Rates and Risk Factors for Arterial Ischemic Stroke Recurrence in Children

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Abstract:

Background and Purpose: Recurrent ischemic events are common in children with arterial ischemic stroke (AIS), and put patients at risk for further neurological impairment. This study sought to identify rates and risk factors for recurrent AIS or transient ischemic attack (TIA) in a cohort of children seen after index AIS and uniformly investigated and managed using contemporary clinical guidelines.

Methods: Case note and radiology review of children >28 days and <18 years who presented to Great Ormond Street Hospital (GOSH) from 2005 to 2015 with index AIS. Demographic characteristics, medical history, index AIS features, radiological findings, and neurological outcome were examined. Recurrence was identified from clinical records and coded as AIS (if there was associated new cerebral infarction) or TIA.

Results: Eighty-four children (43 girls, median age at index AIS = 4.1 years) were identified. Cumulative AIS recurrence was 5% at 1 month, 10% at 3 months, 12% at 6 months, 12% at 12 months, and 15% at 60 months after index event. Factors that independently predicted AIS recurrence were referral to GOSH from outside the catchment area, a prior relevant diagnosis, bilateral arteriopathy and AIS CASCADE category 3.a. or 3.b. Multiple infarcts and evidence of mature, as well as acute, infarcts on first brain imaging, while independently associated with AIS recurrence were also associated with bilateral arteriopathy. Only CASCADE categories 3.a. and 3.b. (bilateral cerebral arteriopathy with or without collaterals) remained significant in multivariate analysis. AIS recurrence was not associated with poor neurological outcome.

Conclusions: AIS recurrence remains a significant problem despite the wide use of antithrombotic medications. AIS subtypes should direct clinicians and future trials to use stratified management strategies and durations of treatment. Bilateral cerebral arteriopathies are especially sinister and consensus criteria should be developed to improve consistency of management.

Introduction

Arterial ischemic stroke (AIS) is an important cause of childhood morbidity and mortality.[1-3] Treatment to limit acute brain injury remains limited and clinical effort is focused on preventing recurrence and accrual of additional injury. Although several childhood stroke clinical guidelines have been published,[4, 5] most are based on expert consensus rather than trial evidence. The impact of these in a clinical population has not been examined. Estimates of recurrence risk vary widely[6, 7] and design and execution of trials of secondary prevention are a major current focus of research in pediatric AIS.[8]

The aims of this study were to describe rates of and risk factors for recurrence in a recent single centre cohort of children with AIS, investigated and managed in a uniform manner according to contemporary clinical guidelines.[4]

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Arterial ischemic stroke was defined as acute focal neurological deficit with radiological evidence of cerebral infarction in a corresponding arterial distribution. Children aged >28 days and <18 years presenting to Great Ormond Street Hospital (GOSH) with index AIS between 2005 – 2015 were included. GOSH serves as the tertiary paediatric neurology centre for North London and does not have an emergency department; all patients would have been initially assessed in one of the feeder general paediatric units. Those with transient ischemic attack (TIA)

presentation (without brain infarction), or those only referred after recurrence, were excluded. Over this period, patients were investigated and managed in compliance with the Royal College of Physicians (RCP) Childhood Stroke Guidelines 2004.[4] This review of existing clinical and radiological data was categorized as clinical audit by the hospital, without requirement for ethical committee review.

Case notes and brain imaging studies were reviewed retrospectively. All imaging studies had been acquired for clinical assessment and selected at clinician discretion. All patients had had brain magnetic resonance imaging (MRI) and angiography (MRA) of the cerebral and cervical arterial circulation at presentation and follow-up, that had been clinically reported by a consultant neuroradiologist at GOSH. Although some patients may have had other imaging studies (head computed tomography or digital subtraction angiography) during clinical assessment, only the MRI/A were assessed here.

Clinical, laboratory, and radiological parameters recorded are summarized in table 1. These were selected following review of the literature, to examine factors previously implicated in index or recurrent AIS. The category "relevant prior diagnosis" included miscellaneous co-existing conditions previously reported to be associated with childhood AIS (listed separately in table 1). Referring hospital was coded as either within or outside of the GOSH north London catchment area to assess for any influence of referral centre bias.

