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AHC Media

Stroke: It's Not Just for Grown-Ups

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An 80-year-old woman presents with sudden onset left hemiparesis. She has a history of hypertension. Diagnosis — stroke.

A 15-year-old male ingests some "bath salts" obtained from a friend and shortly thereafter develops the sudden onset of a left hemiparesis. Diagnosis — stroke.

A 5-year-old male presents with sudden onset of left hemiparesis. He has a history of sickle cell disease. Diagnosis — stroke.

When an elderly patient presents with new neurologic changes, the diagnosis of stroke is easy to make. However, increasingly we are seeing stroke in much younger patients, even in children. This monograph describes stroke in children and emphasizes those populations that are at highest risk.

Many of you work in stroke centers and are required to complete a set number of hours of CME in the area of stroke. We continue to search for new and different topics on stroke to broaden your understanding and clinical competence.

— Sandra M. Schneider, MD, Editor

Defining the Problem

Pediatric stroke remains one of the top 10 causes of death in children, with a mortality rate of 0.6 deaths per 100,000 strokes, and almost all of those affected have a residual neurologic deficit.[2] This figure increases to 5.3 deaths per 100,000 during the first year of life.[2] The incidence of pediatric stroke in the general population is about six cases per 100,000 children per year.[3] Furthermore, a recent study published in the *Annals of Neurology* suggests that this number is increasing, especially among boys. In comparing one-year periods starting in 1995 and 2007, George et al found a 51% increase of ischemic stroke in boys aged 5 to 14 years.[4]

Several studies have found that even when excluding trauma, boys are at a higher risk than girls, and African-American children are at higher risk than their Caucasian and Asian counterparts. Strokes are also slightly more common in children younger than 2 years old, placing the age group least able to communicate clinical symptoms at the highest risk.[5]

Etiology

The adult risk factors of high blood pressure, elevated cholesterol, smoking, alcohol use, and obesity do not exist in most children. However, about one-half of the children presenting with stroke have other previously identified risk factors that predispose them to stroke. Another one-third of the patients have one or more risk factors that are uncovered during the initial workup, and up to one-fifth have no known etiology.[1] Understanding the risk factors that contribute to stroke in children will help expedite a diagnosis in the emergency department. (*See Table 1.*)

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes

Executive Summary

- AIS is a leading cause of acquired brain injury in children, with the perinatal period carrying the highest risk.
- In AIS, the most common underlying conditions are sickle cell disease and congenital or acquired heart disease.
- Common identifiable risks can be broken down as cardiac (CHD), hematologic (SCD, prothrombotic disorders), vascular (inflammatory and noninflammatory), metabolic (homocystinuria, Fabry disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL], mitochondrial encephalopathy, lactic acidosis, and stroke [MELAS]), and ingestions (cocaine, ecstasy, methamphetamines, and glue).

involve the middle cerebral artery (MCA) territory more frequently than either the anterior or posterior cerebral arteries. Acute ischemic stroke (AIS) is the focal brain infarction that results from occlusion of these arteries or their branches. AIS is a leading cause of acquired brain injury in children, with the perinatal period carrying the highest risk.[6]

In AIS, the most common underlying conditions are sickle cell disease and congenital or acquired heart disease. Transient cerebral arteriopathy due to intracranial arterial wall disease is another frequent cause of pediatric stroke.[7] Head trauma appears to trigger arterial strokes, whereas infections, anemia, leukocytosis, and prothrombotic disease are triggers for both arterial and venous strokes.[1] Specific disease mechanisms implicated in childhood arterial ischemic stroke have received little attention, but an increased understanding of disease pathogenesis could lead to novel targeted treatment approaches.[8]

Cerebral venous drainage occurs via superficial (cortical veins, superior sagittal sinus) and deep (internal cerebral veins, straight sinus) systems that converge at the torcula to exit via the paired transverse and sigmoid sinuses and jugular veins. In cerebral venous thrombosis (CSVT), thrombotic occlusion of these venous structures can create increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction (stroke). CSVT may be more common in children than in adults, and risk is greatest in the neonatal period. Clinical presentations are often more gradual, variable, and nonspecific compared to AIS.[6] In CSVT, major risk factors include heart disease, chronic anemia, and dehydration.[1]

Hemorrhagic stroke (HS) includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location within the brain. Intraventricular hemorrhage may be primary or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces. Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or thunderclap headache, loss of consciousness, and nuchal rigidity, in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus, cranial bruit, macrocephaly, and high-output heart failure may be present. Diagnosis relies on imaging, and CT is highly sensitive to acute HS.[6]

Common identifiable risks can be categorized as cardiac, hematologic, vascular, metabolic, and ingestions, and are described below.

Cardiac

Congenital heart disease (CHD) is one of the most common birth defects in the United States and is a risk factor for a cardio-embolic stroke. Strokes from cardiac disease account for approximately 20-30% of childhood strokes.[9] Strokes may result from mural thrombi in a dyskinetic atrium or ventricle, clot, valve vegetation, or as a consequence of cardiopulmonary bypass. Most strokes due to CHD occur during the perioperative period or following catheterization or cardiopulmonary bypass.

Hematologic

Diseases of the blood, including sickle cell disease (SCD) and prothrombotic disorders, predispose children to strokes. SCD is an autosomal recessive disorder affecting red blood cells and is the most common hemoglobinopathy associated with pediatric stroke.

