last known normal at 11 PM and found with right-sided weakness and facial droop at 1 AM. In the local hospital, stroke was suspected and he was flown to a tertiary care center with MRI and neurological expertise available 24 hours a day. On arrival, his National Institutes of Health Stroke Scale was 12. He had a right partial hemianopia, severe right hemiparesis, moderate dysarthria and aphasia. Emergent MRI demonstrated diffusion restriction in the left lentiform nucleus and a small area in the anterior temporal lobe with apparent diffusion coefficient correlate suggestive of acute ischemia. Magnetic resonance angiography (MRA) revealed left middle cerebral artery bifurcation occlusion, and a perfusion scan showed a large perfusion/diffusion mismatch (Figure [A] and [B]). Consent was obtained from the parents and intravenous tissue-type plasminogen activator (tPA) administered. In addition, the patient was immediately taken for endovascular thrombectomy. Conventional angiogram confirmed distal middle cerebral artery occlusion, and a Solitaire stent retriever was used to recanalize the left middle cerebral artery (Figure [C] and [D]). The patient improved dramatically over the next few hours and was discharged with an National Institutes of Health Stroke Scale of 4. The patient had an atrial septal defect, which had previously been repaired. Echocardiography showed a right to left shunt on bubble study, and he subsequently had this closed using the Amplatzer device. The rest of his work-up was negative. Note: for the purposes of this discussion, we define pediatric patients as aged <18 years although in some countries this might be defined differently.

Stroke in Pediatric Patients

Although not as prevalent in pediatric populations as in adults, stroke is an important cause of mortality and disability in children. It is among the top 10 causes of mortality in children aged 5 to 25 years. Improved neuroimaging has led to increased detection of childhood ischemic stroke, and the current estimated incidence of childhood arterial ischemic stroke is 1.6 per 100,000 children/y.1

Causes of Stroke in Children

Causes of stroke in children are varied and differ from those seen in adults. One or more risk factors can be identified in up to three fourths of children with ischemic stroke and an even greater percentage in children with hemorrhagic stroke. Only 10% to 25% of childhood strokes remain cryptogenic. Although high rates of childhood obesity and associated traditional stroke risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, have led to increased pediatric stroke rates,1 additional factors, such as congenital heart disease, prothrombotic states, nonatherosclerotic arteriopathies, head and neck trauma, and infection, are important contributors.1,2

Cardiac disease is identified in almost one third of pediatric stroke patients. Major cardiac risk factors include congenital heart disease, acquired heart disease, and patent foramen ovale.2 In addition, evaluation and treatment of cardiac disease via surgery and catheterization account for one fourth of ischemic strokes in this group of patients. Extracorporeal membrane oxygenation and the use of left ventricular assist devices are also potential causes.2 Paradoxical embolism through a patent foramen ovale or atrial septal defect may allow right to left shunt and are the most common cause of stroke in congenital cardiac and vascular malformations. Cyanotic heart disease leads to polycythemia, further increasing the risk of thrombosis and ischemia.

The incidence of prothrombotic conditions in children with ischemic stroke is reported to be as high as 5% to 13%,1,2 much higher than found in adult patients (4%). The most common reported prothrombotic conditions include protein C, protein S, plasminogen and antithrombin III deficiencies, antiphospholipid antibodies, homocystinuria, factor V leiden, and prothrombin G20210A mutations.5 Most patients with a prothrombotic state have a single cause, but in 23% of cases, multiple prothrombotic risk factors are identified.1 Unlike adults, in whom the vast majority of events related to thrombophilies are venous, there seems to be an equal incidence of arterial and venous events in children.2

Sickle cell disease is an important cause of pediatric stroke. Children, especially those <15 years, tend to have a high risk of cerebral ischemia, whereas adults with sickle cell disease are at increased risk for hemorrhage. High velocity on transcranial Doppler ultrasonography (>200 cm/s) indicates stenosis and can be used to predict which children are at high risk for stroke and should receive prophylactic transfusions to reduce the percentage of hemoglobin S, thereby lowering...
their risk. These children are also at risk for arteriopathies, such as moyamoya.

Arteriopathies are the most common sources of stroke in children. Vasculitis of the intracranial vessels secondary to meningitis, collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, Behcet disease), intravenous drug abuse (commonly cocaine and amphetamine), and primary vasculitic conditions such as polyarteritis nodosa and Wegner arteritis can cause thrombotic occlusion resulting in ischemic stroke. Ischemic infarction because of intracranial focal arteriopathy after varicella infection and herpes zoster ophthalmics are also important causes of stroke in children. Traumatic arterial dissection and subsequent embolization, secondary to sports injuries or motor vehicle accidents in children and adolescents are relatively common causes of stroke in this age group.1

Moyamoya disease is a chronic noninflammatory vasculopathy of the head and neck vessels, which causes progressive stenosis and occlusion of the distal internal carotid arteries/proximal middle cerebral arteries. This inherited disease is one of the more common vasculopathies causing stroke in children and is associated with Down’s syndrome, neurofibromatosis type I, and sickle cell disease. Surgical procedures, such as encephaloduroarteriosynangiosis, can provide additional blood flow.2

**Stroke Mimics**

The diagnosis of stroke is particularly challenging in children because of the prevalence of stroke mimics. History and physical examination alone cannot reliably distinguish stroke and mimics. Neuroimaging, usually MRI, is required to diagnose stroke in children definitively. A prospective, consecutive cohort study found that 30 of 143 (21%) patients had conditions other than cerebrovascular disease. Of these 30 patients, 37% had benign diagnoses, including complicated migraine, psychogenic weakness, and musculoskeletal abnormalities. The remaining 67% of patients with stroke mimics had more serious conditions, such as acute disseminated encephalomyelitis, intracranial hypertension, postictal paralysis, acute cerebellitis, and intracranial abscess.4 In contrast, only 4% to 9% of adult patients with an admission diagnosis of stroke were found to have an alternate diagnosis.4

**Reperfusion Strategies in Children**

The only Food and Drug Administration–approved therapy for acute ischemic stroke in adults is intravenous tPA. tPA has not been rigorously studied in children age <18 years, and potential benefits remain unproven. The American Heart Association Stroke Council outlined guidelines for management of pediatric patients with acute ischemic stroke and did not recommend the use of the intravenous tPA use outside clinical trials (class III, level of evidence C). Unfortunately, clinical trials of pediatric patients have proved difficult because of the low enrollment and are unlikely to provide definitive evidence on reperfusion strategies in children.

Although individual case reports suggest benefit, prospective registries and clinical trials have not confirmed this. Case reports from 17 children treated with intravenous thrombosis (n=6), intra-arterial thrombolysis (n=10), or mechanical thrombolysis (n=1) found no symptomatic intracranial hemorrhages. Sixteen children (94%) survived and 12 (71%) had a good outcome (modified Rankin Scale score 0 or 1), suggesting a possible beneficial role of reperfusion strategies in pediatric strokes.5 On the contrary, a retrospective review of 9257 children showed that only 0.7% of pediatric stroke patients received thrombolysis. These patients had increased mortality and intracerebral hemorrhage rates.6 A national study of 2904 children with ischemic strokes found that 1.6% received thrombolytic therapy. Those who received tPA were less likely to be discharged home and had higher rates of death and dependency.7 Importantly, these studies did not control for stroke severity, the strongest predictors of outcome. The International Pediatric Stroke Study, a multicenter, prospective registry included 687 children with acute ischemic stroke. Only 2% received tPA (9 received intravenous tPA, whereas 6 received intra-arterial tPA). Children receiving tPA were younger, more likely to receive tPA outside the established adult time frame, and tended to have poorer neurological outcomes than children in previously published case reports. It should be noted that there was a low number of patients in the International Pediatric Stroke Study, and the findings did not reach statistical significance.8

The Thrombolysis in Pediatric Stroke trial attempted to test the safety and feasibility of intravenous tPA in children with acute ischemic stroke. This open-label, prospective, 5-year multicenter international safety and dose-finding study was designed to determine the maximal safe dose of intravenous tPA (0.75, 0.9, or 1.0 mg/kg) for children aged 2 to 17 years.
Within 4.5 hours from symptom onset. Unfortunately, poor enrollment forced premature study termination.\textsuperscript{9}

Although data on the use of intravenous tPA are sparse, evidence for endovascular therapy is even sketchier. Mechanical reperfusion devices (Merci retrievers, Penumbra, and stent retrievers) are Food and Drug Administration approved for the use in adults based on data from single-arm studies, concluding that the devices were safe and effective at revascularizing occluded vessels. Pediatric patients were excluded from these studies. When used in children, Ellis et al.\textsuperscript{10} found a recanalization (partial or complete) rate of 74\% with a relatively high complication rate of 29\%. The cause of the high complication rate was not discussed, but one can speculate that smaller pediatric vessels likely contribute. Most patients in this review received intra-arterial tPA alone, whereas a minority received mechanical thrombectomy.\textsuperscript{10} Although mechanical thrombectomy is an option for children with significant neurological deficits and arterial occlusion, it remains experimental and should only be undertaken when families are aware of the risks.

**TAKE-HOME POINTS**

- Potential causes of childhood stroke are diverse and often differ from those seen in adults.
- Diagnosis of acute ischemic stroke is particularly challenging in children because of a high number of stroke mimics.
- Reperfusion strategies, including intravenous tPA and endovascular thrombectomy, have been used but remain unproven in children.

**Disclosures**

None.

**References**


**Key Words:** thrombectomy ■ thrombolytic therapy
Acute Ischemic Stroke in Pediatric Patients
Shivam Om Mittal, Sreenath ThatiGanganna, Benjamin Kuhns, Daniel Strbian and Sophia Sundararajan

Stroke. 2015;46:e32-e34; originally published online December 11, 2014;
doi: 10.1161/STROKEAHA.114.007681

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/2/e32

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/