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Risk of Recurrent Arterial Ischemic Stroke in Childhood: A Prospective International Study

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Abstract

Background and Purpose—Published cohorts of children with arterial ischemic stroke (AIS) in the 1990s to early 2000s reported five-year cumulative recurrence rates approaching 20%. Since then, utilization of antithrombotic agents for secondary stroke prevention in children has increased. We sought to determine rates and predictors of recurrent stroke in the current era.

Methods—The Vascular effects of Infection in Pediatric Stroke (VIPS) study enrolled 355 children with AIS at 37 international centers from 2009–2014, and followed them prospectively for recurrent stroke. Index and recurrent strokes underwent central review and confirmation, as well as central classification of stroke etiologies, including arteriopathies. Other predictors were measured via parental interview or chart review.

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*Appendix (for print and cross-referencing in PubMed)

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Results—Of the 355 children, 354 survived their acute index stroke, and 308 (87%) were treated with an antithrombotic medication. During a median follow-up of 2.0 years (interquartile range, 1.0–3.0), 40 children had a recurrent AIS, and none had a hemorrhagic stroke. The cumulative stroke recurrence rate was 6.8% (95% CI 4.6–10%) at one month and 12% (8.5–15%) at one year. The sole predictor of recurrence was presence of an arteriopathy, which increased the risk of recurrence 5-fold compared to an idiopathic AIS (hazard ration 5.0, 95% CI 1.8–14). The one-year recurrence rate was 32% (95% CI 18–51%) for moyamoya, 25% (12–48%) for transient cerebral arteriopathy, and 19% (8.5–40%) for arterial dissection.

Conclusions—Children with AIS, particularly those with arteriopathy, remain at high risk for recurrent AIS despite increased utilization of antithrombotic agents. Therapies directed at the arteriopathies themselves are needed.

Keywords

ischemic stroke; arteriopathy; vasculopathy; children; pediatric

INTRODUCTION

Childhood arterial ischemic stroke (AIS) causes lifelong disabilities in the majority of affected children.[1, 2] Prior studies suggest that the cumulative rate of recurrent AIS is high in these children, approaching 20% at five years after the index stoke, compounding disability.[3, 4] However, these studies evaluated earlier cohorts (study periods 1978–2000[4]; 1993–2004[3]), and were geographically limited (set in England[4] and Northern California[3]). Treatment with anti-thrombotic medication (antiplatelet or anticoagulation) for prevention of recurrent childhood stroke has, historically, varied dramatically by both epoch and country;[5] a third to half of the children in these two earlier cohorts received *no* anti-thrombotic medication.[3, 4] Since then, recurrence rates may have declined alongside improvements in pediatric stroke care and increased use of antithrombotic medications. Hence, the first goal of our current study was to measure the rate of recurrent AIS in a contemporary and internationally representative cohort of children with AIS.

Understanding risk factors for recurrent AIS is critical for improving strategies for secondary stroke prevention. Prior recurrence studies focused on childhood arteriopathies as a major predictor of recurrence, but were generally underpowered to perform more detailed analyses of risk factors. Recent studies of risk factors for *first* AIS in children provide evidence that minor infections act as a stroke trigger.[6] In the case-control component of our multicenter, prospective “Vascular effects of Infection in Pediatric Stroke” (VIPS) study, we confirmed this association, found that most infections preceding stroke are upper respiratory infections, and found that routine childhood vaccinations protect against childhood stroke.[7] Hence, the second goal of our study was to determine whether the same measures of infection and vaccinations affect risk of *recurrent* AIS.

To measure rates and predictors of recurrent AIS in a contemporary cohort, we prospectively followed 355 children with centrally-confirmed AIS enrolled in VIPS.

