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Challenges in the diagnosis and treatment of pediatric stroke

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Abstract

The onset of stroke in children rarely owes to traditional stroke risk factors such as hypertension or diabetes. Rather, stroke in this patient group typically results from the simultaneous occurrence of multiple stroke risk factors, the presence of which necessitates a thorough evaluation. Several challenges exist in the care of children with stroke. Of note, recognition of pediatric stroke onset by parents and caregivers is often delayed, highlighting the need for increased awareness of and education regarding this condition. In terms of diagnostic challenges, various neurological conditions resemble stroke in pediatric patients and definite diagnosis of stroke will require MRI; adding to the challenge, young children may need to be sedated to undergo acute MRI. Perhaps the most significant challenge is the need for clinical research studies focusing on pediatric stroke treatment, so as to allow evidence-based treatment decision-making. A final challenge is standardizing outcome assessment after stroke across a wide range of ages and developmental levels. In this Review, we examine recent findings and diagnostic issues pertaining to both arterial ischemic stroke and hemorrhagic stroke in children.

Introduction

Pediatric stroke is an important cause of long-term disability, with children often living for many years with significant neurological deficits. This condition is also associated with notable acute and chronic health-care costs (Box 1). An often quoted fact is that in children, stroke occurs as frequently as brain tumor.¹ Data suggest, however, that stroke is slightly more common than brain tumor in this patient group, with an incidence of 2–13 per 100,000 person-years.^{2–5} Despite efforts to raise awareness regarding stroke in children, this condition is often overlooked as a cause of symptoms by health-care providers and families.^{6,7} Delay in diagnosis is just one of the issues relating to the care of children with stroke. This Review will focus on challenges in the diagnosis and treatment of arterial ischemic stroke (AIS) and hemorrhagic stroke in children, highlighting recent advances in the field and areas where further research is critically needed. AIS is defined as cerebral ischemia conforming to an arterial vascular distribution, while hemorrhagic stroke is defined as spontaneous intraparenchymal hemorrhage, intraventricular hemorrhage or subarachnoid hemorrhage. Arterial ischemic perinatal stroke and hemorrhagic perinatal stroke were

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excluded from this article, as these entities have different presentations, risk factors and recurrence risk to stroke in older children. Cerebral sinovenous thrombosis was excluded primarily to limit the scope of this work and because an excellent review covering this condition was recently published.⁸

Box 1

The cost of pediatric stroke

Using the 2003 data from the Kid's Inpatient Database, researchers estimated the mean cost of acute hospital care for patients aged 3 months to 20 years with any new stroke to be US\$20,927 per discharge.⁹³ When these data were separated by stroke type, the mean cost of acute care for patients with ischemic stroke was \$15,003 and for patients with intracerebral hemorrhage was \$24,117. Another study examined the 5 year direct costs of stroke in a Northern Californian health-maintenance organization from 1996–2003, encompassing inpatient and outpatient health-service costs (including costs from out-of-plan facilities).⁹⁴ The investigation found that the average adjusted 5 year cost for childhood stroke was \$135,161, and that the average cost of a pediatric stroke admission was \$81,869. Moreover, the health-care costs of children with stroke were 15-fold greater than the health-care costs of children without stroke. Although post-hospital costs declined after the first year, they continued to exceed the costs of the age-matched stroke-free control children, even 5 years poststroke.⁹⁴

The health-care costs discussed above are only applicable to children in North America; however, these data emphasize that pediatric stroke has both economic and personal costs, as children with stroke often receive treatment for and will live with the resulting functional deficits for many years.

Etiology and risk factors

Arterial ischemic stroke

The most common etiologies for pediatric AIS include cerebral arteriopathies (Figure 1),⁹ which are believed to be present in 50–80% of childhood AIS cases,^{9–11} congenital or acquired cardiac disease, and sickle cell disease.¹² Thrombophilias are also important causes of AIS.^{13, 14} Significant infections such as varicella, sepsis or meningitis have been recognized for many years to be causes of pediatric stroke as well.^{12, 15} By contrast, the discovery that minor infection is a potential risk factor for childhood AIS constitutes a more recent addition to the literature. A nested case–control study from the Kaiser Pediatric Stroke Study compared non-neonatal cases of pediatric AIS ($n = 97$) with controls (three controls per case) matched for birth year and primary care facility.¹⁶ Exposure was defined as an outpatient visit for a minor infection up to 4 weeks before an ischemic stroke or a visit over the same time period to the care facility by the controls. Encounters for minor infection were documented in 26.6% of AIS cases and 13% of controls (odds ratio (OR) 2.93, 95% CI 1.51–5.68; $P > 0.001$). An additional nine AIS cases but no controls had a serious infection causing meningitis or sepsis. The OR for the association of any infection (major or minor) with AIS was 5.01 (95% CI 2.64–9.54; $P < 0.0001$).¹⁶ The possibility that minor infection is a potential risk factor for stroke in children represents a challenge to physicians, given the high incidence of such infections in this patient group. Children who present with AIS often have multiple risk factors for this condition, and the nature of these risk factors shows high variability between individuals.¹⁷ Examples of apparently healthy children presenting with acute AIS who are then found to have multiple, unexpected stroke risk factors have been reported, such as a healthy, athletic school-aged boy found to have atrial fibrillation and a clotting disorder after an embolic AIS in the setting of a febrile illness.¹⁸ One challenge for

clinicians is to determine when all the appropriate risk factors for AIS have been identified in an individual child, so as to initiate appropriate treatment.

