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Anticoagulation in Childhood-Onset Arterial Ischemic Stroke with Non-Moyamoya Arteriopathy: Findings from the Colorado and German (COAG) Collaboration

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Abstract

Background and Purpose—Childhood arterial ischemic stroke (AIS) treatment guidelines recommend extended anticoagulation in cardioembolism and dissection. We sought to investigate the safety of extended anticoagulation in childhood AIS with non-moyamoya arteriopathy, for which the risk of recurrent stroke is high.

Methods—Thirty-seven childhood-onset AIS patients with acute arteriopathy (excluding moyamoya) were diagnosed between 1999 and 2007 and treated with anticoagulation for at least four weeks. Patients were followed in hospital-based cohort studies at two centers and systematically assessed for bleeding episodes and recurrent events.

Results—Over a cumulative anticoagulation duration of 1,329 patient-months, there were no major bleeding episodes and two clinically relevant bleeding episodes. Cumulative probability of recurrent AIS at one year was 14%.

Conclusions—Anticoagulation can be used safely for secondary AIS prevention in children with acute non-moyamoya arteriopathy. Anticoagulation is worthy of evaluation in future randomized controlled treatment trials in this disease.

Keywords

Childhood Stroke; Arteriopathy; Anticoagulation

Introduction

Arterial ischemic stroke (AIS) occurs in 1–2/100,000 children per year, with acute[1] and long-term[2, 3] neurologic sequelae in approximately 70%. Recurrent stroke is a major cause

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of morbidity, occurring in 15% within one year post-event.[3] Risk of recurrent AIS is markedly increased among childhood AIS patients with arteriopathy, a common subtype of childhood AIS involving cerebral/cervical arterial stenosis.[3] This includes moyamoya patients, in whom risk of brain hemorrhage is also elevated.

Currently, anticoagulation is recommended for secondary prevention of childhood AIS in cardioembolism or dissection, wherein the risk of recurrence is increased.[4] Given the high prevalence of thrombophilia in childhood AIS,[5] children with arteriopathy might also be candidates for anticoagulation, if bleeding risk were shown to be low. The objective of the present work, therefore, was to investigate bleeding complications and recurrent AIS in children anticoagulated for AIS with non-moyamoya arteriopathy.

Materials and Methods

Data on demographic characteristics, risk factors, neuroimaging findings, antithrombotic treatments, clinically significant bleeding episodes and recurrent cerebrovascular events were systematically collected in children with acute AIS diagnosed between January 1, 1999 and December 31, 2007 at The Children's Hospital, Colorado and University Children's Hospital, Münster, Germany. In this combined retrospective-prospective hospital-based cohort study, all patients with AIS were followed prospectively from stroke onset, with the exception of five patients diagnosed with acute AIS before February 28, 2006 in Colorado (for whom data were retrospectively collected prior to this date and prospectively thereafter). Written informed consent was uniformly obtained for study participation. Inclusion criteria were: 1) age 29 days through 18 years; 2) sudden-onset focal neurologic deficit; 3) acute neuroimaging (computed tomography [CT], magnetic resonance [MR]) demonstrating recent ischemia/infarct of arterial distribution; 4) cerebral/cervical arterial stenosis demonstrated on MR angiography employing a 1.5 or 3T magnet, CT angiography, or conventional angiography; 5) acute treatment with anticoagulation for a minimum duration of four weeks. Patients with moyamoya, as previously defined,[6] were excluded.

Neurovascular imaging findings were characterized at each center into one of four arteriopathy subtypes (Table 1), confirmed by an independent rater. Anticoagulant therapy employed one of several regimens (Table 2). All decisions regarding type, intensity, and duration of anticoagulation were made on clinical grounds, and were not protocol-driven. Typical reasons for administration of anticoagulation in arteriopathy included dissection, thrombophilia, concomitant cardioembolism,,or development of recurrent AIS/TIA on antiplatelet therapy.

Descriptive analyses involved proportions for categorical data and median values with ranges for continuous data. Proportions were compared between groups using chi-square or Fisher's exact testing, as appropriate. Cumulative duration of anticoagulation was expressed in patient-months (total months of exposure across all patients). Kaplan-Meier survival functions were used to calculate cumulative probability of recurrent AIS over time. All statistical analyses employed SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Among 102 childhood AIS patients with arteriopathy seen at the two centers during the study period, 37 met eligibility criteria of receiving anticoagulation for at least four weeks. Arteriopathy subtypes and overall thrombophilia findings are shown in Table 1.

Table 3 summarizes treatment and outcomes data. Therapeutic anticoagulation was administered in 43% of patients and prophylactic anticoagulation in 57%. Median duration of anticoagulation was 6 months (range: 1 month – 4 years). Over the cumulative treatment duration of 1,329 patient-months of anticoagulation for the study population, there were no major bleeding episodes (including no intracranial hemorrhages) and two non-major clinically relevant bleeding episodes (one outpatient evaluation each for menorrhagia and soft-tissue hematoma). Kaplan-Meier analysis revealed a cumulative probability of recurrent AIS of 14% at one year among all children.

Discussion

Previous studies in adult AIS have reported intracranial hemorrhage in 8% of patients with atherosclerotic intracranial arterial stenosis in whom anticoagulation was administered.[7] To what extent these observations may apply to intracranial large vessel stenosis in childhood AIS remains unclear. To date, knowledge of the safety of anticoagulation in childhood AIS remains limited, particularly in the common subtype of childhood AIS with acute arteriopathy.

