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The roles of anatomic factors, thrombophilia, and antithrombotic therapies in childhood-onset arterial ischemic stroke

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Abstract

Childhood-onset arterial ischemic stroke (AIS) is a rare disorder with high risks of both recurrent stroke and life-long neurological morbidity. Anatomic risk factors for primary and/or recurrent AIS include a venous thrombotic source for paradoxical embolism via a patent foramen ovale, primary cardioembolism, extracranial dissection, and intracranial arteriopathies, among others. Genetic and acquired thrombophilias are common, some of which have been shown to have prognostic influence on risk of recurrent AIS. While knowledge of childhood AIS risk factors has grown considerably in recent years, an evidence-based understanding of optimal antithrombotic therapy strategies has not yet been attained. Consensus-based guidelines have been developed, but future research must emphasize identification of additional prognostic factors and the initiation of cooperative randomized controlled clinical trials.

Introduction

Childhood-onset arterial ischemic stroke (AIS) is characterized by findings of arterial-distribution ischemia in a child age 29 days to 18 years. Patients typically present with sudden-onset neurological deficits, but are often not diagnosed until over 24 hours thereafter [1]. The frequent delay in diagnosis may in large part be explained by the rarity of this disease, which occurs in 2 per 100 000 children per year [2]. Although underlying cardiac or sickle cell disease (SCD) account for many cases of childhood AIS, there remains a large group of patients without major medical illness. In these cases the identified risk factors are distinct from those of both perinatal AIS (in whom AIS occurs before 29 days of life) and adult AIS. In approximately 80% of previously healthy cases, neurovascular imaging reveals cervical/cerebral arteriopathy, characterized by dissection, occlusion, or stenosis in the cerebral vasculature [3]. In addition, in all subtypes of childhood AIS and irrespective of previous medical history, genetic and acquired thrombophilias are common [4,5]. These thrombophilias likely interact in concert with other identified risk factors to initiate and/or propagate thromboembolism in childhood AIS patients.

Despite recent advances in understanding childhood AIS risk factors, the efficacy of antithrombotic, anti-inflammatory and other therapies remains largely unknown. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) provides a valuable example of a

multicenter effort to establish safety and efficacy of preventive measures against childhood-onset AIS in populations at high risk [6]. Secondary prevention strategies are currently being evaluated in SCD in the Stroke With Transfusions Changing to Hydroxyurea (SWITCH) trial, where standard therapy with transfusion and iron chelators is compared to hydroxyurea and phlebotomy [7]. Unlike SCD – where chronic transfusion is used as primary prevention in selected cases and secondary prevention trials are underway – the utility of preventative or therapeutic interventions in other subtypes of childhood AIS remains understudied.

Effective treatments for childhood AIS are urgently needed as 70% of patients suffer life-long neurological morbidity which is both costly and adversely impacts quality of life [8–12]. In addition, there is a high rate of recurrence (7–20% at 5 years) [2,13,14]. Antithrombotic therapies (whether antiplatelet or anticoagulant) are often employed as secondary prevention strategies. Presently, however, the current standard of care is highly-variable world-wide and within the U.S. itself [15], largely due to a paucity of evidence regarding the types and durations of therapy that appear most beneficial, and in which groups of childhood AIS patients.

The present narrative review was undertaken to discuss anatomic considerations of cerebrovascular thromboembolism, the contribution of blood-based thrombophilia factors, and published treatment experience in childhood AIS. While efforts were made to be comprehensive in literature review to inform the manuscript, the presentation of literature herein is necessarily selective; for this reason, the interested reader is encouraged to consult the literature in additional detail.