METHODS

The study setting and methods for identifying, confirming, and characterizing cases of childhood AIS in VIPS have been previously published.[7–9] VIPS centers are all academic institutions with local expertise in pediatric stroke and a history of participation in the International Pediatric Stroke Study, which was the enrollment network for VIPS.[5] The 37 VIPS centers were located in nine countries. After ethics approvals were obtained at each site, they prospectively enrolled 355 children (aged 29 days through 18 years at stroke ictus) between 1/2010 and 3/2014 with acute AIS in the preceding three weeks. Enrolling sites collected and submitted for central analysis (1) clinical data from chart review and parental interview, (2) mandatory brain and cerebrovascular imaging studies, and (3) biological samples. A central case confirmation team of two neuroradiologists and one neurologist reviewed the clinical presentation and brain imaging of every enrolled case to confirm the index AIS diagnosis, defined *a priori* as an acute infarction in an arterial territory with corresponding clinical signs and symptoms. A central stroke classification team of two neuroradiologists and two neurologists reviewed extensive clinical data and all available imaging to classify stroke subtype.[7, 9] Cases were first classified as having definite, possible, or no arteriopathy affecting the cervical or cerebral vessels. Those with "definite arteriopathy" were then further classified as transient cerebral arteriopathy, arterial dissection, moyamoya (primary or secondary, such as due to sickle cell disease), vasculitis (primary or secondary, such as due to bacterial meningitis), or other arteriopathy, including those that could not be classified. Those with "no arteriopathy" were then further classified as idiopathic, cardioembolic (spontaneous or iatrogenic, such as due to a cardiac procedure), or other identified etiologies.

Exposure to infection prior to the index stroke was measured through a structured parental interview, performed within three weeks of the stroke ictus, which included questions about clinical infections prior to the index stroke.[7] Detailed information regarding routine childhood vaccinations was also collected; as a general marker of vaccination status, parents were asked whether their child had received all, most, some, few, or none of the routine vaccines expected for his/her age. "Poorly vaccinated" was defined as some/few/none of routine vaccines. Antithrombotic therapies used for secondary stroke prevention after the index AIS diagnosis were recorded and included any type of antiplatelet medication or anticoagulation.

Patients were followed for a minimum of 12 months after their index stroke. Our *a priori* definition of recurrent AIS included two criteria: (1) imaging evidence of a new acute infarction in a territory of brain that was unaffected on the baseline parenchymal imaging; and (2) new or worsening clinical signs and symptoms corresponding to the new area of infarction. Hemorrhagic stroke after the index AIS was also considered a form of recurrence and was defined as a symptomatic intracerebral or subarachnoid hemorrhage; hemorrhagic transformation of an infarction was not considered a recurrent stroke, even if symptomatic. Transient ischemic attacks (TIAs) were recorded, but not included in our definition of recurrent stroke. Recurrent strokes were ascertained through a multitier process. First, because the VIPS site investigators were the pediatric stroke experts at their institutions, they were typically involved in the clinical care of children with recurrent AIS. Second, site

investigators and study coordinators performed follow-up assessments at pre-specified time points (4 months, 8 months, 12 months, and annually thereafter until 3/2015). These assessments were performed in person if they coincided with a clinical visit, or else via telephone, and included the administration of the Pediatric Stroke Recovery and Recurrence Questionnaire (RRQ), which includes questions about recurrent stroke.[10] Finally, at the end of the study observation period, 3/2015, sites attempted to contact the guardians of all enrolled patients to inquire about recurrent strokes. They also performed a final review of all available in-patient and out-patient medical records at their institution. Once a possible recurrent stroke was ascertained, the enrolling site obtained the relevant medical records and cerebrovascular imaging documenting the recurrence. After locally confirming that the event met criteria for a recurrent stroke, they completed and submitted a follow-up data collection form, including clinical presentation and therapies at the time of recurrence. The same central case confirmation team applied the same methodologies to confirm the recurrent stroke as used for the index stroke: two investigators independently reviewed the clinical data and all available imaging to confirm that both clinical and imaging criteria for recurrence were met, and a third adjudicated any disagreements. This team also classified the recurrent strokes as ischemic or hemorrhagic.