Sickle Cell Disease (SCD). The incidence of stroke in SCD is estimated at 7-11%, which is more than 300 times higher than those without the disorder and occurs most frequently before the age of 10 years.[10] Under deoxygenated conditions, cell density increases and makes the red blood cell susceptible to collapse or sickling, and the resultant congestion of blood may lead to cerebral infarction. In the sickle cell populations, 50% of the patients who experience a stroke will have a recurrence, which makes therapeutic prevention paramount.[11]

Prothrombotic Disorders. Numerous other inherited or acquired prothrombotic disorders have been associated with pediatric stroke. The strongest evidence supporting a correlation between prothrombotic disorders and stroke

Table 1: Risk Factors and Causes of Childhood Stroke

Cardiac	Vasculopathy	Metabolic
Congenital heart disease (CHD)	*Noninflammatory*	Homocystinuria
Cardiac surgery	Transient cerebral arteriopathy of childhood (TCA)	Fabry disease
Cardiac catheterization	Moyamoya	Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Extracorporeal membrane oxygenation	Dissection	Mitochondrial encephalopathy, lactic acidosis, and stroke syndrome (MELAS)
Cardiomyopathy	Neurofibromatosis type 1	Menkes disease
Endocarditis/myocarditis	Fibromuscular dysplasia	Shock/dehydration
Dysrhythmias	Connective tissue disorders	Dyslipidemia
Artificial valves		
Rheumatic heart disease	*Inflammatory*	**Ingestions**
	Takayasu arteritis	Cocaine
Hematologic	Giant cell arteritis	Ecstasy
Sickle cell disease (SCD)	Polyarteritis nodosa	Methamphetamine
Leukocytosis	Kawasaki disease	
Prothrombotic disorders	Varicella	**Other**
Thrombophilia	Syphilis	Trauma
Anemia	Tuberculosis	Fat/air emboli
Pregnancy	Meningitis	
Oral contraceptives	HIV	
Leukemia/malignancies	Lupus	
	Fungal	

was a meta-analysis by Kenet and Lutkhoff. The analysis concluded that risk for acute ischemic stroke was significant for the following traits: two or more genetic thrombophilias, protein C deficiency, antiphospholipid antibodies/lupus anticoagulant, elevated lipoprotein, factor V leiden mutation, prothrombin gene mutation, and MTHFR TT genotype. It also found a nonstatistical correlation of protein C deficiency and antithrombin III deficiency. Because of these strong correlations, there is a higher index for suspicion for stroke when a child has a past medical history of a prothrombotic disorder.[12] Therefore, the initial emergency room workup consists of obtaining coagulation studies, including a PT, PTT, and INR. After a stroke is diagnosed, it is recommended that blood be analyzed for these respective disorders.[13]

Vasculopathy

Abnormalities of a child's cerebral vasculature predispose to stroke. In reviewing vascular imaging of children with acute ischemic stroke, nearly one-half had an arteriopathy.[14] Vasculopathy can be inherited or acquired and is broken down into inflammatory and noninflammatory. Noninflammatory causes include transient cerebral arteriopathy of childhood (TCA), moyamoya, and arterial dissection. Moyamoya is a hereditary disease, most often seen in people of Japanese descent, which causes cerebral vasoconstriction. Inflammatory causes are further divided into primary or secondary vasculitis.

Transient Cerebral Arteriopathy of Childhood (TCA). TCA is the most common vasculopathy. It is an idiopathic unilateral stenosis in the distal arteries and proximal circle of Willis. The stenosis of the vessels causes hypoperfusion and stroke. While the etiology of this disorder is unknown, a post-infection inflammatory mechanism has been proposed, given the strong association with a preceding varicella infection.[15]

Moyamoya. Moyamoya is a progressive bilateral stenosis of the arteries of the circle of Willis and internal carotid artery, which leads to the development of the collateral vessels that represent the "puff of smoke." It is primarily seen in children of Asian descent and accounts for only about 6% of childhood stroke in Western countries.[1]

Dissection. Dissection results from a tear in the internal wall of the blood vessel. Symptoms typically arise from an embolism at the site of a tear or in complete occlusion of the dissected vessel. It is often associated with trauma or a connective tissue disease such as Ehlers-Danlos or Marfan syndrome.[9]

Inflammatory Vasculopathy. Vasculitis or inflammatory changes to cerebral vessel walls affect arterial flow, causing hypoperfusion and stroke. Primary vasculitis associated with stroke includes Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, and Kawasaki disease. Secondary vasculitis can be associated with varicella, syphilis, tuberculosis, fungi, and autoimmune disorders such as HIV and lupus. A study by Askalan found a strong correlation between stroke and varicella. In the study, 31% of pediatric stroke

Table 2: At-a-Glance Signs and Symptoms of Childhood Stroke Syndromes

Acute Arterial Ischemic Stroke or TIA		
Medical Description	**Lay Description**	**Comment**
Hemiparesis	Weak arm or leg, facial droop, paralyzed on one or more sides	Combination of face with arm, or face, arm, and leg strongly suspicious for stroke
Aphasia	Stopped speaking, talking nonsense, won't follow commands	Sometimes mistaken for confusion or oppositional behavior
Visual field cut	Loss of vision, can't see right	Often causes gaze preference toward the side of intact vision, away from the hemiparetic side
Ataxia	Unsteady gait, can't walk straight, seems drunk, can't sit steady, uncoordinated reach/grasp	Often associated with headache, complaint of dizziness, vomiting
Dysarthria	Speech is slurred, although word choice and comprehension are correct	
Hemisensory loss	Numbness, tingling on one side of body	Usually involves one side of the body and more than one body region (face + arm, or face + arm + leg)
New-onset focal seizure with atypical prolonged (> 1 hr) postictal deficit		No previous diagnosis of epilepsy, now has several focal seizures followed by persisting weakness in location of the seizure (usually face + arm or face + arm + leg)
Acute Cerebral Sinovenous Thrombosis		
Medical Description	**Lay Description**	**Comment**
Triad of unremitting and escalating headache, repeated vomiting, and decreased mental status	Lethargic, vomiting, irritable, headache	Frequently has sixth nerve palsy and papilledema
In newborn, lethargy and fever	Lethargic, poor feeding, seizure	
Primary Intracranial Hemorrhage (IVH, Subarachnoid Hemorrhage, AVM)		
Medical Description	**Lay Description**	**Comment**
Hyperacute severe headache	"Worst headache of my life"	Often quickly followed by decreased mental status
Sudden sustained loss of consciousness	"Collapsed," hard to wake up	Often preceded by c/o headache, vomiting, and/or seizure
One or both of above with new focal deficit	Paralyzed on one side, eyes going to one side, face drooping	

