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Childhood Arterial Ischemic Stroke: A Review of Etiologies, Antithrombotic Treatments, Prognostic Factors, and Priorities for Future Research

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Abstract

Childhood arterial ischemic stroke (AIS) is a rare, but serious, medical condition, which is fatal in approximately 3% and associated with both acute and long-term neurologic impairment in over 70% of cases. Common etiologies include sickle cell disease, congenital heart disease, arterial dissection, prothrombotic conditions, and preceding viral infections; however, one in four cases is considered idiopathic. To date, no randomized controlled clinical trials (RCTs) have been conducted to establish evidence for current therapeutic strategies outside of sickle cell disease, thus, treatment strategies are largely shaped by consensus-based guidelines, in which, beyond the acute period, aspirin is the mainstay of therapy and anticoagulation is reserved for select circumstances. In recent years, evidence on prognostic factors has accumulated, helping to inform the future design of prognostically stratified RCTs. In this narrative review, we discuss the current understanding of etiologies, consensus-based treatment recommendations, contemporary treatment data, and prognostic factors in childhood AIS. We also identify priorities for future research.

Keywords

Childhood arterial ischemic stroke; pediatric stroke

Childhood arterial ischemic stroke (AIS) is a rare, but serious, medical condition affecting children (age range, 29 days to 18 years), which is associated with high morbidity. The overall annual incidence is estimated at 1.2 to 8 per 100,000 children, however, it is likely that this is an underestimate, as the index of suspicion for AIS is typically low in the pediatric population and data contributing to incidence estimates rely mainly on retrospective studies.^{1–3} Although risk factors for AIS in the adult population have been well described,

there is still a limited understanding of all the risk factors in the pediatric population, and a large minority of cases is designated as idiopathic.

The acute and long-term outcomes related to childhood AIS are concerning, including mortality, recurrent events, and neurologic sequelae, which have been previously reviewed in detail.^{4,5} In the International Pediatric Stroke Study (IPSS), a multicenter, international observational study evaluating risk factors, treatment options, and outcomes, 22 of 612 children (3%) died before hospital discharge.⁶ The mortality rate, however, appears to increase with a recurrent event and has been reported in a prospective cohort study to be as high as 15% among patients with recurrent stroke.⁷ In general, the risk of recurrence is ~7 to 20% within 5 years of the initial event; however, the risk increases substantially for children with moyamoya or other arteriopathies.^{7–10} In a retrospective cohort, Fullerton and colleagues reported a 5-year cumulative recurrence rate of 66% in children with identified vascular abnormalities.¹⁰ Similarly, Sträter et al reported an increased risk of recurrent AIS in children with vascular abnormalities.⁷ A considerable number of children with AIS will also suffer from neurologic impairments. In the largest published cohort study, Goldenberg and colleagues noted that 74% of children had a neurologic deficit at the time of hospital discharge.⁶ This is similar to the observed rate of neurologic deficits in several studies with follow-up beyond 1 year.^{11–14} Childhood stroke is also associated with an increased risk of seizures, behavioral disorders, and cognitive impairments.^{13–15}

While recent publications in the field of childhood AIS have begun to investigate the utility of prognostic indicators and the safety of therapeutic regimens, there remains an insufficient understanding of optimal therapeutic strategies to improve outcomes. In this narrative review, we discuss the current understanding of etiologies, consensus-based treatment recommendations, recent treatment data, and prognostic factors in childhood AIS. We also identify priorities for future research.

ETIOLOGIES

Known risk factors for childhood AIS include sickle cell disease, congenital heart disease, arterial dissection, prothrombotic conditions, and preceding viral infections. Approximately 24% of cases are still classified as idiopathic.¹⁰ The etiologies and pathophysiologic mechanisms of childhood AIS may impact consensus-based therapeutic decisions in the absence of high-quality evidence from clinical trials.^{16–18} Based largely upon earlier work establishing associations with AIS for congenital heart disease, sickle cell disease, arterial dissection, and moyamoya, the IPSS group separates AIS etiologies broadly into the following six categories: cardiac disease, sickle cell disease, arterial dissection, moyamoya, other arteriopathy, and other causes.⁶