Data analysis

We used survival analysis techniques to estimate rates of recurrent stroke; the primary outcome variable was the time from index stroke to recurrent stroke (the “failure” event). Cases were censored (i.e., withdrawn from the time-to-event analysis) at either death or loss to follow-up using the date when they were last known to be stroke-free either by telephone interview with the guardians, or by chart review, whichever came later. In our primary analysis, we included centrally-confirmed recurrent strokes as well as a small number of recurrent strokes reported by the enrolling sites for which central review could not be performed (typically because confirmatory brain imaging was performed at an outside institution and DICOM files could not be obtained). We derived cumulative recurrence rates from hazard functions.

In our analyses of predictors of recurrent stroke, we used the same definitions for all predictor variables as described in prior VIPS publications.[7–9] The primary measure of infectious exposure was parental report of clinical infection in the week prior to index AIS, which was found to be a risk factor for childhood AIS in the VIPS case-control study.[7] We also used previously established definitions for the other predictors of interest: age at the time of index AIS (categorical), lower-and-middle-income (LAMI) country of enrollment (i.e., Philippines, Serbia, China), and markers of socio-economic status (household income, urban/suburban/rural residence, and highest level of maternal education). To compare recurrence-free survival rates between subgroups, we first constructed stratified Kaplan-Meier survival curves and performed log-rank tests. We then used Cox proportional hazards regression techniques to model predictors of recurrent stroke. To construct our multivariable model, we used a univariate p-value cut-off of <0.10, and included age and sex. All analyses were conducted using Stata v13 (Stata Corp., College Station, TX) with alpha set at 0.05.

RESULTS

Of 355 children with AIS, one died within the first week; the 354 survivors were followed for a median of 2.0 years (interquartile range 1.0, 3.0). A total of 278 had at least 12 months of follow-up; 14 died and 63 were lost to follow-up during the first 12 months. Overall, 308 (87% of all cases) were treated with an anti-thrombotic agent after their index stroke diagnosis: 147 received an antiplatelet agent, 98 received anticoagulation (heparin or warfarin), and 63 received both.

Recurrent Stroke

The enrolling sites identified and confirmed recurrent strokes in 42 children; all were AIS (no hemorrhagic stroke). Of the 42 site-confirmed first recurrences, 37 underwent central review and 35 (95%) of those were confirmed (Figure 1). The other five children with site-confirmed stroke did not have DICOM imaging available for central review; however, because the rate of central confirmation of a site-confirmed recurrence was high, we included these as recurrences. Hence, a total of 40 children had a recurrent stroke at a median of 23 days (range 2–372 days) after the index stroke; and six children had more than one recurrence, with a median of three recurrences (range 2, 3). The cumulative rate of first recurrent stroke was 6.8% (95% CI 4.6–10%) at one month and 12% (95% CI 8.5–15%) at one year (Figure 2A). At the time of the first recurrent stroke, 26 of 40 (65%) were receiving an anti-thrombotic agent: 10 were receiving an antiplatelet agent, 13 anticoagulation (heparin or warfarin), and three both. Of the 16 children on anti-coagulation, all but two were considered therapeutic at the time of the recurrence. Of the 13 children on antiplatelet therapy, all but one were on a standard daily dose of aspirin (81 mg in nine, 325 mg in one, and ≈3.5 mg/kg in two smaller children), and one was also on clopidogrel (75 mg). Of the 14 children on no therapy at the time of recurrence, 12 had previously received an anti-thrombotic agent after their index stroke.

Other Outcomes

A total of 27 children had a transient ischemic attack (TIA) after their index AIS, including 11 (28%) of the 40 children with recurrent stroke and 16 (5.1%) of the 315 without recurrent stroke. Hence, a total of 56 children (16% of the cohort of 355) experienced some recurrent ischemic event (stroke or TIA) during the follow-up period. There were a total of 16 deaths: the aforementioned one in the first week after the index stroke, five between one week and one month, and 10 after the first month. Death occurred in four (10%) of the 40 children with recurrent stroke, and 12 (3.8%) of the 315 without recurrent stroke.