Used with permission from: Rebecca Ichord, MD. Children's Hospital of Philadelphia Stroke Program Stroke Care at CHOP: The Bare Essentials for Primary Care and ED Physicians March 2007. *Developed by the Stroke Team at Children's Hospital of Philadelphia, for screening and triage by nursing staff and emergency medicine providers. Available at www.chop.edu/stroke.

patients had an associated varicella infection in the preceding 12 months vs. 9% of the healthy cohort.[16]

Metabolic Disorders

Several congenital metabolic conditions predispose children to stroke due to the effect on the vascular wall structure. These medical disorders include homocystinuria, Fabry disease, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS).

Homocystinuria. Homocystinuria is a metabolic disorder of homocysteine and metathionine metabolism. It is a rare condition resulting in elevated plasma homocysteine. Moderately elevated plasma homocysteine concentration is independently associated with an increased risk for thrombosis, atherosclerosis, coronary artery disease, and ischemic stroke.[17]

Fabry Disease. Fabry disease is an X-linked lysosomal storage disorder, which results in vessel narrowing and infarction in young adults.

Cerebral Autosomal-dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). CADASIL is caused by a mutation in the Notch3 gene, which leads to progressive degeneration of smooth muscle cells in the vascular wall. Patients with CADASIL may present in late childhood or early adulthood with migraine, TIA, or ischemic stroke.

Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke Syndrome (MELAS). MELAS can present with recurrent stroke. It is a result of a point mutation on mitochondrial DNA and exhibits a pattern of maternal inheritance.[10] One of the original diagnosis criteria for MELAS required stroke-like episodes before age 40. The hallmark of the syndrome is the occurrence of stroke-like episodes that result in hemiparesis, hemianopsia, or cortical blindness.[18]

Ingestion

Ingestion of sympathomimetic drugs and inhalants such as cocaine, ecstasy, methamphetamines, and glue can lead to a stroke. They can induce hypertension, vasospasms, toxic vasculitis, a prothrombotic event, or an exacerbation of unrecognized cardiac disease, leading to hypoperfusion or hemorrhage. Adolescent drug users are at high risk. The stroke rate has been reported as high as 6.5 per 100,000 in young adult drug users.[19]

Clinical Features

Recognition of stroke is often delayed or even missed in most children. On average, it takes 12 to 24 hours for an adult to present to the hospital after the first onset of stroke symptoms. For children, it may take 48 to 72 hours from symptom onset to diagnosis.[20] Many clinical symptoms are often overlooked due to the widespread misconception that strokes do not occur in children. It is imperative that an emergency physician understands the sometimes subtle symptoms in order to make a timely diagnosis.

The clinical presentation of an ischemic, hemorrhagic, and CVST stroke varies according to age, etiology, and location. Although less common in the adult stroke, seizures often herald stroke in the infant population. In infancy, the typical presentation includes seizure, lethargy, and/or apnea, often without a focal neurologic deficit.[21] Therefore, due to the paucity of symptoms in the newborn period, the diagnosis of stroke may be delayed until 4-6 months of age when asymmetry in reaching or the use of the hand is first noted.

Outside the infant population, a focal neurological deficit is the most common symptom associated with an ischemic stroke. A child may present with hemiparesis, hemisensory loss, cranial nerve palsy, aphasia, or dysarthria, and strokes in the posterior circulation can manifest as cerebellar signs such as ataxia, vertigo, and vomiting.[13]

The main symptoms of hemorrhagic stroke include headache, vomiting, seizure, impaired consciousness, and/or focal neurological deficit.[18] In contrast, few patients with a confirmed ischemic stroke presented with impaired consciousness.

The clinical manifestations of CSVT are subtle, nonspecific, and may overlap predisposing conditions such as infection and dehydration. Clinical symptoms again include headache, nausea, vomiting, seizure, altered consciousness, and focal neurologic deficit.[22]

In the clinical environment of the emergency department, a useful tool used to evaluate the neurologic status of a child is the acronym FAST. It is a clever way to remember to think fast when time is brain.[1]

Face: Ask the child to smile. Does one side of the face droop?

Arms: Ask the child to raise both arms. Does one arm drift downward?

Speech: Ask the child to repeat a simple sentence. Are the words slurred? Is the sentence repeated correctly?

Time: If the child shows any of the symptoms, time is important.

Another useful tool to use as clinical guide is Table 2: At-A-Glance Signs and Symptoms of Childhood Stroke Syndromes. It is a screening tool developed by the Stroke Team at Children's Hospital of Philadelphia for providers to quickly recognize the symptoms of pediatric stroke.

Differential Diagnosis

Pediatric stroke has a very broad differential because numerous other conditions present with acute neurologic deficit, headache, seizure, or lethargy. These conditions range from a benign hemiplegic migraine to more serious conditions such as meningitis and brain tumors.

Todd's paralysis, hemiplegic migraines, alternating hemiplegia of infancy, demyelinating disorders, along with hypoglycemia must be considered in the differential diagnosis. A more detailed list is found in Table 3. Todd's paralysis is a neurologic condition experienced by patients with epilepsy. It is a temporary unilateral paralysis that occurs after a seizure and can last for up to 36 hours. Hemiplegic migraine is a classic migraine that is accompanied by hemiparesis during the aura phase. The condition is benign and completely resolves. Alternating hemiplegia of infancy is a rare neurological disorder presenting before 18 months that has transient episodes of hemiplegia. These episodes are unique in that they resolve with sleep and recur when the child is awake. Because children younger than 2 years of age have a greater incidence of stroke, neuroimaging and an extensive pediatric stroke evaluation would need to be conducted before the diagnosis of alternating hemiplegia of infancy could be entertained.

Initial Diagnostic Evaluation and Management

Essential to the emergency department treatment of an acute stroke is rapid assessment,

Table 3: Differential Diagnosis of Child with Suspected Stroke

Vascular	Nonvascular
Focal cerebral ischemia	Cerebral abscess
Intracranial hemorrhage	Encephalitis (herpes simplex virus)
Cerebral sinovenous thrombosis	Meningitis
Aneurysm	Brain tumor
Arteriovenous malformation	Alternating hemiplegia of infancy
	Multiple sclerosis (demyelination)
	Malingering/conversion disorder
	Epilepsy: Postictal Todd's paralysis or a focal inhibitory seizure
	Complicated/hemiplegic migraine
	Hypoglycemia
	Head trauma

stabilization, and anticipation of the next steps in management. A careful history and physical exam must be performed and baseline studies should be obtained to look for any infectious process, coagulopathies, cardiac abnormalities, and drug ingestions. Baseline studies include a complete blood count, prothrombin time, partial thromboplastin time, liver and renal function tests, serum glucose, electrocardiography, erythrocyte sedimentation rate, antinuclear antibody, urinalysis, and chest radiography, along with a toxicology screen.

Upon the child's arrival, a rapid airway assessment should be performed. A rapid neurologic exam should be carried out to determine if the child is alert, responsive to vocal or painful stimuli, or completely unresponsive (AVPU). Maintain a low threshold for intubating a child with clinical evidence of an acute ischemic stroke or intracranial hemorrhage, as these children are at high risk for neurologic deterioration and loss of airway protective reflexes. Once the airway is secured, it is important to continue providing adequate analgesia and sedation to prevent hyperventilation and excessive elevation of the blood pressure, as well as to facilitate imaging and continued evaluation and management. Imaging should be quickly obtained to identify an intracerebral hemorrhage or significant edema with mass effect that could be the cause of the child's neurological decompensation.

If an ischemic stroke occurs in a child with SCD, then urgent IV hydration with normal saline and urgent exchange transfusion at an experienced center is indicated to reduce the hemoglobin S fraction to less than 30%. Exchange transfusion, rather than simple transfusion, is recommended for acute emergencies, in part because it avoids the risk of transfusion-associated volume/circulatory overload (TACO) syndrome and associated pulmonary edema. In addition, exchange transfusion avoids the theoretical risk of increased blood viscosity associated with simple transfusion. Simple transfusion may be indicated when there is severe anemia due to an aplastic crisis or if there will be a long delay in receiving the therapy.

After the initial airway assessment and rapid imaging, continued aggressive supportive therapy becomes the mainstay of treatment. It is essential to maintain normal oxygenation, allow for modest hypertension, seek to normalize the blood glucose, and reduce fever, if present, with antipyretics.

Another neuroprotective strategy essential to preventing progressive ischemic brain injury is aggressive maintenance of cerebral perfusion pressure, with systolic blood pressures maintained in the high normal range. Malignant cerebral edema in the initial 72 hours is life-threatening and more common in children; emergency surgical decompression can be life-saving.[6]

The initial resuscitation fluid used should be an isotonic solution, such as normal saline, as it offers the advantage of maintaining homeostasis by exerting little osmotic effect on the surrounding tissues. The goal of the fluid resuscitation should be to keep the patient euvolemic. Adequate resuscitation can be assessed by maintaining a urine output of 0.5-1 mL/kg/hr. Anticonvulsant medications are indicated if seizures are present. As supportive therapy is instituted and the child is stabilized, additional imaging studies and workup are simultaneously obtained to determine the cause of the stroke and potential treatment options.

As previously stated, upon clinical suspicion for a stroke, neuroimaging of the brain is imperative to confirm the diagnosis. Because the causes of stroke vary and multiple risk factors increase recurrence risk, further investigation for cardiac, hematologic, and vascular causes should also be conducted; a full evaluation should be completed even if one risk factor is identified.[23]

An initial CT to rule out hemorrhagic stroke is appropriate; however, diffusion-weighted MRI is the most sensitive diagnostic study in evaluating an acute ischemic stroke. It is more sensitive in the hyperacute time period and provides better visualization of the posterior fossa than CT. In children, head CT is generally considered inadequate since MRI is required to reliably exclude stroke mimics.[23,24] The sensitivity of MRI over CT was illustrated in an Australian study conducted by Srinivasan. In the study, 84% of patients with a confirmed stroke by MRI had a negative initial head CT.[25] Head CT is considered an acceptable initial alternative only if brain MRI is not available within 48 hours of admission or if hemorrhagic stroke is suspected.[26]

Vascular imaging of the head and neck should be incorporated with the diffusion-weighted MRI. It allows

the visualization of both the clot and infarct in the vessel. Magnetic resonance angiography (MRA) is the first-line examination, followed by magnetic resonance venography (MRV) if venous infarct or cerebral sinovenous thrombosis is suspected. The benefit over CT angiography (CTA) is the lack of ionizing radiation and iodinated contrast.[27]

As previously mentioned, a noncontrast head CT is sensitive in identifying a hemorrhagic stroke; however, a blood-sensitive echo gradient added to the standard MRI can also be used to assess for brain hemorrhage. Even when a head CT identifies intracranial bleeding, an MRI/MRA is needed to identify vascular malformations requiring surgical intervention.[28]

Cardiac monitoring for the first 24 hours is indicated to look for atrial fibrillation and other potentially serious cardiac arrhythmias. Once the patient is admitted to the hospital, a more detailed workup is warranted. This includes an echocardiogram, TCD and/or carotid Doppler, hemoglobin electrophoresis, and a more extensive hypercoagulable evaluation. Table 4 outlines the initial evaluation of a pediatric stroke.[13]

Table 4: Diagnostic Evaluation of Childhood Stroke[13]

First Line: On Presentation	Second Line: Within 48 Hours as Indicated
CT/MRI of brain	Echocardiogram
MRA	Holter monitor
Complete blood cell count	TCD and/or carotid Doppler
PT/PTT/INR	CT angiography
Electrolytes, Ca, Mg, Phos, Glucose, renal function (Bun/Cr)	EEG
Blood culture	Hypercoagulable evaluation
Liver function test	Antithrombin III activity assay
ESR, ANA	Protein C and S activity assay
Urinalysis, urine drug screen	Factor V mutation
ECG	Antiphospholipid antibodies
	Lupus anticoagulant
	Screening metabolic disorders
	Serum amino acids
	Urine for organic acids
	Serum lactate/pyruvate
	Plasma ammonia levels
	Lipid profile
	Serum homocysteine
	Hemoglobin electrophoresis
	Complement profile
	VDRL
	HIV testing
	Rheumatoid factor
	Lumbar puncture: cell count, protein, glucose, lactate

Abbreviations: ANA, antinuclear antibody; BUN, serum urea nitrogen; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

Additional Treatment Considerations

Antiplatelet drugs such as aspirin and clopidogrel are generally indicated as initial therapy for most children with an acute arterial ischemic stroke when the etiology is being investigated or when there is a noninflammatory vasculopathy. These agents limit the migration and aggregation of platelets and reduce ischemic injury. Aspirin at a dose of 3 to 5 mg/kg per day is recommended, with a reduction to 1 to 3 mg/kg per day in response to gastric distress or prolonged epistasis. There have been no reports of Reye's syndrome in children taking aspirin, most likely due to the low dose. However, vaccinations for varicella and the annual influenza vaccine are recommended to reduce the risk of Reye's syndrome, and it is reasonable to halt aspirin during suspected influenza or varicella infections.[1] Clopidogrel at a dose of 1 mg/kg per day can be used in patients unable to tolerate aspirin.

Aspirin is also used to prevent secondary infarct in children who have experienced a first stroke or TIA. Aspirin is not indicated if the stroke is due to a hypercoagulable state, sickle cell disease, intracranial hemorrhage, or if the child is already anticoagulated at the time of initial presentation.

Anticoagulants such as heparin and warfarin limit the ability of the platelets to clot and consolidate and can prevent future thrombus extension. They are used in conditions in which there is a high risk of recurrence and low risk of secondary bleeding. Anticoagulants are indicated for children who have sustained a stroke secondary to a hypercoagulable state, confirmed cardiogenic emboli source, a dural sinus thrombosis, or an arterial dissection.[20] Anticoagulants are used for a longer period of time when there is fixed constant risk of stroke such as a tight arterial stenosis.

Heparin. A heparin loading dose of 75 units/kg IV over 10 minutes is recommended, with maintenance dose depending on the child's age. The target APTT is 60 to 80 seconds. It may be administered up to one week after an ischemic stroke, pending further evaluation.[1]

Low Molecular Weight Heparin (LMWH). LMWH should be used only in the clinical situation where rapid reversal of anticoagulation is not anticipated. The dosing depends on product, age, and weight of child. Lovenox can be dosed 1 mg/kg every 12 hours.

Table 5: Comparison of Guidelines for Acute Management of Ischemic Stroke in Children by Subtype of Stroke

	UK guidelines: 2004 recommendation	G	S	Chest guidelines: 2008 recommendations	G	S	American Heart Association: 2008 recommendations	G	S
General	Aspirin 5 mg/kg	WPC	1	UFH or LMWH or aspirin 1-5 mg/kg/day until cardioembolic and dissection subtypes excluded	1B	1	UFH or LMWH (1 mg/kg every 12 h) up to 1 week until cause determined	2B-C	3
Sickle cell disease	Exchange transfusion to HBS < 30%	WPC	1	Intravenous hydration and exchange transfusion to HBS < 30%	1B	1	Optimal hydration, correction of hypoxemia and hypotension Exchange transfusion to HbS < 30%	1C 2A-B	1 2
Cardiac	Anticoagulation should be discussed by senior pediatric neurologist and cardiologist	WPC	1	LMWH for over 6 weeks	2C	3	Therapy for heart problem	1C	1
Dissection of neck vessels	Anticoagulation for extracranial with no hemorrhage	WPC	1	LMWH for over 6 weeks	2C	3	UFH or LMWH as a bridge to oral anticoagulation	2A-C	3
Alteplase in children	Not recommended	—	1	Not recommended	1B	1	Not recommended	3C	1
Alteplase in teenage years	Not addressed	—	—	Not addressed	—	—	No consensus on use	—	3
Cerebral sinovenous thrombosis	Anticoagulation until recanalization for up to 6 months	—	C3	Initial UFH or LMWH, then LMWH for 3 months plus another 3 months if not fully recanalized	1B	1	Initial UFH or LMWH followed by warfarin for 3-6 months	2A-C	3

Childhood is defined as 28 days to 18 years (Chest), or 1 month to 16 years (UK). G = grade of evidence or recommendation; HbS = sickle cell hemoglobin; LMWH = low molecular weight heparin; S = strength of evidence or recommendation; UFH = unfractionated heparin; WPC = working party consensus

DeVeber G, Kirkham F, et al. Guidelines for the treatment and prevention of stroke in children. *Lancet Neurol* 2008;7:983-985, with permission from Elsevier.

Warfarin. For anticoagulation lasting weeks or months, low molecular weight heparin or warfarin is recommended.[1] Warfarin is initially dosed at 0.2 mg/kg orally and then titrated to maintain a target international normalized ratio at 2.0 to 3.0.[29] Because of low levels of vitamin K in breast milk, dosing may be more difficult in breast-fed infants. The concern that active children could have an increased risk of hemorrhage due to trauma seems to be largely unfounded; however, it is recommended that children avoid activities that carry a high risk of injury, such as contact sports.

Thrombotic Therapy. Thrombotic agents such as tPA act to dissolve clots that have already formed and are currently the mainstay of treatment in adult stroke. But due to lack of safety and efficacy studies beyond those described in isolated case reports, adult guidelines cannot be extrapolated to children. There is ample reason to seek new treatments for children with ischemic cerebral infarction because 55% of children have serious neurological sequelae.[20] The Thrombolysis in Pediatric Stroke (TIPS) study is the current clinical trial to assess the safety of intravenous intra-arterial tPA in children with acute ischemic stroke. Inclusion criteria were adapted from the adult tPA trial and include 0-3 hours from stroke onset for treatment with intravenous tPA, and 3-6 hours from stroke onset for intra-arterial tPA.[30]

The basis of pediatric treatment is mainly supportive with the use of antithrombotic and anticoagulation agents to prevent secondary stroke. Guidelines for treatment outlined in Table 5 are mainly based on consensus and expert opinion set forth by the American College of Chest Physicians, the Royal College of Physicians, and the American Heart

Association. Accumulated experience suggests these agents can be used safely on children, although efficacy and proper dosage need to be established by controlled trials. Newer mechanical recanalization devices also have the potential to provide instant recanalization under optimal circumstances and may be a future treatment alternative in children.

For hemorrhagic strokes (HS), including arteriovenous malformations and leaking intracranial aneurysms, specific treatments such as coil embolization and aneurysmal clipping are performed by pediatric neurosurgeons.[31] Management of childhood HS may include emergent neurosurgical intervention for large or rapidly expanding lesions. The same principles of neuroprotection for vulnerable brain suggested for ischemic stroke also apply to HS. Reversal of anticoagulant therapy may be required (e.g., vitamin K, fresh frozen plasma), but the role of other medical interventions, such as factor VII, are unstudied in children.[6]

Other disease-specific treatments include immunosuppression in vasculitis and revascularization surgery in moyamoya disease.[6]

Transcranial Doppler. High velocity on transcranial Doppler (TCD), low hemoglobin, leukocytosis, and hypertension are all risk factors for ischemic stroke in the sickle cell patient.[11]

Elevation of cerebral blood flow to maximal rates makes it more difficult to increase in times of further metabolic demand; therefore, children with cerebral blood flow rate with an average mean velocity greater or equal to 200 cm/s have a stroke risk of at least 10% per year.[32] Identifying high-risk children by using TCDs is an opportunity to prevent a first stroke. The landmark stroke prevention trial in sickle cell anemia (STOP) identified such patients and conducted a randomized, controlled study of a prevention strategy. By reducing hemoglobin S to less than 30% using blood transfusion, there was a 92% reduction of first stroke in children with sickle cell disease. The current recommendation is to consider a transfusion regimen in children with two abnormal TCD ultrasound studies.[32]

Summary and Conclusion

Despite the neural plasticity present in children, the majority of children with stroke have persistent disability. Studies indicate that up to 55% of children develop sensory or motor problems, seizure, developmental delay, or cognitive disorders.[33] There are some stroke-related disabilities unique to pediatric stroke, including cerebral palsy, mental retardation, and epilepsy.[3] These disabilities require extensive physical, speech, and occupational therapy that can last decades, in contrast to the shorter duration of impact for adult stroke survivors. While children who suffer stroke have good educational and mobility outcome, they have poorer outcomes when it comes to communication, socialization, and the activities of daily living.[33] Pediatric stroke is expensive, and the lifetime cost of care is likely greater for a child than an adult. The cost to the family and the larger society underscores the importance of pediatric stroke treatment and prevention.

Key Points

- Recognition of stroke in the pediatric population is often delayed or missed. Stroke can occur in neonates, infants, children, and young adults with devastating sequelae.
- Fifty percent of children presenting with stroke have a previously identified risk factor such as congenital heart disease, sickle cell disease, prothrombotic disorders, vasculopathy, or metabolic disorders.
- Sickle cell disease is the most common hemoglobinopathy associated with pediatric stroke, and the rate of first stroke can be reduced by blood transfusions.
- Seizure is often a clinical sign of a stroke in the infant population.
- Ischemic strokes commonly present with a focal neurological deficit, while hemorrhagic strokes usually present with impaired consciousness.
- Diffusion-weighted MRI is the most sensitive neuroimaging to evaluate an acute ischemic stroke.
- Inpatient diagnostic workup for pediatric stroke includes an echocardiogram and hypercoagulable evaluation.
- Numerous conditions present with an acute neurologic deficit, headache, seizure, or lethargy. The diagnosis of stroke needs to be excluded in most cases.
- Treatment of pediatric stroke is largely supportive with antiplatelet and anticoagulation therapy to prevent recurrent stroke.
- Aspirin, 3-5 mg/kg/day, is recommended to prevent recurrent ischemic stroke.
- Heparin, LMWH, and warfarin are recommended with stroke associated with heart disease, hypercoaguble state, dissection, and dural sinus thrombosis.
- In arterial ischemic stroke associated with sickle cell disease, hydration and urgent transfusion is recommended.
- In children, tPA is not recommended. The current TIPS clinical trial is investigating the safety and efficacy of tPA in the pediatric population.
- Despite neural plasticity, the majority of the children who survive a stroke have persistent disabilities.
- For most cases of pediatric stroke, there is no evidence-based treatment.
- More resources need to be devoted to researching causes and treatment of pediatric stroke.