Hemorrhagic stroke

Hemorrhagic stroke typically includes spontaneous intracerebral hemorrhage (ICH)—parenchymal and intraventricular hemorrhage—and nontraumatic subarachnoid hemorrhage. The most common causes of pediatric hemorrhagic stroke are cerebral vascular abnormalities ranging from 40 to 90% of children with hemorrhagic stroke;^{11, 19} these abnormalities include arteriovenous malformations (AVMs), cavernous malformations, and aneurysms. Other causes of hemorrhagic stroke such as a bleeding disorder, thrombocytopenia and brain tumor (hemorrhagic stroke may constitute the presenting symptom of brain tumor) are less common.^{11, 19, 20} Hypertension has also been identified to be a risk factor for ICH in children, but occurs less frequently (and, hence, is a less important risk factor) in this patient group than in adults.^{21, 22} Recent cohort studies have revealed that, even after thorough patient evaluations, 9–23% of childhood ICH is still considered idiopathic.^{11, 21}

Diagnostic challenges

Delay in diagnosis and stroke mimics

The average time from symptom onset to presentation to the hospital for children with AIS has been reported in older literature to be 24 h.²³ More-recent work suggests that much of the delay to diagnosis in children with this condition now occurs within hospitals.^{6, 7} Rafay *et al.* found that while the median prehospital delay from symptom onset to presentation in cases of pediatric AIS was 1.7 h, the median in-hospital delay from presentation to diagnosis in such cases was 12.7 h.⁶

Symptom onset is often rapid and dramatic in children with hemorrhagic stroke, occurring over minutes to hours. At times, however, symptoms of this condition can be insidious, developing over several hours to days.²² In a cohort of children with intraparenchymal hemorrhage, the median time to presentation in hospital was 70 min, although 23% of children presented after 24 h.¹¹

Pediatric stroke is often under-recognized by health-care providers. In the study by Rafay and colleagues, for example, AIS was only suspected on initial assessment in 38% of children.⁶ One reason healthcare providers may overlook stroke in children is that there is a broad differential diagnosis for many of the non-specific presenting symptoms of childhood stroke such as seizures, headache, and hemiparesis. In fact, a pediatric stroke team examined their acute stroke calls and found that only 21% of children had stroke mimics.²⁴ Among these children, one-third had benign conditions, while two-thirds had serious diagnoses unrelated to stroke, including reversible posterior encephalopathy syndrome, intracranial infection, inflammatory disease and tumor. Note that, in children, hemorrhagic stroke can have a similar presentation to AIS, so it is likely that the information on stroke mimics of AIS apply to hemorrhagic stroke as well.

Neuroimaging challenges

Arterial ischemic stroke—Diffusion-weighted MRI of the brain is the most sensitive method to diagnose acute AIS; however, in children aged <8 years old, sedation or anesthesia may be required to undergo such imaging, as individuals must hold still for an extended period of time. One challenge in imaging pediatric stroke is, therefore, having an appropriate team available at all times for urgent sedation of patients. Delays in neuroimaging may result from the need for sedation.

In general, head CT generally does not require patient sedation, but the sensitivity of this method to detect acute AIS is low. In fact, a study from a large tertiary children's medical center in Australia found that ischemic stroke was not visualized on head CT in 62 of 74 (84%) children with this condition; all of these children had their stroke confirmed by MRI of the brain.⁷

Neuroimaging is always tailored to the individual patient with AIS or hemorrhagic stroke, although general guidelines are available. Brain imaging should occur as soon as possible after the stroke. Investigations should include MRI (the gold standard) of the brain, incorporating diffusion-weighted imaging (Figure 1). Vascular imaging of the brain and neck vessels should also be undertaken. In most cases of pediatric AIS, such imaging will involve magnetic resonance (MRA) angiography as the first-line examination, with the addition of magnetic resonance venography (MRV) if venous infarction or cerebral venous sinus thrombosis (CVST) is suspected. CT angiography (CTA) and CT venography (CTV) may also be used to identify vascular abnormalities.

The disadvantages of CTA and CTV, in comparison with MRA and MRV, include exposure to ionizing radiation and iodinated contrast agents. New CTA protocols can reduce the amount of radiation to which a child is exposed. Nevertheless, CTA presents another difficulty; the delivery of intravenous contrast has to be accurately timed to achieve a high quality image. In a child with a small intravenous line, it may not be possible to inject contrast quickly enough to allow imaging.²⁵ Another issue associated with CTA is that some nonsedated children move when the contrast agent is injected, and this movement can reduce the quality of the scan. Advantages of CTA over MRA are that that former is often more widely available and, at many centers, offers excellent and possibly superior visualization of vascular structures.²⁶ Conventional, digital subtraction angiography (DSA) remains the gold standard for vascular imaging²⁷ and may be required for a definitive diagnosis of small-vessel vasculitis, moyamoya disease, arterial stenosis or cervicocephalic arterial dissection.

Hemorrhagic stroke—In a child presenting with stroke-like symptoms, AIS and hemorrhagic stroke are both possible differential diagnoses. If a head CT is not obtained before brain MRI, 'blood-sensitive' MRI sequences (that is, gradient echo or susceptibility-weighted imaging [SWI]) can be added to standard MRI protocols to assess for brain hemorrhage. These MRI sequences have not been studied in children with stroke, but in adults with this disorder, these sequences are at least as sensitive as head CT for the detection of blood²⁸ and are often helpful in demonstrating cerebral cavernous malformations (Figure 2). Given the importance of vascular abnormalities as causes of hemorrhagic stroke in children, detailed vascular imaging in this patient group is particularly important. When possible, a complete MRI sequence (including MRI, MRA and MRV) should be performed to look for unusual causes of hemorrhagic stroke, such as high-grade brain tumor or CSVT with hemorrhagic venous infarction. If noninvasive imaging fails to detect the cause of the hemorrhage or a vascular malformation is suspected, DSA should be performed.²⁹

Sometimes brain AVMs are not evident on MRI, MRA or even DSA immediately after an acute hemorrhage. Thus, when vascular imaging is normal or inconclusive in the acute setting, studies should be repeated once the parenchymal hematoma has been reabsorbed; the reabsorption process often takes 2–8 weeks.

Laboratory and cardiac evaluation

Arterial ischemic stroke—As cardioembolic stroke is a major cause of AIS in children, use of echocardiography would seem to be a logical step to identify undetected congenital

heart disease. However, the role of patent foramen ovale (PFO) in childhood stroke and the proper echocardiographic technique to detect a PFO or other intracardiac shunt that might predispose to stroke in children is controversial.^{10, 30} An electrocardiogram (ECG) should be obtained to document the cardiac rhythm in all children with AIS. If arrhythmia is suspected on the basis of the patient's history or ECG, then longer, Holter or telemetry monitoring is indicated.

The laboratory evaluation of childhood AIS should assess markers of inflammation, hyperlipidemia, rheumatologic disease and thrombosis. Thus, tests for complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, the fasting lipid profile and antinuclear antibody levels should be conducted. A basic thrombophilia evaluation should also be performed.³¹

A meta-analysis has estimated the impact of thrombophilia on the risk of first-ever childhood stroke, and the resultant findings may prove helpful to clinicians as they decide what tests should be conducted.³¹ Analysis of data from 22 studies meeting strict methodologic inclusion criteria revealed that several thrombophilia risk factors had a significant association with first-ever stroke in children. An antithrombin deficiency, a protein C deficiency, a protein S deficiency, the factor V (*F5*) gene mutation 1691G>A (Leiden allele), the factor II (*F2*) gene mutation 20210G>A and high plasma lipoprotein(a) levels were identified as risk factors for both AIS and CSVT. By contrast, the presence of antiphospholipid antibodies was strongly associated with AIS only (OR 6.95, 95% CI 3.67–13.14). The methylene tetrahydrofolate reductase (*MTHFR*) gene mutation 677C>T was also associated with AIS only, albeit weakly (OR 1.58, 95% CI 1.20–2.08). Combined thrombophilias had the strongest association with pediatric stroke and CSVT (OR 11.86, 95% CI 5.93–23.73).³²

The meta-analysis reveals the strong associations between particular thrombophilia risk factors and pediatric AIS and the importance of multiple concurrent clotting risk factors in determining stroke risk. This analysis possessed, however, several important limitations, as acknowledged by the study's researchers. The study mostly examined white children; thus, the detected associations may not be applicable to other patient groups. Indeed, *F5* 1691G>A and *F2* 20210G>A are rare in black and Asian populations.^{33, 34} In adult thrombophilia, *MTHFR* mutations only confer a high risk of AIS in the presence of high homocysteine levels. Homocysteine data were not available in the pediatric cohort examined in the meta-analysis, but the authors of the study advised clinicians to test for homocysteinemia rather than *MTHFR* mutations, based on adult data.³⁵ Finally, only limited data were available on the risk of recurrent stroke in children with thrombophilia in the cohort of patients examined.

In addition to a careful laboratory evaluation for thrombophilia in suspected cases of pediatric AIS, consideration should be given to performance of both a toxicology screen, particularly for cocaine, and a pregnancy test in girls and young women of childbearing age as these are additional AIS risk factors.

Hemorrhagic stroke—A meta-analysis similar to the one in AIS has not been conducted for hemorrhagic stroke to identify risk factors for bleeding. Thus, recommendations for the laboratory evaluation of childhood hemorrhagic stroke are rudimentary. In a child with this condition, tests should include a platelet count, basic clotting studies (such as determination of the prothrombin time or international normalized ratio) and determination of the activated partial thromboplastin time, with further testing being guided by the family's history of bleeding disorders and the clinical picture.²⁹ Additional studies, such as metabolic testing

and more-detailed testing for inflammatory or rheumatological markers, should be decided on an individual basis.

Treatment options and challenges

Three sets of pediatric stroke guidelines have been published: the Royal College of Physicians guidelines,³⁶ the American College of Chest Physicians guidelines,³⁷ and the American Heart Association (AHA) guidelines.²⁹

Among these guidelines, only those from the AHA discuss hemorrhagic stroke. Several articles have reviewed and compared these guidelines.^{38, 39} The three sets of guidelines are all limited by the lack of treatment studies that have been conducted for pediatric stroke (with the notable exception of studies focusing on sickle cell disease). Overall, further research into the management of stroke in children is needed.

Supportive care

Supportive measures that have shown benefit in adults with stroke are recommended for children who develop this condition. These measures include maintenance of normal body temperature (via acetaminophen administration and use of cooling blankets), provision of sufficient intravenous fluids to maintain euolemia,⁴⁰ and avoidance of hyperglycemia.⁴¹

Blood pressure management

The AHA guidelines suggest “control of systemic hypertension” in children with AIS and hemorrhagic stroke.²⁹ This recommendation is based on expert opinion and is reasonable, but specific guidelines for blood pressure values are absent.

