Pediatric Stroke

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KEYWORDS

- Pediatric stroke • Thrombolytic therapy • Risk factors • Arterial ischemic stroke

KEY POINTS

- Stroke is rare in children but leads to significant morbidity and mortality.
- Emergency department physicians are likely to be the first to evaluate children suffering from a stroke and it is, therefore, important for them to recognize common presenting features and risk factors for pediatric stroke.
- Further research is needed on the acute and preventative treatments of pediatric stroke because merely applying our knowledge of stroke in adults to children is insufficient.

INTRODUCTION

Stroke is uncommon in the pediatric population. Children from neonates to adolescents may suffer from strokes, with the stroke type varying according to age. Certain children with underlying disorders are at a particular risk. Furthermore, stroke may present differently in children compared with adults. The World Health Organization defines stroke as a clinical syndrome of rapidly developing focal or global disturbance in brain function lasting more than 24 hours or leading to brain tissue death with no obvious nonvascular cause.[1] This definition excludes much of what defines stroke in children. In children, brain infarction may occur on imaging despite only transient symptoms; antecedent or ongoing infection may be associated with stroke; and in cerebral venous sinus thrombosis, isolated headache without focal neurologic disturbance may occur.[1]

Emergency department (ED) physicians are likely to be the first physicians to evaluate these patients and it is, therefore, important for them to recognize common presenting features and risk factors for pediatric stroke. The following review is intended to describe the epidemiology, clinical presentations, stroke types, associated risk

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factors, evaluation, treatment, and prognosis of pediatric stroke. A review of the literature on the use of thrombolytics in children and other therapies for stroke in children are discussed.

EPIDEMIOLOGY OF PEDIATRIC STROKE

A recent estimate of the incidence of pediatric stroke is 2 to 13 per 100,000 children per year.[1] Agrawal and colleagues[2] used a retrospective search strategy of radiology studies in addition to a search based on diagnostic coding for stroke to look at a population of 2.3 million children aged younger than 20 years in Northern California from 1993 to 2003 and found that the incidence of arterial ischemic stroke was 2.4 per 100,000 children per year, which is significantly higher than prior estimates.[2] Hemorrhagic stroke accounts for approximately half of all childhood stroke, whereas childhood cerebral venous sinus thrombosis (CVST) is rare, with an incidence of 0.67 per 100,000 children per year.[1] Gender and ethnic disparities are noted in several studies, with boys and black children at a higher risk for stroke than girls and other ethnic groups.[3,4]

PEDIATRIC ARTERIAL ISCHEMIC STROKE

Significant prehospital and in-hospital delays often exist in diagnosing children with stroke, stressing the need for educating ED physicians about pediatric stroke. In a study of 209 children aged 1 month to 18 years with arterial ischemic stroke (AIS) at the Hospital for Sick Children in Toronto, the median interval from symptom onset to AIS diagnosis was 22.7 hours. Prehospital delay (symptom onset to hospital arrival) was 1.7 hours, whereas the in-hospital delay (presentation to diagnosis) was 12.7 hours. The diagnosis of AIS was suspected on the initial assessment in only 38% of these children and only 20% were diagnosed within 6 hours. Obstacles to timely diagnosis included the lack of experience with pediatric stroke in the ED, frequent nonfocal presentations of stroke in children, a wider differential diagnosis for focal neurologic deficits in childhood, and the poor sensitivity of acute computed tomography scanning for the diagnosis of pediatric AIS.[5]

AIS in Infants and Older Children

Presentation
Children aged less than 1 year with AIS may present with focal weakness but are more likely than older children to present with seizures and altered mental status. As in adults, older children usually have hemiparesis or other focal neurologic signs, such as aphasia, visual disturbance, or cerebellar signs. Speech abnormalities and headache are difficult to detect in children aged less than 1 year because of minimal or absent expressive speech ability in this age group.[6]

Cause
Approximately half of the children presenting with AIS have at least one identifiable predisposing cause. The International Pediatric Stroke Study (IPSS) prospectively enrolled 676 children aged 29 days to 18 years with AIS. In 9% of the children, no identifiable risk factor was present. The most frequent risk factors included arteriopathies (53%), cardiac disorders (31%), and infection (24%). Other common risk factors include blood disorders and genetic conditions.[7]

In other studies, up to 30% of children with AIS have no known risk factor. The most common underlying conditions are sickle cell disease (SCD) arteriopathy and

congenital or acquired heart disease. The presence of multiple risk factors may compound the stroke risk for some children (**Box 1**).[1]

Outcome

Clinical and radiological recurrence of AIS is seen in 10% to 30% of children.[1,8,9] The mortality rate from AIS is approximately 0.08 deaths per 100,000 children per year in the United States, with a higher mortality rate found in the Southeastern United States (referred to as the stroke belt) for reasons that remain unclear.[10] Despite the neural plasticity present in children, most children with stroke have persistent disability.

Risk factors

Arteriopathies Arteriopathies are the conditions most frequently associated with pediatric AIS and may be acute, transient, or progressive. Common arteriopathies include focal cerebral arteriopathy (FCA) of childhood, moyamoya, cervicocephalic arterial dissection, and sickle cell disease.[11]

   Focal cerebral arteriopathy FCA is the term used by the IPSS group to describe an unexplained focal arterial stenosis in a child with AIS, including transient cerebral arteriopathy of childhood (TCA). In the IPSS, the only independent factor associated with FCA was recent upper respiratory tract infection.[12]

   TCA is characterized by unilateral focal or segmental stenosis of the distal carotid arteries and proximal circle of Willis vessels. The stenosis may worsen for several months after the stroke but then stabilizes and can even improve by 6 months after the presentation.[13] AIS associated with TCA typically occurs in the distribution of the lenticulostriate branches of the proximal middle and anterior cerebral arteries. Antecedent viral infections may be found in some cases of TCA, although the exact cause is unknown. Possible causes include inflammation and vasculitis caused by infection or autoimmune disease, thromboembolic arterial occlusion or stenosis, intracranial dissection, arterial spasm, and prothrombotic factors.[13]

   Postvaricella arteriopathy Varicella-associated AIS accounts for nearly one-third of childhood AIS. The most plausible mechanism is intraneuronal migration of the virus from the trigeminal ganglion along the trigeminal nerve to the cerebral arteries.[14] In a prospective study of children aged 6 months to 10 years with neuroimaging-confirmed AIS from 1992 to 1999 in Canada, 22 of 70 (31%) children with AIS had a varicella infection in the preceding year compared with 9% in the healthy population. The mean interval from varicella infection to AIS was 5.2 months. The presentation of varicella-associated strokes is less variable than nonvaricella-related AIS, with hemiparesis significantly more likely than seizures. Recurrent AIS occurred in 10 (45%) children in the varicella cohort compared with 8 (20%) children in the group without recent varicella.[14]