Cardiac Abnormalities

Cardiac procedures including surgery, catheterization, and extracorporeal membrane oxygenation are all considered risk factors for childhood AIS, likely mediated through cardioembolism.^{18,19} Congenital heart disease and other cardiac abnormalities including valvular heart disease, cardiac arrhythmias, and cardiomyopathy also appear to be risk factors for childhood AIS, independent of invasive cardiac procedures.^{18,20–22} Alterations of the cardiac valves, major vessels, and myocardium may result in aberrant blood flow and formation of a thrombus that can embolize to the cerebral vessels, especially in the case of right-to-left shunting. Lo et al noted that congenital heart disease was the most frequent comorbidity in children with AIS in a retrospective national database review.²⁰ Nearly 25% of children diagnosed with AIS in the Canadian Registry had cardiac disease at presentation.²³ Similarly, Ganesan and colleagues observed that 28% of children in their childhood AIS cohort study had cardiac abnormalities.²⁴

An additional cardiovascular concern is the role of hypertension in childhood AIS. Ganesan and colleagues reported an association with vasculopathy and systolic hypertension.²⁴ Similarly, Lo et al found hypertension as a risk factor for pediatric stroke.²⁰ Although the mechanism is not well delineated, it is hypothesized that an elevated blood pressure may be a systemic response to an acquired vasculopathy.²³ Alternatively, hypertension may be related to chronic anemia or other comorbid medical conditions.

It is still uncertain if a patent foramen ovale (PFO) is a significant risk factor for childhood AIS. In a small prospective study, Benedik and colleagues reported abnormal findings with transcranial Doppler with Valsalva maneuver suggesting a right-to-left shunt in four of six children with idiopathic AIS.²⁵ While the mechanism of a paradoxical embolism resulting in AIS via a PFO is plausible and supported in the adult literature, the underlying incidence of PFO in healthy children is still unknown.²⁶

Sickle Cell Disease

Sickle cell disease is one of the most common causes for AIS in childhood, particularly among individuals such as African-Americans, of recent historical descent from populations inhabiting malaria-endemic regions. The Baltimore-Washington Cooperative Young Stroke Study, a retrospective, regional, hospital-based study noted sickle cell disease as the most common comorbidity at the time of presentation. The incidence was reported as 280 per 100,000 children/year, significantly higher than the rate in the general pediatric population.²⁷ In a retrospective/prospective cohort study of childhood AIS, Ganesan and colleagues also observed that 16% of the children had sickle cell disease.²⁴ AIS in sickle cell disease typically results from cerebrovascular changes induced by progressive narrowing of the distal internal carotid artery and the proximal middle cerebral artery, termed moyamoya. Pathologic features of sickle cell-associated moyamoya are characterized by intimal hyperplasia of the large cerebral arteries, often associated with thrombotic occlusion and the presence of collateral vessels.^{28–30} Although sickle cell-associated moyamoya likely accounts for the majority of AIS in sickle cell disease, other risk factors may be present, as demonstrated by a recent case-control study reporting an increased incidence of PFO in these patients.^{18,31}

Arteriopathies

Arteriopathy is one of the most common findings on diagnostic evaluation in children with AIS, occurring in up to 80% of previously healthy cases.^{24,32} In a retrospective/prospective childhood AIS cohort study, 79% of children who underwent neurovascular imaging had evidence of arterial abnormalities, while 78% of previously healthy children who were imaged also had cerebral arterial abnormalities.²⁴ The IPSS study also noted that the majority of children with arterial imaging had evidence of arteriopathy.³³ Subtypes of arteriopathy in childhood AIS include dissection, moyamoya, and focal cerebral arteriopathy (FCA), although the nomenclature and classification for these subtypes are still in evolution. Each is discussed further in the sections below.

DISSECTION—Arterial dissection is identified in up to 20% of children with AIS.^{11,34} While many cases may be attributed to significant or even mild traumatic events,^{35–37} and some to connective tissue disorders such as Ehlers-Danlos or Marfan syndrome, a proximate cause for dissection is often unclear.^{38–41} The diagnosis of arterial dissection as proposed by Sebire and colleagues requires the identification of one of the three following clinical scenarios using magnetic resonance imaging (MRI)/magnetic resonance angiogram (MRA) or conventional angiography: “(1) angiographic findings of a double lumen, intimal flap, or pseudo aneurysm, or, on axial T1 fat saturation MRI images, a bright crescent sign in the arterial wall; (2) the sequence of cervical or cranial trauma, or neck pain, less than 6 weeks

preceding angiographic findings of segmental arterial narrowing (or occlusion) located in the cervical arteries; (3) or angiographic segmental narrowing (or occlusion) of the vertebral artery at the level of the C2 vertebral body, even without known traumatic history.”⁴²