Anatomic factors for cerebral thromboembolism

In some cases of childhood-onset AIS, the site of thrombus generation is identifiable. Several possible scenarios are observed. Deep venous thrombosis of the limbs or central vasculature (e.g., vena cavae) may result in paradoxical embolism through a patent foramen ovale (PFO) or other right-to-left shunting intracardiac lesion. Left-sided cardiac thrombi (such as those that are free-floating or pedunculated, and less commonly those that are muralized) can directly embolize to the cerebral arterial circulation. This is also a hypothesized mechanism for embolization from sites of endocardial injury in cases of acute AIS in the first 7–10 days following cardiac catheterization in children, in the absence of overt intracardiac thrombus. *In situ* arterial thrombosis may also arise from dissection of extracranial vessels, causing a local and/or embolized thrombus. Lastly, *in situ* thrombosis may also develop in children with cerebral arteritis (e.g., in the setting of systemic lupus erythematosus) and in those with cerebral arteriopathy (including idiopathic as well as those with identified causes such as classic varicella-associated cerebral arteriopathy).

With regard to extracranial sources for cerebrovascular thromboembolism, it is likely that in many cases of complex congenital heart disease, impaired cardiac function and/or turbulent blood flow may provide sufficient circumstance for thrombus generation. Outside of complex congenital cardiac anomalies, intra-cardiac shunting may be particularly relevant to paradoxical embolism when it exists in the setting of underlying thrombophilia. Indeed, multiple studies demonstrate that patent foramen ovale (PFO) is associated with as much as a 4 to 6-fold increase in risk of AIS among young adults (<55 years), and others have demonstrated a higher prevalence of PFO in young AIS patients (40%) as compared to controls (10%) [16,17]. A recent single center prospective cohort of children with SCD and stroke demonstrated a higher prevalence of PFO in this group (25%) as compared to children with stroke without SCD (12%), suggesting that paradoxical embolism may also contribute to risk of AIS in SCD (where elevated cerebrovascular flow velocity on transcranial Doppler and moyamoya syndrome already serve as important risk factors). Several centers

have reported that congenital heart defects and/or cardioembolic sources of thrombus account for approximately 12–15% of childhood-onset AIS patients [3,14], and a recent publication from the International Pediatric Stroke Study (involving 661 childhood-onset cases) found that 20% were associated with cardiac disease (including known heart disease, cardiac procedure, or both, but excluding isolated patent foramen ovale).

Another key extracranial anatomic consideration, dissection, has been shown in one large series from the International Pediatric Stroke Study (IPSS) to account for 7% of childhood-onset AIS cases [15]. However, criteria for and technical expertise in diagnosis of dissection are variable, and a recent single center study from the University of California San Francisco suggests that dissection is under-diagnosed [18]. Furthermore, the aforementioned studies in dissection and cardioembolism are generally limited by the potential for referral, selection, and observation biases, such that the true contribution of extra-cranial thrombus formation to childhood-onset AIS remains unclear.

Arteriopathy has been reported in 78% of previously-healthy patients with childhood-onset AIS [3]. A retrospective cohort study by Fullerton and colleagues demonstrated a cumulative probability of recurrent stroke of 66% at five years in this subset of patients. Similar findings have been reported by Sträter and colleagues in Germany [14]. Table 1 summarizes evidence for recurrence risk in relation to various arteriopathies (as well as cardiac disease), based upon selected reports. Although moyamoya disease or syndrome (characterized by bilateral progressive stenosis of the internal carotid and middle cerebral arteries with lenticulostriate collaterals) accounts for some cases of arteriopathy, the majority involves unilateral focal stenosis of a large cerebral artery of uncertain etiology. Varicella-associated arteriopathy (which is often transient) is well-established, but the majority of cases of unilateral focal stenosis of a large cerebral artery cases are not accompanied by evidence of recent systemic varicella infection [19]. Nevertheless, a recent study from the IPSS revealed recent upper respiratory infection as an independent risk factor for focal cerebral arteriopathy [20], providing clues that viral infection and/or a secondary inflammatory response may be involved in the pathophysiology of this highly prevalent finding. With regard to natural history of focal large-vessel cerebral arterial stenosis, a recent three center cohort study in Europe demonstrated that the vast majority (94%) of unilateral cases do not progress beyond 6 months, and among these, 23% completely resolve [19]. Finally, local small vessel vasculitis can also cause stroke in children with systemic rheumatologic conditions, as well as in primary inflammatory diseases of the cerebral vasculature [21,22]. In many instances, cerebral angiitis (whether small vessel or large arterial) in the setting of rheumatologic conditions is superimposed upon a background of systemic inflammation [21], that may act together with antiphospholipid antibodies, other acquired thrombophilias and anatomic considerations of arterial stenosis to promote *in situ* thrombus formation.