   Additionally, children in the varicella cohort were more likely than children in the nonvaricella cohort to have an infarct located in the basal ganglia, limited to the anterior circulation, or stenosis of a large vessel. The vascular abnormalities in the varicella cohort consisted nearly exclusively of areas of stenosis in the proximal portion of the major cerebral arteries.[14]

   Another study demonstrated that approximately one-third of children experience recurrent varicella-associated AIS up to 33 weeks after presentation despite antithrombotic prophylaxis.[15] Postvaricella arteriopathy generally takes a monophasic course with spontaneous regression of the stenosis. Occasionally, stenosis may progress for up to 6 months after stroke. AIS rarely recurs with antithrombotic prophylaxis after stenosis regression occurs, which suggests that AIS recurrence relates to acute vascular injury and thrombosis associated with the progression of vascular stenosis.[15]

Box 1
Risk factors for pediatric stroke

Cardiac

    Congenital heart defects

    Valvular heart disease

    Right-to-left shunts

    Cardiomyopathy

    Endocarditis/myocarditis

    Arrhythmia

    Cardiac tumors

    Cardiac surgery

Hematologic disorders and coagulopathies

    Anemia

    Sickle cell disease

    Dehydration

    Idiopathic Thrombocytopenia Purpura (ITP)/Thrombotic Thrombocytopenic Purpura (TTP)/Hemolytic Uremic Syndrome (HUS)

    Thrombocytosis

    Polycythemia

    Disseminated intravascular coagulation

    Leukemia or other neoplasm

    Congenital and acquired coagulation disorders

    Pregnancy and the postpartum period

Vasculitis/Vasculopathies

    Systemic lupus erythematosus

    Polyarteritis nodosa

    Takayasu arteritis

    Kawasaki disease

    Moyamoya syndrome/disease

Infection

    Meningitis/encephalitis

    Mastoiditis/otitis media

    HIV

    Varicella

    Syphilis

    Tuberculosis

    Systemic infection

Metabolic/Miscellaneous

    Homocystinuria

    Fabry disease

Organic acidemia

Hyperlipidemia

Mitochondrial encephalopathy with lactic acidosis and strokelike episodes syndrome

Menkes disease

Other Vascular

Vasospasm (subarachnoid hemorrhage)

Migraine

Carotid ligation (eg, extracorporeal membrane oxygenation)

Fibromuscular dysplasia

Cervicocephalic arterial dissection

Arteriovenous malformation

Arteriography

Hereditary hemorrhagic telangiectasia

Sturge-Weber syndrome

Intracranial aneurysm

Trauma (including nonaccidental)

Blunt and penetrating cervical trauma

Brain tumor

Drugs

Cocaine

Amphetamines

Oral contraceptives

L-asparaginase

There are no specific accepted treatment protocols for varicella-associated stroke in children. The use of steroids or antiviral drugs is controversial and is not commented on by the American Heart Association (AHA) Stroke Council Guidelines. The prevention of varicella infection via vaccination will decrease the morbidity associated with postvaricella arteriopathy. Varicella vaccine contains live attenuated virus and was recommended in 1996 as a routine immunization for young children. A retrospective study of more than 3 million children found no association between varicella vaccine and ischemic stroke.[16]

Moyamoya disease and moyamoya syndrome Moyamoya syndrome is characterized by progressive stenosis of the distal intracranial internal carotid artery (ICA) and, less often, the proximal anterior cerebral artery (ACA), middle cerebral artery (MCA), basilar artery, and posterior cerebral artery. The term moyamoya is a Japanese word meaning "puff of smoke" and refers to the appearance of deep, fine, collateral vessels seen on conventional angiography. In the United States, the incidence is 0.086 per 100,000 children. All ethnic groups can be affected by moyamoya.[17]

Children with an associated medical condition are categorized as having moyamoya syndrome, whereas those with no known risk factors are said to have moyamoya disease. Moyamoya syndrome is seen in association with neurofibromatosis, Down syndrome, Williams syndrome, sickle cell disease, and after cranial irradiation.[1]

Moyamoya disease typically presents in children, with a peak incidence at 5 years of age. Recurrent transient ischemic attacks or ischemic strokes are common during childhood. Ischemic symptoms may be triggered by hyperventilation, crying, coughing, straining, or fever. Later in early adulthood, patients may more commonly suffer from intracranial hemorrhage.[17]

Absent flow voids in the ICA, MCA, and ACA coupled with abnormally prominent flow voids from basal ganglia and thalamic collateral vessels may be demonstrated on magnetic resonance angiography. These imaging findings are virtually diagnostic of moyamoya syndrome.[17]

Moyamoya disease results in recurrent strokes with gradual neurologic and cognitive deterioration in 50% to 60% of patients if untreated. Mortality rates of up to 4.3% are seen in moyamoya disease.[17] Surgical revascularization procedures are widely used for moyamoya syndrome, particularly for patients with cognitive decline or recurrent or progressive symptoms. Direct anastomosis procedures, most commonly a superficial temporal artery to MCA anastomosis, are often technically difficult to perform in children because of the small size of scalp donor vessels or MCA recipient vessels. For this reason, newer procedures, including encephaloduroarteriosynangiosis and encephalomyoarteriosynangiosis, have been developed for indirect bypass.[1]

A modification of the encephaloduroarteriosynangiosis procedure, called pial synangiosis, has been used with encouraging results. In this procedure, the superficial temporal artery is transposed and affixed to the brain surface to promote neovascularization. A review of 143 children with moyamoya syndrome treated with pial synangiosis demonstrated marked reductions in their stroke frequency after surgery. Although 67.8% had strokes preoperatively, 7.7% had strokes in the perioperative period and only 3.2% had strokes after at least 1 year of follow-up.[18] Potential complications of surgery for moyamoya include postoperative ischemic stroke, infection, spontaneous or traumatic subdural hematoma, and intracranial hemorrhage.[17]

Cervicocephalic arterial dissection Cervicocephalic arterial dissection (CCAD) is an underrecognized cause of stroke in children. A retrospective review of 213 children aged 1 month to 18 years with AIS who were included in the Canadian Pediatric Ischemic Stroke Registry from 1992 to 2002 demonstrated that CCAD accounts for 7.5% of children with AIS.[19] Warning symptoms, including headache, vomiting, dizziness, vertigo, diplopia, confusion, neck pain, and recurrent transient ischemic attacks, were present in 37.5% of those with CCAD. One-half had a history of head or neck trauma. The clinical presentation included headache (44%), altered consciousness (25%), seizures (12.5%), and focal deficits (87.5%).[19]

The predisposing factors for CCAD include trauma, connective tissue abnormalities, fibromuscular dysplasia, and anatomic variations. Migraine, infection, and hyperhomocysteinemia have also been considered risk factors. CCAD occurs both spontaneously and after blunt or penetrating trauma. Unlike adults, CCAD in children is most commonly found intracranially. Spontaneous anterior circulation arterial dissections (ACAD), in particular, tend to be intracranial, whereas posttraumatic ACAD is more often extracranial.[20]