MOYAMOYA—Moyamoya is an arteriopathy characterized by bilateral stenosis of the distal internal carotid arteries with lenticulostriate collateralization that results in the pathognomonic “puff of smoke” appearance on conventional cerebral angiogram and is diagnosed in up to 20% of childhood AIS.^{4,33,43} Children with neurofibromatosis, sickle cell disease, trisomy 21, and history of central nervous system radiation are at an increased risk for developing moyamoya (classified as secondary moyamoya or moyamoya syndrome).^{44–47} Moyamoya may also occur in previously healthy children, most commonly healthy Japanese, in whom it was first described (classified as primary moyamoya or moyamoya disease). It is suggested that the etiology of moyamoya has a genetic basis with the presence of familial cases, ethnic differences, and reported studies implicating specific genetic loci; however, these results have not been conclusive and a single causal gene is yet to be identified.⁴⁸

Sebire and colleagues proposed definitions to aid in the diagnosis of moyamoya. To diagnose “possible” moyamoya one of the following criteria is sufficient: “(1) narrowing and/or occlusion of the distal part of both internal carotids, but without excessive collateral network of vessels; (2) unilateral narrowing and/or occlusion of the distal part of one internal carotid artery with excessive collateral network of vessels distal to the occluded artery.”⁴² To diagnose “definite” moyamoya, MRA or conventional angiography must demonstrate both of the following: “narrowing or occlusion of the terminal portion of both internal carotid arteries, and unilateral or bilateral collateral network of small vessels distal to the occluded arteries.”⁴²

FCA—FCA is recognized as focal cerebral arterial stenosis without an identified etiology and represents ~25% of all arteriopathies.³³ Historically, nondissective, nonmoyamoya arteriopathies were described as idiopathic arteriopathies in pediatric AIS literature. Unilateral cases were further classified retrospectively as transient cerebral arteriopathy (when improving over time) or chronic cerebral arteriopathy (if persistent). Given the need to establish consistent nomenclature at AIS diagnosis, the IPSS group has used the term FCA more recently for such cases without an apparent cause.³³ Further efforts to unify classification are underway by the IPSS.

It is likely that several mechanisms may contribute to the development of FCA, as the nomenclature is merely descriptive. Recent observations from the IPSS suggest that an inflammatory or parainfectious process may play a role, as a preceding mild upper respiratory infection is significantly associated with the presence of FCA.³³ Previous evidence from case series and cohort studies also suggest infectious etiologies such as varicella or other viral illnesses as the inciting factor in AIS with arteriopathy, particularly focal unilateral stenosis of a large cerebral artery.^{33,49–52} Postvaricella arteriopathy is a subset of FCA marked by unilateral stenosis and AIS within 1 year of varicella infection.^{50,52} An additional consideration in the causal pathway of FCA is a history of trauma, as a subset of children with FCA may actually have arterial dissection that was misclassified at diagnosis, as reported recently in a small case series.⁵³

The typical course of FCA is an initial worsening of the cerebral arterial stenosis within the first 3 to 6 months, followed by stabilization or improvement. Braun et al characterized this pattern in 94% of the 79 children with unilateral intracranial arteriopathy and AIS, while 6% progressed to moyamoya. Of the cases with non-moyamoya AIS, complete resolution

occurred in 24%, improvement without resolution occurred in 45%, and stabilization occurred in 32%.⁵⁴

Hypercoagulable States

Although the subject of some debate, several prothrombotic conditions appear to contribute to the risk of childhood AIS.^{55–60} As noted by Sträter and colleagues, it is likely that in many instances, thrombophilia is a permissive factor rather than an isolated cause for AIS.⁵⁷ A recent meta-analysis of 22 observational cohort studies reported a statistically significant association between a first AIS in childhood and the following prothrombotic conditions: inherited deficiency of protein C, protein S, or antithrombin, the factor V G1691A (Leiden), factor II G20210A, or methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism, elevated level of lipoprotein(a), and presence of antiphospholipid antibodies.⁵⁸ These results support previous findings of a systematic review.⁵⁹ Thrombophilia may also confer an independent risk of AIS, as demonstrated by Nowak-Göttl et al in a multicenter case-control study in which elevated lipoprotein(a) level, the factor V G1691A, factor II G20210GA, and MTHFR polymorphisms, and protein C deficiency were significant independent risk factors for childhood AIS, after excluding patients with other AIS risk factors.⁶⁰