Predictors of Recurrent Stroke

In univariate analysis, the only significant predictor of recurrent stroke was definite arteriopathy, which increased the hazard of a recurrence 5-fold compared to idiopathic AIS (Table 1). The cumulative risk of recurrence at one year was 4.5% (95% CI, 1.7–12%) for children with idiopathic stroke (n=90), 8.1% (3.4–18%) for spontaneous cardioembolic stroke (n=65), 12% (4.8–30%) for possible arteriopathy (n=34), and 21% (14–29%) for definite arteriopathy (n=127) (Figure 2B). Among those with definite arteriopathy, the one-year recurrence rate was 32% (18–51%) for moyamoya (n=34), 25% (12–48%) for transient

cerebral arteriopathy (n=25), 19% (8.5–40%) for arterial dissection (n=26), and 6.7% (1.0–39%) for secondary vasculitis (i.e., vasculitis in the setting of infectious meningitis; n=15). (There were no cases of primary vasculitis in VIPS.) Because not all children had follow-up vascular imaging, we could not assess arteriopathy progression as a predictor of recurrence. However, among the 26 children with definite arteriopathy and recurrent stroke, 19 had follow-up vascular imaging; the arteriopathy improved in four, remained stable in three, progressed in six, and progressed and then later improved in six.

Risk factors for childhood AIS identified in the VIPS case-control study—low socioeconomic status, recent infection, and under-vaccination—did not predict risk of recurrent AIS (Table 1). In a multivariable model adjusting for age and sex, definite arteriopathy remained a strong predictor of recurrent stroke (Table 2).

DISCUSSION

In this contemporary international cohort of children with AIS, we found high rates of recurrent stroke, particularly in children with arteriopathies. This occurred despite enrollment at academic centers with pediatric stroke expertise and increased utilization of antithrombotic medications for secondary stroke prevention compared with previously published cohorts. In a retrospective population-based cohort of 97 children with AIS in Northern California (1993–2004), 51% were treated with aspirin or anti-coagulation, and the one-year cumulative recurrence rate was 15% (95% CI, 12–30%).[3] In a single-center British cohort of 212 children with AIS (mixed retrospective and prospective; 1978–2000), 46% were treated with an antithrombotic, and the 5-year cumulative recurrence rate was 18% (95% CI 11–25%).[4] In the VIPS cohort, 87% were treated with an antithrombotic after the baseline stroke, yet the overall 1-year cumulative recurrence rate was 12% (95% CI 8.5–15%). However, of the 40 children who suffered a recurrent stroke, only 65% were on an anti-thrombotic therapy at the time of recurrence. Because VIPS sites are tertiary care centers, the VIPS cohort may include higher risk patients than those included in the population-based Californian study. The British study was set at a more similar tertiary care center (Great Ormand Street Hospital), but did not report the 1-year stroke recurrence rate. These differences preclude direct comparisons between studies; however, there is no clear indication that rates of recurrent childhood AIS are declining.

The VIPS case-control study identified risk factors for childhood AIS, including recent infection, under-vaccination, and low socio-economic status;[7] none of these factors independently affected risk of *recurrent* AIS. The only significant risk factor for recurrence was arteriopathy: one in five children with a definite arteriopathy had a recurrence by 1 year. (The risk for children with “possible” arteriopathy was intermediate between that of the definite and no arteriopathy groups, consistent with that representing a mixed group of children with and without arteriopathy.) Although prior studies of recurrent childhood AIS have varied considerably in their ability to detect and classify arteriopathy (for example, the Californian study reviewed reports of vascular imaging, but not the vascular imaging itself), all have consistently suggested the importance of arteriopathies as the major factor defining recurrent stroke risk in children.[3, 4, 11] One additionally found that *progressive* arteriopathies conferred a particularly high risk;[12] although we could not assess this as a predictor in our

statistical models, 12 of the 19 children with definite arteriopathy, follow-up vascular imaging and recurrent stroke had a progressive arteriopathy. Another study demonstrated that severity of arterial stenosis predicts recurrence.[13]