High-resolution magnetic resonance imaging (MRI), with fat-saturated T1 imaging of the neck, and contrast-enhanced magnetic resonance angiography can help diagnose CCAD, although conventional angiography is the gold standard for diagnosis. Arteriographic features of CCAD include the presence of a string sign; double-lumen sign; short, smooth, tapered stenosis; and vessel occlusion of a parent arter.[1]

The recurrence rate of CCAD is about 1% per year.[1] Outcomes include complete recovery in 43%, mild to moderate deficits in 44%, and severe deficits in 13%. Follow-up angiography shows the resolution of abnormalities in 60% of vessels.[19]

The goal of therapy for CCAD is to prevent additional ischemic strokes until the vessel has healed. Options include immediate anticoagulation with intravenous unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by a 3- to 6-month course of warfarin, continued LMWH, or platelet antiaggregant therapy. For patients who do not respond to medical management, proximal ligation, trapping procedures, and extracranial-intracranial bypass procedures have been attempted.[1]

SCD SCD is one of the most common causes of childhood stroke, with a rate that is approximately 300 times higher than that seen in children without SCD.[21] Eleven percent of patients with SCD have a clinically apparent stroke by 20 years of age.[22] SCD contributes to stroke development because of the persistent endothelial injury from hypoxia, increased sheer stress, abnormal endothelial adherence of sickled red blood cells, and inflammation induced by reperfusion injury.[21] Stroke is a leading cause of death in children with SCD.[23]

The risk of stroke varies with the genotype. The Cooperative Study of Sickle Cell Disease (CSSCD) reported an age-adjusted incidence of first stroke of 0.61 per 100 patient-years in SCD hemoglobin SS (Hb SS), which is higher than that for hemoglobin SC (Hb SC), hemoglobin S-beta (+) thalassemia, and hemoglobin S-beta (0) thalassemia (0.15, 0.09, and 0.08, respectively, per 100 patient-years).[22] Among these first strokes, 54% were caused by cerebral infarction, 34% by intracranial hemorrhage, 11% by transient ischemic events, and 1% had features of both infarction and hemorrhage.[22] AIS is most common in children aged between 2 years and 9 years, whereas hemorrhagic stroke is most frequent in individuals aged between 20 and 29 years.[22]

In most cases of symptomatic stroke, infarction results from large vessel occlusion usually in the distribution of the distal ICA, proximal MCA, and ACA. Moyamoya syndrome, resulting from progressive narrowing of these vessels with compensatory collateral vessel development, occurs in about one-third of patients with stroke.[21] Children with this syndrome are at a higher risk of recurrent stroke, including hemorrhagic stroke caused by the rupture of moyamoya vessels or aneurysms. The site of bleeding may be subarachnoid, intraparenchymal, intraventricular, or a combination of these locations.[22]

With the availability of better imaging techniques, like MRI and angiography and transcranial Doppler, subtle subclinical injury to the brain caused by sickle cell-related vascular compromise has been demonstrated in approximately 20% of children with SCD.[21] The cause of these ischemic lesions is small vessel occlusion, mainly in arterial border zones. These lesions are known as silent infarcts because they are asymptomatic but appear as punctate lesions in the deep white matter of the brain on MRI. However, these lesions may not truly be silent because an increasing lesion burden correlates with significant neuropsychological deficits.[21]

Symptoms of AIS in SCD may include hemiparesis, dysphasia, gait disturbance, or altered consciousness. Children with SCD do not generally die acutely of AIS, although substantial morbidity may occur. In contrast, hemorrhagic stroke commonly presents with severe headache, vomiting, stiff neck, and altered consciousness. One-quarter to one-half of children with SCD will die within 2 weeks of a hemorrhagic stroke.[22]

The major identified risk factors for AIS with relative risks (RR) in the CSSCD are prior TIA (RR 56), low steady state hemoglobin (RR 1.9 per 1 g/dL decrease), rate of acute chest syndrome (RR 2.4 per event per year), episode of acute chest syndrome within the previous 2 weeks (RR 7.0), and elevated systolic blood pressure (RR 1.3 per 10 mm Hg increase).[22] The major risk factors identified for hemorrhagic stroke are low steady state hemoglobin (RR 1.6 per 1 g/dL decrease) and increased steady state leukocyte count (RR 1.9 per 5000/μL increase).[22]

TCD is an important tool in predicting the risk for stroke in children with SCD. It is a noninvasive procedure that measures the time-averaged mean velocity of blood flow in the large intracranial vessels, which is inversely related to arterial diameter. A focal increase in velocity usually suggests arterial stenosis. Because of their anemia, children with SCD generally have higher TCD flow velocities (130–140 cm/sec) than children without SCD (90 cm/sec).[24] In children with SCD, a mean velocity greater than 170 cm/sec is considered marginal, whereas values greater than 200 cm/sec in the middle cerebral or internal carotid artery are highly associated with an increased risk of stroke. The TCD can pick up abnormalities before lesions become evident on magnetic resonance angiography.[24] TCD has become part of routine screening for children with SCD. Children at a high risk for stroke on multiple studies should be started on a stroke-prevention protocol of chronic transfusion.[25]

The ability to identify patients with SCD at a high risk for stroke provides the opportunity to prevent a first stroke in children with SCD. The Stroke Prevention Trial in Sickle Cell Anemia (STOP I trial) included 130 children with SCD with no prior history of stroke and all had a blood flow velocity greater than 200 cm/sec on 2 repeated studies. The children were randomly assigned to observation or a chronic transfusion program with a goal HbS fraction of less than 30% of total hemoglobin. The trial was prematurely terminated because of a marked benefit in the prophylactic chronic transfusion group. There was one infarct in the transfusion group compared with 10 infarctions and one intracerebral hemorrhage in the control group.[26]

Once a patient starts a chronic transfusion protocol, stopping it results in a reversion back to a high risk for stroke. This point was demonstrated in the STOP II Trial, which was similarly terminated early when a significant number of patients who stopped receiving chronic transfusion reverted to a high risk of stroke and 2 patients had a stroke. There were no strokes or reversion to high stroke risk in the patients assigned to continue transfusion.[27]

For those children with SCD presenting acutely with ischemic stroke, urgent transfusion therapy followed by immediate exchange transfusion to achieve a HbS fraction of less than 30% and hemoglobin level of approximately 10 g/dL is recommended (**Box 2**). Initial treatment also involves administering intravenous normotonic fluids to prevent dehydration. Early consultation with the hematology department is important to determine the best protocol to follow regarding hydration and transfusion. After the acute episode, these children should be treated with chronic transfusion therapy to prevent stroke recurrence, which occurs in approximately two-thirds of patients within 2 years of the initial stroke.[21,25]

At this time, no effective alternative to chronic transfusion therapy is available. Special care should be taken to minimize the adverse consequences of transfusion, which include iron overload, alloimmunization, and infection.[25] Hydroxyurea, the only Food and Drug Administration–approved drug for treating SCD, failed to show effectiveness in preventing stroke recurrence in a large multicenter trial (Stroke With Transfusions Changing to Hydroxyurea [SWiTCH] trial).[28]

Box 2
Acute management of ischemic stroke in children with SCD

- Hydration
- Urgent transfusion therapy followed by immediate exchange transfusion
- Goal HbS fraction of less than 30% and hemoglobin level of approximately 10 g/dL
- Initiation of chronic transfusion protocol to prevent stroke recurrence

Angiography should be considered carefully in all patients with SCD because angiography might promote sickling. The treatment of subarachnoid hemorrhage in children with SCD involves administering intravenous normotonic fluids to prevent dehydration. In adults, nimodepine, a calcium antagonist that improves outcomes by counteracting delayed arterial vasospasm, is indicated; the use in this setting in young children is not approved but is reasonable on an empiric basis. The adult dosage of 60 mg orally every 4 hours should be adjusted for weight. Aneurysms may be repaired when possible, either surgically or endovascularly. In children with SCD and moyamoya syndrome, surgical treatment has been used to restore the circulation of the ischemic brain area, thereby reducing the risk of ischemic stroke.[25]

Cardiac disease One-fourth to one-third of AIS in children results from cardiac disease.[1,7] Most of these occur in children already known to have a cardiac lesion at the time of their stroke. Stroke has been described with most types of cardiac lesions, although complex congenital heart lesions with right-to-left shunting and cyanosis (eg, atrial or ventricular septal defects with pulmonary hypertension) are particularly prone to cause stroke. Children with heart disease who have a low hemoglobin concentration resulting from iron deficiency seem to have a higher risk of arterial stroke. In contrast, those with a markedly elevated hematocrit may be at more risk for cerebral venous sinus thrombosis.[1] The significance of a patent foramen ovale (PFO) in a child with stroke is uncertain and finding one on diagnostic echocardiogram should not exclude further etiologic investigation.[1] Children can develop a stroke as a result of acquired disorders of the myocardium or cardiac valves. Infective endocarditis involving the left side of the heart increases the risk of stroke.[1] Although cardiac arrhythmias are an uncommon cause of stroke in children, specific types of arrhythmias have been described in children with stroke. Cardiomyopathy or myocardial infarction from various causes can lead to cardiac arrhythmia or decreased left ventricular wall motion predisposing to cerebral embolism.[1] Cardiomyopathy can occur with mitochondrial disorders, various forms of muscular dystrophy, Friedreich ataxia, some congenital myopathies, and Fabry disease. Myocardial infarction in children most often occurs in the setting of childhood polyarteritis nodosa, homozygous type II hyperlipoproteinemia, or Kawasaki disease.[1] Congestive heart failure with reduced ejection fraction increases the risk of embolism. The risk of stroke is increased for children receiving extracorporeal membrane oxygenation (ECMO).[1] Intracranial bleeds and infarction may be caused by ligation of the carotid artery and internal jugular vein, systemic heparinization, thrombocytopenia, coagulopathies, or systolic hypertension. The long-term risks of ligation of the carotid artery are not known, so an increased risk of stroke may occur as the person ages. Venous-venous (VV) ECMO does not require tying off the carotid artery. Although this may prove to have fewer risks, not all people are candidates for VV ECMO. Thromboembolic stroke can complicate cardiac catheterization and cardiac surgery. A study from the Hospital for Sick Children in Toronto found that among 5526 children less than 18 years of age with congenital heart disease who underwent cardiac surgery, the risk for AIS/CVST was 5.4 strokes per 1000 children.[29]

Anticoagulation is recommended for those children who are thought to have a high risk of embolism from cardiac disease. Surgical repair or transcatheter closure is indicated for major atrial septal defects, both to reduce the stroke risk and to prevent long-term cardiac complications.[1]

Hypercoagulable disorders One or more prothrombotic states have been identified in 20% to 50% of children presenting with AIS.[30] The presence of a prothrombotic state is often combined with other mechanisms for thrombotic vascular occlusion

and is rarely an isolated cause.[30] Children with other risk factors for stroke who also have a hypercoagulable disorder are at the highest risk for stroke.

Prothrombotic abnormalities reduce the threshold for the development of thrombosis and may be important in the pathogenesis of childhood AIS. It is valuable to identify a prothrombotic abnormality in children with AIS to provide appropriate treatment, prevent recurrences, and provide information on the risk of thrombosis in family members.[31]

In some cases, the abnormality is inherited, such as the deficiencies of coagulation inhibitors or increased activity of coagulation proteins. A recent meta-analysis of 22 observational studies that included 1526 children with AIS, 238 with cerebral venous sinus thrombosis, and 2799 control subjects, estimated the impact of thrombophilia on the risk of first childhood stroke. The highest odds ratios (OR) were found for combined genetic traits, deficiency of protein C, the presence of antiphospholipid antibodies, and elevated lipoprotein (a) (**Table 1**).[32]

Screening for inherited thrombophilia in children should be done under the guidance of a pediatric hematologist. Many of the tests are time sensitive, and interpreting the results of the screening tests can be challenging because of the variability of normative reference values in children.

In some children, acquired thrombophilia caused by underlying illness may lead to stroke such as occurs in systemic lupus erythematosus, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, malignancy, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, polycythemia rubra vera, essential thrombocythemia, and disseminated intravascular coagulation. Homocystinuria is an uncommon but well-recognized cause of both arterial and venous occlusion. Medications, including L-asparaginase and oral contraceptives, may be prothrombotic.[1]

Pregnancy is a stroke risk factor in adolescent girls. Alterations of multiple coagulation factors occur during pregnancy. The risk of both brain infarction (usually venous) and hemorrhage is increased during the 6 weeks after delivery but not during pregnancy. Although the incidence is low, ischemic stroke and intracranial hemorrhage account for at least 4.0% to 8.5% of maternal mortality in the United States. Eclampsia remains the leading cause of both hemorrhagic and nonhemorrhagic stroke.[1]

Iron deficiency anemia Previously healthy children with stroke are 10 times more likely to have iron deficiency anemia (IDA) than healthy children without stroke. Several studies suggest that IDA is a significant risk factor for stroke in otherwise healthy

Table 1 Prothrombotic conditions associated with pediatric AIS	
Condition	**OR (CI)**
Two or more genetic thrombophilias	18.8 (95% 6.5–54.1)
Protein C deficiency	11.0 (95% 5.1–23.6)
Antiphospholipid antibodies/lupus anticoagulant	7.0 (95% 3.7–13.1)
Elevated lipoprotein (a)	6.5 (95% 4.5–9.6)
Factor V Leiden mutation G1691A	3.7 (95% 2.8–4.9)
Factor II G20210A (prothrombin) mutation	2.6 (95% 1.7–4.1)
MTHFR TT genotype	1.6 (95% 1.2–2.1)

Abbreviations: CI, confidence interval; MTHFR, methylenetetrahydrafolate reductase T677T.