Anticonvulsants and EEG monitoring

Seizures are a common complication of pediatric stroke, affecting 25% of children with AIS and 20% of children with ICH.⁴² When they occur, seizures should be treated aggressively.²⁹

Prophylactic anticonvulsants are often used in the setting of intraparenchymal or subarachnoid hemorrhage in adults, although this approach is not evidence-based practice. The AHA pediatric stroke guidelines recommend against prophylactic anticonvulsant use in ischemic stroke but do not make recommendations in the setting of hemorrhagic stroke.²⁹ Note that no studies to support treatment or non-treatment with anticonvulsants have been conducted in children.

A study by Messé *et al.* analyzed data from CHANT for neuroprotection in adults with ICH.⁴³ The researchers found that prophylactic anticonvulsant use in adults with acute intraparenchymal hemorrhage was associated with poor outcomes: however, only 8% of the study participants ($n = 23$) were placed on prophylactic medication. Similar findings were seen in a prospective observational study of prophylactic anticonvulsant use in 98 adults with ICH.⁴⁴ In this study, five of seven patients with a clinical seizure had their seizure on the day of their intraparenchymal hemorrhage. Use of phenytoin but not levetiracetam was associated with a longer hospital stay and a poorer score on the modified Rankin Scale (mRS) at 14 days, 28 days, and 3 months compared to patients who were not treated with anticonvulsants. Note that selection bias existed in these studies, as patients who had the largest hemorrhages or who were critically ill were most likely to receive prophylactic anticonvulsants.

Continuous EEG monitoring is often utilized in intensive care units, although the benefit of this technique remains unproven. One study examined 100 children who had continuous

EEG monitoring for a diverse array of clinical indications, not specifically ischemic stroke or ICH. Seizure detection via EEG monitoring led to the initiation or escalation of antiseizure medications in 43 patients.⁴⁵ In many of these children, the indication for EEG monitoring was prolonged unresponsiveness after a clinical seizure. The application of these data to children with acute stroke and no history of seizure is unclear. Nevertheless, continuous EEG monitoring should be considered in children who exhibit a persistently altered mental status that is not clearly explained by their stroke (AIS or hemorrhagic stroke) or demonstrate movements or vital sign changes that are suggestive of seizure but cannot be captured on a routine EEG.

Management of intracranial pressure

A decline in mental status in a child with AIS or hemorrhagic stroke is a worrisome sign, which may indicate a rise in intracranial pressure (ICP). Other symptoms and signs of increased ICP include positional headache (a headache that intensifies when a patient is in a supine position, but improves when they are upright), vomiting, irritability or combativeness, sixth nerve palsies, and papilledema. Cushing's triad of signs for elevated ICP, comprising hypertension, bradycardia and irregular respirations, is usually a late finding. With AIS, increased ICP may develop several days after stroke onset as infarcted brain tissue becomes edematous. In hemorrhagic stroke, increased ICP may occur acutely, owing to mass effect from a hemorrhage. Increased ICP may also occur in the acute phase or subacutely if an intraventricular hemorrhage is accompanied by communicating hydrocephalus. An intraventricular catheter (IVC) may prove advantageous in some cases of pediatric hemorrhage stroke, providing both a means to measure ICP and, via drainage of cerebrospinal fluid, to manage ICP. As this sort of monitoring requires ventricular enlargement for placement, the insertion of an IVC is not an option for all children with hemorrhagic stroke. A subdural bolt is available for children who cannot have an IVC but require ICP monitoring. In a recent series of children with hemorrhagic stroke, 27% required a ventriculostomy.¹¹

Nonsurgical methods for acutely lowering elevated ICP include keeping the head of a patient's bed at 30°, so as to promote good cerebral venous drainage, hyperventilation to a pCO₂ of 25–30 mmHg to constrict cerebral blood vessels slightly as a means to reduce intracranial blood volume, and hyperosmolar therapy—with either mannitol or hypertonic saline—to promote osmotic diuresis. Plasma osmoles and electrolytes must be monitored frequently when osmotic agents are used to avoid hypovolemia, hypo or hypernatremia and renal failure. In some cases, sedation may be required to help manage elevated ICP. Hyperosmolar therapy and particularly hyperventilation are generally avoided. Corticosteroids should be avoided, since their efficacy for lowering increased ICP has not been demonstrated in adult studies,^{46, 47} and hyperglycemia resulting from corticosteroid treatment has been associated with poor outcomes in adults with ICH and AIS.^{41, 48}

AIS-specific treatments

Antithrombotic therapy—Antithrombotic therapy includes both antiplatelet (typically aspirin) and anticoagulant (unfractionated heparin, low molecular weight heparin, and warfarin) medications. Of note, the only treatments that limit brain injury after stroke are therapies that promote reperfusion, for example, tPA and mechanical clot retrieval, or reduce metabolic demands (avoiding hyperpyrexia or hyperglycemia); all other interventions are designed for secondary stroke prevention. In non-neonates, treatment with antithrombotic therapy is recommended for secondary stroke prevention.²⁹ Neonates with first-ever AIS but showing no evidence of an ongoing cardioembolic source are not, however, typically treated with antiplatelets or anticoagulants.³⁷

Children with sickle cell disease (SCD) are the exception amongst older children with AIS; aspirin and anticoagulation aren't typically recommended. Instead, transfusions are recommended to lower the percentage of sickle hemoglobin to <30%; this evidence-based guideline encompasses both secondary stroke prevention and primary stroke prevention.^{49–51} Evidence for acute transfusion in the setting of first-ever AIS is not as strong, although acute transfusions are commonly performed in clinical practice.⁵²

For non-SCD-related childhood stroke, the American College of Chest Physicians guidelines recommend initial anticoagulation or aspirin therapy at 1–5 mg/kg/day until cervicocephalic arterial dissection or cardioembolic causes have been excluded, followed by long-term aspirin therapy for a minimum of 2 years.³⁷ All major guidelines recommend consideration of anticoagulation (3–6 months treatment with low molecular weight heparin or warfarin) for confirmed cervicalcephalic artery dissection or cardioembolic stroke.²⁹ Anticoagulation is not typically recommended for children with moyamoya disease (Figure 3) or moyamoya syndrome, given the small risk of spontaneous intracerebral hemorrhage.⁵³

Overall, the choice of anticoagulation or antiplatelet therapy for children with AIS varies geographically, with centers in the US using anticoagulation less often than centers in Australia, Europe and Canada.⁵⁴ Some investigators argue that these geographic differences in care comprise an equipoise that would allow a randomized clinical trial of aspirin versus anticoagulation for pediatric AIS to be conducted.^{54, 55}

Thrombolytic therapy—Much effort has been devoted to the education of physicians and the public regarding thrombolytic therapy in adult stroke since the landmark National Institute of Neurological Disorders and Stroke trial of intravenous tissue plasminogen activator (tPA),⁵⁶ however, use of thrombolytic therapy for patients aged <18 years is much more controversial. The current AHA guidelines recommend that tPA use in young children is limited to a clinical trial, and no consensus has been reached regarding the use of this thrombolytic agent in older adolescents who meet standard adult criteria for tPA therapy.²⁹ Evidence for the safety and efficacy of thrombolysis in children with stroke is extremely limited, and existing studies of this treatment approach for systemic clots suggest a high risk of hemorrhagic complications.⁵⁷ Amlie-LeFond *et al.* compared published case reports of tPA use in children with tPA use reported as part of the International Pediatric Stroke Study (IPSS).⁵⁸ The researchers found that children receiving tPA in the IPSS were younger, had a longer time to treatment, and had poorer outcomes than individual cases reported in the medical literature.⁵⁸ The bias towards publishing cases with the best outcomes is well known. Thus, while some children with AIS may benefit from tPA, good reason exists for a safety and dosing-finding tPA study in children (Figure 4). Such a study is now planned and will require radiological confirmation of acute ischemia or vessel occlusion before tPA is administered.⁵⁹

Surgical therapy—Hemicraniectomy may be both life-saving and function-sparing in adults with a large AIS who display a rapid deterioration in level of consciousness or progress to signs and symptoms of impending herniation.^{60–62} In children, no formal studies of hemicraniectomy have been performed. In a recent case series of 10 children with malignant middle cerebral artery infarction,⁶³ seven underwent hemicraniectomy, all of whom survived and had moderately good recovery (all seven had hemiparesis but were able to walk and had fluent speech despite left-sided infarcts). In this study, time to surgery ranged from 23–291 h in survivors. The lowest Glasgow Coma Scale scores ranged from 4 to 9 in children who survived. The three children who died in this case series did not undergo hemicraniectomy and died of increased ICP. The recommendation was to consider hemicraniectomy in children with malignant middle cerebral artery infarction even in the presence of deep coma.

Hemorrhagic stroke-specific treatment

The role of surgical evacuation of hemorrhage in children and young adults, <45 years of age with ICH is yet another controversial area of stroke therapy. STICH demonstrated that in adult patients with spontaneous supratentorial ICH, emergent surgical evacuation of hematoma within 72 h of bleeding onset did not improve patient outcomes over best medical management.⁶⁴ STICH required that the local investigator have clinical equipoise for surgical versus medical management. Younger patients (<45 years) with lobar hemorrhages may not have been enrolled in STICH because a small retrospective study had already provided some evidence that early surgery was beneficial in young adults with ICH.⁶⁵ For these reasons, it is unlikely that the results of the STICH trial are applicable to children. Further, children with ICH may require more urgent intervention than adults with hemorrhage to reduce elevated ICP and to prevent brain herniation (expansion of a hematoma or cerebral edema may rapidly cause such herniation) because they do not have cerebral atrophy that is present in many older adults with ICH.

Recurrence risk and neurological outcomes

Arterial ischemic stroke

Recurrence risk—Among children who suffer a first-ever AIS outside the neonatal period and go untreated, the risk of recurrence is $\approx 10\text{--}25\%$,^{12, 66, 67} although this value may be as low as 6% in those with 1 risk factors¹⁷ or as high as 90% in those with SCD.⁶⁸

The underlying stroke AIS mechanism seems to be particularly influential in regard to recurrence risk and timing of recurrence. In the Great Ormond Street series, genetic thrombophilia was significantly more common in children with cryptogenic stroke who recurred than in those who did not recur.⁶⁶ Along the same lines, children with cardiac disease, moyamoya disease or a systemic disease that predisposes to stroke may have recurrence many years after the original stroke, whereas children with transient cerebral arteriopathy or dissection are most likely to have an early recurrence of stroke.⁶⁹ In a study of children with AIS ($n = 97$) in CA, USA, the 5 year cumulative risk of AIS recurrence in older children was 19% (95% CI 12–30%), with 12 of the 15 cases of recurrent stroke occurring in children with arteriopathy.¹² Thus, a comprehensive evaluation of children with AIS for potential stroke risk factors may allow stratification of children into high-risk and low-risk groups for recurrent stroke, and may afford information about the timing of stroke recurrence.

Neurological outcomes—Neurological sequelae of stroke are present in more than half of children after AIS.^{70, 71} Motor deficits are the most recognizable deficits after childhood AIS, with cognitive impairments being more subtle. Up to 25% of children with acute stroke will have seizures; however, clear data on the persistence of seizures and development of epilepsy are lacking. Cortical lesions and persistence of seizures beyond 2 weeks of the acute insult have previously been identified as risk factors for secondary epilepsy.⁷² Young age, male sex and bihemispheric infarction predict poor outcome after AIS.⁷³

The idea is often touted that young brains exhibit more plasticity than adult brains and, therefore, have more capacity for recovery after injury. In studies of childhood AIS however, the younger the age at stroke onset, the poorer the cognitive and behavioral outcomes that have been observed.^{67, 74, 75} Note that these studies are limited by sample size, their cross-sectional design and the use of age-matched normal controls rather than matched sibling controls.

Hemorrhagic stroke

Recurrence risk—Few studies have commented on the incidence of rebleeding in cases of pediatric hemorrhagic stroke. In one retrospective cohort from Switzerland, comprising of 34 children who presented with hemorrhagic stroke between 1990 and 2000, recurrent ICH occurred in three children (9%).²² All three recurrences occurred within the first year of the incident ICH and were in children with unrepaired vascular anomalies (two individuals) and unknown cause of hemorrhage (one individual). In a population-based cohort of 116 children in Northern California who presented between January 1993 and December 2004, 11 individuals (9.5%) had recurrent ICH.⁷⁶ The recurrences occurred at a median of 3.1 months from the incident hemorrhage (among all the recurrences, >60% occurred within 6 months of the initial hemorrhage and >90% occurred within 3 years of the incident ICH). Of the children with recurrent ICH, none had idiopathic ICH and nine had vascular anomalies, six of which were never treated. The two children with medical etiologies of ICH both recurred within 1 week of the incident hemorrhage. One child with recurrent ICH had endstage renal disease leading to hypertensive ICH, the other child was a term neonate with idiopathic thrombocytopenia.

Neurological outcomes—Outcome studies in hemorrhagic stroke have been sparse. One study pooled data from non-population-based studies and reported an average mortality rate of 25% in children with hemorrhagic stroke.⁷³ Estimates of the mortality rate from individual studies range from 7–54%.^{21, 72} A more-modern, population-based study found a hemorrhagic stroke case fatality rate of 5.2%.⁷⁷

Predictors of poor outcome in hemorrhagic stroke include infratentorial hemorrhage location, Glasgow Coma Score (GCS) ≤ 7 at admission, aneurysm, age < 3 years, and underlying hematological disorder.²² A retrospective study showed that in children with this form of stroke, a large ICH volume predicted a poor outcome.²¹ A prospective series confirmed the importance of ICH volume for predicting patient outcomes and demonstrated that altered mental status within 6 h of hospital presentation was an added risk factor for poor short-term neurological outcome.¹¹ Bedside methods to estimate hemorrhage volume in children and, thus, to aid clinical outcome prediction have recently been developed.^{77, 78}

One important point to consider is that although children often ‘walk and talk’ after AIS or hemorrhagic stroke, the functional impact of their impairments on daily life may be significant. Similarly, lesions in the developing brain may result in impairments (such as cognitive deficits) that only emerge at the appropriate developmental stage.

Rehabilitation

Like traditional physical, occupational and speech therapies, neuropsychological testing with educational support does not have a strong evidence base, but should still be included in the recommended treatment plan for children with stroke. The AHA and RCP guidelines both support this view as these evaluations are useful in planning educational programs after a child’s stroke.^{29, 36} Newer, less traditional therapies for pediatric stroke are also available. Constraint-induced movement therapy (CIMT), which involves restraining a patient’s good arm and hand and intensive therapy for the weaker arm and hand, has been shown to be beneficial in adults undergoing rehabilitation for stroke.^{79, 80} To date, each pediatric CIMT study has involved no more than 55 participants. Nevertheless, together these small studies showed that CIMT was moderately effective in improving use of the stroke-affected upper extremity.^{81–84}

Botulinum toxin A (BoNT-A) injections for spasticity have not been studied specifically for children with stroke, but good evidence exists that this agent, when administered as

adjunctive therapy to standard physical and occupational therapy, can improve upper extremity function in children with hemiplegic cerebral palsy.⁸⁴ Predictors of good response to BoNT-A are good grip strength before commencement of treatment and, potentially, young age.⁸⁵

A small randomized controlled trial ($n = 10$ in each treatment arm) of repetitive transcranial magnetic stimulation (rTMS) versus sham rTMS in children with subcortical AIS suggested that inhibition of the contralesional cortex could improve hand function.⁸⁶ A larger study of this technique for the treatment pediatric AIS is ongoing. Transcranial direct-current stimulation has the advantage of not carrying a risk of seizure.⁸⁷ This technique has shown promise in adult stroke for both motor and language recovery, but has not yet been studied in children.⁸⁸

Unfortunately, few studies have been undertaken to guide the use of the various techniques discussed above in children. Families of children with stroke understandably desire rehabilitation techniques that will improve function, but the lack of data means that health-care providers have little to base recommendations on. Additionally, health-care benefits from third-party payers are often limited or nonexistent for unproven therapies. Further study of rehabilitation techniques for childhood stroke is critically needed.

Future directions

Clinical trials are a priority in pediatric AIS, including studies of antithrombotic medications (aspirin versus anticoagulation), acute antithrombotic or antifibrinolytic therapy, and rehabilitation methods. Clinical trials of treatments for hemorrhagic stroke are perhaps more distant but are equally necessary.

The NIH stroke scale (NIHSS) has been used successfully to quantify initial stroke severity in adults. The NIHSS has advanced clinical trials for stroke in this patient group because the score provides a baseline measure against which stroke outcomes may be compared and treatment effects may be assessed. A pediatric version of this scale (PedNIHSS) will be available soon (a study to validate the PedNIHSS is nearing completion).⁸⁹ Hopefully, the PedNIHSS will have similar impact in childhood stroke to the impact NIHSS has had in adult stroke.

Also of great importance is the ability to accurately measure outcome after pediatric stroke across a wide range of ages and developmental levels. The pediatric stroke outcome measure (PSOM) is a validated measure suitable for children aged 2–18 years and comprises a standardized neurological examination performed by a neurologist.⁹⁰ Nevertheless, a simpler functional scale, similar to the mRS, which is used in adults is also needed.⁹¹ The strength of the mRS is that it is a checklist that can be completed by a nurse or other health-care provider.⁹² A validated pediatric version of this scale or a similar outcome scale would be particularly helpful in clinical trials. More detailed outcome measures to adequately assess for cognitive deficits and behavioral problems will be necessary for more comprehensive outcome assessment.

Conclusions

Pediatric stroke is an important cause of childhood disability. The factors responsible for stroke in children are quite different from those that cause stroke in adults. Arteriopathy, cardiac disease and SCD represent just a few of the potential causes of stroke in children. Many challenges exist in the evaluation and treatment of these children, including nonrecognition of stroke by families and health-care providers, the frequent need for anesthesia support for diagnostic MRI in children, and the absence of treatment studies

outside of SCD. The PedNIHSS validation study results will be reported this year. This scale will quantify initial stroke severity and will provide a baseline measure against which stroke outcomes may be compared. Treatment trials are needed and will include a dose-finding and safety study of acute AIS treatment with tPA, starting this year, as well as ideally, a trial comparing aspirin versus warfarin or low molecular weight heparin for secondary stroke prevention in the future. To assess properly whether various treatments truly improve outcome, well-validated, easily applied outcome measures will need to be developed.

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Key points

Common risk factors for pediatric arterial ischemic stroke include cerebral arteriopathies, congenital or acquired cardiac disease, and sickle cell disease

Cerebral vascular abnormalities are the most common causes of hemorrhagic stroke in children

A combination of multiple, seemingly minor risk factors may lead to stroke in childhood Delayed recognition of stroke in children by families and health-care providers is a significant issue for both medical care and clinical trials

Clinical trials examining treatment strategies—particularly antithrombotic medications (aspirin versus anticoagulation) and rehabilitation methods—are needed for pediatric stroke

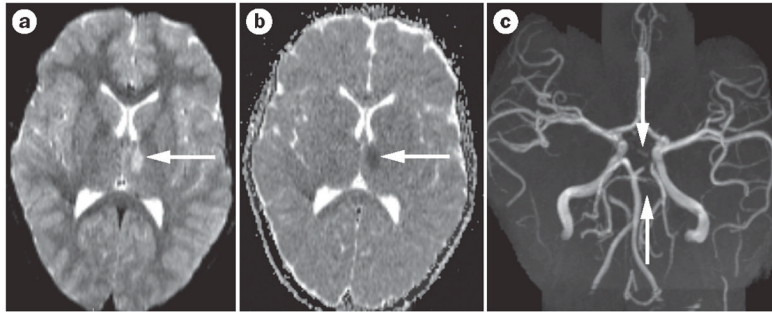


Figure 1.

Arteriopathy in pediatric stroke. a| Diffusion-weighted MRI shows an acute thalamic stroke (bright area; arrow) in a previously healthy 8 year-old girl. b | The apparent diffusion coefficient map is dark and confirms the acute stroke (arrow). c | Time-of-flight, noncontrast magnetic resonance angiography shows narrowing (near occlusion) of the posterior cerebral artery and superior cerebellar arteries on the same side (arrows). Extensive evaluation showed no cause for this arteriopathy.

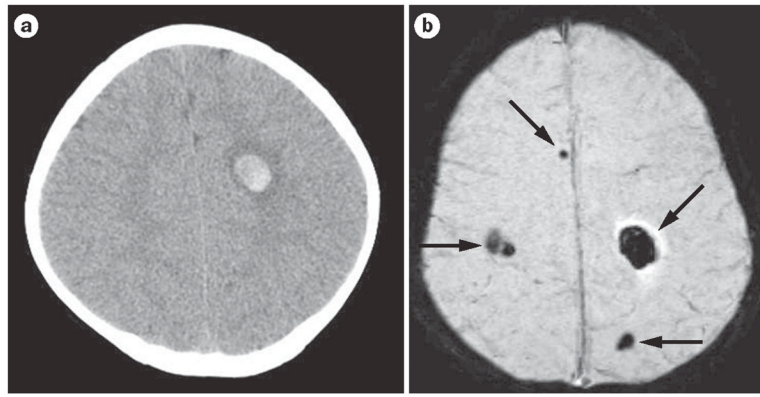


Figure 2. Acute hemorrhagic stroke and susceptibility-weighted imaging. a | The head CT shows a single, small right frontal acute parenchymal hemorrhage. b | The MRI susceptibility-weighted image shows the right frontal hemorrhage as well as multiple additional hemorrhages not visualized on head CT. This child has multiple cerebral cavernous malformations.