Childhood arteriopathies are heterogeneous, ranging from genetic disorders, like many of the primary and secondary forms of moyamoya, to acquired arteriopathies, like arterial dissection and vasculitis secondary to meningitis.[9, 14] Transient cerebral arteriopathy (TCA) is a monophasic childhood arteriopathy that affects the intracranial internal carotid artery, and/or its proximal branches, unilaterally.[15, 16] It one of the most common arteriopathies in a previously healthy child with AIS, and conferred a high risk of recurrence in the VIPS cohort, yet its mechanism remains elusive. Reduction in stroke recurrence rates in children depends on a better understanding of all childhood arteriopathies so that secondary stroke prevention strategies can move beyond anti-thrombotic agents towards therapies directed at the arterial pathology itself. For example, studies using advanced techniques for imaging vessel walls suggest that TCA may be inflammatory in etiology,[17] and hence immunosuppressant medications may prove effective at reducing recurrent stroke risk in children with that disease.

Although parental report of clinical infection prior to the index AIS did not affect risk of recurrent stroke in our study, infection may play a role in the pathogenesis of childhood arteriopathies that do themselves confer a high risk of recurrence. Varicella zoster virus (VZV) is a well-established cause of TCA,[18] and recent evidence suggests it may play a role in other arteriopathies, such as giant cell arteritis.[19] TCA continues to occur in children vaccinated for VZV,[7] suggesting other pathogens may contribute to this disease; a better understanding of this relationship is needed before immunosuppression is used for secondary stroke prevention.

Our study also provides important data on the timing of recurrent stroke in children: 75% occurred within the first 12 weeks after the index stroke, and only one occurred beyond a year (at 372 days after the index stroke). Prior studies of recurrent childhood AIS have demonstrated similar findings.[3, 4, 11] This implies that a secondary stroke prevention trial in children would require a relatively short duration of follow-up.

Limitations of this study include loss to follow-up, lack of repeat vascular imaging in all cases, lack of long-term follow-up, and the lack of continuous assessment or validation of the use of antithrombotic medications. Another limitation is the study setting, with children enrolled solely at tertiary care centers; hence, the results may not be generalizable to children who receive stroke care in a community setting. Because of unavailability of DICOM images when some children received care for their recurrent AIS at an outside hospital, we were unable to centrally review and confirm all recurrent strokes; however, the central confirmation rate was high for the site-confirmed recurrences. Predictors related to history of clinical infection and vaccinations were measured through parental report; however, because they were measured at the time of the index stroke, there should not have been recall bias related to the recurrent stroke outcome. Strengths of VIPS are that it is international and prospective, and that the stroke etiologies, particularly arteriopathy, were

carefully classified through central review of clinical and imaging data. It is also the largest study of recurrent stroke in childhood.

CONCLUSIONS

Despite increased treatment with antithrombotic agents compared to cohorts from the 1970s to early 2000s, rates of recurrent stroke in children with AIS remain high, with more than one in ten children suffering a recurrence within one year. Arteriopathy is both common and the strongest risk factor for recurrence, indicating a clear direction for future research aimed at improving secondary stroke prevention in this age group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Dowling, Michael M(University of Texas Southwestern Medical Center, Dallas), Benedict, Susan L (Primary Children's Medical Center, Salt Lake City), Bernard, Timothy J (Denver Children's Hospital), Fox, Christine K (UCSF), DeVeber, Gabrielle A (The Hospital for Sick Children, Toronto), Friedman, Neil R (Cleveland Clinic Children's Hospital), Lo, Warren D (The Ohio State University and Nationwide Children's Hospital, Columbus OH), Ichord, Rebecca N (Children's Hospital of Philadelphia), Tan, Marilyn A (University of the Philippines-Philippine General Hospital, Manila), Mackay, Mark T (Royal Children's Hospital Melbourne), Kirton, Adam (Alberta Children's Hospital), Hernandez-Chavez, Marta I (Pontificia Universidad Catolica de Chile), Humphreys, Peter (Children's Hospital of Eastern Ontario), Jordan, Lori C (Vanderbilt University Medical Center, Nashville), Sultan, Sally (Columbia University Medical Center, New York), Rivkin, Michael J (Boston Children's Hospital), Rafay, Mubeen F (Children's Hospital, Winnipeg, University of Manitoba), Titomanlio, Luigi (L Hôpital Robert Debré-Paris), Kovacevic, Gordana S (Mother and Child Health Care Institute, Serbia), Yager, Jerome Y (Stollery Children's Hospital), Amlie-Lefond, Catherine (Seattle Children's Hospital), Dlamini, Nomazulu (Evelina London Children's Hospital), Condie, John (Phoenix Children's Hospital), Yeh, Ann (Women and Children's Hospital of Buffalo), Kneen, Rachel (Alder Hey Children's Hospital), Bjornson, Bruce (British Columbia Children's Hospital), Pergami, Paola (West Virginia University), Zou, Li Ping (Chinese PLA General Hospital, Beijing), Elbers, Jorina M (Stanford Children’s Health, Palo Alto), Abdalla, Abdalla (Akron Children's Hospital),