Thrombophilia

As discussed above, it is believed that thrombus generation is the proximate cause for arterial-distribution brain ischemia in the majority of cases of childhood onset AIS, whether the clot originates in the venous circulation, the heart, the cervical arteries or the intracranial arteries. At the same time, it must be pointed out that an intra-arterial thrombus is not commonly visualized at the time of initial diagnostic cerebrovascular imaging in acute childhood-onset AIS. In addition, in rare cases, findings suggest that ischemia is secondary to an alternative cause, such as metabolic defects (e.g., mitochondrial encephalopathy, lactic acidosis and stroke-like episodes [MELAS] syndrome) or vasospasm following intracerebral hemorrhage. Because thrombotic/embolic phenomena predominate in the pathophysiology of childhood-onset AIS, investigation of the contribution of thrombophilias to risk of

incident and recurrent AIS in childhood is warranted. Indeed, several studies have demonstrated various thrombophilias as risk factors for childhood onset AIS, as further described below, and summarized in Table 2 (based upon selected reports).

Genetic thrombophilias

Genetic thrombophilias have been associated with both incident and recurrent AIS. Several studies have demonstrated the increased frequency of heterozygous factor V Leiden (FVL) polymorphism in childhood-onset AIS case as compared to healthy controls [23–25]. In a German case-control study of 148 childhood-onset AIS patients and 296 age matched controls, 20% of AIS cases possessed FVL, as compared to 4% of controls (OR 6; 95% CI 2.97–12.1) [25]. The same study found the prothrombin G20210A polymorphism in 6% of patients as compared to 1 % of controls (OR 4.7; 95% CI 1.4 to 15.6) [25]. Protein S deficiency has been reported in multiple case reports of childhood-onset AIS, as well as in association with an antibody mediated response to varicella (see also *Acquired thrombophilias*, below) [26–28]. Protein C deficiency has been demonstrated as a risk factor for incident AIS in multiple case-control studies [4,25,29], and in one consecutive cohort series of 310 German children protein C deficiency demonstrated a relative risk of recurrent childhood-onset AIS of 3.5 (95% CI 1.1–10.9) [14]. The same series reported an even higher recurrence risk for elevated lipoprotein(a) (RR=4.4, 95% CI=1.9–10.5). Lipoprotein(a) elevation has also been associated with cardioembolic subtype of childhood-onset AIS [4,25].

The recent meta-analysis of Kenet and colleagues demonstrated that the MTHFR C677T mutation was found in more childhood-onset AIS patients than healthy controls; [30] however, it is uncertain whether this serves as an independent risk factor relative to plasma homocysteine levels. This meta-analysis confirmed many of the associations reported above, and also demonstrated a significant association between multiple thrombophilia traits and incident pediatric AIS [30]. It determined a significant association with AIS for FVL (OR 3.70; CI 2.82–4.85), factor II G20210A (OR 2.60; 95% CI 1.66–4.08), protein C deficiency (OR 11.0; 95% CI 5.13–23.59), lipoprotein (a) (OR 6.53; 95% CI 4.46–9.55) and MTHFR C677T mutation (OR 1.58; 95% CI 1.20–2.08) [30]. Neither protein S deficiency nor antithrombin deficiency were significantly associated with incident pediatric AIS. It is important to note that the meta-analysis was an aggregate of both studies of childhood-onset AIS (the subject of this review) and neonatal AIS (AIS occurring before 29 days of life).