Hemoglobin concentration (within two weeks) and coagulation profile were coded as either normal or abnormal at index AIS. Coagulation profile included values for coagulation screen

(prothrombin time, activated partial thromboplastin time, fibrinogen), dilute Russell's viper venom time, and levels of protein C, protein S, antithrombin, Factor VIII, and Factor XII. Follow-up data for patients with acute coagulation abnormalities were used to assess for definite thrombophilia.

Initial brain MRI/A were reviewed as to site(s) of infarction (right/left/bilateral, anterior circulation/posterior circulation/both), multiplicity of infarcts (single/multiple), evidence of mature infarcts at the time of index event/scan (from previous clinically silent infarction), and arteriopathy location (right/left/bilateral carotid/vertebral circulation, anterior/posterior/both circulation). A patient with multiple infarcts within a single vessel territory was considered to have multiple infarcts.

Follow-up brain MRI and MRA were reviewed to identify any change in brain appearance (new infarcts and/or extension of previous infarct(s) from index AIS) and evolution in arteriopathy categorised as progressive (longer segment involved of previously abnormal artery or involvement of new arteries)/reversible/stable. AIS subtype was categorised according to the CASCADE classification.[9]

Recurrence was considered any cerebral ischemic event occurring after the index AIS, including further AIS (with new brain infarction), TIA (reversible event judged by treating clinician to be significant, without new infarcts) or clinically "silent" infarcts. Neurological outcome was scored from case notes using the Recurrence and Recovery Questionnaire[10] (RRQ) and dichotomized into "good" and "poor" categories as previously described.[2]

Survival analysis was used to find rates of first recurrence in the sample. Cases were censored at death or on the date of last documentation for patients without recurrence. Kaplan-Meier survival curves were used to visualize the proportion of patients who remained recurrence free. To investigate predictors of recurrence, hazard ratios and 95% confidence intervals were found using univariate Cox regression; significant and clinically relevant factors were entered into a multivariable model. Chi-square tests were used to find associations between outcomes, recurrence, and bilateral disease, and between bilateral disease and infarct characteristics. These tests used an adjusted critical p-value found by dividing 0.05 by the number of comparisons made. All analyses were performed with SPSS version 24 (IBM Corporation, Armonk, NY).

Results

Eighty-four children (43 girls), were identified. Sixty were referred from within the GOSH north London catchment area. Median age at index AIS was 4.1 years (interquartile range (IQR): 2.4 – 7.0 years), and patients were followed for a median of 2.4 years (IQR: 1.5 – 4.0 years). Data on medical history, acute investigations, and imaging studies at index AIS are summarised in table 1.

Nearly all patients (82/84) had received a medical intervention after index AIS, in accordance with the RCP clinical guidelines; the two who did not experienced recurrent AIS, and it was unclear from notes review why they were not initially treated. Data on interventions after index AIS are summarised according to CASCADE classification in table 2.

Figure 1 shows survival curves for children with recurrent AIS and any clinical recurrence. For full details on recurrence risk at specific time points, see http://stroke.ahajournals.org. The median interval to AIS recurrence was 2.3 months; 77% of recurrent AIS occurred within the first 6 months after index AIS. AIS recurred in 10/17 children specifically with bilateral arteriopathy (CASCADE 3.a. n=10; 3.b. n=6; 4.a. n=1), all of which occurred within 12.5 months of index event (figure 2). Two patients with no arteriopathy had another AIS; one of these patients had a cardiac condition and factor V Leiden mutation, the other had a cardiac condition and a relevant prior diagnosis (antiphospholipid antibodies). Of the 16 children with TIA recurrence, 5 also had recurrent AIS (CASCADE 3.a. n=1; 3.b. n=3; 6.a. n=1). The number of clinical recurrences (AIS and/or TIA) ranged from 1 – 11, with 12 patients experiencing multiple clinical recurrences. Seven children with more than one clinical recurrence were classified as CASCADE 3.a. or 3.b. Bilateral disease was significantly associated with both multiple acute infarcts ($p<0.001$) and mature infarcts at index AIS ($p<0.001$) in chi-square analysis.

