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STROKE (H ADAMS, SECTION EDITOR)

Arterial Ischemic Stroke in Children: Risk Factors and Etiologies

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Abstract Stroke is increasingly recognized as a significant cause of morbidity and mortality in children, and as a financial burden for families and society. Recent studies have identified and confirmed presumptive risk factors, and have identified novel associations with childhood arterial ischemic stroke. A better understanding of risk factors for stroke in children, which differ from the atherosclerotic risk factors in adults, is the first step needed to improve strategies for stroke prevention and intervention, and ultimately minimize the physical, mental, and financial burden of arterial ischemic stroke. Here, we discuss recent advances in research for selected childhood stroke risk factors, highlighting the progress made in our understanding of etiologic mechanisms and pathophysiology, and address the future directions for acute and long-term treatment strategies for pediatric stroke.

Keywords Pediatric stroke · Cerebral arteriopathy · Cranial radiation · Sickle cell disease · Congenital heart disease · Patent foramen ovale

Introduction

Stroke has become an increasingly recognized cause of morbidity and mortality in children. Population-based studies of arterial ischemic stroke (AIS) in children (defined by age 29 days to 18 years) estimate an annual incidence of 2.4 per 100,000 persons, with a case fatality rate approaching 4 % [1, 2]. Over 50 % of survivors have persistent neurologic, cognitive, or psychiatric deficits, with significant financial costs to families and society [5–9]. Epilepsy develops in nearly a third of young stroke survivors within the first decade after stroke, which may place further strain on families caring for child with disabilities [10].

Hospitalizations for AIS in children rose in the last decade [3, 4]. The rising rates of pediatric AIS hospitalization may be related, in part, to the increasing availability and use of better diagnostic techniques, such as magnetic resonance imaging (MRI) [11]. An improving public stroke awareness and recognition of stroke symptoms may also contribute. Finally, incidence rates of childhood stroke may actually be rising as the prevalence of important stroke risk factors in children change over time. Traditional cardiovascular risk factors of obesity and hypertension are becoming more prevalent among children at younger ages [12, 13]. Concurrently, the prevalence of diabetes, hypertension, lipid disorders, alcohol abuse, and tobacco use has increased among both adolescents and young adults hospitalized with AIS [4]. The prevalence of congenital heart disease (CHD) in adolescents hospitalized with AIS has also increased, perhaps reflecting improvement in the overall care and longer survival of children with cardiac anomalies, who then may be vulnerable to stroke as a delayed complication. On a more hopeful note, the prevalence of sickle cell disease has decreased among children with AIS as effective stroke prevention strategies have become available and are implemented [14, 15].

In contrast to adults, in whom modifiable risk factors such as cigarette smoking, hypertension, diabetes, and hypercholesterolemia have been well-documented, risk factors for pediatric AIS are less well understood. Traditional pediatric stroke risk factors were initially identified in case series describing the high

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prevalence of CHD, sickle cell disease, infection and hypercoaguable states among children with stroke [16–18]. As with other uncommon conditions, studies of childhood stroke have often been limited by sample size. Recently, the International Pediatric Stroke Study (IPSS), a multicenter, international observational cohort study reported on the prevalence of a spectrum of medical conditions associated with 676 children with AIS across broad geographical regions [19••, 20]. This prospective, collaborative, international effort is the largest series of childhood strokes to date and has provided greater details on presumptive childhood AIS risk factors. However, the children in this study remain a selected population enrolled predominantly from tertiary pediatric centers. The Kaiser Pediatric Stroke Study (KPSS), a population-based, case–control study, provided complementary data, confirming estimates of stroke risk in 2.5 million children and young adults in a single geographic region (Northern California) (Table 1) [21, 22••]. Identifying and quantifying risk factors for childhood AIS allows focused future research in stroke mechanisms for specific stroke etiologies.