A limitation of some of the previously cited studies on anticoagulant deficiencies (e.g., protein C, protein S, antithrombin) as well as lipoprotein(a), and a challenge for future investigation, is the distinction between genetic and acquired abnormalities. In anticoagulant deficiencies, an influence of severity of deficiency has also been rarely distinguished, and is made difficult by the rarity of these conditions.

Acquired thrombophilias

Investigation of acquired thrombophilia in AIS has mainly emphasized factor VIII (FVIII) activity and antiphospholipid antibodies (APA). While evidence suggests that a heritable contribution exists for elevated FVIII activity [31], most cases appear to be acquired. One retrospective case-control study demonstrated elevated factor VIII activity in 65% of childhood AIS patients tested four months post-stroke as compared to 12.5% of controls [32], but the association between FVIII and childhood stroke requires further investigation.

With regard to APA, early studies in childhood AIS investigated anticardiolipin antibodies (ACA). Initial evidence on the prevalence of ACA (IgG or IgM) yielded an estimate of 10% in the subgroup of children with cardioembolic AIS [4]. An Israeli case-control study by

Kenet and colleagues reported a greater than 6-fold increase in the odds of stroke in patients with antiphospholipid antibodies (lupus anticoagulant or ACA, using cutoffs for the latter of 18 GPL units for IgG and 10 MPL units for IgM) in childhood-onset AIS cases as compared to healthy controls [24]. A single study investigating a subset of antiphospholipid antibody syndrome (specifically, persistence of ACA—defined as ACA IgG > 15 GPL units on more than two occasions separated by greater than 6 weeks, in the clinical setting of a history of childhood-onset AIS), conducted by Lanthier and coworkers, suggested that such patients are not at increased risk of recurrent AIS [33]. In Kenet and colleagues' meta-analysis, a pooled examination of antiphospholipid antibodies of multiple types demonstrated a significant association between antiphospholipid antibodies and incident pediatric AIS (neonates included - OR 6.95; CI 3.67–13.14) [30]. Age-appropriate normative values for APA remain unclear, however, and further well-controlled studies are needed to evaluate whether persistent APA are prognostic factors for recurrent stroke in childhood-onset AIS [34]. Furthermore, additional work to develop functional assays modeling prothrombotic effects of APA may afford better prognostic utility for thromboembolic disease, including childhood-onset AIS. Despite these initial studies evaluating APS in childhood-onset AIS, data about APS in children remains scarce. Although a few retrospective case series in childhood VTE have also explored APS in children, data regarding outcomes and patient characteristics are still limited [35,36]. In addition, determination of appropriate cutoffs for “positive” APA testing remains challenging, as such thresholds should both exclude values observed in healthy subjects, as well as demonstrate prognostic potential for development of incident or recurrent thromboembolic events. Present criteria for antiphospholipid syndrome [37] utilize thresholds that are not informed by robust pediatric data, and it is possible that the presence of APA is associated with incident AIS, beyond the more restrictive definition of APS.

Beyond acquired thrombophilia *per se*, other coagulative markers have been proposed as putative prognostic factors in childhood-onset AIS. Recent work in a small cohort study has demonstrated that D-dimer (a marker of ongoing coagulation activation, given its rapid production during physiologic fibrinolysis of newly-formed fibrin) is acutely elevated in patients with childhood-onset AIS, especially patients with cardioembolic stroke [38]. The investigation of D-dimer and other clinically and laboratory-based putative prognostic factors in childhood-onset AIS remains in its infancy; such efforts are vital to the development of future risk-stratified antithrombotic therapeutic approaches in childhood-onset AIS.

Outside of thrombophilia and coagulative markers, suggested risk factors for childhood-onset AIS have included leukocytosis [13], thrombocytosis, and iron deficiency anemia (IDA) [39]. IDA, which has received increased emphasis in the past several years, has been reported as an associated condition at AIS onset in several case reports [40,41]. Furthermore, in a recent Canadian case-control study, IDA was disclosed in 53% of cases, as compared to 9% of controls [39]. The mechanism(s) by which iron deficiency anemia contributes to AIS risk remain unclear, but initial investigation suggests that it may be independent of the thrombocytosis observed in many chronic cases of IDA [39].