Follow-up brain and cerebrovascular imaging studies were available for 78/84 children after a median of 2.0 years (IQR: 1.1 – 4.0 years). Five children without follow-up imaging had not experienced any recurrence, and 1 further child was diagnosed with recurrent TIA but no recurrent AIS. Hence, all 13 children with recurrent AIS were re-imaged during follow-up and showed either new infarction or an extension of a previous infarct. No changes in brain imaging were seen in the 10 children with recurrent TIA only and follow-up scans, or in the 55 re-imaged children with no clinical recurrence.

Fifty-three of the 54 children with arteriopathies at presentation were re-imaged during follow-up: 11 children showed arteriopathy progression (CASCADE 3.a. n=2; 3.b. n=5; 4.a. n=1; 6.b. n=3), while arteriopathy had improved in 14 and remained stable in 28.

Thirty-five of 84 children had a poor neurological outcome on the RRQ. Of note, inspection of the raw RRQ scores showed that most patients were assigned a low level of impairment in most domains, with only a few scored as having a major functionally limiting impairment – however, on the RRQ assignment of anything other than a "no impairment" score in any domain allocates the child to the "poor" outcome group. Children with no or unilateral arteriopathy generally had good outcome, although these factors were not significantly associated with outcome. There was a significant association between bilateral arteriopathy and poor outcome (p=0.007); the risk of poor outcome was 71% for these children. Poor outcome was also more common among children with AIS recurrence but not significantly so (chi-square=2.5; p=0.11).

In univariate Cox regression children referred to GOSH from hospitals outside the north London catchment area, a previous diagnosis known to be associated with AIS and bilateral cerebral arteriopathy were significantly more likely to experience recurrent AIS. With regard to AIS subtype, bilateral cerebral arteriopathy with (CASCADE 3.a.) and without collaterals (3.b.) significantly predicted recurrence. Those with established, mature infarcts at the time of index clinical presentation, and those with multiple infarcts were also more likely to experience recurrence. In contrast to previous studies, co-existence of multiple risk factors for index AIS and arteriopathy progression were not significantly predictive of recurrence[11, 12] (table 3).

Multivariate Cox regression, adjusted for age, also included data on referring hospital, prior diagnoses, and CASCADE classification. Infarct characteristics were not included because of their association with bilateral disease. Only CASCADE categories 3.a. (hazard ratio: 13.2 (95% CI 1.4 – 122.7); p=0.02) and 3.b. (HR: 25.3 (95% CI 2.6 – 243.8); p=0.005) remained predictive of recurrent AIS.

Discussion

In this contemporary group of uniformly managed children with AIS, AIS recurrence rate was 12% within 6 months, and 15% within 5 years. The 5-year cumulative risk of AIS and/or TIA was 29% (24/84 children), with 12 multiple recurrences. Imaging predictors of recurrent AIS were bilateral arteriopathy (CASCADE 3.a./3.b.), also associated with mature/multiple infarcts at presentation.

Referral bias was evident, with more recurrences in children from outside the GOSH catchment area. Bias is also evident in other studies, with population-based cohorts having fewer patients with high risk diagnoses such as moyamoya.[6] Other limitations here include retrospective and missing data, and limited power. The latter likely explains the fewer posterior circulation/cardioembolic categories compared with previous cohorts, though this may also relate to inconsistency of diagnostic definitions between studies. Whilst it is surprising that recurrence was not significantly associated with outcome, it is important to acknowledge limitations of the dichotomized RRQ outcomes used, namely that children with very minimal functional deficit could still be classified as poor outcome. The key finding here is that recurrence risk, and its trajectory, varies according to AIS subtype, a key point to consider in future trial design.

The recurrence rate of 15% compares with an 18% rate in an older GOSH cohort[13] of whom only 62% received prophylaxis. The impact of consensus-derived clinical guidelines and more use of anti-thrombotics on recurrence rate appears to be limited, although compliance cannot be guaranteed. The 2017 Royal College of Paediatrics and Child Health childhood stroke guidelines are largely similar to 2004 guidelines, so it seems unlikely these will materially alter recurrence rates.[14] Thus the need for more effective, and targeted, interventions is clear.