Although not derived from a clinical trial, the present findings suggest that anticoagulation, whether administered by therapeutic or prophylactic regimen, may be a safe treatment option for secondary AIS prevention in these patients. Over a cumulative treatment duration of greater than 1,000 patient-months of anticoagulation, there were no major bleeding episodes and only two non-major clinically relevant bleeding episodes. This work substantiates prior experience that anticoagulation can be safely administered in childhood AIS,[8] and extends such experience to AIS in children with non-moyamoya arteriopathy. Furthermore, the low risk of major bleeding observed here compares favorably with the published cumulative incidence of major bleeding of approximately 5% for children with venous thromboembolism receiving a therapeutic course of LMWH.[9]

A few limitations of this study are notable. While the cumulative probability of recurrent AIS at one year, at 14%, was appreciably lower than the recently published risk of approximately 60% among arteriopathy cases in a population-based retrospective cohort of childhood AIS in which anticoagulation was used sparingly,[3] this observation must be strongly qualified in that: (1) moyamoya patients were included in the aforementioned analysis but not in the present one; and (2) neither investigation directly compared use versus non-use of anticoagulation. Furthermore, because heparin was limited to the acute hospitalization period of AIS in these patients, and the minimum duration of anticoagulation was four weeks, the present findings are most applicable to extended anticoagulant therapy with LMWH or warfarin. Lastly, this study involved a relatively small population, such that bleeding and recurrence risks may be imprecise.

Notwithstanding these qualifications, this is the largest series yet reported for therapeutic and prophylactic dosing of anticoagulation in childhood AIS. The high prevalence of identified thrombophilia in these children provides further rationale for study of anticoagulation. The present cohort-level evidence of safety and potential for efficacy of anticoagulation in childhood AIS with acute non-moyamoya arteriopathy adds growing evidence in support of randomized controlled trials of anticoagulation versus aspirin in this disease.

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Table 1

Age, stroke characteristics, arteriopathy subtypes, and thrombophilia findings.

	Prophylactic Group	Therapeutic Group	Total
N	21	16	37
Age at diagnosis (median and range)	5 y (7 m–14 y)	6 y (6 w–17 y)	5 y (6 w–17 y)
Stroke characteristics			
Intracranial hemorrhage at presentation	0 (0%)	2 (13%)	2 (5%)
Anterior circulation only	14 (67%)	13 (81%)	27 (73%)
Posterior circulation only	3 (14%)	2 (13%)	5 (14%)
Anterior and posterior	4 (19%)	1 (6%)	5 (14%)
Arteriopathy subtypes			
Intracranial large vessel stenosis	13 (62%)	8 (50%)	21 (57%)
Dissection	6 (29%)	5 (31%)	11 (30%)
Vasculitis	1 (5%)	2 (13%)	3 (8%)
Other arterial abnormality	1 (5%)	1 (6%)	2 (5%)
Thrombophilia findings *			
Mild thrombophilia only	14 (67%)	6 (38%)	20 (54%)
Potent thrombophilia†	0 (0%)	7 (44%)	7 (19%)
Total (any thrombophilia)	14 (67%)	13 (82%)	27 (73%)

* Comprehensive thrombophilia testing was performed at each site in accordance with international recommendations from the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis.

† "Potent thrombophilia" was defined by any one of the following: 1) severe anticoagulant deficiency (<30% antithrombin; <20% protein C or protein S; 2) homozygosity for the factor V Leiden or prothrombin G20210A polymorphisms; 3) antiphospholipid antibody syndrome; or 4) multi-trait thrombophilia. All other single-trait thrombophilia states were characterized as "mild thrombophilia only." In addition to testing noted above, thrombophilia assessment included plasma factor VIII activity, serum homocysteine concentration, and plasma lipoprotein(a) level.

Table 2

Anticoagulant therapy regimens.

	Prophylactic Regimen		Therapeutic Regimen	
	Frequency	**Monitoring goal***	**Frequency**	**Monitoring goal***
LMWH	Once-daily	0.50–1.00 anti-Xa U/mL	Twice-daily	0.50–1.00 anti-Xa U/mL
UFH	--	--	Continuous infusion	0.30–0.70 anti-Xa U/mL
Warfarin	--	--	Once-daily	INR 2.0–3.0

Abbreviations: LMWH, low molecular weight heparin; UFH, unfractionated heparin; INR, international normalized ratio

*For LMWH: anti-Xa measured 4 hours post-dose.

Table 3

Treatments and outcomes.

	Prophylactic Group	Treatment Group	Total
Total patient-months of anticoagulant therapy	728	601	1,329
Clinically relevant bleeding episodes			
Major	0% (0/21)	0% (0/16)	0% (0/37)
Non-major	9% (2/21)	0% (0/16)	5% (2/37)
Cumulative probability of recurrent AIS at 1 y (95% confidence interval)	15% (5–40%)	13% (3–41%)	14% (6–30)
Cumulative probability of recurrent AIS/TIA at 1 y (95% confidence interval)	25% (15–55%)	20% (7–50%)	23% (14–44%)

Abbreviations: AIS, arterial ischemic stroke; TIA, transient ischemic attack