Approach to diagnostic evaluation

The approach to diagnostic evaluation of childhood-onset AIS is challenging. Although multiple anatomic and thrombotic risk factors in childhood-onset AIS have been clearly delineated, their significance on outcome and treatment selection is still poorly understood. Hence, the approach to diagnostic evaluation of childhood-onset AIS remains controversial and diverse. It is crucial to identify anatomic causes of clot formation through imaging modalities, although weighing the risks and benefits of each approach to testing is a

challenging task with little supporting data. As an example, conventional angiography provides gold standard vascular imaging of the head and neck, but carries a small chance of transient global amnesia, secondary vascular injury and/or stroke (up to 1.4% in one series of 137 patient aged 5–24) [42]. Similarly, computed tomography with angiography (CTA) exposes the child to increased radiation burden, but contains less artifact than magnetic resonance angiography (MRA). At a minimum, children with AIS should have cerebral imaging, vascular imaging of the head and neck, as well as echocardiography, with consideration of bubble study to detect a patent foramen ovale. American Heart Association (AHA) pediatric stroke guidelines suggest that “the least invasive study that will provide an adequate assessment is usually the test to perform, but whether to do a test and the order in which a study is performed will vary with the clinical situation” [43].

MRA, CTA and conventional angiography are the most commonly used imaging modalities employed to visualize vascular anomalies in childhood onset AIS. Local expertise, degree of suspicion for a vascular abnormality and age of the patient all inform the study choice. As arteriopathies can sometimes present after the acute onset of stroke (<3 months post stroke) and often change over time [19], repeat vascular imaging is usually performed. Although MRA is the least invasive procedure (no radiation or stroke risk), according to the AHA recommendations “some conditions, including extracranial arterial dissections, particularly involving the posterior circulation, and small-vessel vasculitis, are difficult to exclude on MRA.” [43] Detection of extracranial dissection is improved with fat-saturated T1 imaging.

At our center, MRA of the head and neck (with T1 fat saturated images of the neck) is the first line modality for vascular imaging in acute childhood-onset AIS. We have recently added contrast to our studies to reduce false positives. CTA is considered in patients with large vessel anomalies that are uncertain on MRA. Conventional angiography is considered in cases of clinically suspected dissection, moyamoya, or possible vasculitis. Repeat imaging at 3–12 months is essential, as 19% of unilateral vascular anomalies will transiently worsen, 6% can progress, and only 23% of non-progressive disease will completely normalize [19]. Although some studies suggest that PFO and right to left shunt in cryptogenic stroke are detected more often with transesophageal echocardiography (TEE) and transcranial Doppler ultrasonography (TCD), than in patients with transthoracic echocardiography (TTE); [44] the implications of a PFO in childhood-onset AIS remain unknown. AHA pediatric stroke guideline suggest, “in some series, the prevalence of a patent foramen ovale (PFO) is greater in young adults with unexplained ischemic stroke than in normal individuals, and the significance of a PFO in a child with stroke is even less certain. Optimal treatment of paradoxical embolism associated with PFO is not known” [43].

Although multiple types of genetic and acquired thrombophilia are established as independent risk factors for incident AIS, data supporting significant prognostic impact upon recurrence risk are limited to a few individual traits such as elevated lipoprotein (a), protein C deficiency, and the presence of multiple risk factors [14,45]. AHA pediatric stroke guidelines suggest, “although the risk of stroke from most prothrombotic states is relatively low, the risk tends to increase when prothrombotic disorder occurs in children with other risk factors. Thus, it is reasonable to evaluate for the more common prothrombotic states even when another stroke risk factor has been identified.” [43] Given the lack of adequately powered studies to detect the impact of thrombophilia on recurrence risk in childhood-onset AIS, our approach is to comprehensively evaluate for both genetic and acquired thrombophilias. One approach, outlined by the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH), suggests an initial evaluation of: complete blood count, antithrombin, protein C activity, free and total protein S antigen, FVL and/or

functional activated protein C resistance assay, prothrombin G20210A, homocysteine level +/- MTHFR, lipoprotein (a), lupus anticoagulant, anticardiolipin antibodies, and hemoglobin electrophoresis (for sickle cell disease screening) [46]. Typically, abnormal potentially-acquired thrombophilia findings should be retested at about 12 weeks from initial testing.

In addition to consideration of anatomic and thrombotic risk factors, diagnostic evaluation for alternative etiologies also needs to be considered, including pharmacological causes (such as cocaine), rheumatologic disease (such as lupus), metabolic disease (such as Fabry Disease), mitochondrial disease (such as MELAS), and other genetic conditions (such as CADASIL).

Antithrombotic treatments

Treatment of non-SCD-associated childhood-onset AIS, particularly with regard to antithrombotic therapies, is largely based upon extrapolation from adult evidence. Three consensus-based guidelines have been developed to assist in clinical care: the American Heart Association (AHA) Scientific Statement on management of stroke in infants and children, the American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy in neonates and children, and the Royal College of Physicians (RCP) clinical guidelines for diagnosis, management and rehabilitation in pediatric stroke [43,47,48]. Given that salient risk factors and pathophysiological processes in adult AIS—atherosclerosis, hypertension, and hyperlipidemia—are infrequent in childhood-onset AIS, prospective studies and cooperative trials investigating the safety and efficacy of antithrombotic therapeutic modalities (both antiplatelet and anticoagulant) are urgently needed to better inform clinical care for children.

With regard to therapies administered in the hyperacute phase of AIS, evidence on systemic intravenous (IV) and catheter-direct intra-arterial (IA) thrombolysis is particularly lacking. Multiple case reports have been published involving the use of thrombolysis in childhood AIS [49–54], and it is estimated that 1.6% of childhood-onset AIS patients in the United States receive thrombolytic therapy [55]. A recent IPSS series of 15 children receiving IV or IA tissue-type plasminogen activator (tPA) reported intracranial hemorrhage after tPA in 2/9 IV patients and 2/6 IA cases [54]. It is notable that many of these patients received therapy beyond time-windows established for thrombolytic therapy in adult AIS [54]. Given the lack of data, ACCP and RCP guidelines emphasize that the risk/benefit ratio of thrombolytic therapy for AIS is unclear [47,48]. The AHA guidelines further suggest that, “Until there are additional published safety and efficacy data, tPA generally is not recommended for children with AIS outside a clinical trial. However, there is no consensus about the use of tPA in older adolescents who otherwise meet standard adult tPA eligibility criteria.” [43] A dose-finding trial of IV tPA in childhood-onset AIS has been proposed through the IPSS [56].

Antithrombotic therapies (whether antiplatelet or anticoagulant) are often employed as secondary prevention strategies, initiated in the acute phase of childhood-onset AIS. Presently, however, the current standard of care is highly-variable world-wide and with the U.S. itself [57]. In a recent IPSS analysis involving over 600 childhood-onset AIS cases from over 30 centers world-wide, frequencies of acute antiplatelet therapy, anticoagulation, and no antithrombotic therapy administration were balanced (at 27–30% each) [57]. Furthermore, management varied by geographical region, with acute anticoagulation utilized less frequently in U.S. than non-U.S. centers (38% of cases as compared to 50%) [57].

Several studies have explored the preliminary safety and efficacy of antiplatelet and anticoagulant therapies in the secondary prevention of childhood onset-AIS. A single-center, nonrandomized, prospective cohort study by Sträter and colleagues compared aspirin (4 mg/

kg) and low-dose low-molecular-weight heparin (LMWH) in 135 childhood-onset AIS patients, and found no significant differences in the rates of recurrent stroke or clinically-significant bleeding between the two approaches. [58] A recent collaborative cohort study from the pediatric stroke programs in Colorado and Munster, Germany evaluated the safety of anticoagulation in patients with arteriopathy (excluding those with moyamoya), and found that over a cumulative anticoagulation duration of 1329 patient-months, there were no major bleeding episodes and only two minor bleeding episodes [5]. Both of the aforementioned studies are limited by a nonrandomized (and in the latter case, non-comparative) design. Furthermore, the influences of stroke subtype, stroke size and comorbidities upon safety and efficacy of anticoagulation and antiplatelet therapy remain insufficiently studied.