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Physician CME Questions

1. In pediatric ischemic stroke, all of the following are common underlying conditions *except*:
   A. congenital/acquired heart disease
   B. transient cerebral arteriopathy
   C. prolonged QT interval
   D. sickle cell disease

2. All of the following are true regarding pediatric stroke *except*:
   A. Stroke is slightly more common in children younger than 2 years of age.
   B. Boys are at a higher risk than girls.
   C. African-American children are at higher risk than those of Caucasian and/or Asian descent.
   D. Almost all of the children affected with this condition recover without neurologic deficit.

3. About half of the children presenting with a stroke have previously identified risk factors that predispose them to it.
   A. true
   B. false

4. A 14-year-old boy presents to the emergency department with right-sided facial droop and weakness of the right upper extremity. As an emergency physician, you are suspicious for pediatric stroke. All of the following tests would be part of the initial workup *except*:
   A. diffusion-weighted MRI of brain
   B. urine drug screen
   C. hypercoagulation evaluation for factor V mutation
   D. ECG

5. The majority of pediatric patients with a confirmed ischemic stroke present with impaired consciousness.
   A. true
   B. false

6. A mother presents with her 18-month-old African-American boy. She witnessed one episode of right-sided seizure activity that lasted less than five minutes. The patient is otherwise healthy with no past medical conditions. At the time of examination, the patient is nontoxic, appearing playful, with normal vital signs and no apparent neurological deficits. An appropriate initial treatment would be:
   A. Order a transcranial Doppler (TCD) to determine if the average velocity of the cerebral blood flow is greater than or equal to 200 cm/s. If the TCD is elevated, admit patient for blood transfusion to reduce hemoglobin S to less than 30%.
   B. Place patient on a cardiac monitor, establish IV access, order ECG, CBC, CMP, PT, PTT, INR, NS bolus at 20 mL/kg, and MRI brain. Discuss with mother the possible need to sedate the child to conduct the MRI.
   C. Place patient on a cardiac monitor, establish IV access, initiate loading dose of heparin of 75 units/kg IV

over 10 minutes prior to neuroimaging.
D. Observe patient for 4-6 hours. If patient is seizure free with no signs of neurological deficit, discharge patient with neurology referral.

7. The typical presentation of stroke during infancy includes all of the following *except*:
   A. lethargy
   B. focal neurologic deficit
   C. seizure
   D. apnea

8. Strokes in the posterior circulation can manifest with all of the following signs *except*:
   A. ataxia
   B. vertigo
   C. visual field loss
   D. vomiting

9. Aspirin at 3 to 5 mg/kg/day is generally indicated therapy to prevent secondary stroke when:
   A. Stroke is due to intracranial hemorrhage.
   B. Stroke is due to a hypercoagulable state.
   C. Stroke is due to sickle cell disease.
   D. The etiology is being investigated or patient experiences TIA.

10. Ischemic strokes commonly present with a focal neurological deficit, while hemorrhagic strokes commonly present with impaired consciousness.
   A. true
   B. false

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Strokes in Children

Risk Factors and Causes of Childhood Stroke

Cardiac
Congenital heart disease (CHD)
Cardiac surgery
Cardiac catheterization
Extracorporeal membrane oxygenation
Cardiomyopathy
Endocarditis/myocarditis
Dysrhythmias
Artificial valves
Rheumatic heart disease

Hematologic
Sickle cell disease (SCD)
Leukocytosis
Prothrombotic disorders
Thrombophilia
Anemia
Pregnancy
Oral contraceptives
Leukemia/malignancies

Vasculopathy
Noninflammatory
Transient cerebral arteriopathy of childhood (TCA)
Moyamoya
Dissection
Neurofibromatosis type 1
Fibromuscular dysplasia
Connective tissue disorders

Inflammatory
Takayasu arteritis
Giant cell arteritis
Polyarteritis nodosa
Kawasaki disease
Varicella
Syphilis
Tuberculosis
Meningitis
HIV
Lupus
Fungal

Metabolic
Homocystinuria
Fabry disease
Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Mitochondrial encephalopathy, lactic acidosis, and stroke syndrome (MELAS)
Menkes disease
Shock/dehydration
Dyslipidemia

Ingestions
Cocaine
Ecstasy
Methamphetamine

Other
Trauma
Fat/air emboli

At-a-Glance Signs and Symptoms of Childhood Stroke Syndromes

Acute Arterial Ischemic Stroke or TIA		
Medical Description	**Lay Description**	**Comment**
Hemiparesis	Weak arm or leg, facial droop, paralyzed on one or more sides	Combination of face with arm, or face, arm, and leg strongly suspicious for stroke
Aphasia	Stopped speaking, talking nonsense, won't follow commands	Sometimes mistaken for confusion or oppositional behavior
Visual field cut	Loss of vision, can't see right	Often causes gaze preference toward the side of intact vision, away from the hemiparetic side
Ataxia	Unsteady gait, can't walk straight, seems drunk, can't sit steady, uncoordinated reach/grasp	Often associated with headache, complaint of dizziness, vomiting
Dysarthria	Speech is slurred, although word choice and comprehension are correct	
Hemisensory loss	Numbness, tingling on one side of body	Usually involves one side of the body and more than one body region (face + arm, or face + arm + leg)
New-onset focal seizure with atypical prolonged (> 1 hr) postictal deficit		No previous diagnosis of epilepsy, now has several focal seizures followed by persisting weakness in location of the seizure (usually face + arm or face + arm + leg)
Acute Cerebral Sinovenous Thrombosis		
Medical Description	**Lay Description**	**Comment**
Triad of unremitting and escalating headache, repeated vomiting, and decreased mental status	Lethargic, vomiting, irritable, headache	Frequently has sixth nerve palsy and papilledema
In newborn, lethargy and fever	Lethargic, poor feeding, seizure	
Primary Intracranial Hemorrhage (IVH, Subarachnoid Hemorrhage, AVM)		
Medical Description	**Lay Description**	**Comment**
Hyperacute severe headache	"Worst headache of my life"	Often quickly followed by decreased mental status
Sudden sustained loss of consciousness	"Collapsed," hard to wake up	Often preceded by c/o headache, vomiting, and/or seizure
One or both of above with new focal deficit	Paralyzed on one side, eyes going to one side, face drooping	

Used with permission from: Rebecca Ichord, MD. Children's Hospital of Philadelphia Stroke Program Stroke Care at CHOP: The Bare Essentials for Primary Care and ED Physicians March 2007. *Developed by the Stroke Team at Children's Hospital of Philadelphia, for screening and triage by nursing staff and emergency medicine providers. Available at www.chop.edu/stroke.

Differential Diagnosis of Child with Suspected Stroke

Vascular	Nonvascular
Focal cerebral ischemia Intracranial hemorrhage Cerebral sinovenous thrombosis Aneurysm Arteriovenous malformation	Cerebral abscess Encephalitis (herpes simplex virus) Meningitis Brain tumor Alternating hemiplegia of infancy Multiple sclerosis (demyelination) Malingering/conversion disorder Epilepsy: Postictal Todd's paralysis or a focal inhibitory seizure Complicated/hemiplegic migraine Hypoglycemia Head trauma

Comparison of Guidelines for Acute Management of Ischemic Stroke in Children by Subtype of Stroke

	UK guidelines: 2004 recommendation	G	S	Chest guidelines: 2008 recommendations	G	S	American Heart Association: 2008 recommendations	G	S
General	Aspirin 5 mg/kg	WPC	1	UFH or LMWH or aspirin 1-5 mg/kg/day until cardioembolic and dissection subtypes excluded	1B	1	UFH or LMWH (1 mg/kg every 12 h) up to 1 week until cause determined	2B-C	3
Sickle cell disease	Exchange transfusion to HBS < 30%	WPC	1	Intravenous hydration and exchange transfusion to HBS < 30%	1B	1	Optimal hydration, correction of hypoxemia and hypotension Exchange transfusion to HbS < 30%	1C 2A-B	1 2
Cardiac	Anticoagulation should be discussed by senior pediatric neurologist and cardiologist	WPC	1	LMWH for over 6 weeks	2C	3	Therapy for heart problem	1C	1
Dissection of neck vessels	Anticoagulation for extracranial with no hemorrhage	WPC	1	LMWH for over 6 weeks	2C	3	UFH or LMWH as a bridge to oral anticoagulation	2A-C	3
Alteplase in children	Not recommended	—	1	Not recommended	1B	1	Not recommended	3C	1
Alteplase in teenage years	Not addressed	—	—	Not addressed	—	—	No consensus on use	—	3
Cerebral sinovenous thrombosis	Anticoagulation until recanalization for up to 6 months	—	C3	Initial UFH or LMWH, then LMWH for 3 months plus another 3 months if not fully recanalized	1B	1	Initial UFH or LMWH followed by warfarin for 3-6 months	2A-C	3

Childhood is defined as 28 days to 18 years (Chest), or 1 month to 16 years (UK). G = grade of evidence or recommendation; HbS = sickle cell hemoglobin; LMWH = low molecular weight heparin; S = strength of evidence or recommendation; UFH = unfractionated heparin; WPC = working party consensus

DeVeber G, Kirkham F, et al. Guidelines for the treatment and prevention of stroke in children. *Lancet Neurol* 2008;7:983-985, with permission from Elsevier.

Diagnostic Evaluation of Childhood Stroke

First Line: On Presentation	Second Line: Within 48 Hours as Indicated
CT/MRI of brain MRA Complete blood cell count PT/PTT/INR Electrolytes, Ca, Mg, Phos, Glucose, renal function (Bun/Cr) Blood culture Liver function test ESR, ANA Urinalysis, urine drug screen ECG	Echocardiogram Holter monitor TCD and/or carotid Doppler CT angiography EEG Hypercoagulable evaluation Antithrombin III activity assay Protein C and S activity assay Factor V mutation Antiphospholipid antibodies Lupus anticoagulant Screening metabolic disorders Serum amino acids Urine for organic acids Serum lactate/pyruvate Plasma ammonia levels Lipid profile Serum homocysteine Hemoglobin electrophoresis Complement profile VDRL HIV testing Rheumatoid factor Lumbar puncture: cell count, protein, glucose, lactate

Abbreviations: ANA, antinuclear antibody; BUN, serum urea nitrogen; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

Supplement to *Emergency Medicine Reports*, November 19, 2012: "Stroke: It's Not Just for Grown-ups." *Authors:* **Dale S. Birenbaum, MD, FACEP, FAAEM,** Academic Chairman, Program Director, Florida Hospital Emergency Medicine Residency Program, Assistant Professor, Florida State University and University of Central Florida Schools of Medicine, Orlando; **Dennis A. Hernandez, MD, FAAEM, FACEP**, Medical Director, Pediatric Emergency Services, Florida Hospital for Children, Assistant Professor, Florida State University School of Medicine, Assistant Professor, University of Central Florida School of Medicine, Orlando; and **Kevin Steinwachs, MD**, Florida Hospital Emergency Medicine Residency, Orlando.