Pediatric stroke is still an emerging field of study, and the recent literature identifying and confirming childhood stroke risk factors is of great importance. However, only about half of the children with a stroke have an underlying condition that predisposes to stroke, and etiology remains undetermined in a significant number of children, even after workup. Further, many of the risk factors discussed in this review may overlap or have a common mechanism. For example, cerebral arteriopathy is a leading mechanism for childhood stroke, but may be the result of various underlying genetic conditions such as sickle cell disease, PHACE syndrome, or fibromuscular dysplasia, an acquired condition from trauma or infection, or develop in a previously healthy child without any other known risk factors. In this review, we discuss recent advances in research for selected childhood stroke risk factors, highlighting the progress made in our understanding of etiologic mechanisms and pathophysiology, and address the future directions for acute and long-term treatment strategies for pediatric stroke.

An Evolving Understanding of Children at Risk for Ischemic Stroke

Congenital Heart Disease

Cardiac anomalies, both congenital and acquired, are reported in a large proportion of children with stroke. In the Great Ormond Hospital series, 15 % of children had a history of a cardiac disorder prior to stroke. In the IPSS, 31 % were reported to have a cardiac disorder. In contrast, only of the 8 % of the children in KPSS had a history of CHD. This discrepancy may reflect differences between series from primarily tertiary referral centers and population-based data. Abnormal cardiac anatomy may increase risk of AIS through a number of mechanisms, including paradoxical shunting of emboli, a prothrombotic state secondary to inflammation, iron-deficient anemia, and depressed cardiac function [23, 24]. Cardiopulmonary bypass, circulatory arrest, or other factors related to cardiac surgical repair may also be mediators of increased stroke risk [25, 26].

The use of new pediatric-specific ventricular assist devices and smaller extracorporeal life support systems has risen over the last decade for children with CHD, serving as a bridge to transplant or recovery [27]. As care for children with complex CHD has increased overall life expectancy, more children are surviving into adulthood. Both before and after surgical repair, children with CHD may be susceptible to acquired conditions such as infective endocarditis or arrhythmias [28]. Stroke remains a long-term risk, particularly in patients with cyanotic heart lesions [29]. In a cohort of 135 patients with CHD and incident stroke, 27 % had stroke recurrence by 10 years of follow-up [30]. Over half of those with stroke recurrence

Table 1 Risk factors for arterial ischemic stroke in children reported in the Great Ormond Street Hospital series, the International Pediatric Stroke Study (IPSS), and the Kaiser Pediatric Stroke Study (KPSS)

	Ganesan et al. [16]	IPSS [19••]	KPSS [37]	
	n=212*	n=674*	n=126	
	n (%)	n (%)	n (%)	OR (CI)
Cardiac disorders	26 (12)	204 (31)	10 (8)	7.5 (2.4–23.9)
Infection	43 (37)	165 (24)	50 (40)	13.2 (3.6–11.4)
Prothrombotic disorders	24 (11)	87 (13)	N/A	N/A
Head and neck trauma	23 (11)	70 (11)	15 (12)	1.6 (2.9–19.3)
Sickle cell disease	35 (17)	39 (6)	2 (2)	N/A
Genetic disorders/IEM	3 (1)	34 (5)	N/A	N/A
Cancer	7 (3)	33 (5)	N/A	N/A
Autoimmune/inflammatory	2 (0.9)	4 (0.6)	13 (0.5)	39 (5.1–298)

IEM inborn errors of metabolism

*Denominators for reported risk factor categories vary slightly

were already on treatment with an antiplatelet agents and/or anticoagulation, emphasizing the need for optimization of therapeutic strategies in this population.