Whereas the AHA, RCP and ACCP guidelines all recommend exchange transfusion to reduce sickle hemoglobin to less than 30% total hemoglobin in the setting of acute SCD-related AIS [43,47,48], the three guidelines differ in their recommended approach to acute (0–7 days) antithrombotic management of non-SCD-associated childhood-onset AIS. ACCP guidelines indicate that, “for children with non-SCD related acute AIS, we recommend UFH or LMWH or aspirin (1 to 5 mg/kg/d) as initial therapy until dissection and embolic causes have been excluded.” In contrast, RCP recommendations advocate for initiating therapy with aspirin (5 mg/kg) acutely, with anticoagulation administered only when/if dissection or cardioembolism is disclosed. AHA recommendations support the consideration of anticoagulation (LMWH or UFH) for up to 1 week after idiopathic childhood onset AIS, and also suggest that 3–5 mg/kg/day of aspirin is a reasonable option for secondary prevention [43]. It is hoped that the equipoise embodied by these consensus-based recommendations for acute treatment will facilitate the commencement of randomized controlled clinical trials of acute antithrombotic therapy for childhood-onset AIS. Of note, while all three guidelines call for extended anticoagulation in dissection and cardioembolic subtypes of childhood-onset AIS, optimal duration of anticoagulation is also unclear and insufficiently studied.

Conclusion

Antithrombotic management in childhood-onset AIS is largely based upon consensus-based guidelines and evidence from adult AIS literature. Evidence suggests that numerous thrombophilias may serve as risk factors for incident or recurrent AIS. Findings from the International Pediatric Stroke Study indicate that antiplatelet and/or anticoagulation therapy is employed in over 80% of childhood-onset AIS as a secondary prevention strategy. Recent data from observational studies suggest that aspirin and anticoagulation can each be used safely in childhood-onset AIS, although definitive evidence from clinical trials is urgently needed. Future studies should also evaluate anatomic factors, thrombophilia, and other putative prognostic factors in childhood-onset AIS, as a risk-stratified approach to antithrombotic therapy will likely be necessary in order to optimize the balance between bleeding and recurrence risks.

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Table 1

Published associations between anatomic factors and recurrent childhood-onset AIS (selected reports).
Abbreviations: *OR*, odds ratio; *HR*, hazard ratio.

Anatomic Factor Identified	Comparison Group	Recurrent AIS	
		Magnitude of association	Reference
Cardiac disease	All other childhood AIS	OR=0.3 (95% CI=0.03–3.4)	Sträter [14]
Abnormal Vascular Imaging ^b	Normal Vascular Imaging	P<0.0001 ^a	Fullerton [2]
Vascular Stroke ^c	All other childhood AIS	OR=3.9 (95% CI=1.4–10.6)	Sträter [14]
Occlusion	All other childhood AIS	HR=1.07 (95% CI=0.45–2.57)	Ganesan [13]
	Non-occlusive unilateral arteriopathy	OR=2.8 (95% CI=0.9–8.5)	Braun [19]
Stenosis	All other childhood AIS	HR=1.43 (95% CI=0.71–2.87)	Ganesan [13]
Moyamoya	All other childhood AIS	HR=3.26 (95% CI=1.55–6.84)	Ganesan [13]
Dissection	All other childhood AIS	HR=0.75 (95% CI=0.21–2.68)	Ganesan [13]
Progressive cerebral arteriopathy	Stable or improved unilateral arteriopathy	OR=18.8 (95% CI=1.9–182)	Braun [19]
	Stable or improved non-moyamoya arteriopathy	HR=3.2 (95% CI=0.5–20.3)	Danchaivijitr [59]

^a As determined by log-rank test, comparing abnormal vascular imaging to normal vascular imaging.

^b Consisted of large vessel stenosis, moyamoya syndrome, vasculitis and/or arterial dissection.

^c Included dissection or trauma, fibromuscular dysplasia, moyamoya, stenosis, or vasculitis.

Table 2

Published associations between thrombophilia and childhood-onset AIS, including both incident and recurrent events (selected reports). Abbreviations: *OR*, odds ratio; *RR*, relative risk or risk ratio; *APA*, antiphospholipid antibodies.

Genetic Thrombophilia	Incident AIS		Recurrent AIS	
	Magnitude of association (relative to healthy controls)	Reference	Magnitude of association (relative to all other childhood AIS)	Reference
Factor V Leiden polymorphism	OR=9.7 (95%CI: 1.1–84.7) ^a	Duran [23]	RR=0.4 (95%CI: 0.05–2.8)	Sträter [14]
	OR=4.8 (95%CI: 1.4–16.5)	Kenet [24]		
	OR=6.0 (95%CI: 3.0–12.1)	Nowak-Göttl [25]		
	OR=3.6 (95%CI: 0.9–14.9) ^b	Sträter [4]		
	OR=1.2 (95%CI: 0.8–1.9) ^c	Haywood [29]		
Factor II G20210A polymorphism	OR=4.7 (95%CI: 1.4–15.6)	Nowak-Göttl [25]	RR=1.3 (95%CI: 0.2–9.6)	Sträter [14]
	OR=1.3 (95%CI: 0.2–8.2)	Kenet [24]		
	OR=1.1 (95%CI: 0.5–2.3) ^c	Haywood [29]		
Antithrombin deficiency	OR=1.0 (95%CI: 0.3–3.7) ^c	Haywood [29]	n/a	–
Protein S deficiency	OR=1.1 (95%CI: 0.3–3.8) ^c	Haywood [29]	RR=2.9 (95%CI: 0.8–11.3)	Sträter [14]
Protein C deficiency	OR=18.5 (95%CI: 2.2–16.0) ^b	Sträter [4]	RR=3.5 (95%CI: 1.1–10.9)	Sträter [14]
	OR=9.5 (95%CI: 2.0–44.6)	Nowak-Göttl [25]		
	OR=7.0 (95%CI: 0.8–65.1)	Kenet [24]		
	OR=6.5 (95%CI: 3.0–14.3) ^c	Haywood [29]		
Activated protein C resistance	OR=9.7 (95%CI: 1.1–84.7) ^a	Duran [23]	n/a	–
	OR=1.3 (95%CI: 0.2–11.5) ^c	Haywood [29]		
Lipoprotein(a) elevation	OR=7.2 (95%CI: 3.8–13.8)	Nowak-Göttl [25]	RR=4.4 (95%CI: 1.9–10.5)	Sträter [14]
	OR=4.3 (95%CI: 1.3–14.4) ^b	Sträter [4]		
MTHFR mutation	OR=2.4 (95%CI: 1.5–4.5)	Nowak-Göttl [25]	n/a	
	OR=1.7 (95%CI: 1.2–2.3) ^c	Haywood [29]		
Factor VIII elevation	OR=4.9 (0.5–46.8) ^a	Duran [23]	n/a	–
Acquired Thrombophilia				
APA (any)	OR=6.1 (95%CI: 1.5–24.3)	Kenet [24]	n/a	–
Lupus anticoagulant	n/a	–	n/a	–
Anti-β2-gp-I antibody	n/a	–	n/a	–
Anticardiolipin antibody	n/a	–	OR=0.6 (95%CI: 0.3–1.4) ^a	Lanthier [33]

^aOR and corresponding 95% CI calculated by the present authors based upon data provided in the original report.

^bCases included cardiac patients only.

^cData obtained by systematic review of observational studies.