A recent physician survey suggests that combined corticosteroid-antithrombotic treatment for focal cerebral arteriopathy (FCA) is the highest priority for interventional studies in childhood AIS.[8] However, in contrast to other groups, FCA patients did not have a high recurrence rate in our study, nor did we find progressive arteriopathy to predict recurrence.[7, 11, 15-18] Though these differences likely partially relate to power, they emphasise the importance of AIS subtyping in calculating risk and power for trials, that will need to be tailored to AIS subtype, rather than having a "one size fits all" design.

A major difficulty in comparing data between studies is that radiological features of conditions with differing pathophysiology may be indistinguishable – for example FCA and primary angiitis of the central nervous system – that would be predicted to have differing natural histories. While CASCADE enables categorization of *all* AIS patients using predefined criteria, and is therefore a useful research tool, using radiology to subtype patients may falsely group patients with differing pathophysiology and natural history, again relevant to proposed interventions.

A population screening study in Japan suggested that moyamoya could be more benign than previously suggested, including asymptomatic cases.[19] However, it appears that outside Japan, bilateral arteriopathy in children with AIS is almost universally a malignant radiological signature and that within that group CASCADE 3.a. and 3.b. have differing disease trajectories.[20] Whilst a trial of surgical revascularization in these patients is unlikely to materialize, prospective multi-centre data collection and analysis could help refine decision making. In parallel, improving understanding of disease biology would contribute significantly to development of disease-targeted interventions, and would form a useful antecedent to clinical trials.

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Ethics Approval

Clinical audit #2149

Disclosures: None

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Figure legends:

Figure 1. Whole cohort Kaplan-Meier survival curves for first recurrence. Figure shows survival functions for both any ischemic recurrence (bold) and AIS recurrence groups.

Figure 2. Kaplan-Meier survival curves for the patients with either bilateral (bold, solid), unilateral (thin, solid), or no arteriopathy (dotted).

Tables:

Table 1. Clinical, Laboratory, and Radiological Investigations after Index AIS. FCA=Focal cerebral arteriopathy of childhood. *Includes genetic mutations and definite thrombophilia.

Medical History	N (% of cohort)
Cardiac Conditions	18 (21%)
Infections	33 (39%)
Chickenpox in past 12 months	17
Other infections in past 4 weeks	16
Relevant Prior Diagnosis	18 (23%)
Trisomy 21	5
Sickle cell disease or sickle cell trait	2
Pulmonary hypertension	2
ACTA2 mutation	2
Meningitis	1
Neuroblastoma	1
Raynaud's	1
Antiphospholipid antibodies	1
Hypothyroidism	1
Superior vena cava thrombus	1
Acute multi-focal placoid epitheliopathy	1
Other Medical History	
Head trauma in past 2 weeks	10 (12%)
Extracorporeal membrane oxygenation (ECMO)	2 (2%)

Number of medical history risk factors*	
None	19 (23%)
Single	32 (38%)
Multiple	33 (39%)
Acute AIS Investigations (N Investigated)	N Abnormal (%)
Echocardiography (84)	13 (15%)
Genetic Thrombophilia Mutations (66)	30 (45%)
Acute Hemoglobin Concentration (69)	23 (33%)
Acute Coagulation Profile (77)	20 (26%)
Definite thrombophilia at follow-up	2
Brain Imaging	N
Number of infarcts	
Single	54
Multiple	30
Anterior circulation	77
Posterior circulation	6
Anterior and posterior circulation	1
Uni/bilaterality of brain region affected	
Left	34
Right	35
Bilateral	15
Evidence of mature infarct at time of index AIS	18
Arterial Imaging	N

No arteriopathy	30
Anterior circulation	49
Posterior circulation	3
Anterior and posterior circulation	2
Uni/bilaterality of arteriopathy	
Unilateral	37
Bilateral	17
CASCADE AIS subtype	N (% of cohort)
2.a. Unilateral FCA - Anterior circulation with collaterals	6 (7%)
2.b. Unilateral FCA - Anterior circulation without collaterals	22 (26%)
2.d. Unilateral FCA - Other	1 (1%)
3.a. Bilateral cerebral arteriopathy – With collaterals	10 (12%)
3.b. Bilateral cerebral arteriopathy – Without collaterals	6 (7%)
4.a. Aortic/cervical arteriopathy - Dissection	3 (4%)
5.a. Cardio-embolic – Definite	3 (4%)
6.a. Other – undetermined etiology	25 (30%)
6.b. Other – other	8 (10%)

Table 2. Interventions after index AIS by CASCADE classification.