In a combined retrospective/prospective study of 50 children with AIS followed for a mean duration of 21 months, elevated D-dimer levels were noted most frequently in children with cardiac disease.⁴⁹ As D-dimer is a marker of coagulation activation, this finding suggests an underlying thrombophilia state (whether acquired or inherited) in pediatric cardiac disease, which is also supported by the high prevalence of thrombophilia traits identified in children with AIS and cardiac disease by Straäter et al.⁵⁷

Additional hematologic factors that may confer an increased risk of AIS include sickle cell disease (discussed above), iron deficiency anemia, thrombocytosis (independent of iron deficiency anemia), and polycythemia.^{24,61,62}

Genetic/Metabolic Conditions

Numerous inherited metabolic disorders appear to be associated with AIS in childhood. Some examples include Fabry disease, an X-linked deficiency of α -galactosidase; cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; Menkes syndrome, a copper transport disorder; and homocystinuria, a deficiency of cystathionine- β -synthase that results in hyperhomocysteinemia.^{63–66}

Sympathomimetic Drugs

Recreational drug use is a possible etiologic factor in childhood AIS; among adolescents in particular. Although typically reported in adults, AIS may be associated with cocaine or amphetamine use, likely as a result of hypertension and vasospasm.^{67,68} The extent to which other sympathomimetic agents, including some used commonly in children for treatment of migraine or attention deficit disorder, contribute to AIS risk remains undefined.

ANTITHROMBOTIC TREATMENTS

To date, no randomized controlled clinical trials (RCTs) have been published to guide therapeutic strategies in children with AIS beyond the setting of sickle cell disease; thus, optimal antithrombotic treatments are unknown. These treatments are in large part shaped by consensus-based guidelines published by the American College of Chest Physicians (ACCP), the Royal College of Physicians (RCP), and the American Heart Association (AHA).^{16–18} In sickle cell disease, primary management consists of red blood cell exchange

transfusion (erythrocytapheresis). In metabolic disease, the mainstay of therapy is correction of the underlying metabolic defect. In moyamoya, first-line therapy is surgical revascularization to establish an alternative source of vascular flow to hypoperfused territories, although often not immediately poststroke. The following discussion focuses upon antithrombotic therapies in non-sickle cell disease-associated, nonmetabolic, non-moyamoya childhood AIS. With the exception of thrombolysis, these therapies are generally aimed at secondary prevention, that is, the prevention of AIS progression/recurrence.

Acute (Including Hyperacute) Phase

ANTICOAGULATION OR ANTIPLATELET THERAPY—Three observational studies to date have suggested that anticoagulation therapy can be given safely in children with AIS.^{69–71} Given the frequency of cardioembolism and dissection as etiologic factors in childhood AIS, as well as the high prevalence of prothrombotic conditions, the ACCP guidelines recommend initiation of therapy with either unfractionated heparin or low molecular weight heparin (LMWH) and continuing anticoagulation until cardioembolic sources and extracranial dissection have been excluded.¹⁶ RCP guidelines adopt an approach of withholding anticoagulation (i.e., utilizing antiplatelet therapy instead) until cardioembolism or extracranial dissection is diagnosed.¹⁷ AHA guidelines support either approach.¹⁸ In either scenario, heparin-based anticoagulation, when employed, is best monitored with anti-factor Xa activity with a therapeutic range of 0.3 to 0.7 anti-factor Xa activity U/mL for unfractionated heparin and 0.5 to 1.0 U/mL for LMWH. These recommendations support the use of anticoagulation in cardioembolism and extracranial dissection for the acute and subacute period after childhood-onset AIS. In adult dissection this practice has recently been called into question, based upon a recent retrospective analysis of 298 patients with carotid dissection, suggesting that aspirin may be as effective as anticoagulation in preventing recurrence.⁷²

