An Update on Pediatric Stroke Protocol

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Abstract: Pediatric stroke is relatively rare, with approximately 1000 childhood strokes in the United States per year. However, the occurrence of stroke in children leads to significant morbidity and mortality, warranting the development proven screening tools, protocols, and treatment options. Because significant delays in seeking medical attention can occur, time to recognition of pediatric stroke in the emergency department is uniquely challenging and critical. Once recognized, a trained multidisciplinary team with a multifaceted approach is needed to provide the best possible outcome for the patient. Key elements of the pediatric stroke protocol should include recognition tools, stroke alert mechanism, stroke order sets, timely imaging, laboratory evaluation, and treatment options. Substantial advancements have been made in the field of pediatric stroke protocols mainly due to formation of international consortiums and clinical trial. Despite significant progress, treatment options remain controversial.

Key Words: pediatric emergency department, pediatric stroke protocol, stroke imaging, stroke order set

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TARGET AUDIENCE

This CME activity is intended for pediatric emergency medicine practitioners, pediatric critical care physicians, and emergency management personnel.

LEARNING OBJECTIVES

After completing this CME activity, the reader should be better able to:

1. Assess the basic elements in pediatric emergency department acute stroke management
2. Value the importance and time sensitive need for definitive neuroimaging in pediatric stroke
3. Analyze the epidemiology, signs, and symptoms of pediatric and neonatal stroke
4. Interpret current literature regarding pediatric acute stroke protocol

The incidence of pediatric stoke is low, with most estimates around 2 to 3 per 100,000 every year accounting for approximately 1000 childhood strokes in the United States per year.[1] Stroke incidence is higher in neonates (25–40/100,00) and is highest in premature infants, with estimates up to 100 per 100,000 births.[2]

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Stroke can be defined as an abrupt loss of brain function that is caused by decreased cerebral blood flow. Stroke can occur at all stages of life, but presentation is variable depending on age, involved artery, and underlying risk factors. Younger children usually present with nonspecific symptoms such as seizure and altered mental status, especially those younger than 1 year, whereas older children present with focal neurologic deficits such as hemiplegia. Seizures have been reported in 20% to 48% of cases and are present regardless of age and independent from stroke subtype.[3]

Although stroke management guidelines exist for the pediatric population, wide institutional variations exist in care, and interventions to minimize morbidity are not applied consistently. To improve long- and short-term outcomes in pediatric stroke, extrapolation for the experience in adults suggests that the formation of an acute stroke team with multidisciplinary representation and written protocols is an important step in delivering emergent pediatric stroke care.

RISKS

Risk factors for stroke in children differ from those in adults. Adult risk factors are centered mainly on obstructive atherosclerotic arteriopathies, cardiovascular disease, and arrhythmias, which are seldom found as risk factors in children. Stroke in children occurs primarily through 2 mechanisms, ischemic and hemorrhagic. The most common cause of ischemic stroke is thrombotic, which occurs more commonly in children, representing 30% to 60% of cases. Although less common in children, hemorrhagic stroke is mainly caused by arteriovenous malformation.[1]

Studies such as the International Pediatric Stroke Study (IPSS) have reported systemic risk factors for pediatric stroke including sickle cell disease, cardiac disorders, trauma, and major infections such as meningitis, sepsis, and encephalitis, but in most cases, no systemic disease was found.[3,4]

EPIDEMIOLOGY

Stroke incidence can be stratified by age in children: 13/100,000 per year in children older than 1 month, 25 to 40/100,000 in neonates, and 100/100,000 in premature infants.[2] Many studies have shown that pediatric ischemic stroke is more common in boys than in girls and that male predominance was consistent regardless of age, history of trauma, or type of stroke. In one large international study including 30 centers across 10 countries with 1187 children, male predominance persisted after stratification by age (61% for neonates, $P = 0.011$; 59% for later childhood, $P = 0.002$) and stroke subtype (58% for arterial ischemic stroke [AIS], $P = 0.004$; 65% for cerebral sinovenous thrombosis, $P = 0.002$).[5]

Stroke in children occurs less frequently than in adults; however, the societal cost inherently has greater impact.[6] Arterial ischemic stroke in children has been shown to be associated with decreased quality of life in greater than 50% of cases, death in 12%, and disability in greater than 60% of survivors.[7,8] It has been estimated that 50% of neonates and 65% of children older than 1 month will incur lasting motor deficits after suffering from stroke.[2]

STROKE ASSESSMENT AND DETECTION

Delays in detection of pediatric stroke can adversely influence long- and short-term outcomes.[9] In the pediatric emergency department (PED), the goal for door to actual physician assessment should be less than 15 minutes, when the chief complaint is highly specific for acute stroke, such as the abrupt onset of hemiplegia.[10] The estimated time between presentation of children with stroke and the actual diagnosis is 24 hours, with most of that interval consisting of delays in seeking medical attention and the duration of the in-hospital evaluation.[11] There is an emerging consensus that screening protocols and recruitment, education, and organization of emergency department (ED) personnel are vital in stroke assessment and detection. Protocols and tools used by emergency staff to accurately and expeditiously detect stroke must be developed with an understanding of child versus adult presentation differences. Communication among ED personnel, as well as collaboration/consultation with neurology, radiology, and critical care, is essential.

When a child arrives in the PED, many diagnoses can mimic pediatric stroke, which can complicate detection, including migraine, febrile, or afebrile seizures, Bell palsy, conversion disorder, and syncope.[1,12] Up to one third of pediatric focal neurologic deficits are due to these stroke mimics.[7] Delays in detection of pediatric stroke can affect outcomes because treatment is time sensitive. Therefore, validated stroke recognition tools are needed to improve door to pediatric stroke recognition and treatment time. Many instruments exist in the adult arena including the Face Arm Speech Test, the Cincinnati Pre-Hospital Stroke Scale, the Los Angeles Pre-Hospital Stroke Screen, and the Recognition of Stroke in the Emergency Department.[13]

Although stroke recognition tools have been validated for adult patients, limited studies have been performed to validate these tools in pediatric stroke. One study aimed to describe signs and symptoms of radiologically confirmed pediatric stroke and also determine whether adult stroke recognition tools are applicable. The study results indicated that face, arm, or leg weakness and speech disturbance were the most common signs and noted 2 adult tools; namely, the Face Arm Speech Test and Recognition of Stroke in the Emergency Department had sensitivity of 76% and 81%, respectively, for detection of stroke symptoms.[13] Of note, stroke topography has been shown to affect the accuracy of these tools because they cannot assess defects due to interruption of the posterior circulation. The posterior circulation affects visual fields, perception, and balance, which are not integral parts of these assessment tools. In this particular study, one quarter of these pediatric strokes involved posterior circulation.

In addition to these matrix- and list-based stroke recognition tools, technology has also shown a promising role in the detection of pediatric stroke. Near-infrared spectroscopy, now called "cerebral oximetry," has been used during adult and pediatric cardiothoracic surgery for detection of low cerebral perfusion states, ischemic and hemorrhagic insults, and an increased hypoxic brain injury risk from surgery.[14,15] Recently, this hemispheric cerebral oximetry monitoring premise has been substantiated in adult stroke studies and in one pediatric stroke study. In the pediatric stroke cerebral oximetry study, hemispheric regional cerebral oxygen saturation less than 60% and an interhemispheric discordance hemispheric regional cerebral oxygen saturation reading greater than 10 correlated with the abnormal hemispheric cerebral pathology, with high positive predictive value for stroke occurrence, stroke location, and stroke type (hemorrhagic or ischemic).[16] In pediatric patients with suspected signs and symptoms of a potential stroke, cerebral oximetry has shown that it can detect pediatric stroke, stroke location, and stroke type.[6,14–17] When used as an adjunct neurologic screening tool, cerebral oximetry has potential to support expediting stroke alert process, neuroimaging, and neuroresuscitation.

NEUROIMAGING

A review of the literature supports brain magnetic resonance imaging (MRI) as more sensitive than computed tomography (CT) in diagnosis and detection of pediatric stroke. Head CT without contrast is the study of choice for identifying acute hemorrhage but may be normal in the cases of ischemic stroke in the first 12 to 24 hours after the event.[10,11,18] Therefore, MRI is a more sensitive modality for stroke including AIS, vascular malformations, and central nervous system inflammatory changes. Noncontrast CT used for the detection of brain ischemia is more sensitive after the initial 24 hours.

Any child with suspected acute stroke should have an MRI performed with diffusion-weighted imaging as well as magnetic resonance angiography (MRA) of the head and neck. In addition, magnetic resonance venography imaging should be given consideration if hemorrhage has occurred secondary to cerebral venous sinus thrombosis. In order for expeditious MRI imaging to occur, part of pediatric stroke protocol requires an MRI technologist and physicians with deep sedation privileges be available 24/7. The actual imaging time is only seconds to a few minutes. In the event that the treating facility does not have MRI capability, CT with angiography (CTA) may be substituted.

DEVELOPMENT OF PEDIATRIC STROKE PROTOCOL

To ensure the best outcome after pediatric stroke, most literature supports the development of an acute stroke team augmented with written clinical care and screening protocols. Although there is no consensus delineated for membership, most teams are multidisciplinary, with a minimum of an emergency physician, a neurologist, and a neuroradiologist, with ongoing-targeted training for recognition, diagnosis, and treatment. It is beneficial to develop a stroke council that will take an iterative approach to stroke alert, protocol, quality, and outcome improvement. The council should meet regularly to discuss quality improvement goals as well as needed educational activities such as early stroke recognition.[19] These activities should include but not limited to case discussion, lecture, simulation, and protocol discussion to continually refine and improve quality measures.[20]

Once a child has been identified as having a potential stroke, per-protocol stroke activation must optimally address patient care and treatment based on the capabilities of the facility. Activation may include a single page or a combination of communication methods including text and phone call(s) to allow for coordination of multidisciplinary care. In fully staffed tertiary facilities, communication may include neurology, neurosurgery, imaging team, intensive care team, nursing, cardiologist, MRI technician, pharmacist, and hematologist. In resource-limited facilities, initial communication may include a select subset of the team such as the on-call stroke neurologist who triages the call and decides the appropriate disciplines to include in the activation.

The most important aspect in creation and implementation of a pediatric stroke protocol is formation of a team of specialists, including stroke neurologists that can provide rapid response around the clock.[20]

ACUTE CHILDHOOD STROKE NOTIFICATION SYSTEMS

After the approval of tissue plasminogen activator (tPA) in treatment of acute AIS in the adult population, multiple stroke

organizations including the National Stroke Association published guidelines recommending establishment of primary stroke centers, or PSCs. The goal of these PSCs was to provide standardized acute stroke care with efficient diagnosis and initiation of tPA therapy when indicated. Essential elements of PSCs include acute stroke teams capable of bedside assessment ideally within 15 minutes, standardized written care protocols, emergency medical services, an ED with stroke monitoring protocol, a stroke unit, neurosurgical service, imaging capabilities, laboratory services, and rehabilitation services for post–stroke care.[10] As a result, there was a significant increase in availability of PSCs to the adult American population from 2000 to 2010.[21]

The Thrombolysis in Pediatric Stroke (TIPS) trial was crucial in the development of similar stroke centers specific to pediatrics. The TIPS trial was intended to be a 5-year, prospective multicenter trial funded by the National Institute of Neurological Disorders and Stroke to study the use intravenous tPA in pediatric patients with acute ischemic stroke (AIS). Although it was halted in 2013 because of low recruitment, the TIPS trial helped optimize acute pediatric stroke care and lead to development of primary pediatric stroke centers. The trial served as a catalyst for significant resource investment in participating centers as evidenced in Figure 1. As delineated in Figure 1, a significant growth trend was seen at participating TIPS sites in the quantity of pediatric subspecialties, sedated MRI availability, and targeted electronic medical record order sets. Evaluation of potential TIPS sites before study initiation in 2010 assessed each facility's incidence of pediatric stroke as well as ability to rapidly diagnose and treat pediatric stroke. This analysis revealed significant variability among these sites in clinical, radiographic, and overall facility preparedness to manage pediatric stroke. The search for TIPS sites highlighted a need to standardization of pediatric stroke care.[20]

In response to these findings during site investigation, the TIPS steering committee established requirements that TIPS sites have pediatric intensive care units for post–stroke care, 24-hour emergent neuroimaging capability (MRI/MRA or CT/CTA), pediatric anesthesia, and pediatric neurosurgery services.[9] Pediatric stroke alerts or stroke codes were also instituted at many facilities. These alert systems involve a central paging system notification to initiate multidisciplinary evaluation of and treatment for pediatric patients with potential AIS.[11] Patients are seen within 15 minutes and have appropriate neuroimaging immediately. Establishment of pediatric stroke alert systems helps increase the ED staff sensitivity for stroke diagnosis, as well as provide comfort in managing acute childhood AIS.[1]

ED PEDIATRIC STROKE ORDER SETS

Prompt recognition and diagnosis of pediatric stroke is essential in the pediatric ED. However, because of the relative infrequency and lack of data on treatment of pediatric AIS, management can be difficult for providers. To maximize efficiency and streamline diagnostic evaluation of pediatric stroke, stroke order sets or pathways for management have developed. In 2004, only 6% of TIPS primary sites had an ED order set for acute pediatric stroke.[20] As a result of TIPS preparation and steering committee recommendations, all 13 TIPS had implemented a formal stroke order set by 2013. Establishment of pathways for childhood AIS increases provider comfort in managing these patients.[9] Rapid diagnosis and treatment of acute stroke in pediatrics is essential and often challenging. Median time to diagnosis of pediatric AIS from symptom onset is nearly 24 hours.[1] Overall outcomes are best with efficient diagnosis, especially because of a limited window of opportunity for thrombolytic therapy. As mentioned previously, cerebral oximetry has been shown to noninvasively detect changes in cerebral hemispheric physiology correlating with stroke activity and thus has the potential to expedite stroke activation, imaging, diagnosis, and treatment.

An important component of the order set is emergent neuroimaging—with either MRI or noncontrast CT. Computed tomographic imaging is readily available, fast, and sensitive for intracranial hemorrhage; however, it can miss early ischemic infarction especially in the first 6 to 12 hours.[3,11,22] Magnetic resonance imaging is more sensitive than CT imaging for ischemic changes seen in AIS and is therefore the gold standard in pediatric AIS.[1] Angiography, usually MRA, is essential for definitive evaluation of cerebral vasculature.

Laboratory investigation must be thorough and assess for underlying etiology or contributing factors to stroke, such as hypercoagulable states or drug use. Evaluation must include serum chemistry, electrolytes, complete blood cell count, and coagulation factors. Table 1 details standard components to initial ED evaluation of pediatric AIS. The radiographic imaging can be tailored to individual patient presentation. In addition, frequent reassessment of blood glucose is essential because hyperglycemia can worsen cerebral ischemia.[4,23] Glucose monitoring should occur at least every 2 hours if within normal parameters, more frequently if abnormal.

ED TREATMENT OF PEDIATRIC STROKE

Substantial advancements in the recognition and treatment of pediatric stroke have been made in the past decade partially
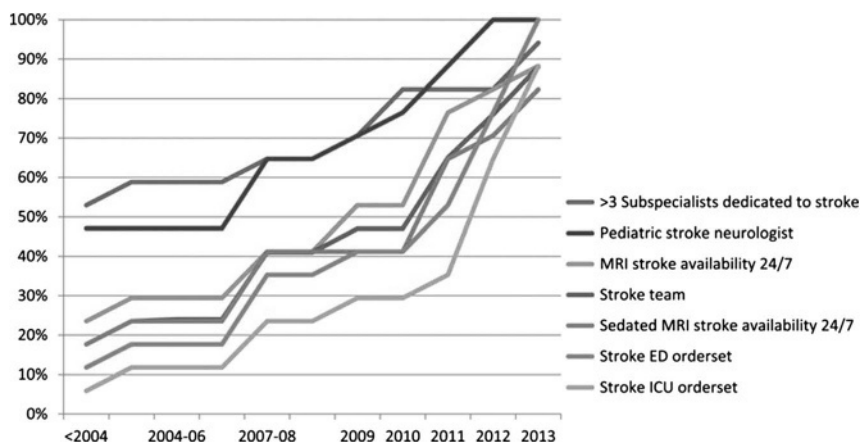

FIGURE 1. Development of site readiness for acute stroke in TIPS sites from 2003 to 2013.[20]

TABLE 1. ED Pediatric Stroke Order Set Components

Laboratory
    CBC
    Erythrocyte sedimentation rate
    Electrolytes
    Blood glucose
    Renal function studies
    Prothrombin time
    Partial thromboplastin time
    Lipid Profile
    Toxicology screen
    Pregnancy test
    Protein C
    Protein S
    Antithrombin III
    Anticardiolipin antibody
    Lupus anticoagulant
    Factor V Leiden mutation
    Coagulation factors
    Homocysteine
    Lipoprotein
    β_2-Glycoprotein antibody blood type and screen
Radiographic (Presentation Specific)
    Noncontrast MRI of the head
    Noncontrast CT of the head if MRI not available
    MRA of the head and neck
    CTA of the head and neck if MRA not available
    Echocardiogram (with bubble study)
    Chest x-ray
Other (Optional)
    Electrocardiogram
    Lumbar puncture
    Blood culture if history of febrile illness
    TEG if on aspirin at presentation
    Anti-FXA (LMWH) level if on enoxaparin at presentation

CBC indicates complete blood count; FXA, factor Xa; LMWH, low-molecular-weight heparin; TEG, thromboelastogram.

because of the formation of groups such as the IPSS consortium and clinical trials, namely, TIPS trial. Although progress has been made, pediatric stroke treatment decisions remain controversial with the decision to administer tPA at the heart of the discussion.

The formation of primary pediatric stroke centers has improved uniformity and efficiency of pediatric stroke management.[9] The majority of pediatric stroke management has been extrapolated from adult literature owing to limited studies on pediatric stroke. However, the organization of the TIPS trial (although discontinued) and formation of pediatric stroke consensus organizations have created more standardized pediatric stroke care. As with any pediatric patient, priority must be given to maintenance of airway, breathing, and circulation. Patients with stroke have significant aspiration risk and should be kept nil per os. Physicians should evaluate patients with suspected stroke using the Pediatric National Institutes of Health Stroke Scale before neuroimaging. In addition, frequent monitoring and reassessment is vital to pediatric stroke care. Patients should be on continuous monitoring, and nursing or support staff should obtain frequent vital signs to assess for changes in clinical condition. As part of the acute pediatric stroke protocol at Arkansas Children's Hospital, nurses obtain vital signs every 30 minutes for the first 90 minutes then hourly while in the ED. Neurologic status should be evaluated at least hourly, and any immediate changes in mental status require prompt reassessment given risk of high stroke recurrence.

Neuroprotective Measures

All pediatric patients with stroke should receive certain neuroprotective measures to help minimize cerebral ischemia and further neurologic damage. Most patients with childhood AIS present outside the accepted time window for acute tPA administration. Therefore, early treatment to maintain euvolemia, address hyperthermia and antithrombotic therapy, and prevent hyperglycemia may be more important in improving childhood AIS outcomes.[9] The head of the bed should be kept flat for 24 to 72 hours to maximize cerebral perfusion pressure, unless increased intracranial pressure is a concern.[11] Patients should also be placed on supplemental flow to maintain adequate oxygenation.[22] Goal oxygen saturations should be 94% or greater. Euvolemia should be maintained with intravenous fluids (normal saline) at 1 to 1.5 times maintenance fluid requirement, and use of hypotonic fluids should be avoided.[11] Prevention and treatment of hyperthermia is recommended with liberal acetaminophen use or application of cooling blanket to maintain temperature less than 37.5°C.[11]

Reactive increase in blood pressure is common in patients with stroke due to stress, change in cerebral perfusion pressure, and increased sympathetic activity. Persistent hypertension (>95th percentiles for age) within the first 3 days after AIS has been associated with increased risk of death; therefore, it is recommended to maintain blood pressure between the 50th and 95th percentile for age and height.[2] However, permissive hypertension up to 20% above the 95th percentile is acceptable and it can help maintain adequate cerebral perfusion pressure.[11,22] Labetalol (0.2 mg/kg) is the recommended antihypertensive agent and when administered should aim to lower blood pressure by 25% within 24 hours. Antihypertensive therapy must be used cautiously to prevent precipitous decreases in blood pressure and subsequent worsening of cerebral ischemia.[22]

Seizures may be an initial presenting symptom of AIS. Seizure activity can potentially worsen cerebral ischemia and cause hypoglycemia. Treatment of seizures with anticonvulsant medications is recommended along with consideration of electroencephalogram monitoring if concern for altered mental status, subclinical seizures, or status epilepticus.[2] Up to 23% of childhood AIS may have nonconvulsive seizures detected on electroencephalogram.[24]

Antithrombotic Therapy

Patient should receive anticoagulation with unfractionated heparin (UFH) or antiplatelet therapy with aspirin in the acute setting after hemorrhagic stroke has been ruled out.[11,22] Other notable possible contraindications for anticoagulation include Moya Moya disease, thrombocytopenia, surgery within the past 24 hours, active bleeding, methotrexate toxicity, thrombocytopenia with platelet count less than 50,000/mm³, or history of heparin-induced thrombocytopenia. There are limited data for anticoagulation in pediatrics AIS. At Arkansas Children's Hospital, the stroke center order set recommends aspirin dosing of 3 to 5 mg/kg orally every 24 hours. Unfractionated heparin is given with an initial loading dose of 30 units/kg for 10 minutes with a maximum of 5000 units. Next, heparin maintenance therapy is given with dosing based on age: 28 units kg^{-1} h^{-1} if younger than 1 year and 20 units kg^{-1} h^{-1} (maximum 1000 units/h) in those 1 year or older. Blood activated partial thromboplastin time (UFH) level or heparin anti-Xa UFH assay is obtained 4 hours after the initial dose to keep UFH level between

65 and 100 seconds or anti-Xa UFH 0.35 to 0.7 units/mL. There are standardized nomograms to adjust dosing based on these levels. Specific choices and titrations can be discussed with pediatric hematologist.

Thrombolytics

Tissue plasminogen activator is well established for use in adult stroke because it promotes degradation of fibrin in a thrombus that can lead to recanalization of a previously occluded artery in AIS.[2] In the United States, approximately 2% of children with acute stroke received tPA therapy.[20] Another positive impact of the TIPS trial has been more standardized tPA treatment in children. Before TIPS, the IPSS reported in a retrospective study of pediatric AIS patients receiving tPA from 2003 to 2007 that many received treatment outside the accepted adult treatment guidelines.[25] Given the time-sensitive nature of pediatric AIS, candidates must be identified expeditiously for possible thrombolytic treatment. Pediatric AIS patients must be identified within 4.5 hours of symptom onset to be considered for thrombolytic treatment or thrombectomy.[2] Delays in presentation, delays in diagnosis, and comorbidities limit the number of candidates for thrombolysis. Thrombolytic therapy with tPA should be considered in pediatric AIS if children are at least 2 years old, present with acute onset of neurologic symptoms and with neurologic imaging that confirms absence of intracranial hemorrhage, and displays early ischemic brain injury in the distribution of an arterial obstruction.[2] Acute neurologic symptoms concerning for stroke include unilateral weakness or sensory deficit, vision change, aphasia, and gait difficulty.[26] In addition, patients must not have any contraindications to tPA administration. Recommended dosing of tPA in AIS in children meeting previously discussed criteria is 0.9 mg/kg, which is the standard adult dosing as well. The first 10% should be given as a bolus and the rest within 1 hour. Administration of tPA is not without risks and adverse effects including nausea, vomiting, bradycardia, fever, allergic reaction, arrhythmias, and hypotension. Hemorrhage of the central nervous, gastrointestinal, or genitourinary systems is a life-threatening concern.[2] Incidence of intracranial hemorrhage after tPA in young adults may be less than seen in the older adult population though.[11] All pediatric patients with stroke who receive thrombolytic therapy should be admitted to a pediatric intensive care unit for post–stroke care. The risk of pediatric stroke recurrence ranges from 10% to 30% and is highest immediately after, emphasizing need for close monitoring.[11]

INTERNATIONAL ORGANIZATIONAL GROUPS DEVELOPED TO ADDRESS STROKE DETECTION AND TREATMENT

There are numerous stroke organizations worldwide that target both community and medical professional stroke education. In the past, most of these groups focused on recognition and treatment of stroke in the adult population, such as the American Heart Association Stroke Council and Brain Attack Coalition. However, more recently pediatric stroke organizations have been established. Management of pediatric AIS can be challenging given relative infrequency and lack of data outside adult stroke studies.[9] Development of integrated research networks has helped further pediatric stroke research, as the overall purpose of these groups is to improve recognition, community awareness, and treatment of pediatric stroke. One example is the International Alliance for Pediatric Stroke, which was established to facilitate collaboration between pediatric stroke communities. The emergence of pediatric stroke consortiums may be due to higher prevalence of pediatric stroke than previously believed.

CONCLUSIONS

Pediatric stroke is relatively rare but can lead to significant morbidity and mortality. Because incidence is much lower than the adult population and presentation is distinctly different, ongoing challenges exist in development of proven screening tools, protocols, and treatment options. In the PED, early recognition is paramount and requires the use of screening tools, effective communication, protocols, and trained personnel to provide optimal outcomes. Once a potential stroke is identified, there is an emerging consensus that a multidisciplinary team with a multifaceted approach is needed including stroke alert, stroke order sets, timely imaging, laboratory evaluation, and treatment options.

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