	2.a.	2.b.	2.d.	3.a.	3.b.	4.a.	5.a.	6.a.	6.b.	Total
Antiplatelet only	6	19	0	7	4	1	2	25	4	68
Anticoagulation only	0	2	0	0	0	0	0	0	0	2
Both antiplatelet and anticoagulation	0	1	1	0	0	2	0	0	3	7
Surgery and antithrombotic	0	0	0	1*	0	0	1†	0	1‡	3
Blood transfusions	0	0	0	1	1	0	0	0	0	2
No treatment	0	0	0	1	1	0	0	0	0	2

*Revascularization surgery and antiplatelet. †: Mitral valve repair and antiplatelet. ‡: Fenestrated atrial septal defect closure and anticoagulation.

Table 3. Univariate Cox regression for AIS recurrence.

Factor	No AIS recurrence (n=71); n	AIS recurrence (n=13); n	HR (95% CI)	P-value
Age at index AIS (median)	4.0	4.8	1.02 (0.91 – 1.14)	0.74
Referring hospital outside catchment area (vs. within)	16	8	4.31 (1.4 – 13.2)	0.01
Number of AIS risk factors				
None	17	2	Ref	Ref
Single	26	6	1.84 (0.37 – 9.10)	0.46
Multiple	28	5	1.34 (0.26 – 7.0)	0.73
Prior relevant diagnosis (vs. no prior diagnosis)	11	7	5.0 (1.7 – 15.0)	0.004
Progressive Arteriopathy (vs. stable or improved)*	7	4	2.43 (0.71 – 8.32)	0.16
Arteriopathy Uni/bilaterality				
No arteriopathy	28	2	Ref	Ref
Unilateral	36	1	0.39 (0.04 – 4.35)	0.45

Bilateral	7	10	11.6 (2.52 – 53.14)	0.002
AIS Classification (CASCADE)				
2.a.	6	0	0.00 (0.00)	0.99
2.b.	21	1	1.12 (0.07 – 17.91)	0.94
2.d.	1	0	0.00 (0.00)	0.99
3.a.	4	6	20.1 (2.4 – 167.9)	0.006
3.b.	2	4	24.1 (2.7 – 216.7)	0.004
4.a.	3	0	0.00 (0.00)	0.99
5.a.	3	0	0.00 (0.00)	0.99
6.a.	24	1	Ref	Ref
6.b.	7	1	3.1 (0.19 – 49.5)	0.42
Multiple infarcts at index AIS (vs. single)	21	9	4.42 (1.36 – 14.38)	0.013
Evidence of mature infarcts at index AIS	11	7	5.16 (1.73 – 15.41)	0.003

Figure 1:

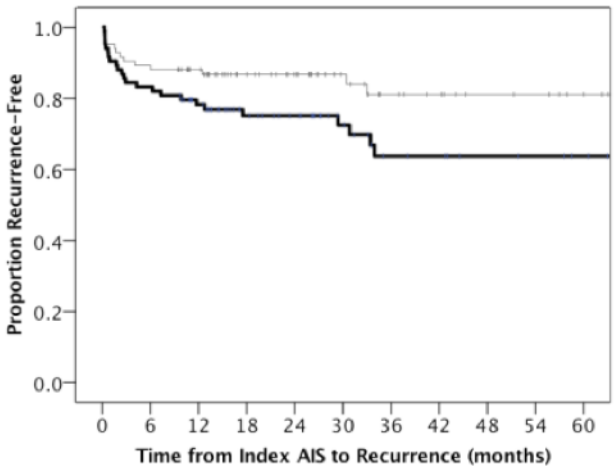

Figure 2: