Stroke in Neonates and Children

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Education Gaps

1. Pediatricians should be aware of the appropriate initial evaluation of suspected stroke in children to combat documented delays in diagnosis of greater than 24 hours. (1)

2. Pediatricians should be aware of primary and secondary prevention measures for stroke in at-risk populations, such as transcranial Doppler ultrasonography screening for children with sickle cell disease.

3. Pediatricians must recognize the clinical findings associated with childhood stroke, including ischemic and hemorrhagic stroke, understand the prognosis for each type of stroke, and delineate optimal ongoing management and rehabilitation.

Objectives   After completing this article, readers should be able to:

1. Describe the pathophysiology of stroke in infants, children, and adolescents.

2. Recognize the clinical findings associated with childhood stroke and with arteriovenous malformations and other cerebrovascular abnormalities predisposing to childhood stroke.

3. Delineate the appropriate initial evaluation of suspected stroke in children.

INTRODUCTION

Stroke in children is surprisingly common, affecting 1 in 1,600 to 4,000 neonates at birth (2)(3) and 2.3 to 13 per 100,000 older children per year. (4)(5)(6) Strokes can occur in seemingly healthy infants, children, and adolescents. Despite the plasticity of the developing brain, stroke in children carries substantial morbidity. Early recognition of childhood stroke by pediatric clinicians is crucial for the rapid implementation of targeted and neuroprotective therapies. Clinicians should be familiar with risk factors for pediatric stroke and appropriate prevention strategies. Finally, pediatricians are key members of an integrated, multidisciplinary approach to stroke treatment and rehabilitation.

This review begins with a discussion of stroke in children older than 28 days, followed by a discussion of perinatal stroke (before 28 days of age) because strokes in these 2 age groups have distinct mechanisms and presentations. We conclude with a discussion of long-term prognosis and systems of care for infants and children who experience stroke. Although evidence to guide treatment of pediatric stroke is growing, many recommendations remain based on expert consensus. Developmental and etiologic differences in children limit extrapolation from the adult stroke experience to pediatric patients. Registries such as the International Pediatric Stroke Study have provided a wealth of knowledge, and clinical trials in pediatric stroke have begun.

CHILDHOOD STROKE: DEFINITIONS AND PATHOPHYSIOLOGY

As with adult stroke, pediatric stroke can be divided into ischemic and hemorrhagic stroke. Ischemic stroke is defined as focal damage to an area of brain tissue within a vascular territory due to loss of blood flow or oxygenation. It differs from diffuse hypoxic-ischemic injury in its mechanisms and distribution. Ischemic stroke, which represents 55% of pediatric strokes, can be subdivided into injuries caused by arterial ischemic stroke (AIS), which is due to loss of arterial flow, or venous infarction, which is due to loss of flow in a draining cerebral vein or venous sinus. Cerebral sinovenous thrombosis (CSVT), which involves obstruction by clot of a major venous sinus draining the brain parenchyma, can lead to infarcted brain parenchyma; other components of the venous system such as the deep medullary veins or cortical veins can also thrombose. Finally, the arterial occlusion in AIS can be by 1 of 2 mechanisms. Localized ("in situ") thrombus formation may result from hypercoagulable states or develop in response to localized endothelial damage and luminal narrowing such as from arterial dissection, inflammation, or vasculopathy. Thromboembolism occurs when a clot formed elsewhere in the body, such as the heart, other arteries (as from dissection), or in the venous system in the presence of a venous-to-arterial shunt, travels and becomes lodged in a cerebral artery. Transient ischemic attack (TIA) has been defined in adults as the sudden onset of focal neurologic symptoms that resolve fully within 24 hours without radiologic evidence of ischemia. TIA has been less studied in children, but in 1 series, 6% of children with transient neurologic symptoms had ischemia on acute imaging and 13% of children with TIA eventually had strokes. (7)

Hemorrhagic stroke includes spontaneous hemorrhage within the brain parenchyma (intraparenchymal hemorrhage) and spontaneous (nontraumatic) subarachnoid hemorrhage immediately adjacent to the surface of the brain. Hemorrhage produces focal brain damage through localized mass effect and ischemia of adjacent tissues. Causes include CSVT, trauma, rupture of vascular malformations, and hemorrhage into the area of an ischemic stroke (arterial or venous) due to impaired vasoregulation and vessel friability. Subdural and extradural hemorrhages are not typically considered a type of stroke. (8)

CHILDHOOD STROKE: CLINICAL MANIFESTATIONS

Sudden-onset focal neurologic deficits constitute the clinical hallmarks of stroke, but they occur in only 85% of affected children. As in adults, sudden onset of lateralized motor deficits, speech disturbance, or fixed gaze deviation could indicate a stroke in the anterior arterial circulation (anterior cerebral and middle cerebral arteries arising from the internal carotid artery) on 1 side. However, posterior circulation strokes (from the vertebrobasilar circulation supplying the posterior cerebral, cerebellar, and brainstem arteries) can produce alteration of mental status, dizziness, vomiting, ataxia, and eye movement abnormalities. Figure 1 shows selected symptoms of stroke in major affected vascular territories; other symptoms or symptom combinations may also be seen.
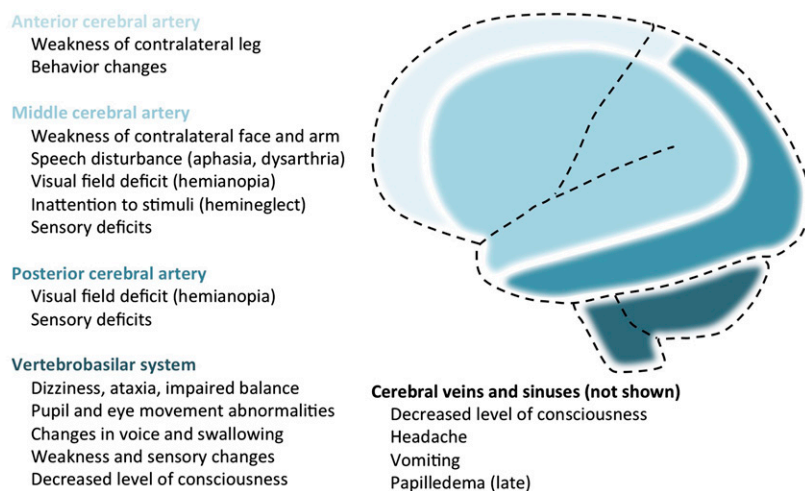
Despite the definition of stroke as a focal injury, more than 60% of children with ischemic or hemorrhagic stroke have been reported to display generalized signs and symptoms that are less readily localized to a single vascular territory or brain region. Approximately 50% of children with AIS present with altered mental status. Headache has been observed in 40% of children with AIS, 46% with hemorrhagic stroke, and 51% with TIA.

Finally, seizure serves as a sentinel sign of acute stroke in 31% of children, including up to 46% of younger children, compared with only 5% of adult strokes producing early seizure. In 1 study, postictal Todd paralysis occurred in only 13.4% of adult patients with known focal epilepsy, typically resolving within minutes. Based on the estimated incidence of new-onset focal epilepsy in children of 12.5 to 25 per 100,000 per year, the incidence of new-onset focal epilepsy with Todd paralysis is approximately comparable to the incidence of pediatric stroke. Accordingly, Todd paralysis should remain a diagnosis of exclusion. Hemiparesis lasting more than a few minutes after a seizure and/or a first-time focal seizure in a child without a history of focal epilepsy should prompt consideration of acute stroke. Seizures arising from an area of infarction may also rapidly generalize, obscuring their focal onset.

CHILDHOOD STROKE: EPIDEMIOLOGY AND ETIOLOGY

Stroke incidence across the lifespan follows a U-shaped curve: the risk of stroke during the neonatal period (see the section

Figure 1. Selected symptoms of stroke in children. The symptoms vary by the vascular territory affected. This figure depicts major manifestations of stroke in the anterior, middle, and posterior cerebral arteries as well as the vertebrobasilar system that supplies the cerebellum and brain stem. Venous stroke and cerebral sinovenous thrombosis may cause focal and/or diffuse deficits. Stroke may also produce other symptoms, and a stroke in a given vascular territory may not produce all of the listed symptoms.

Anterior cerebral artery
Weakness of contralateral leg
Behavior changes

Middle cerebral artery
Weakness of contralateral face and arm
Speech disturbance (aphasia, dysarthria)
Visual field deficit (hemianopia)
Inattention to stimuli (hemineglect)
Sensory deficits

Posterior cerebral artery
Visual field deficit (hemianopia)
Sensory deficits

Vertebrobasilar system
Dizziness, ataxia, impaired balance
Pupil and eye movement abnormalities
Changes in voice and swallowing
Weakness and sensory changes
Decreased level of consciousness

Cerebral veins and sinuses (not shown)
Decreased level of consciousness
Headache
Vomiting
Papilledema (late)

on Perinatal Stroke in this article) is nearly as high as in older adulthood. Among children older than age 1 month through adolescence, the combined incidence of ischemic and hemorrhagic stroke in the United States has been reported to be 2.3 to 4.6 per 100,000 children per year (4)(5); a population-based study in France found an incidence of 13 per 100,000 children per year. (6) This is comparable to the incidence of pediatric brain tumors. Some of these incidence figures exclude stroke in the setting of trauma and meningitis, and there remains a concern that some children with stroke remain undiagnosed or that available research tools do not capture all cases.

About 50% of patients with pediatric AIS are known to have a risk factor predisposing to stroke at the time of stroke diagnosis (Table 1). Ultimately, after thorough evaluation, approximately 40% of children with AIS will be found to have 1 clinical factor associated with AIS, and about 50% will have 2 or more factors, often with a combination of longstanding and newly discovered factors. In at least 10% of cases, however, no risk factor can be identified. (9) Similarly, 90% of children with hemorrhagic stroke have at least 1 identifiable risk factor (Table 2). (9)

Given the prevalence of identifiable risk factors for pediatric stroke, an evaluation in search of a cause of stroke is warranted. Identification of underlying causes is important not only to direct immediate management and long-term preventive therapy but also to understand prognosis, including risk of recurrence. For example, genetic or acquired abnormality of the cerebral arteries is referred to as arteriopathy, which is the most common risk factor for pediatric AIS, occurring in 53% of cases. Consequently, all children with acute stroke should receive vascular imaging to assess for arteriopathy. The presence of arteriopathy can change acute

and ongoing medical therapy and increases the recurrence risk to 66%.

The next section discusses the most important conditions associated with childhood stroke, but clinicians should note that many conditions can predispose to more than 1 of the classification categories of stroke. For example, among the major causes of AIS are sickle cell disease and cardiac disease, but these conditions or their therapies can also predispose to hemorrhage in some cases. Major causes of both arterial and venous ischemic stroke include prothrombotic conditions and infection. Finally, although underlying vascular anomalies are the major cause of hemorrhagic stroke in children, hemorrhage can also occur subsequent to ischemic stroke, called hemorrhagic conversion.

CHILDHOOD STROKE: MAJOR ASSOCIATED CONDITIONS

Sickle Cell Disease
One of the most common arteriopathies associated with childhood stroke is sickle cell disease (SCD), a disorder of hemoglobin affecting 1 in 5,000 US children, including 1 in 365 children of African ancestry. Mutations in the *HBB* gene produce the S form of hemoglobin, with 95% of hemoglobin in the form of HbS in children homozygous for the sickle cell allele (HbSS) or with sickle β-zero thalassemia (HbSβ°). The HbS molecules polymerize, leading to the characteristic "sickle" shape of red blood cells. This leads to stroke in 3 ways. First, sickled cells cannot pass easily through small arterial and capillary beds, leading to vaso-occlusion in the brain and other parts of the body. Second, sickled cells hemolyze or sequester in the spleen, leading to anemia and diminished oxygen-carrying capacity supply relative to demand that further worsens ischemia. Third, SCD is a disorder not

only of erythrocytes but also of arteries, with chronic inflammation and vascular damage, which can adversely affect blood flow.

Ischemic stroke occurs in 11% of patients with SCD by age 20 years, which is 200 times greater than children without SCD. Further, the risk of recurrence is 70%. Stroke in small vessels is due to microvascular occlusion with platelet activation and fibrin deposition. Stroke in large vessels is related to endothelial damage that activates the coagulation cascade and stimulates hyperplasia of the vessel wall with luminal narrowing. This sickle cell-associated arteriopathy is the strongest predictor of stroke risk in children with SCD due to arterial stenosis, occlusion, or friability. Hemorrhagic stroke occurs more in older adolescents and young adults with SCD due to vascular fragility, development and rupture of aneurysms, or the hemorrhagic conversion of a large ischemic stroke. Clinically silent strokes, detected on magnetic resonance imaging (MRI) in up to 30% of children with SCD, contribute to neurocognitive deficits.

The standard of care for stroke prevention in children ages 2 to 16 years with SCD is annual screening with transcranial Doppler ultrasonography (TCD). TCD measures the velocity of blood flow, which increases as arteries narrow. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) randomized children with high-risk TCD velocity greater than 200 cm/second to monthly transfusions or standard care. Transfusion reduced the annual incidence of stroke from 10% to less than 1%. The National Heart, Lung, and Blood Institute, therefore, recommends TCD screening no less than annually, with increased screening frequency if there are abnormal results and initiation of regular transfusion if TCD velocities are repeatedly elevated. The Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) showed that transfusion also decreases recurrence of silent strokes. Recently, the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial evaluated hydroxyurea for secondary stroke prevention as an alternative to transfusion for children with transfusional iron overload but found it not to be effective. Finally, stem cell transplantation may be considered and can be curative. (10)

Other Arteriopathies

Moyamoya syndrome is a progressive narrowing of the distal internal carotid or proximal anterior or middle cerebral arteries. Its name is derived from the Japanese term for the "puff of smoke" appearance of the compensatory collateral vessels found on conventional angiography. Moyamoya vasculature may be idiopathic, especially in people of East Asian descent. It may also be seen in association with sickle cell disease, neurofibromatosis type 1, after head and neck

TABLE 1. Medical Conditions Associated With Childhood Arterial Ischemic Stroke and Cerebral Sinovenous Thrombosis

Vasculopathy:
- Sickle cell disease
- Moyamoya syndrome
- Alagille syndrome
- Radiation vasculopathy
- Arterial dissection
- Collagen vascular disorders:
  o Ehlers-Danlos type IV
  o Marfan syndrome
  o *COL4A1* mutations
  o Fibromuscular dysplasia
- Focal cerebral arteriopathy
- Primary angiitis of the central nervous system
- Systemic vasculitides and autoimmune disorders:
  o Wegener granulomatosis
  o Microscopic polyangiitis
  o Polyarteritis nodosa
  o Takayasu arteritis
  o Systemic lupus erythematosus
  o Mixed connective tissue disease
  o Henoch-Schönlein purpura
  o Hemophagocytic lymphohistiocytosis
  o Kawasaki disease
  o Inflammatory bowel disease
  o Human immunodeficiency virus
- Vasospasm:
  o Reversible cerebral vasoconstriction syndrome
  o Subarachnoid hemorrhage
  o Cocaine use

Prothrombotic conditions:
- Polycythemia
- Deficiency of protein C, protein S, antithrombin III
- Factor V Leiden mutation/activated protein C resistance
- Prothrombin 20210 gene mutation
- Elevated factor VIII
- Elevated von Willebrand factor antigen

Continued

TABLE 1. (Continued)

- Hyperhomocysteinemia; if present, assess for the methyltetrahydrofolate reductase gene polymorphism
- Elevated lipoprotein(a)
- Antiphospholipid antibodies
- Migraine with aura
- Estrogen-containing oral contraceptive use
- Pregnancy and postpartum
- Malignancy
- L-asparaginase and other chemotherapeutics

Cardiac disorders:

- Congenital heart disease, especially with right-to-left shunt
- Cardiac catheterization or surgery
- Extracorporeal membrane oxygenation
- Left ventricular assist devices
- Endocarditis
- Valvular abnormalities
- Cardiomyopathy

Genetic/metabolic disorders:

- Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Homocystinuria
- Fabry disease
- Organic acidemias:
  - Glutaric aciduria type II
  - Methylmalonic acidemia
  - Propionic acidemia
  - Isovaleric acidemia
- Congenital disorders of glycosylation
- Adenosine deaminase 2 deficiency
- Sulfite oxidase deficiency

Infection:

- Meningitis
  - *Streptococcus pneumoniae*
  - Tuberculosis
  - *Aspergillus* species
- Varicella vasculopathy
- Sinusitis
- Mastoiditis
- Sepsis

irradiation, and in trisomy 21. Children with moyamoya syndrome may present with stroke or recurrent TIA, especially after hyperventilation or dehydration. Revascularization surgeries use the external carotid branches to revascularize the obstructed intracranial circulation.

Arterial dissection disrupts the vessel wall, with resultant extravasation of blood into the wall. It causes luminal narrowing and exposes thrombogenic wall components that can lead to vessel obstruction. Predisposing injuries involve a sudden, rapid torsion of the head and neck, as can occur in sports, motor vehicle crashes, and with chiropractic neck manipulation. The injury may precede symptoms by days or weeks. However, dissection may occur spontaneously in healthy children or in those with connective tissue disorders. Clinicians should pay attention to personal or family history of joint hypermobility, unusually distensible skin with impaired wound healing, easy bruising, or abnormalities of other arteries or the heart.

TABLE 2. Medical Conditions Associated With Childhood Hemorrhagic Stroke

Vascular anomalies:

- Arteriovenous malformation
- Arteriovenous fistula
- Aneurysm
- Cavernous malformation
- Capillary telangiectasia
- Venous angioma

Vasculopathy:

- Sickle cell disease
- Moyamoya syndrome

Coagulation disorders:

- Thrombocytopenia
- Hemophilia
- Hepatic failure
- Vitamin K deficiency
- Anticoagulant therapy

Other:

- Brain tumor
- Hemorrhage due to cerebral sinovenous thrombosis*
- Hemorrhagic transformation of ischemic infarction*

See tables of conditions associated with these conditions.

Vasculitis is a relatively rare inflammation of the blood vessels that may be isolated to the cerebral vasculature (primary angiitis of the central nervous system [PACNS]) or associated with systemic vasculitides. One type of vasculitis, large-to-medium-sized vessel PACNS, leads to irregularity and stenosis of large- and medium-sized vessels, sometimes leading to stroke. PACNS may progress over time. Focal cerebral arteriopathy of childhood is a transient arterial narrowing found in 13% of children who have AIS. This may be linked to current or recent infections with varicella or other common childhood pathogens.

Cardiac Disorders

Cardiac disorders are the second most common risk factor for pediatric AIS, found in 18% of neonates and 31% of non-neonates with AIS. The presence of cardiac disorders, especially congenital heart disease, is likely to be known before the stroke. Consequently, affected children can be treated prophylactically to prevent stroke. Further, parents should receive education regarding signs and symptoms that might warrant rapid evaluation for acute stroke.

Most cardiac disorders produce embolic strokes from either intracardiac thrombi or paradoxic embolism via right-to-left shunts across atrial or ventricular septa, with a higher rate of multiple infarcts often involving both hemispheres and/or both anterior and posterior circulations. This is especially true of children with cyanotic congenital heart disease. Children with cardiac disorders treated with systemic anticoagulation are also at higher risk of hemorrhagic stroke. Acquired cardiac disease such as cardiomyopathy, valvular disease, or endocarditis can lead to stroke in up to 20% of cases. Anticoagulation of stroke in infective endocarditis is not generally recommended because of the high risk of hemorrhage of septic aneurysms. (11)

Children with heart disease also have an increased risk of stroke associated with surgical repair requiring bypass (5.4 AIS or CSVT per 1,000 surgeries) or during cardiac catheterization (AIS in 0.38%-1.3%). Diagnosis of stroke during these times may be delayed due to postsurgical sedation and medical fragility. Hemorrhagic stroke or AIS occurs in 7% to 11% of children requiring extracorporeal membrane oxygenation and 28% to 34% of those who receive ventricular assist devices.

Prothrombotic Conditions

Thirteen percent of children with arterial stroke and up to 67% with venous stroke are found to have a hereditary thrombophilia, a genetic tendency toward thrombus formation. A 3-generation family history may be suggestive, with stroke or myocardial infarction before age 50 years, unprovoked deep vein thrombosis or pulmonary embolus, or women with 2 or more miscarriages as indicators. Even in the absence of a family history of thrombophilia, testing for specific conditions is reasonable because their presence may affect the type or duration of therapy selected for stroke prophylaxis (Table 1 and Fig 2).

Several acquired conditions also predispose to stroke. Migraine with aura, but not migraine without aura, has been shown to double the risk of stroke in adults, and data suggest similar increases in adolescents. Estrogen-containing oral contraceptive pills are associated with a 2- to 2.5-fold increased risk of ischemic stroke, although the risk is dose-dependent. Stroke risk is also increased during pregnancy. Young women should be counseled about these risks and encouraged to avoid modifiable risk factors such as smoking. Progestin-only pills, implants, depot injections, and intrauterine devices are recommended for young women at a high risk of thrombosis.

Both systemic malignancy and its treatment increase stroke risk in children. Malignancy can be an acquired hypercoagulable state promoting formation of in situ thrombosis or thromboembolism. Cranial irradiation can lead to radiation vasculopathy with stenosis of vessels in the radiation field that produces ischemic stroke as well as to the formation of cavernous malformations that can result in hemorrhagic stroke. Chemotherapeutic agents, particularly L-asparaginase, predispose to venous thrombosis. Foreign bodies such as arterial or venous catheters in children with malignancy or other major medical conditions can act as a nidus for formation of thrombi that may then embolize.

Infection

Concurrent infection is a common scenario for stroke that is present in as many as 1 in 3 affected children. Head and neck infections outside the brain, such as otitis media, sinusitis, and neck infections, may promote thrombus formation in adjacent arteries and veins, some of which communicate with the intracranial system. Meningitis is complicated by stroke in up to 25% of cases; cerebral vessels coursing through inflamed meninges may develop vasculitis, vasospasm, and consequent thrombosis. The inflammatory or hypercoagulable state in the 3 days following even a minor infection has been found to increase the odds of stroke 12-fold. Infection may also act, in part, by triggering focal cerebral arteriopathy.

Cerebrovascular Abnormalities

Vascular anomalies (Table 2) account for about 45% of nontraumatic hemorrhagic strokes in children. Arteriovenous malformations (AVMs), in which abnormal arteries connect directly to draining veins without an intervening capillary bed, are especially common (Fig 3). Children may
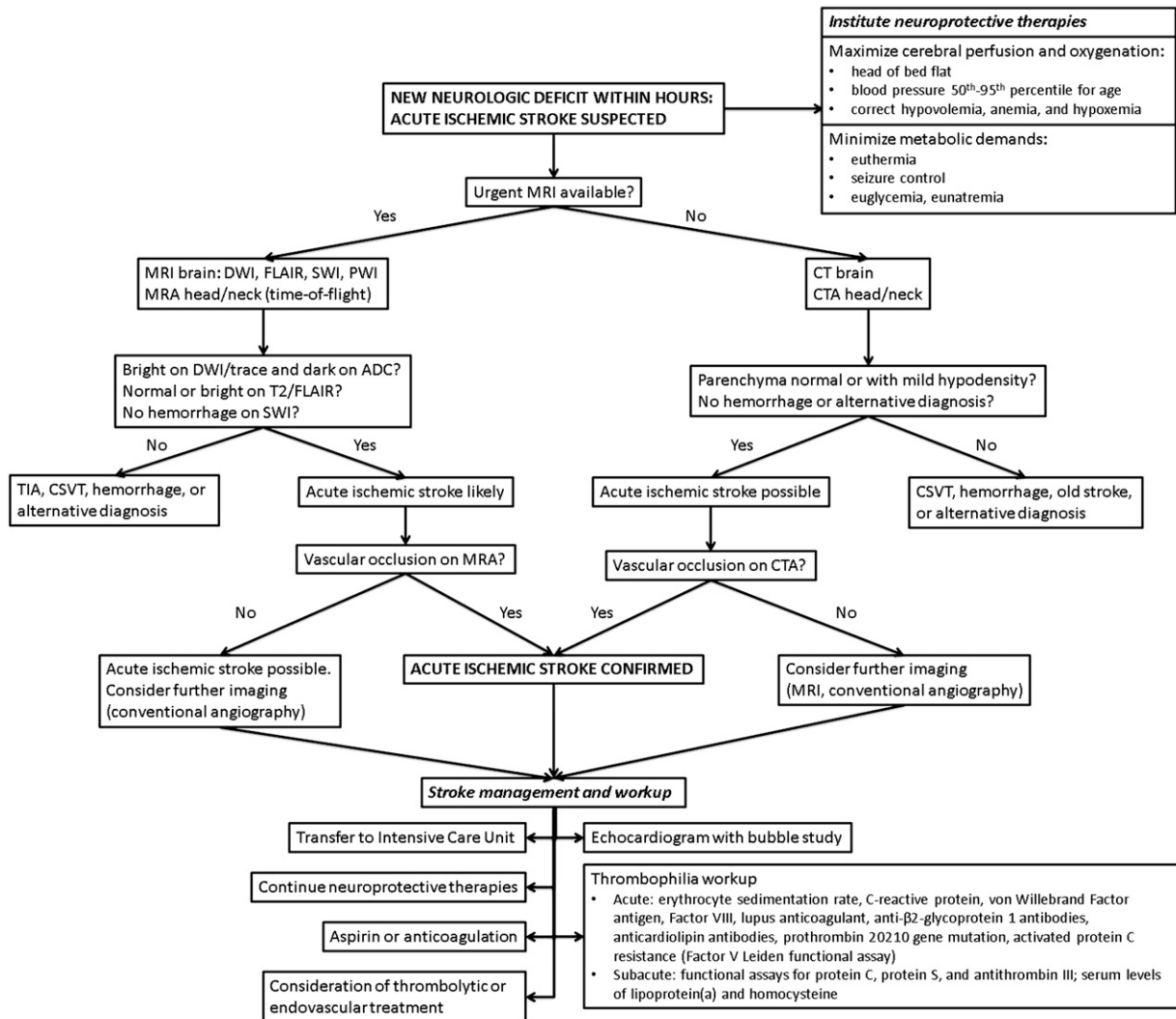
NEW NEUROLOGIC DEFICIT WITHIN HOURS: ACUTE ISCHEMIC STROKE SUSPECTED

Institute neuroprotective therapies

Maximize cerebral perfusion and oxygenation:
- head of bed flat
- blood pressure 50th-95th percentile for age
- correct hypovolemia, anemia, and hypoxemia

Minimize metabolic demands:
- euthermia
- seizure control
- euglycemia, eunatremia

Urgent MRI available?

Yes → MRI brain: DWI, FLAIR, SWI, PWI / MRA head/neck (time-of-flight)

No → CT brain / CTA head/neck

MRI branch: Bright on DWI/trace and dark on ADC? Normal or bright on T2/FLAIR? No hemorrhage on SWI?
- **No** → TIA, CSVT, hemorrhage, or alternative diagnosis
- **Yes** → Acute ischemic stroke likely → Vascular occlusion on MRA?
  - **No** → Acute ischemic stroke possible. Consider further imaging (conventional angiography)
  - **Yes** → **ACUTE ISCHEMIC STROKE CONFIRMED**

CT branch: Parenchyma normal or with mild hypodensity? No hemorrhage or alternative diagnosis?
- **Yes** → Acute ischemic stroke possible → Vascular occlusion on CTA?
  - **Yes** → **ACUTE ISCHEMIC STROKE CONFIRMED**
  - **No** → Consider further imaging (MRI, conventional angiography)
- **No** → CSVT, hemorrhage, old stroke, or alternative diagnosis

Stroke management and workup
- Transfer to Intensive Care Unit
- Continue neuroprotective therapies
- Aspirin or anticoagulation
- Consideration of thrombolytic or endovascular treatment
- Echocardiogram with bubble study

Thrombophilia workup
- Acute: erythrocyte sedimentation rate, C-reactive protein, von Willebrand Factor antigen, Factor VIII, lupus anticoagulant, anti-β2-glycoprotein 1 antibodies, anticardiolipin antibodies, prothrombin 20210 gene mutation, activated protein C resistance (Factor V Leiden functional assay)
- Subacute: functional assays for protein C, protein S, and antithrombin III; serum levels of lipoprotein(a) and homocysteine

Figure 2. Suggested diagnostic approach to ischemic stroke in children. The diagnosis of acute ischemic stroke (within hours of onset) in children is ideally established by urgent stroke-protocol magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head and neck. Computed tomography (CT) scan with computed tomography angiography (CTA) showing a vessel occlusion is an alternative when MRI or MRA is unavailable. Supportive and diagnostic measures should be instituted simultaneously. ADC=apparent diffusion coefficient, CSVT= cerebral sinovenous thrombosis, DWI=diffusion-weighted imaging, FLAIR=fluid-attenuated inversion recovery, PWI=perfusion-weighted imaging, SWI=susceptibility-weighted imaging, TIA=transient ischemic attack.

have multiple AVMs, especially in genetic syndromes such as hereditary hemorrhagic telangiectasia, or an AVM with associated aneurysm. Symptomatic aneurysms are relatively rare in children but are associated with conditions such as aortic coarctation, polycystic kidney disease, sickle cell disease, Ehlers-Danlos type IV, and fibromuscular dysplasia.

Unruptured AVMs or other direct arteriovenous connections such as fistulas and vein of Galen malformations may present in infancy with high-output heart failure due to arteriovenous shunting and hydrocephalus due to mass effect. Older children with AVMs or clusters of thin-walled capillaries called cavernous malformations may develop seizures, headache, or focal neurologic deficits. The annual hemorrhage risk for known AVMs is 2% to 4% and for cavernous malformations is 4.5%, so close monitoring by a pediatric neurosurgeon with serial imaging and the assessment of surgical risk/benefit, depending on size and symptoms, is advisable.

CHILDHOOD STROKE: DIAGNOSIS

Differential Diagnosis

The differential diagnosis for pediatric stroke is broad (Table 3). Urgent MRI is an important aid for identifying "stroke mimics" that are nevertheless important to diagnose promptly, including hemorrhage, intracranial infection,
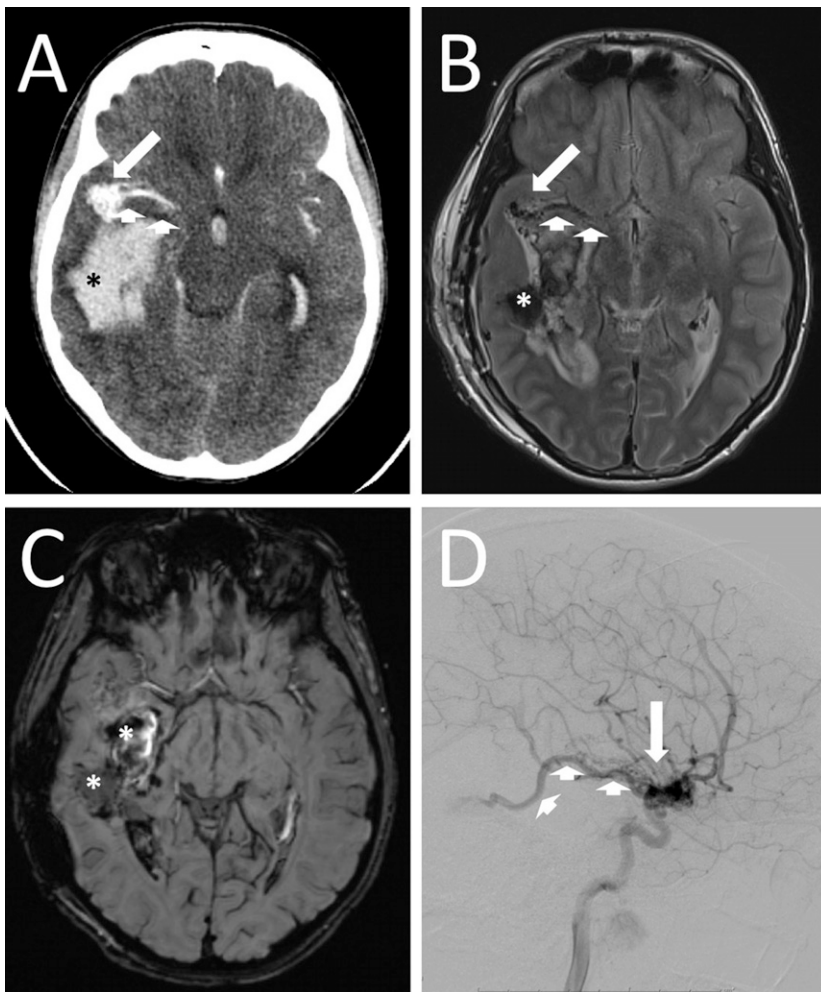
Figure 3. Hemorrhagic stroke due to ruptured arteriovenous malformation. A 14-year-old previously healthy boy developed headache and emesis that progressed to obtundation. A. Axial computed tomography scan with contrast shows a right temporal arteriovenous malformation (arrow) fed by branches of the middle cerebral artery (arrowheads), with intraparenchymal hemorrhage (asterisk). B. Axial T2-weighted magnetic resonance imaging better delineates the nest of abnormal vessels (arrow) fed by an enlarged middle cerebral artery (arrowheads) and adjacent intraparenchymal and intraventricular hemorrhage (asterisk). C. Hemorrhage is also visible on postoperative axial susceptibility-weighted magnetic resonance imaging. D. Conventional angiography shows the malformation (arrow), with rapid contrast filling of a draining vein (arrowheads). He has a left hemiparesis and hemianopia.

inflammatory diseases, posterior reversible leukoencephalopathy syndrome, malignancy, and other causes of elevated intracranial pressure. (12) Seizure with or without postictal deficits is part of the differential diagnosis but is also a presenting feature of childhood stroke. Complicated migraine is a diagnosis of exclusion, and headache is common at stroke presentation; the level of suspicion for stroke should remain high, particularly in children with identified risk factors or without prior history of migraine.

The first step toward recognition of stroke in a child is, therefore, its inclusion in the differential diagnosis of sudden-onset neurologic deficits, including seizure and nonfocal deficits, even in a child without predisposing risk factors. Despite the prevalence of stroke in children, difficulty with prompt recognition by parents can delay the presentation of affected children to the hospital for evaluation. In addition, failure to consider stroke as an etiologic possibility by clinicians can contribute to further delay in diagnosis. When studied, the average delay from symptom

onset to diagnosis of AIS in children repeatedly exceeds 24 hours. (13) Median time from symptom onset to hospital arrival was only 1.7 hours in 1 study of non-neonates, but an average of 29 hours elapsed from symptom onset to diagnosis of stroke, nearly 13 hours of which elapsed in hospital. Common themes in studies of delay in diagnosis include lack of parent and clinician recognition, lack of utilization of emergency transportation, delay in imaging acquisition, and use of nondefinitive imaging such as computed tomography (CT) scan rather than MRI. In a study of 88 children ultimately confirmed to have AIS, the first physician to assess the patient documented a suspicion of stroke in only 23 cases (26%), despite nearly all children having previously recognized risk factors. (14)

Recommended Diagnostic Approach

Once stroke is considered, further examination, initiation of imaging, and institution of supportive therapy should proceed concurrently. The Pediatric National Institutes of Health

TABLE 3. Selected Differential Diagnoses of Pediatric Stroke

- Complicated migraine
- Seizure/postictal symptoms not due to stroke
- Hemorrhage (hemorrhagic stroke, traumatic hemorrhage)
- Intracranial infection (meningitis, abscess)
- Trauma
- Tumor
- Demyelinating disease (multiple sclerosis, acute disseminated encephalomyelitis)
- Posterior reversible encephalopathy syndrome (PRES)
- Toxic exposure
- Metabolic derangement
- Idiopathic intracranial hypertension (pseudotumor cerebri)
- Postinfectious process (cerebellitis, acute cerebellar ataxia)
- Musculoskeletal cause of weakness
- Somatoform disorder

Stroke Scale (PedNIHSS) is an 11-item scale to assess the severity of stroke. It has been validated for use in children and infants and is available online for free (http://stroke.ahajournals.org/content/42/3/613/suppl/DC1).

Our recommended approach to patients with suspected acute stroke is presented in Fig 2. This approach enables rapid identification and differentiation of ischemic and hemorrhagic stroke, which have substantially different acute treatments. Ischemia can be seen within minutes of onset as restricted diffusion on diffusion-weighted MRI. CT scan is less sensitive for ischemic lesions in general and usually demonstrates changes consistent with stroke only hours after its onset. MRI is, therefore, the preferred mode of imaging. Both susceptibility-weighted MRI and CT scan can show hemorrhage. Evaluation of the blood vessels of both the head and neck is important to understand stroke mechanism and can be performed initially by time-of-flight or contrast magnetic resonance angiography (MRA) or contrast CT angiography. Conventional catheter angiography should be considered for patients in whom there is a high level of concern for vasospasm, moyamoya physiology, other vasculopathy, or vascular malformation if noninvasive tests are unrevealing.

CHILDHOOD STROKE: ACUTE CARE

Acute Stroke-directed Treatment

Observational studies report the use of intravenous tissue plasminogen activator (tPA) in pediatric patients, but safety and efficacy have not yet been established by prospective study. The Thrombolysis in Pediatric Stroke (TIPS) Trial was a phase I multicenter study evaluating the safety and pharmacokinetics of tPA in pediatric patients but was closed early due to low enrollment. Currently, 22 centers treat children with tPA according to the TIPS protocol of 0.9 mg/kg (maximum 90 mg) administered within 4.5 hours of symptom onset. Work is ongoing in collecting experiences with tPA from these sites and in planning future trials. Endovascular therapies, including intra-arterial tPA and mechanical thrombectomy, are increasingly used for acute revascularization in adults with ischemic stroke and are used in children on a case-by-case basis.

Three sets of consensus-based guidelines address the use of aspirin versus anticoagulation for initial management of acute stroke in children. The American Heart Association/American Stroke Association guidelines state that anticoagulation with low-molecular weight heparin or unfractionated heparin may be considered for up to 1 week after stroke if dissection, vasculopathy, unrecognized heart disease, or significant hypercoagulability are not yet ruled out. (15) The United Kingdom Royal College of Physicians recommends aspirin in the initial period and anticoagulation if extracranial arterial dissection is confirmed. (16) The American College of Chest Physicians guidelines recommend either aspirin or anticoagulation during the period of initial evaluation. (17)

In children with sickle cell disease, the mechanism of stroke is different and treatment is directed toward reducing the proportion of sickled red cells and reestablishing cerebral vascular patency. Exchange transfusion should be performed urgently to decrease the fraction of HbS to below 30%. Transfusion may also be appropriate in the setting of acute anemia.

For CSVT, anticoagulation with either intravenous unfractionated heparin or subcutaneous low-molecular weight heparin is considered reasonable in patients who do not have significant intracranial hemorrhage in association with thrombosis. About 30% of CSVTs propagate, and of these, 40% develop venous infarction. Of note, in children with CSVT and milder hemorrhage, the benefits of preventing further infarction and hemorrhage by anticoagulation are generally believed to outweigh the risks of worsening the existing hemorrhage. (18)

Other Acute Neuroprotective Care

Stroke entails a mismatch between the available supply of oxygen and energy substrates and the brain tissue's demand for them. Early identification of stroke in children is no less important than in adults because acute neuroprotective strategies (Fig 2) maximize supply and minimize demand,

especially while some tissue may be ischemic but not yet infarcted. Maintenance of blood pressure between the 50th and 95th percentile for age, sex, and height maximizes forward flow through stenotic arteries or collateral vessels to preserve regional cerebral perfusion while minimizing hemorrhage risk from hypertension. Minimization of metabolic demand entails aggressively treating fever and seizures. There is no evidence at this time to support therapeutic hypothermia or prophylactic anticonvulsant use in children with stroke. Metabolic derangements such as serum glucose and sodium abnormalities should be corrected.

Because of their greater brain volume relative to skull size compared to adults, children are at an even higher risk of poststroke edema. Neurosurgical consultation and intracranial pressure monitoring should be considered, especially with large-territory strokes or strokes in the posterior fossa. Hyperosmolar therapy and even decompressive hemicraniectomy may be necessary in severe cases, such as malignant middle cerebral artery syndrome, in which edema within a large area of infarcted tissue leads to life-threatening elevations in intracranial pressure.

CHILDHOOD STROKE: CHRONIC TREATMENT AND SECONDARY PREVENTION

The risk of stroke recurrence varies widely by cause from 6% to 40% for all children to up to 66% 5-year AIS recurrence in children with documented arteriopathy. Between 10% and 20% of children with CSVT have a second systemic or cerebral venous thrombosis. In children with known vascular anomalies or other chronic medical conditions, the risk of recurrent hemorrhagic stroke is 10% to 13%.

In general, the 3 available guidelines recommend anticoagulation for secondary ischemic stroke prophylaxis if there is a confirmed dissection, cardioembolic source, or certain thrombophilias, with the duration of treatment depending on the condition. If these are not present, the recurrence risk is lower, and aspirin (3 to 5 mg/kg per day) is reasonable for secondary stroke prevention. Aspirin should be held during influenza or varicella infections to minimize the risk of Reye syndrome, but in all other cases, disruptions in aspirin therapy should be minimized, with the awareness that stroke risk also increases around biologic stresses such as illness and procedures. The optimal duration of therapy is unknown. Secondary prevention of CSVT and hemorrhagic stroke depends on the cause.

PERINATAL STROKE: DEFINITIONS, PATHOPHYSIOLOGY, AND PRESENTATION

Perinatal stroke denotes central nervous system injury due to focal interruption of blood supply occurring between 20 weeks' gestation and 28 days after birth. Although this includes in utero stroke, most perinatal strokes are believed to occur within hours to days of delivery (Fig 4). Focality differentiates neonatal stroke from the more global hypoxic-ischemic injury, although the risk factors overlap.

Unlike older children, neonates rarely manifest stroke as a unilateral motor deficit. The most common presentation is focal or generalized seizure 12 to 72 hours after delivery, occurring in 70% to 90% of infants. Stroke is the second most common cause of seizure in term neonates. Among neonates who have stroke, 36% to 63% have encephalopathy: they are either irritable and hypertonic or lethargic and hypotonic, and often feed poorly.

"Presumed perinatal stroke" indicates a stroke identified in a child older than 28 days but without a clinical history of an acute neurologic event, thereby implying that the stroke most likely occurred undetected in the perinatal period. Presumed perinatal strokes often manifest as an early hand preference or delayed motor milestones. They may also produce focal seizures or infantile spasms. Imaging shows a chronic focal injury in an appropriate vascular territory (Fig 5).

PERINATAL STROKE: EPIDEMIOLOGY AND ASSOCIATED CONDITIONS

The perinatal period carries the highest risk of stroke in the pediatric age range. Stroke affects about 1 in 1,600 to 4,000 births, (2)(3) including 1 in 140 preterm births (at or before 34 weeks' gestation). Approximately 80% of neonatal strokes are ischemic and 20% are CSVT or hemorrhage. Ischemic strokes may be arterial or venous, and arterial strokes may be due to thromboembolism or in situ thrombosis, as in older children. Neonatal ischemic stroke is believed to result from a confluence of risk factors that involve the mother, the fetus/infant, and the placenta (Table 4); multiple risk factors are often present. Both fetal and maternal coagulability are increased during the peripartum period. Subacute or chronic stressors in utero may decrease tolerance of the stresses of labor, leading to an acute stroke around delivery.

PERINATAL STROKE: DIAGNOSIS

If available, MRI with vessel imaging is the optimal imaging modality to detect and characterize stroke in neonates and to differentiate stroke from diffuse hypoxic-ischemic injury. As in older children and adults, evidence of restricted diffusion is indicative of a stroke occurring within the preceding hours to days, enabling early detection and approximate

Figure 4. Acute perinatal arterial ischemic stroke. A term infant with uncomplicated pregnancy and delivery presented with right eye twitching within 24 hours of birth. Axial magnetic resonance imaging showed restricted diffusion indicating acute ischemia (bright on trace image [A] and dark on apparent diffusion coefficient map [B]) occupying the entire left middle cerebral territory (arrows). C. Sulcal effacement and obliteration of the gray-matter/white-matter junction are seen on the axial T2 sequence. D. Magnetic resonance angiography showed absent flow signal in the expected location of the left middle cerebral artery (MCA) due to occlusion (solid arrows indicate expected course as compared to white outlined arrows that indicate course of right MCA). He developed infantile spasms at 5 months. At 13 months, he had a spastic hemiparesis, could sit but not crawl, and had no specific words.
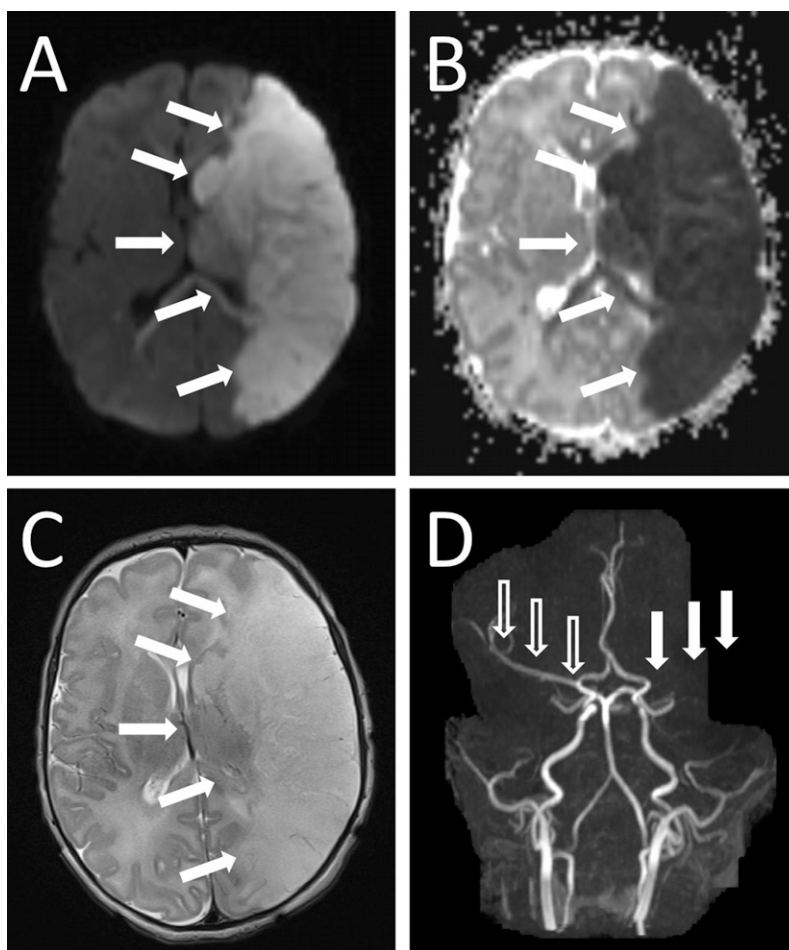
timing of the injury. Optimal visualization is at 2 to 4 days. Susceptibility-weighted imaging can visualize hemorrhage. MRA and venography can readily identify arterial or vascular occlusions.

CT scan is quicker and can detect hemorrhage and some ischemic strokes but may miss venous thromboses and small or early ischemic strokes. CT angiography can identify vascular abnormalities. The ionizing radiation exposure of CT scan, especially with angiography, must be taken into account. Head ultrasonography is the least sensitive modality for detection and characterization of ischemic strokes and CSVT. Conventional angiography is technically challenging in neonates and rarely indicated for stroke.

The evaluation should include assessment for cardioembolic sources and hypercoagulability, as in older children. Echocardiography with bubble study often shows a patent foramen ovale in newborns but should assess for the presence of intracardiac thrombus and right-to-left shunt. Levels

of protein C, protein S, and antithrombin III are normally low in infants but should be evaluated as part of the thrombophilia evaluation, as in Fig 2.

PERINATAL STROKE: ACUTE CARE

Aspirin, anticoagulation, and tPA are not routinely used in perinatal AIS. Anticoagulation may be considered in children with significant cardiac abnormalities or systemic thrombi. In neonates with CSVT, the American Heart Association/ American Stroke Association guidelines recommend anticoagulation only in the setting of thrombus propagation, while the American College of Chest Physicians guidelines recommend anticoagulation for 6 to 12 weeks. More recent data obtained in neonates with CSVT have supported treatment with anticoagulation, although additional prospective study is needed. Otherwise, current treatments for perinatal stroke seek to support homeostasis and avoid seizures.
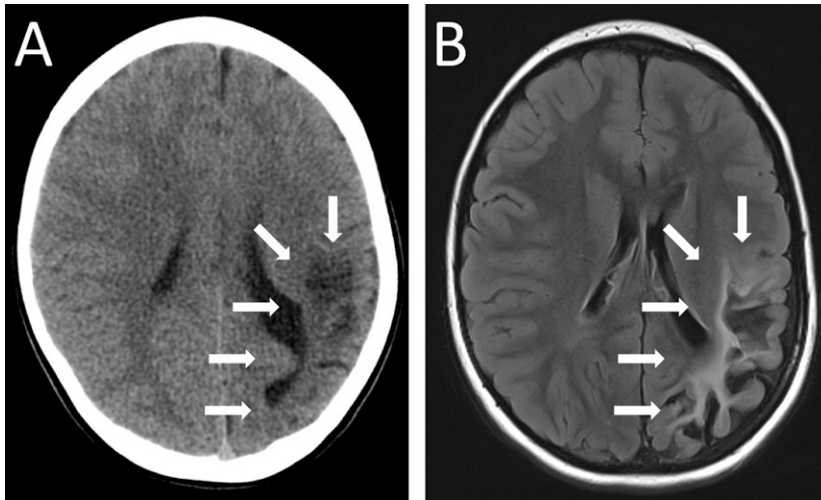
Figure 5. Presumed perinatal arterial ischemic stroke. A previously healthy 6-year-old girl presented with first lifetime right-sided seizure. Physical examination showed hyperreflexia and Babinski sign on the right as well as right arm posturing when running. She had been left-handed since before age 1 year. Axial computed tomography scan (A) and axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging of the brain (B) showed left parieto-occipital encephalomalacia in the territory of a branch of the left middle cerebral artery (arrows). Neuropsychologic evaluation showed mild intellectual disability with global deficits in both verbal and nonverbal skills as well as difficulty with processing and integration.

PERINATAL STROKE: CHRONIC TREATMENT AND SECONDARY PREVENTION

Stroke recurs in 1% to 2% of children who have suffered perinatal stroke. Recurrence is highest in children with identified cardiac, vascular, or coagulation abnormalities.

TABLE 4. Selected Conditions Associated With Perinatal Arterial Ischemic Stroke

Maternal factors:
- Infection
- Thrombophilia, including antiphospholipid antibodies
- Preeclampsia
- Cocaine use
- Smoking
- History of infertility

Fetal/infant factors:
- Infection
- Thrombophilia
- Congenital heart disease
- Need for resuscitation or low Apgar score at 5 minutes
- Arterial injury during delivery from mechanical forces on the head and neck

Placental factors:
- Infarction
- Abruption
- Insufficiency
- Chorioamnionitis

In the absence of those abnormalities, the recurrence risk and risk to future siblings approach that of the general population. Given the low recurrence rate, neither chronic aspirin nor anticoagulation is generally recommended.

PROGNOSIS OF PERINATAL AND CHILDHOOD STROKE

Cerebrovascular disease is among the top 10 leading causes of death for children in the United States. The mortality rate is estimated to be 3% to 20% for AIS, about 12% for CSVT, and up to 40% for hemorrhagic stroke. Although most children survive their strokes, up to 90% endure substantial neurologic morbidity. Because most children with stroke do not die of the injury, the impact is felt throughout the decades that follow. Consequently, the burden of chronic disability to both the individual patient and society is high. Because pediatric stroke occurs in the developing brain, the subsequent damage can interfere with the expected trajectory of postnatal brain development. The full impact of a childhood stroke may not be apparent for years, with deficits unmasked only with developmentally appropriate increased motor or cognitive demands.

One study of children of all ages with either AIS or CSVT found moderate-to-severe deficits in 41%; children with AIS had worse outcomes. Arterial ischemic stroke also has worse outcomes compared to hemorrhagic stroke. Spastic hemiparesis is common, as is dystonic hemiparesis due to frequent involvement of the basal ganglia. Neonatal stroke is the leading identifiable cause of hemiplegic cerebral palsy.

Some studies have found worse outcomes in children who have strokes at older ages. By contrast, other studies

have found worse outcomes in children who are younger at the time of stroke, suggesting an "early vulnerability." Deficits can even emerge over time. Among 26 children with neonatal stroke assessed in preschool and again in grade school, IQ scores did not differ from age norms in preschool, but by grade school, they fell by 5 points on full-scale IQ and showed emerging nonverbal, working memory, and processing difficulties. In addition, mood and attention disorders were common.

Lesion location and size are also important and interact with age. Strokes affecting both cortical and subcortical areas, as opposed to either alone, are associated with worse cognitive outcomes. Both subcortical stroke in neonates and cortical stroke in children age 1 month to 5 years have been associated with subsequent cognitive deficits. Neonatal strokes affecting 2 or 3 brain parenchymal regions among cortex, subcortical white matter, and basal ganglia have worse motor outcomes than those affecting only 1 region; involvement of the posterior limb of the internal capsule alone is also predictive of motor deficits.

Although seizures at presentation of acute stroke typically resolve, remote epilepsy (unprovoked seizures more than 30 days after the stroke) has been observed in as many as 70% of neonates and 30% of older children within the years after stroke. Remote seizures may occur without seizures at onset, as in presumed perinatal stroke. The occurrence of epilepsy in children with stroke correlates with poorer neurocognitive outcome.

SYSTEMS OF CARE FOR CHILDREN WITH STROKE

The Pediatric Primary Stroke Center: Acute Care

Adult stroke practice now provides care in primary stroke centers with dedicated stroke units and multidisciplinary stroke teams that can rapidly evaluate patients with acute stroke and provide thrombolytic or endovascular treatment. In addition, these systems of care in and of themselves have been shown to improve outcomes.

Although the role of tPA in pediatric stroke has yet to be demonstrated systematically, the delivery of pediatric stroke care in coordinated systems is key to rapid diagnosis and the institution of neuroprotective measures for patients. Moreover, some proportion of acute neurologic presentations initially triaged as possible strokes are expected to have other ultimate diagnoses, but two-thirds of these stroke mimics are not benign diagnoses and still warrant urgent evaluation.

The infrastructure created for the TIPS trial resulted in the development of 22 functional pediatric primary stroke centers across North America. These sites can serve as models for other centers interested in developing the framework necessary for the delivery of optimal care to children with acute stroke. The framework includes: (19)

1. Clinicians comprising the acute stroke team with expertise in pediatric stroke, including neurologists, neurosurgeons, interventional radiologists, hematologists, emergency medicine physicians, and pediatric intensivists
2. Continuous coverage by pager to assemble a rapid response acute stroke team and institutional mechanisms for first-line providers to activate a rapid response
3. Order sets or care protocols in the emergency department and intensive care unit for both in-hospital and out-of-hospital patients with acute stroke
4. Urgent neuroimaging protocols with 24/7 availability of either MRI with MRA or CT scan with CT angiography; this requires the availability of pediatric radiologists, anesthesiologists for sedated scans, and radiology technologists
5. Input and support from pharmacy and nursing leadership
6. Cross-disciplinary medical education, quality improvement initiatives, and research infrastructure

Community clinicians serve as the first set of "eyes on the ground" for children with new symptoms that may represent acute stroke. Recognition in the clinic or by phone triage of sudden-onset neurologic deficits, especially but not exclusively in children with known risk factors, should prompt emergent referral to an acute care center with pediatric expertise in stroke. Stroke telemedicine is not yet formalized in the pediatric sphere, but the development and utilization of "hub-and-spoke" community partnerships with tertiary care centers should be encouraged.

Follow-up Care and Rehabilitation

Pediatric primary stroke centers are also well equipped to manage the complex medical and rehabilitation needs of children after a stroke. In addition to the disciplines represented in the rapid response team, patients and families benefit from multidisciplinary clinical teams that include physiatrists, physical and occupational therapists, speech and language therapists, feeding specialists, orthopedists, orthotists, psychologists, and social workers.

Intensive rehabilitation programs should be instituted promptly after stroke. If the patient is a neonate or younger than age 3 years, evaluation and therapy through an Early Intervention Program should be instituted promptly after discharge. Note that many states consider stroke to be an

"established condition" with a high probability of developmental delay, thereby qualifying affected children for Early Intervention services, even if delays are not yet apparent. For older children with stroke, inpatient rehabilitation hospital treatment can be crucially important for recovery of function. Neuropsychological evaluation beginning in late preschool can help identify subtle cognitive deficits that may become more academically disabling over time if not remediated and that might constitute targets for intensive therapies as part of an Individualized Education Plan.

Specific therapies have been developed for children with hemiparesis. Constraint-induced movement therapy improves the function of the paretic arm through restraining, bracing, or casting the nonparetic arm. Bimanual therapy emphasizes the coordinated use of both arms. The role of transcranial magnetic stimulation and transcranial direct current stimulation in stroke rehabilitation is being explored.

Approach to Stroke Management: Integrated Care Models

Although multidisciplinary subspecialty expertise is important for diagnosing and treating pediatric stroke, the primary care clinician and the patient's medical home play crucial roles in both initial and ongoing care for these complex patients. As noted previously, primary care clinicians may be the first to recognize the symptoms of acute or prior stroke in the child presenting with a new neurologic deficit, seizure, or failure to meet developmental milestones.

After stroke occurs in a child, care from pediatric stroke specialists is best complemented by ongoing care by primary pediatricians, with care plans and roles agreed upon by all clinicians and the family. Routine health maintenance such as vaccination is all the more important for children at risk of stroke recurrence in times of illness, such as those with sickle cell disease or moyamoya syndrome. Surveillance is important for secondary medical complications from stroke such as aspiration, complications of pharmacotherapy, and the development of contractures and scoliosis. Developmental and academic progress must be closely monitored. Pediatricians can help families navigate resource needs in their local community, including therapies, orthotics and mobility devices, and special education services or disability accommodations. According to a recent American Academy of Pediatrics policy statement, integrated care models are essential and optimize care quality, patient/family experience, and outcome.

Summary

- On the basis of some research evidence (evidence quality B), pediatric stroke is common, affecting 2.3 to 4.6 per 100,000 children annually. (4)(5) It is most common in neonates, affecting up to 1 in 1,600 to 4,000 term infants and 1 in 140 preterm infants. (4)(5)

- On the basis of strong research evidence (evidence quality A), sickle cell disease is a major risk factor for both ischemic and hemorrhagic stroke. Annual transcranial Doppler ultrasonography screening is the standard of care to evaluate stroke risk and initiate preventive therapies. (10)(15)

- On the basis of some research evidence (evidence quality B), children with acute stroke should have a thorough evaluation for arteriopathy, thrombophilia, and cardiac etiologies. (15)(16)

- On the basis of research evidence (strong in adults, some in children) as well as consensus (evidence quality C), tissue plasminogen activator may be beneficial therapy in the appropriate child who presents with acute arterial ischemic stroke. Other acute interventions are important to minimize brain damage. (19)

- On the basis of strong research evidence (evidence quality A), perinatal stroke usually presents with seizures or encephalopathy rather than focal deficits. (16)

- On the basis of primarily consensus but also on strong research evidence in the adult population (evidence quality C), comprehensive, integrated systems of care involving primary pediatricians working together with subspecialty referral centers can optimize long-term outcomes for children with stroke. (16)(19)

To view PowerPoint slides that accompany this article, visit http://pedsinreview.aappublications.org and click on the Supplemental tab for this article.

Stroke in Neonates and Children

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PIR Quiz

1. A 2-year-old boy with a known vasculopathy presents with sudden onset of focal neurologic deficits. Emergent magnetic resonance imaging (MRI) confirms ischemia in the distribution of the middle cerebral artery. Which of the following is the most likely mechanism of the focal brain injury in this scenario?

    A. Excessive metabolic demands.
    B. Global hypoxia.
    C. Loss of blood flow or oxygenation within a vascular territory.
    D. Metabolic insult.
    E. Proliferation of compensatory collateral vessels.

2. A 4-year-old girl presents with sudden onset of right-sided upper extremity and facial weakness, aphasia, and left-sided gaze preference. MRI confirms ischemia within a vascular territory. Based on the clinical findings, which of the following is the most likely location of the insult?

    A. Brainstem artery.
    B. Cerebellar artery.
    C. Middle cerebral artery.
    D. Ophthalmic artery.
    E. Posterior cerebral artery.

3. A 4-year-old boy with sickle cell disease is seen in your clinic for follow-up evaluation of otitis media. You are concerned that your patient has not been seen in the comprehensive sickle cell clinic for the past 2 years. To screen for stroke risk, which of the following tests should you recommend?

    A. Arteriography.
    B. Computed tomography scan of the brain.
    C. Echocardiography.
    D. Magnetic resonance imaging of the brain.
    E. Transcranial Doppler ultrasonography.

4. A 10-year-old boy with sickle cell disease presents with sudden onset of right-sided weakness, speech abnormalities, and headache. You suspect that your patient is having a stroke. The MRI machine at your facility is currently unavailable. Which of the following is the most appropriate next step in management?

    A. Aspirin.
    B. Exchange transfusion.
    C. Hyperventilation.
    D. Low-molecular weight heparin.
    E. Tissue plasminogen activator (tPA).

5. A 5-year-old boy presents with a history of severe diarrhea and vomiting for 48 hours and sudden onset of change in mental status. On physical examination, you also note hemiparesis and hemisensory loss. Emergent MRI demonstrates cerebral venous sinus thrombosis with venous infarction. In addition to anticoagulation, which of the following is recommended as a neuroprotective strategy?

    A. Anti-inflammatory agent.
    B. Broad-spectrum antibiotics.
    C. Correct metabolic derangements.
    D. Maintain blood pressure in 10th to 40th percentile for age, sex, and height.
    E. Vitamin K.