The importance of patent foramen ovale (PFO) for cryptogenic stroke in the young has received much recent attention. A PFO acts a potential right-to-left shunt, and may allow venous emboli to reach the brain. However, an isolated PFO was reported in only 5 % of children in the IPSS as compared to a prevalence of approximately a quarter of the general population [19••, 31, 32]. The role of an isolated PFO in otherwise cryptogenic childhood stroke remains unclear, and the efficacy of closure of a PFO to prevent recurrent stroke has been hotly debated. Recently, the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial evaluated PFO closure versus medical therapy alone in 980 adults with PFO and a recent diagnosis of cryptogenic ischemic stroke and found no significant benefit of PFO closure in preventing recurrent ischemic stroke in their primary analysis [33•]. However, PFO closure was superior to medical therapy in the per-protocol and as-treated secondary endpoints. Serious adverse event rates were similar between the groups, and subgroup analyses suggested that those with substantial shunt size or atrial septal aneurysm might have an increased benefit. In similarly designed randomized trials, the CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) trial and the PC (Clinical Trial Comparing Percutaneous Closure of the Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism) trial there were no significant differences in stroke recurrence rates between the PFO closure versus medical therapy groups [34•, 35•]. What these results mean for young adults with cryptogenic stroke remains open to interpretation, and extrapolation of that interpretation to children is even less clear. The mean age of patients in all three trials was around 45 years, and both CLOSURE I and RESPECT excluded children younger than 18 years. In the PC trial, the younger participants (under 45 years), showed a trend towards benefit from PFO closure. Further trials are underway that may clarify which, if any, groups might benefit PFO closure after AIS. However, no registered trials include participants younger than 16 years, limiting generalizability of results to children [36, 37].

Infection

Preceding infections are reported in a large proportion of childhood strokes. In KPSS, children with a minor infection in the preceding month had a greater than fourfold increase in risk of AIS compared with controls [22••]. In IPSS, infection was associated with 24 % of AIS cases and the prevalence was inversely proportionate to age, with those younger than 5 years at most risk [19••]. No single location of infection was more likely to be associated with AIS, and patients had varied illnesses, including upper respiratory infection, acute otitis media, and acute gastroenteritis [22••].

The mechanisms for AIS during or after an infection are actively under investigation. Several studies have correlated major infections such as meningitis and sepsis, as well as minor infections with risk of AIS in adults [38–41]. In KPSS, a recent upper respiratory infection was noted in 9 % of those with a cerebral arteriopathy compared with 5 % of those without an arteriopathy. This association was stronger when comparing children with a unilateral, intracranial arterial stenosis, or focal cerebral arteriopathy to those with other arteriopathy (e.g., dissection, moyamoya, sickle cell) [42]. Pathologic changes in post-mortem tissue of patients with infection and AIS have given credence to a role for inflammation. Varicella zoster virus-related arteriopathy is perhaps the best-studied example of a direct vascular infection in association with AIS. Post-mortem tissue in post-varicella arteriopathy and AIS has demonstrated virus in sections of vessel intima and associated lymphocytic cellular infiltration and vascular proliferation [43–46]. Prospective studies are underway to better understand the complex association of infection, inflammation, cerebral vascular injury, and AIS [47].

Trauma

Trauma has been associated with stroke in adults and has been reported as a prevalent exposure preceding stroke in children. In KPSS, a medical encounter for head or neck trauma in the 12 weeks prior to stroke was found in 12 % of patients, but only 1.6 % of controls [22••]. Though the median time from trauma to AIS was 0.5 days, risk of stroke persisted through 3 months after the event. Frequent causes of injury in children with AIS include motor-vehicle accidents, gun-shot wounds, non-accidental trauma, and sports-related injuries [22••]. The major physiologic mechanisms of stroke after head and neck trauma are thought to be stretching or tearing of the vertebral or carotid arteries from sudden and forceful hyperextension and contralateral rotation of the head, a direct blow to the neck or orbit, or laceration by adjacent fractures. Resulting dissection, arteriovenous fistula, or pseudoaneuryms ultimately interrupts blood flow or causes artery-to-artery thromboembolic events to the brain [48, 49]. Current trauma guidelines suggest that patients with significant head trauma who meet clinical criteria should be considered for screening vascular imaging, yet there is no single accepted set of criteria for who should be screened or how a patient should be treated if a vascular abnormality is found. Screening protocols for cerebrovascular injury after blunt trauma in adult populations are based on

expert opinion and data from case-series in large trauma hospitals [50, 51]. Evidence guiding when, how, and who to screen for vascular injury in pediatric trauma populations is even more limited [51]. In a large retrospective, single-institution study of children younger than 18 years with blunt trauma screened with computed tomography angiography (CTA), 0.3 % of patients were diagnosed with cerebrovascular injury. In this group, 28 % of asymptomatic children would have not met adult guidelines for a screening CTA when the adult screening criteria after blunt trauma were applied [52]. Population-based investigations in pediatric cohorts with trauma are needed to identify specific risk factors of cerebrovascular injury and stroke, ascertain the ideal imaging modality for screening, and best practices for intervention to prevent stroke.