Data from Kenet G, Lütkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation 2010;121(16):1838–47.

children.[33,34] Several theories have been proposed to explain this finding: a hypercoagulable state directly related to iron deficiency or anemia, thrombocytosis secondary to IDA, and anemic hypoxia whereby a mismatch of oxygen supply and demand leads to ischemia and infarction.[33,35]

Vasculitis Primary vasculitides associated with stroke include Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease, and primary angiitis of the central nervous system (CNS). Secondary vasculitides are associated with collagen vascular diseases, like lupus or infections. Bacterial meningitis; viral infections, including HIV, varicella, syphilis, and CNS tuberculosis; and fungal infections can cause cerebral vasculitides resulting in stroke. CNS infections, such as meningitis and encephalitis, are associated with up to 10% of all childhood AIS.[1] Vascular inflammation, thrombosis caused by reduced cerebral perfusion in systemic hypotension, raised intracranial pressure, and low cerebrospinal fluid glucose may all contribute to stroke pathophysiology. Hypotension and hypercoagulability secondary to bacteremia or sepsis can lead to AIS.[1]

Metabolic Several metabolic conditions are associated with AIS by affecting changes in the wall of the cerebral vessels. These conditions include cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Fabry disease, Homocystinuria, and Menkes disease.

Some metabolic conditions are associated with metabolic stroke rather than arterial stroke: the syndrome of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, organic acidemias (eg, methylmalonic, propionic, isovaleric), and urea cycle disorders. These metabolic strokes may be associated with systemic illness, persistent vomiting, hypoglycemia, or diabetes.[1]

Acute management of pediatric arterial ischemic stroke

The goals of acute management in pediatric stroke are to preserve neurologic function, limit the extension of the area of infarction, and prevent early recurrent thromboembolic events. Beyond the acute phase, secondary preventative measures are of the utmost importance given the 10% to 30% recurrence rate of stroke in children.[9]

Evidence-based decision making in pediatric AIS is hampered by the lack of randomized controlled data. The current recommendations discussed here reflect the official guidelines from the American Heart Association Stroke Council, the Council on Cardiovascular Disease in the Young, and the American College of Chest Physicians (ACCP).[1,36] These recommendations (**Box 3**) are based on reviews of less-rigorous studies in the literature, expert opinion, and extrapolation from adult studies.

Box 3
Acute treatment of AIS

1. The initial therapy should be instituted with UFH/LMWH until dissection and embolic causes are excluded (AHA Stroke Council recommendation).

2. Aspirin may be an acceptable alternative at a dosage of 1 to 5 mg/kg/d (ACCP).

3. Thrombolysis cannot be endorsed for the treatment of AIS in children outside of clinical trials.

4. The treatment of adolescents who otherwise meet criteria for tissue plasminogen activator is debatable and should be considered on a case-by-case basis with consultation with a neurologist at a tertiary care center. Strict protocol needs to be followed to prevent ICH.

5. The phone number, 1-800-NOCLOTS, may be useful for consultation.

However, it should be emphasized that ischemic stroke in children is fundamentally a different illness than stroke in older adults. The mechanism of thrombus formation in adults is more commonly associated with atherosclerosis-driven platelet activation, whereas illnesses leading to fibrin clot formation are more often responsible for stroke in children. Therefore, the results of antithrombotic trials in adults are not so easily transferable to children.

Unlike adult patients, UFH or LMWH may be initiated for children with acute ischemic stroke pending evaluation of the stroke cause. Children are much more likely to suffer an AIS secondary to cervical artery dissections, vasculopathy, heritable coagulopathies, or nonatherosclerotic cardiac disease. The recommended fist-line therapy for all of these conditions is anticoagulation.[9] For children with SCD or Moyamoya disease, the initial treatment with UFH or LMWH is not indicated.[1,36] Anticoagulation in childhood AIS seems to be safe.[37]

Aspirin and related antiplatelet medications are the mainstay of secondary prevention in adults with AIS but require different consideration in children. Nonrandomized studies have found differing results as to the efficacy of antiplatelet versus anticoagulants for secondary prevention. No randomized trials of antithrombotic use in children for the management of stroke have been conducted. However, studies have demonstrated that treatment with either antithrombotic is superior to no treatment.[38,39] Dosing recommendations for aspirin are 3 to 5 mg/kg/d, with reduction to 1 to 3 mg/kg/d if gastric distress or bleeding occurs.[1,36] Plavix (clopidogrel) may be considered in children with aspirin intolerance or aspirin failure.[1]

Although there are numerous case reports of the successful use of thrombolytics, such as tissue plasminogen activator (tPA) in children with AIS, reliable multicenter randomized controlled data are lacking. There are limited published safety and efficacy data regarding the use of thrombolytics in children.[40,41] For this reason, the AHA Stroke Council and the ACCP do not currently recommend the use of tPA outside of a clinical trial.[1,36] An international multicenter clinical trial (Thrombolysis in Pediatric Stroke) examining safety, dosage, and feasibility of thrombolytics is currently underway.[42]

A gray area exists regarding the use of tPA in adolescent patients who otherwise meet the standard adult tPA eligibility criteria. There is no consensus about the use of tPA in adolescents or a commonly accepted definition as to what age defines adolescence in this circumstance. All guidelines and published data demonstrate that if thrombolytics are to be given, clinicians must adhere to standard adult protocols with regard to the dosage and the timing of therapy. Delays in administration from the onset of stroke past the accepted time ranges are likely to result in unacceptable risks of hemorrhage.[40,43]

For guidance, a pediatric stroke consultation service has been established (1-800-NOCLOTS). The telephone line is based at the Hospital for Sick Children in Toronto and is staffed by pediatric hematologists and neurologists.[44]

Supportive neuroprotective measures are important for the preservation of neurologic function and limitation of the ischemic penumbra (**Box 4**). Supplemental oxygen is recommended only when patients are hypoxemic and has not shown to be beneficial in those who are normoxemic.[1,45] Fever may worsen the degree of brain damage after AIS and should, therefore, be controlled with antipyretics. There are limited data on the role of induced hypothermia in adult patients, and there is not enough information to recommend therapeutic brain cooling for pediatric patients with stroke.[46,47] The treatment of dehydration, anemia, and hyperglycemia are recommended. In adult AIS, permissive hypertension is recommended in all but the most severe blood pressures (>220 mm Hg systolic blood pressure or >120 mm Hg diastolic blood pressure). There

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Box 4
Supportive neuroprotective measures

1. Provide supplemental oxygenation only for patients who are hypoxemic. There is no role for hyperbaric oxygen except in decompression sickness or air embolism.

2. There is no empiric treatment of seizures.

3. Provide adequate hydration with normotonic solutions.

4. Provide normalization of serum glucose.

5. There is permissive hypertension in the acute period unless anticoagulation is to be initiated.

6. Anemia should be treated.

7. Treat fever with antipyretics.

8. Although brain cooling is an appropriate treatment in neonates with hypoxic-ischemic encephalopathy, there is no role in pediatric stroke for therapeutic hypothermia outside of clinical trials.

9. There should be early consultation with neurosurgery if there is a high suspicion for increased intracranial pressure warranting the consideration of decompression.

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are no consensus guidelines addressing permissive hypertension specifically in children, but it seems rational to control excessive hypertension particularly when anticoagulant medications are being administered. Antiepileptic drugs are only recommended in patients with clinical or electrographic seizures.[1] The treatment of increased intracranial pressure in children is similar to therapies used in adults. Neurosurgery should be consulted early for consideration of decompressive surgery if there is a concern for increased intracranial pressure.

Perinatal Ischemic Stroke

Perinatal stroke refers to cerebrovascular events that occur between 20 weeks of fetal life and 28 days after birth. As in older children, strokes in neonates may be AIS, hemorrhagic, or CVST (which can cause both infarction and hemorrhage).[48] AIS is more common in the perinatal period than hemorrhagic strokes, representing approximately 80% of strokes, and may be caused by arterial occlusion, hypoperfusion in watershed territories, or venous outflow obstruction.

Epidemiology

The incidence of perinatal AIS is 10 times greater than that of childhood stroke and ranks second only to the ischemic strokes in the elderly population. Because of the lack of prospective studies on the incidence of perinatal strokes, estimates are based on retrospective cohort studies. The annual incidence of perinatal AIS is 29 per 100,000 live births or 1 per 3500.[2]

Presentation

Unlike older children and adults, the clinical presentation of neonates with cerebral infarction can be subtle and nonspecific. Seizures are the presenting symptom in 85% to 90% of infants with perinatal AIS[49] and may be clonic, tonic, or focal (typically contralateral to the affected hemisphere in unilateral cerebral infarction). Seizure onset from AIS typically occurs on the first day of life, with 90% presenting within the first 3 days of life. Perinatal AIS is diagnosed in 10% to 15% of neonates with seizures.[49]

Most cases of AIS result from arterial infarction in the distribution of the MCA. Therefore, the arm and face are likely to be more affected than the leg.[50] Infants with

unilateral lesions may have a hemiparesis but this can be difficult to detect in infancy. It may appear as asymmetry of spontaneous movements. Mild quadriparesis in the case of bilateral brain lesions is usually not detected until late infancy. Other presentations may include apnea, lethargy, and poor feeding.[48,49]

Cause

The causes of perinatal AIS can be embolic from cardiac origin, thrombotic from disturbed hemostasis, or related to disorders of the cerebral arteries. These disorders may originate from maternal, placental, or fetal/neonatal conditions alone or in combination. Newborns are at risk for emboli to cerebral vessels from thrombosis of placental vessels that may lead to emboli being released into the fetal circulation as the placenta separates at birth. Additionally, venous clots can pass through the PFO and proceed to the cerebral vessels. Other right-to-left shunts can occur in the presence of congenital heart disease. Emboli can also be a result of iatrogenic causes, such as indwelling umbilical vessel catheters.[48]

Coagulation disorders, which have been identified in half of the infants and children with stroke, may be an even greater risk factor in newborns. Inherited prothrombotic disorders that are probable risk factors for perinatal AIS include antiphospholipid antibodies/lupus anticoagulant; factor V Leiden; congenital deficiency of proteins C, S, or antithrombin; increased lipoprotein (a); prothrombin gene mutation; and methylenetetrahydrafolate reductase T677T genotype (MTHFR).[48]

Evaluation

Following a thorough examination and neurologic assessment, the evaluation of a neonate with suspected stroke should include a complete blood count with differential blood and cerebrospinal fluid analysis with cultures, serum electrolyte analysis, and urine toxicology screening. For persistent seizures, studies to detect inborn errors of metabolism should be considered. Herpes encephalitis may have a similar presentation and, if suspected, antiviral therapy should be started and continued until all relevant tests prove normal.[50]

In cases of confirmed infarction, further evaluation includes a cardiac echo to exclude an underlying cardiac abnormality as well as an amplitude integrated electroencephalogram (aEEG) or full EEG. Confirmation of normal clotting status is needed early; although genetic prothrombotic disorders may be tested for at any time, protein-based assays should be performed soon after symptom onset and repeated 3 to 6 months later if abnormal. A detailed maternal, family, pregnancy, and delivery history should be taken and, if possible, placental assessment should be performed.[50]

Outcome

Long-term disabilities after a perinatal stroke include cognitive and sensory impairments, cerebral palsy, and epilepsy.[49,50] The recurrence risk for cerebral events after perinatal AIS is low, roughly 1% to 8%.[1,49] Factors associated with an increased recurrence rate include thrombophilic states and comorbidities, such as congenital heart disease or dehydration. Unilateral AIS is not associated with an increased mortality unless there are other complicating conditions.[50]

Treatment

In the acute phase of perinatal AIS, supportive measures, such as the maintenance of normal hydration, temperature, electrolyte, hematologic, oxygenation, and acid-base status are recommended. Anticonvulsants may be given along with antibiotics or antivirals if sepsis is suspected.[50] Randomized controlled trials addressing the acute or chronic treatment of perinatal stroke are not available. The ACCP recommends the

administration of UFH or LMWH in neonates with a first AIS only if an ongoing cardioembolic source can be documented. The AHA Stroke Council also recommends UFH or LMWH in severe thrombophilias.[1] Otherwise, anticoagulation or antiplatelet therapy is not recommended in neonatal stroke because the risk of recurrent stroke is low and the lesion is not thought to extend further by the time the diagnosis is made.

Hemorrhagic Transformation of Pediatric AIS

There are limited data available regarding hemorrhagic transformation of AIS in children. It may occur within 30 days of symptom onset in 30% of children and is mostly asymptomatic. It has been shown to occur less frequently in children with vasculopathy as the cause of AIS and has not been associated with anticoagulation versus antiplatelet therapy. Similar to adults, larger infarct volume may be associated with hemorrhagic transformation and worse outcome.[51]

CVST

CVST is a rare but important form of stroke that results from thrombosis of the dural venous sinuses, which drain blood from the brain. The incidence of childhood CVST is 0.67 per 100,000 children per year from term birth to 18 years of age, with neonates composing 43% of the patients.[52] Venous congestion can lead to both parenchymal ischemia and hemorrhage. Subarachnoid and subdural hemorrhages are less frequent. The superficial venous system is more frequently involved than the deep system, and the most common sites of CVST are the transverse, superior sagittal, sigmoid, and straight sinuses.[53]

CVST in Neonates

Neonatal CVST presents similarly to perinatal AIS (see section on perinatal AIS presentation). It may arise because of damage to cerebral sinus structures caused by molding of the cranium from birth or from placental lesions that may lead to an inflammatory and prothrombotic state in the placenta and fetus.[50] Neonates also have reduced levels of circulating anticoagulant proteins and relative dehydration and hemoconcentration, which could also lead to a prothrombotic state.[54] Prothrombotic states have been identified in 20% of neonates with CVST.

Risk factors
Perinatal complications (51%) and dehydration (30%) were the most frequent illnesses found in 69 neonates with CVST in the Canadian Pediatric Ischemic Stroke Registry. The perinatal complications included hypoxia at birth, premature rupture of membranes, maternal infection, placental abruption, and gestational diabetes.[52]

Outcome
Among neonates with CVST, neurologic deficits have been observed in 28% to 83% of patients. Studies have demonstrated a mortality rate of 7% to 8%.[54]

Treatment
The role of anticoagulation in neonatal CVST is controversial because recurrent CVST is rare. However, the extension of the initial thrombus in the week following diagnosis occurs less often in neonates on anticoagulation therapy compared with those not treated with anticoagulation.[55] The ACCP and the AHA Stroke Council guidelines recommend treatment of neonates with CVST without significant intracranial hemorrhage using UFH or LMWH initially, followed by LMWH or warfarin for 6 to 12 weeks.[1] For neonates with CVST and significant hemorrhage, radiological monitoring is

recommended with commencement of anticoagulation therapy if extension of the thrombus occurs 5 to 7 days after the initial hemorrhage.[50] The safety of anticoagulation in neonates is yet to be fully studied. However, in a small study of 10 neonates with CVST and unilateral thalamic hemorrhage, 7 were treated with LMWH without any side effects.[56]

CVST in Infants and Older Children

Presentation

The clinical manifestations of CVST in children are subtle and nonspecific. An altered level of consciousness and encephalopathy, focal neurologic deficits (cranial nerve palsies, hemiparesis, hemisensory loss), and diffuse neurologic symptoms (headache, nausea, emesis) may result. Focal and diffuse neurologic signs are more common in older infants and children than seizures.[52]

Risk factors

The conditions that are associated with CVST in children outside of the neonatal period include common childhood illnesses, such as fever, infection, and anemia, and medical conditions, such as congenital heart disease, nephrotic syndrome, systemic lupus erythematosus, and malignancy. Otitis media and mastoiditis, meningitis, head trauma, and recent intracranial surgery are strongly associated with CVST. Prothrombotic states have been identified in 24% to 64% of children with CVST.[53] Dehydration is another important risk factor for pediatric CVST, which can be caused by increased fluid loss or poor oral intake.[53]

Outcome

CVST-specific mortality is less than 10%, but motor and cognitive sequelae may require long-term rehabilitative regimens. Between 10% and 20% of children who have CVST will experience a recurrent symptomatic venous event, at least half of which are systemic rather than cerebral.[53]

Treatment

Many infants and older children receive anticoagulation in the acute setting with UFH or LMWH or oral warfarin. This regimen is often followed by chronic anticoagulation with LMWH or warfarin for 3 to 6 months. There are no randomized data on thrombolysis, thrombectomy, or surgical decompression for CVST.[53]

HEMORRHAGIC STROKE
Presentation

Children younger than 6 years of age with hemorrhagic stroke are more likely to present with altered mental status and seizures, whereas older children more commonly present with headache and focal neurologic signs. The typical pattern of presentation is the abrupt onset of clinical signs followed by progressive neurologic deterioration.[57]

Cause

Childhood hemorrhagic stroke, which includes spontaneous intraparenchymal and nontraumatic subarachnoid hemorrhages, accounts for approximately half of all childhood strokes. It tends to be associated with intracranial vascular anomalies (48%) or medical disorders, such as hematologic abnormalities (10%–30%) or brain tumors (9%), whereas in a significant minority of children, no identifiable cause is identified (19%).[57]

Intracranial vascular anomalies include arteriovenous malformations, aneurysms, and cavernous malformations. Hematologic causes of intraparenchymal hemorrhage include thrombocytopenia, hemophilia, von Willebrand disease, and coagulopathy secondary to hepatic dysfunction or vitamin K deficiency. Brain hemorrhage is estimated to occur in 0.1% to 1.0% of children with idiopathic thrombocytopenia purpura and in 2.9% to 12.0% of children with hemophilia. Hemorrhagic stroke in the context of SCD is common, as described previously in this article.[58]

Hemorrhagic Stroke in Neonates

Hemorrhagic stroke in the perinatal period can occur from conversion of ischemic infarction of arterial or venous origin or via intraparenchymal hemorrhage from vascular anomalies or bleeding diatheses. In a retrospective study from 1993 to 2003 in California, 20 cases of perinatal hemorrhagic stroke were described. The rate of perinatal hemorrhagic stroke in this population was 6.2 per 100,000 live births.[59] All of these patients presented with encephalopathy; 65% had seizures and 5% had focal weakness. Nineteen of the 20 were intracerebral hemorrhages and one was a subarachnoid hemorrhage. No causes for hemorrhage were identified in 15 patients. Four patients had thrombocytopenia and one had a cavernous malformation as the cause. Predictors of perinatal hemorrhage included fetal distress, emergency caesarian section delivery, prematurity, and postmaturity. Birth weight was not found to be a predictor. Neonates with a history of ECMO, coarctation of the aorta, and venous thrombosis are also at risk for hemorrhagic stroke.[59]

Outcome

Hemorrhagic stroke has a higher mortality than AIS. Limited data exist on outcomes. Studies have shown that the ratio of hemorrhage volume to brain volume positively correlates with increasing disability and poorer quality of life. Initial Glasgow Coma Score, hemorrhage location, and ventricular involvement do not seem to predict outcomes.[57]

Approximately one-third of children have a good outcome with little impairment, another third have deficits that range from moderate to severe, and one-third die of acute hemorrhage, recurring hemorrhage, or from an underlying disorder. Very few children develop epilepsy.[57]

The 5-year cumulative recurrence rate for hemorrhage is approximately 10%.[60] To prevent recurrence in children with intracranial vascular anomalies, the anomalies should be corrected when possible. Microsurgery, radiosurgery, and embolization are among the treatment options.

Treatment

A child with acute hemorrhagic stroke should be monitored in a pediatric intensive care unit. Although an awake patient can be monitored noninvasively, those children who demonstrate significant alteration of mental status should have intracranial pressure monitoring with the measurement of cerebral perfusion pressure.[60]

Children should neither be given hypotonic fluids nor be allowed to take anything by mouth to prevent cerebral edema and aspiration respectively. Blood pressure, body temperature, and blood sugar should be kept in the normal range for age. Neurologic examinations to check for signs of increased intracranial pressure and herniation should be conducted frequently. Some patients will require interventions, such as hyperosmotic treatments for elevated intracranial pressure or surgical management.[60]

Repeat computed tomography (CT) scans to look for hydrocephalus, extension of intracerebral hematoma, herniation, or vasospasm, in cases of subarachnoid

hemorrhage, may be needed if further deterioration occurs. Patients who have cardio-pulmonary compromise may need ventilatory or circulatory support.[60] If patients have a known disorder of hemostasis, specific treatment to address this disorder is needed. Patients may also require medications to control seizures.[57]

DIFFERENTIAL DIAGNOSIS OF PEDIATRIC STROKE

The differential diagnosis of pediatric stroke is broad because numerous other conditions can present with acute neurologic deficits (**Box 5**).[61]