THROMBOLYSIS—To date, there have been no interventional studies evaluating the use of thrombolysis in the hyperacute treatment phase (i.e., first 6 to 8 hours) for children with AIS. Several case reports and case series have documented the use of systemic or intra-arterial thrombolytic therapy, but without a rigorous clinical trial, it is not possible to deduce the safety or efficacy of this mode of intervention.^{73–78} Given potential safety concerns, AHA guidelines recommend against routine use of thrombolysis, outside of a clinical trial for children. For adolescent children, no consensus was met regarding the use of thrombolytic therapy when standard adult eligibility criteria are met.¹⁸ Nevertheless, the use of thrombolysis in children remains controversial, and should be evaluated on a case-by-case basis, with providers experienced in treating childhood stroke. Amlie-Lefond and colleagues of the IPSS have proposed the Thrombolysis in Pediatrics Study, a multicenter study evaluating the safety, dosing, and feasibility of thrombolysis in childhood AIS.⁷⁹ A major challenge to thrombolysis is posed by the fact that median time to AIS diagnosis in childhood ranges from 24 to 35 hours, much longer than the recommended 3 to 8 hour interval for this intervention.^{80–82} Several factors may contribute to the delay in diagnosis, including lack of awareness of childhood AIS in the community, lack of recognition of abnormal neurologic signs/symptoms, frequency of “stroke-mimickers,” and delay in consultation of a pediatric stroke specialist.

Subacute and Chronic Treatments

ANTIPLATELET THERAPY—In children with AIS who do not have sickle cell disease, cardioembolic stroke, or arterial dissection, all guidelines (i.e., ACCP, RCP, and AHA) recommend secondary prophylaxis with aspirin. Dosing recommendations for aspirin are 1 to 5 mg/kg/d by ACCP, 1 to 3 mg/kg/d by RCP, and 3 to 5 mg/kg/d by AHA with a

reduction to 1 to 3 mg/kg/d if side effects occur.^{16–18} Duration of treatment remains uncertain, although many practitioners discontinue treatment after 1 or 2 years.

ANTICOAGULATION—Secondary prophylaxis with LMWH or warfarin is recommended by the RCP and ACCP guidelines in children with cardioembolism or extracranial arterial dissection.^{16,17} The AHA guidelines also note to consider anticoagulation in children with a high risk of recurrent cardiac embolism and with some inherited thrombophilias.¹⁸

In a recent combined retrospective/prospective study focusing on the safety of anticoagulation in childhood AIS with non-moyamoya arteriopathy, 37 such children received anticoagulation for at least 4 weeks.⁷¹ During the 1329 patient months of follow-up, clinically relevant bleeding episodes were rare, and not life-threatening. Although preliminary studies suggest that anticoagulation may be safe in children with AIS (even those with arteriopathy), the efficacy and safety of anticoagulation over aspirin has not been evaluated in childhood-onset AIS in the setting of an RCT. Therefore, antiplatelet therapy is currently recommended by all guidelines for subacute/chronic therapy in childhood AIS without cardioembolic AIS or dissection.

PROGNOSTIC FACTORS

The identification of prognostic factors can facilitate risk stratification and has the potential to inform future therapeutic approaches. Abnormal cerebral vasculature at AIS presentation is associated with an increased risk of recurrence, while progressive intracranial arteriopathy on follow-up imaging is also associated with an increased recurrence risk.^{10,32,54} In addition, abnormalities of descending corticospinal tracts on diffusion MRI may also be prognostic of adverse long-term motor outcome.⁸³ The volume of cerebral infarct in AIS also appears to influence early and long-term outcomes.⁸⁴ Goldenberg and IPSS colleagues also reported that the odds of adverse early outcomes including neurologic deficit and/or death were higher with the presence of arteriopathy, bilateral ischemia, or a low level of consciousness at the time of presentation.⁶ Stroke location may confer additional risk: Braun and colleagues noted cortical involvement was associated with poor functional outcomes, while Cnossen et al reported that involvement of the right middle cerebral artery was associated with poor neurologic outcome.^{54,85} Additional adverse prognostic factors may include younger age and presence of fever at AIS presentation.⁸⁵

CONCLUSIONS

In the past several years, significant progress has been made in understanding etiologic and prognostic factors in childhood AIS, and these strides must continue to be made via collaborative cohort studies. An improved understanding of inflammatory and/or infectious mechanisms contributing to the development of AIS, as well as host inflammatory responses, will further enhance AIS classification and identification of appropriate therapies. The safety and efficacy of antithrombotic treatments (including hyperacute thrombolytic approaches as well as acute and subacute anticoagulant vs. antiplatelet therapies) and anti-inflammatory therapies must be appropriately investigated. Ideally, the design of RCTs of anticoagulation versus antiplatelet therapy should adopt a risk-stratified approach informed by etiologic subtypes and prognostic markers, targeting children at heightened risk for AIS progression/recurrence. These efforts will be facilitated by the implementation of a reliable nomenclature and classification of childhood AIS.

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