The pathogenesis of AIS after mild trauma is less clear and may be related to the vulnerable cerebral anatomy present in childhood in combination with an additional risk factor, such as prior central nervous system (CNS) infection, resulting in a milieu where subtle shear or stretch can result in intimal lesions and thrombosis [53, 54]. A subset of children may be susceptible to vertebral artery dissection and posterior circulation stroke after minor trauma due to congenital bony and ligamental abnormalities. Anatomic variations, including arcuate foramen, atlanto-axial subluxation, fibrous soft tissue bands, or acquired bony lesions, may compress the vertebral artery during head rotation [55–59]. From limited studies, an estimated 4% of the population is thought to significantly compress or occlude one of their vertebral arteries during head rotation [60, 61]. Vertebral artery compression with head-turning has been well described as a cause of vertebrobasilar insufficiency in adults. More rarely, posterior circulation strokes may occur in children owing to chronic vertebral artery dissection at the anatomic level of rotational vertebral artery compression [55, 58, 59, 62]. In a series of 12 children with posterior circulation strokes, nine were ultimately found to have unilateral or bilateral arcuate foramen though to contribute to their stroke findings [55].

Sickle Cell Disease

Children with sick cell anemia (SCA) are at risk of stroke owing to the development of progressive large vessel cerebral vasculopathy, moyamoya disease and, possibly, a higher likelihood of intracardiac shunting [63]. Without treatment, the estimated incidence rate is 1 in 416 person-years, with a prevalence of 11 % by 20 years of age [64, 65]. In 1992, abnormal transcranial Doppler (TCD) examination of the middle or internal cerebral artery (timed average mean maximum velocity≥200 cm/s) was found to predict stroke. Among children who had abnormal TCD screening velocities, 40 % had a stroke within 3 years [5, 66]. This finding led to the landmark STOP trial, which found chronic blood transfusion therapy in patients with abnormal TCD velocities reduced primary stroke risk by 92 % [14, 67] Exactly how chronic blood transfusion confers stroke protection is not known, but is thought to be through improvement or halting progression of large vessel cerebral arteriopathy [68]. Typically, these large vessel stenoses affect the distal internal carotid artery, the proximal portions of the middle and anterior cerebral arteries, and can be radiographically evident through imaging with magnetic resonance angiography (MRA), CTA, and conventional cerebral angiograms. A stenotic, diseased vessel lumen can be a nidus for thrombus formation and artery-to-artery emboli, or decrease cerebral perfusion leading to watershed ischemia. Children with severe stenosis experience recurrent transient ischemic attacks as the blood to the brain is more and more compromised, ultimately leading to ischemic stroke or, later in the disease, hemorrhage from these abnormal, delicate collateral vessels [69].

To develop better alternatives for stroke prevention, it has become increasingly important to understand the pathophysiology behind focal cerebral stenosis in sickle cell disease. While incompletely understood, recent research suggests a complex, causal pathway involving chronic intravascular hemolysis, release of pro-inflammatory mediators, activation of endothelial surface, and endothelial dysfunction [70, 71]. Free hemoglobin from chronic hemolysis and reduction of nitric oxide availability are thought to lead to increased vasomotor tone [72]. Adherent erythrocytes, leukocytes, and platelets further contribute to the inflammatory milieu, leading to endothelial damage and proliferation of smooth muscle cells [73]. Post-mortem examinations of cerebral arteries after AIS demonstrate intimal thickening with fibroblast and smooth muscle proliferation in larger arteries with resultant thrombus [74, 75]. In states of chronic anemia, and particularly in vascular territories of diseased stenotic vessels with decreased flow, the brain reacts by auto-regulation of the cerebrovasculature, with blood vessel dilation and increased blood flow to improve perfusion. When episodes of systemic stress lead to sickling, the brain receives a double hit of both increased metabolic demand and decreased oxygen carrying capacity. Blood vessels with a proximal stenosis that are already near maximum dilation have little reserve and are vulnerable to watershed ischemia. Finally, children with SCA may be at increased risk of stroke via a higher prevalence of cardiac shunting. In a single center childhood stroke cohort, children with SCA had twice the prevalence of PFO compared with children without SCA, suggesting a possible vulnerability to paradoxical embolism in additional to cerebral vasculopathy [63].