DIAGNOSTIC EVALUATION OF CHILDREN WITH SUSPECTED STROKE

Children who are suspected of having a stroke should undergo urgent neuroimaging (**Box 6**). If neuroimaging is not immediately available, consideration should be given to transferring the child to a hospital with neuroimaging and neurosurgical and intensive care capabilities. The least invasive study that will provide an adequate assessment is usually the test to perform. If immediately available, general consensus is that MRI is an ideal method to evaluate neonates, infants, and children with suspected stroke.[1]

MRI studies should include sequences to detect hemorrhage, delineate anatomy, characterize focal lesions, and determine if a stroke is acute, subacute, or chronic. These studies may include T1, T2, fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI) sequences.[1]

The temporal evolution of diffusion abnormalities on MRI is distinct in neonates compared with older children and adults. DWI may underestimate the extent of infarct during the first 24 hours and after day 5 in neonates. T2 and FLAIR MRI sequences are more reliable than diffusion at day 7 and later in term newborns.[62]

Box 5
Conditions that mimic stroke in children

Brain tumor

Structural brain lesions

Prolonged postictal paralysis (Todd)

Migraine

Familial alternating hemiplegia

Metabolic stroke

Idiopathic intracranial hypertension

Intracranial infection (brain abscess, meningoencephalitis), acute disseminated encephalomyelitis

Reversible posterior leukoencephalopathy syndrome

Postinfectious cerebellitis

Musculoskeletal conditions

Nonaccidental trauma

Drug toxicity

Psychogenic conditions

Data from Shellhaas RA, Smith SE, O'Tool E, et al. Mimics of childhood stroke: characteristics of a prospective cohort. Pediatrics 2006;118(2):704–9.

> **Box 6**
> **Emergent neuroimaging for suspected pediatric stroke**
>
> *CT brain without contrast to exclude hemorrhage and mass effect if MRI is unattainable*
>
> - Consider CT angiography/venography
>
> *MRI with diffusion-weighted sequences*
>
> - Excludes hemorrhage
> - Defines the extent and territory of infarct
> - Diffusion imaging differentiates acute from chronic infarct
>
> *MR angiography (MRA)*
>
> - Defines vascular anatomy of the circle of Willis vessels and neck vessels
>
> *MR venography (MRV)*
>
> - Excludes CVST
>
> *Axial T1-weighted MRI of the neck with fat saturation sequence*
>
> - Excludes CCAD
>
> *Conventional angiography*
>
> - Consider if normal coagulation and no obvious cause for hemorrhage on MRA and MRV or ischemic stroke with normal MRA, MRV, and T1 MRI with fat saturation of neck
>
> *Data from* Pappachan J, Kirkham FJ. Cerebrovascular disease and stroke. Arch Dis Child 2008;93(10):890.

In addition, MR angiography (MRA) of the head is used to evaluate the intracranial large arteries, whereas MRA of the neck helps evaluate the extracranial large arteries. Axial T1-weighted MRI of the neck with fat saturation should be performed to exclude arterial dissection. MR venography (MRV) should be considered to look for CVST. MRA or conventional angiography (CA) is rarely used in neonates; however, MRA and MRV will provide the best means to evaluate for vascular trauma and congenital vascular anomalies causing perinatal stroke.[62]

Typical MRI sequences require 3 to 5 minutes each to acquire, and the assessment for cerebrovascular disease takes from 15 to 35 minutes. Patient movement during image acquisition will render most sequences useless. Consequently, successful MRI requires considerable patient cooperation, and most children require sedation.[1]

In contrast, CT scans can be completed in a matter of seconds, often reducing the need for sedation. CT uses ionizing radiation, a particular concern for children because recent studies have demonstrated a relative increased lifetime cancer risk even with low radiation doses. Unenhanced CT is a sensitive means of detecting intracranial hemorrhage and mass effect. However in the early acute phase, AIS is often missed until at least 6 hours after onset of symptoms.[1] Although CVST is sometimes evident on unenhanced CT, these lesions are more reliably identified with MRI and MRV by demonstrating a lack of flow in the cerebral veins with or without brain infarction. Unenhanced CT scans may detect deep venous thrombosis as linear densities in the deep or cortical veins. As the thrombus becomes less dense, contrast may demonstrate the empty delta sign, a filling defect, in the posterior part of the sagittal sinus. CT scan with contrast misses the diagnosis of CVST in up to 40% of patients.[53]

CT is the ideal imaging technique in unstable patients or patients in whom acute intracranial hemorrhage is likely. Children who have cochlear implants, cardiac

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Box 7
Studies to consider in the evaluation of children with acute stroke

Brain imaging

Electrocardiogram/echocardiogram

Complete blood count

Coagulation studies

Fibrinogen

Erythrocyte sedimentation rate

Serum electrolytes

Hepatic transaminases

Coagulability studies (with hematology consultation)

Hemoglobin electrophoresis

Cholesterol and triglycerides

Serum amino acids/urine organic acids

Toxicology screen

Pregnancy test (adolescent girls)

Lactate

Lumbar puncture (consider with caution if risk of herniation)

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pacemakers, or other contraindications to MRI are best evaluated with CT. CT angiography and venography may also be performed.[1]

Cranial ultrasound is used routinely for neonatal imaging and can be performed until the closure of the anterior fontanelle. Although ultrasound is often used to detect intraventricular hemorrhage and periventricular leukomalacia, it is less sensitive than CT and MRI in the detection of cerebral ischemic lesions. CVST is a difficult diagnosis to confirm with ultrasound. Ultrasound imaging of the posterior fossa is also limited.[1]

CA can establish the cause of stroke in most children but is the most invasive of imaging options.[58] Most children require general anesthesia to undergo CA. During the first year of life, the risk of CA is increased because of the small size of the vascular tree, so the decision to perform angiography in these younger patients must be weighed carefully. In many instances, MRA or CT angiography will suffice in these patients. Diagnostic CA may need to be done in concert with therapeutic endovascular procedures even in this very young population.[63]

There are no guidelines addressing laboratory or ancillary testing for the assessment of pediatric stroke (**Box 7**). Tests to look for specific causes of stroke, such as coagulopathies, cardiac disease, or hematological disorders, should be considered with guidance from multidisciplinary consultation with pediatric hematologists, neurologists, radiologists, and any other relevant specialists.

SUMMARY

Pediatric stroke is a rare but important entity. There are age-specific differences in the causes, manifestations, and treatment of stroke in children of which ED physicians need to be aware to ensure prompt diagnosis and treatment of children with stroke syndromes. Although large clinical trials are difficult to conduct in children with stroke

because of its low incidence and heterogeneity of causes, continued research and additional experience are needed. Randomized controlled trials are needed to establish the safety and efficacy of acute and preventative treatments of pediatric stroke. It is clear from a review of the literature on stroke in children that merely applying our knowledge of stroke in adults to children with stroke is insufficient.

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