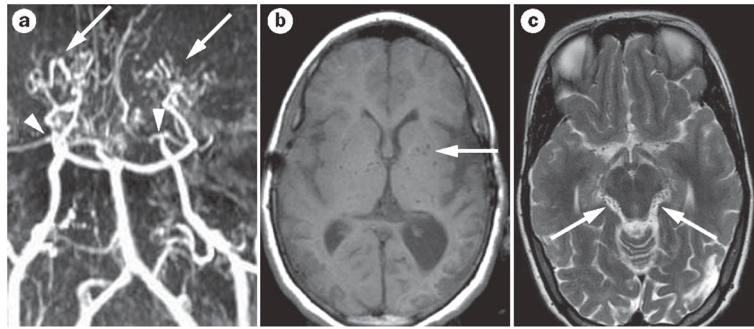


Figure 3.

Idiopathic moyamoya disease. a | Time-of-flight, noncontrast, magnetic resonance angiography shows moyamoya vasculopathy with bilateral occlusion of the internal carotid arteries (arrowheads). Robust lenticulostriate collaterals can also be observed (arrows). b | The lenticulostriate collaterals in moyamoya disease are also seen on the MRI scan, with multiple flow voids piercing the basal ganglia (arrow). c | These moyamoya collateral vessels are also seen as multiple small-flow voids around the brainstem (arrows).

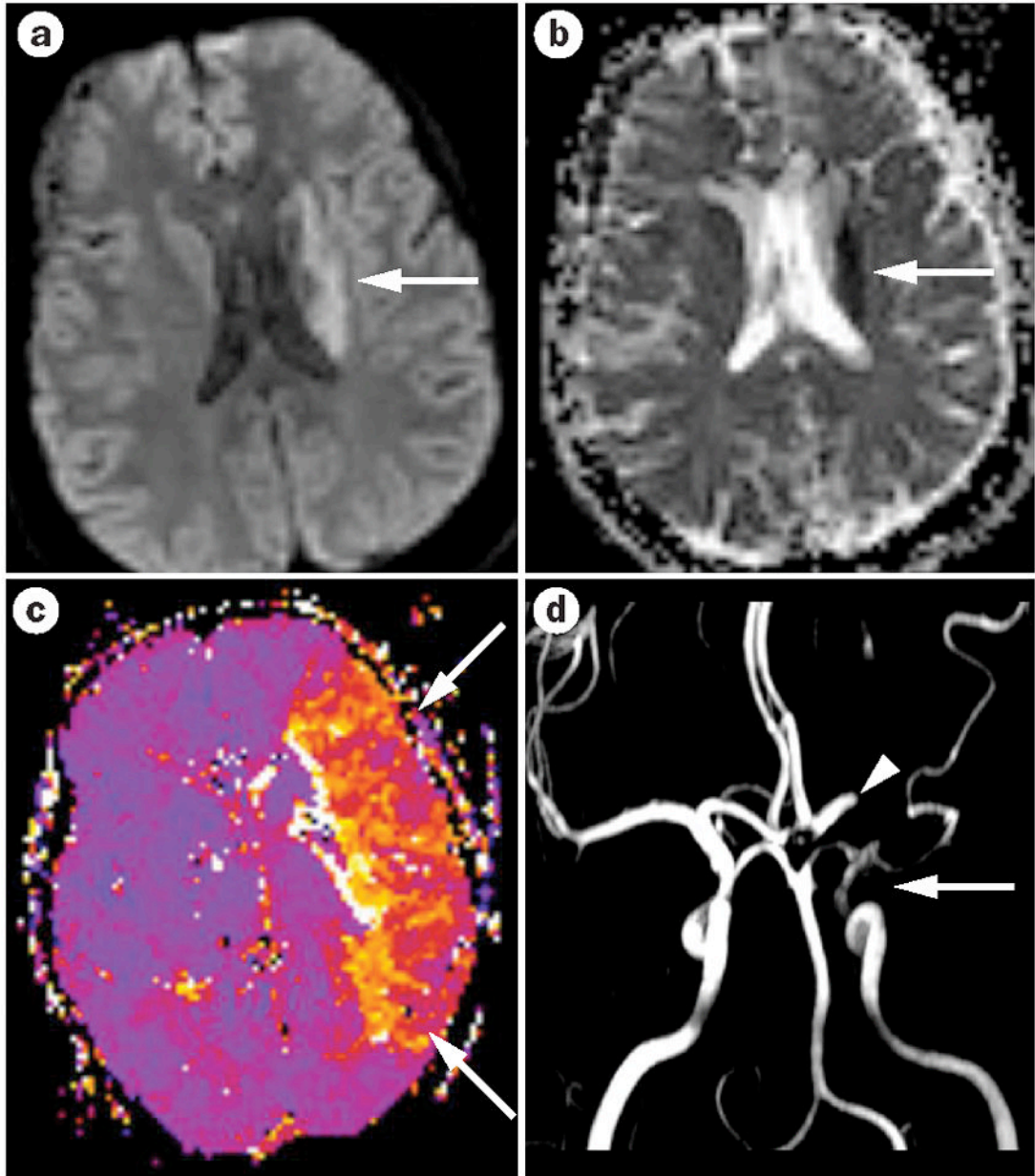


Figure 4.

Acute arterial ischemic stroke with diffusion–perfusion mismatch. **a**| The MRI reveals a small acute stroke that shows restriction on diffusion-weighted imaging in the periventricular region (arrow). **b**| The corresponding apparent diffusion coefficient map confirms the occurrence of acute ischemia (arrow). **c**| The perfusion-weighted image shows a large area of hypoperfusion—basically the entire left middle cerebral artery territory (arrow)—representing diffusion–perfusion mismatch. **d**| This stroke was caused by embolization of a cardiac thrombus that led to partial occlusion of the internal carotid artery—little flow is seen on magnetic resonance angiography (arrow)—and complete occlusion of the middle cerebral artery (arrowhead).