Because chronic transfusions confer the long-term health risks of infection, iron overload, and end-organ damage, alternative methods to reduce stroke risk have been studied. The SWiTCH trial (Stroke with Transfusions Changing to Hydroxyurea) was initiated to study stroke reduction after

transitioning from chronic transfusion to hydroxyurea, an antineoplastic agent that increases hemoglobin F levels [76••]. In this non-inferiority trial, 134 children with SCA, history of stroke, and over 18 months of prior blood transfusions were randomized to receive 30 months of hydroxyurea and phlebotomy (to relieve established iron overload) or continued blood transfusions with chelation therapy. In a planned interim analysis after one-third of patients completed trial exit, there was a 10 % stroke recurrence rate in the hydroxyurea/phlebotomy group and 0 % in the transfusion/chelation group. Moreover, they found no change in liver iron stores between the groups, and the trial was closed early because of safety concerns. Additional roles for hydroxyurea in stroke prevention for children with SCA continue to be studied. A randomized clinical trial comparing hydroxyurea to chronic blood transfusions for the primary prevention of stoke in SCA is underway in the TWiTCH trial (TCD with Transfusions Changing to Hydroxyurea) [77].

Cancer

As survival rates of childhood cancers has improved, so too has our understanding of the long-term effects of radiation therapy. Regardless of underlying malignancy, cranial and cervical radiation increases risk of AIS [78–81]. In 2006, the Childhood Cancer Survivor Study (CCSS) measured a sixfold increase in relative risk of stroke for childhood leukemia survivors compared with sibling controls. Survivors of brain tumors had a nearly 30-fold increased relative risk of stroke compared with siblings [78]. A recent retrospective review of children with CNS malignancy who had received cranial and cervical radiation demonstrated a stroke incidence rate of 2 % at 5 years and 4 % at 10 years [79]. The risk for AIS in this population persists well into adulthood, with an increase in AIS risk of nearly eightfold compared with matched sibling controls in the CCSS cohort after an average of 18.6 years from oncologic diagnosis to AIS [82]. Risk factors for stroke include administration of therapy to the Circle of Willis and escalating doses of radiation [78, 79, 83, 84]. As with other diseases discussed in this review, the mechanism of arterial injury and vasculoapthy after radiation therapy is not well understood. Hypotheses include oxidative stress with chronic inflammation and resultant accelerated atherosclerosis [85, 86].

Currently, the Children's Oncology Group Long-Term Follow-Up Guidelines recommend annual neurologic examinations in those who received over 18 Gray (Gy) of cranial radiation [87]. However, there are no consensus guidelines for treatment of vasculopathy or the use of neuroimaging as a screening tool in asymptomatic patients. An ongoing prospective study of MRI and MRA annually after cranial radiation may improve understanding of the temporal development of vasculopathy, a first step towards primary and secondary stroke prevention strategies in children treated for cancer.

Hypercoagulable States

Many genetic and acquired thrombophilias have been associated with incident AIS in childhood [16, 19••, 88] and elevated lipoprotein(a) has recently been associated with recurrent childhood stroke [89]. Thrombophilias are relatively common in the general population and are often thought to interact with other risk factors in a multi-factorial manner in children who have had a stroke. The association of MTHFR polymorphism homozygosity, elevated homocysteine, and risk of thromboembolic events are debated [90]. Because the effect of MTHFR mutation is mediated through hyperhomocysteinemia, which may be overcome through a folate-rich diet, fasting homocysteine levels may be a more appropriate test than MTHFR genetic testing for thrombotic risk. While management strategies for thrombosis are relatively well defined in adults, recommendations are less clear for children. With the possible exception of antiphospholipid antibody testing, the indications for and benefit of extensive screening for thrombophilia after stroke in children is controversial, particularly because it is unclear how results should alter management. Further studies are needed to evaluate the role of genetic polymorphisms and stroke risk in children, optimize screening practices, and evaluate potential therapeutic strategies for those who may be at increased risk.

Management of AIS

Hyperacute Therapies

When presenting early after a stroke, adult patients have several hyperacute interventional options available that have been studied for efficacy of clot lysis and restoration of brain perfusion, including intravenous or intra-arterial (IA) administration of tissue plasminogen activator (tPA) and endovascular clot retrieval devices. However, children younger than 18 years have generally been excluded from hyperacute stroke interventional studies. In the absence of age-appropriate safety data or dosing guidelines, children who present with an acute stroke are sometimes treated with hyperacute therapy outside of the recommended guidelines for use of tPA. Currently, the international multicenter study entitled "Thrombolysis in Pediatric Stroke" (TIPS) is enrolling children aged 2–17 years with clinically- and radiographically-confirmed AIS within 3 h of symptom onset to assess dose determination, safety, and efficacy of intravenous tPA [93]. Additionally, the study will assess the safety and efficacy of IA tPA in eligible patients 3–6 h after symptom onset. This critical study will help guide the use of tPA in pediatric cohorts. With regards to interventional therapies in

the hyper-acute treatment of childhood stroke, a recent case series of mechanical embolectomy in children with AIS described successful revascularization in four children, aged 4–17 years with large-vessel AIS, using the Merci retriever (Concentric Medical, Mountain View, CA, USA) and/or Penumbra system (Penumbra, Alameda, CA, USA) with concomitant clinical improvement [91]. The median time from stroke onset to arterial puncture ranged from 4 to 20 h. In keeping with adult trials, they observed a 25 % rate of asymptomatic intracranial hemorrhage [92].

Secondary Stroke Prevention

Chronic transfusions are a mainstay for both primary and secondary stroke prevention in SCA [76••]. Beyond this, optimal strategies for secondary stroke prevention in children are debated. After a stroke, children are often treated with anticoagulation or anti-platelet therapy to prevent recurrence. Additional therapies, such as surgical revascularization, are considered for secondary stroke prevention in severe moyamoya arteriopathies, which may be familial, idiopathic, or related to sickle cell disease, neurofibromatosis type 1, and Down syndrome [94–96]. Choice of therapy and duration of treatment are generally guided by the mechanism of injury, presence of comorbidities, and a provider's estimate of recurrence risk. With the exception of SCA, no randomized controlled clinical trials are available to guide practice. Within the IPSS, children post-stroke were treated with anticoagulation alone in 27 % compared with anti-platelet alone in 28 % of cases. Practice varied geographically, and was associated with stroke etiology [97].

Current treatment practices are based on expert opinion and consensus guidelines that are often extrapolated from data in adult stroke trials. The risk and benefit of anticoagulation and antiplatelet therapy likely varies by age and underlying stroke etiology; therefore, further age-specific research for stroke prevention in children should be a priority. Finally, for pediatric stroke research to move forward, further development and validation of systems of stroke classification and outcome scales are essential. The validation of the Pediatric National Institutes of Health Stroke Scale from chart review may allow comparable outcome measures across retrospective studies [98]. Uniform classification of pediatric stroke etiologies using the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria will be critical for future prospective studies targeting interventions for prevention of stroke recurrence [99].

Conclusions

Awareness of the risk of stroke in the young may be improving with the advent of social media, increase in disease-focused websites, and increase in trained sub-specialists. As the appreciation of AIS in pediatric populations grows, so too will our ability to study and understand this potentially devastating illness. Already, the established association of sickle cell disease with AIS has allowed for improvement in therapeutic strategies for primary stroke. Understanding the association of infection or radiation with childhood stroke has begun to shed light on the role of arteriopathies in AIS. Ultimately, advancements in the identification of pediatric populations most at risk for stroke will improve and hasten diagnosis, allowing for targeted studies of stroke prevention.

Compliance with Ethics Guidelines

Conflict of Interest Adam L. Numis declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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