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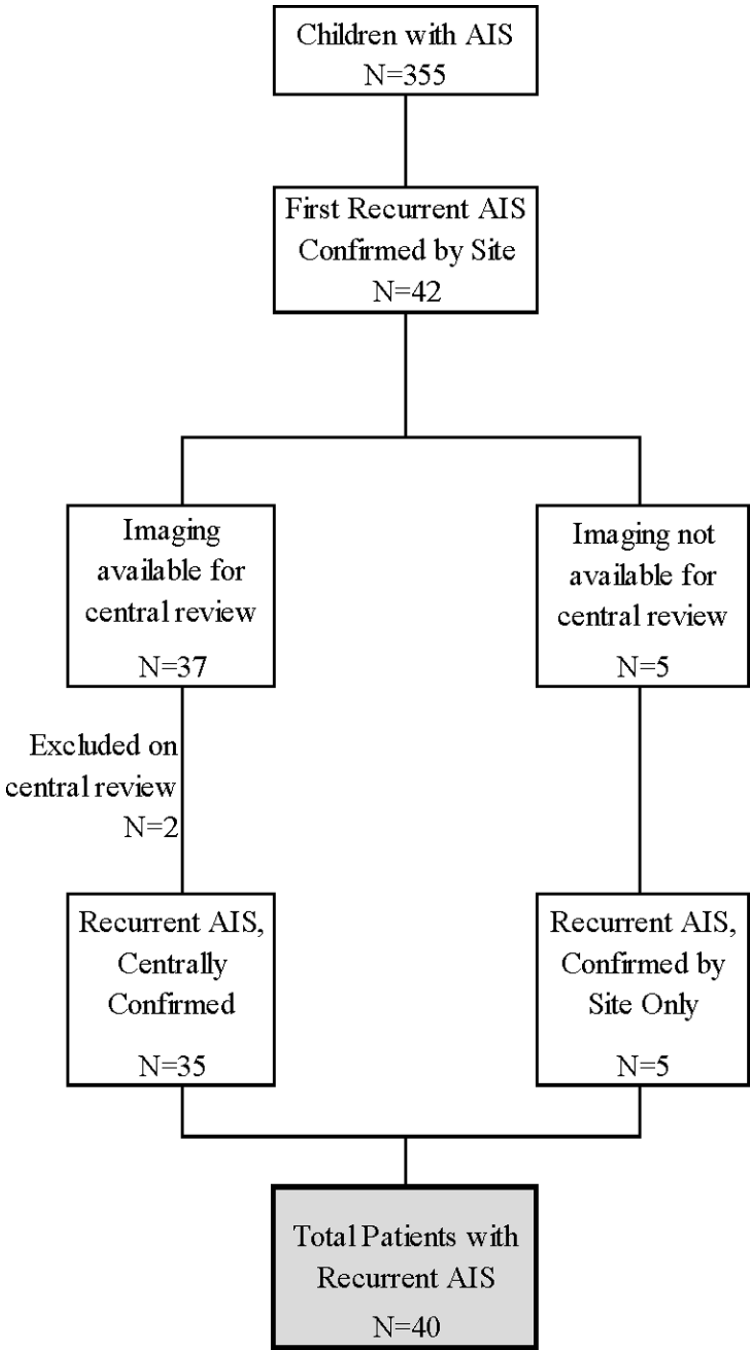
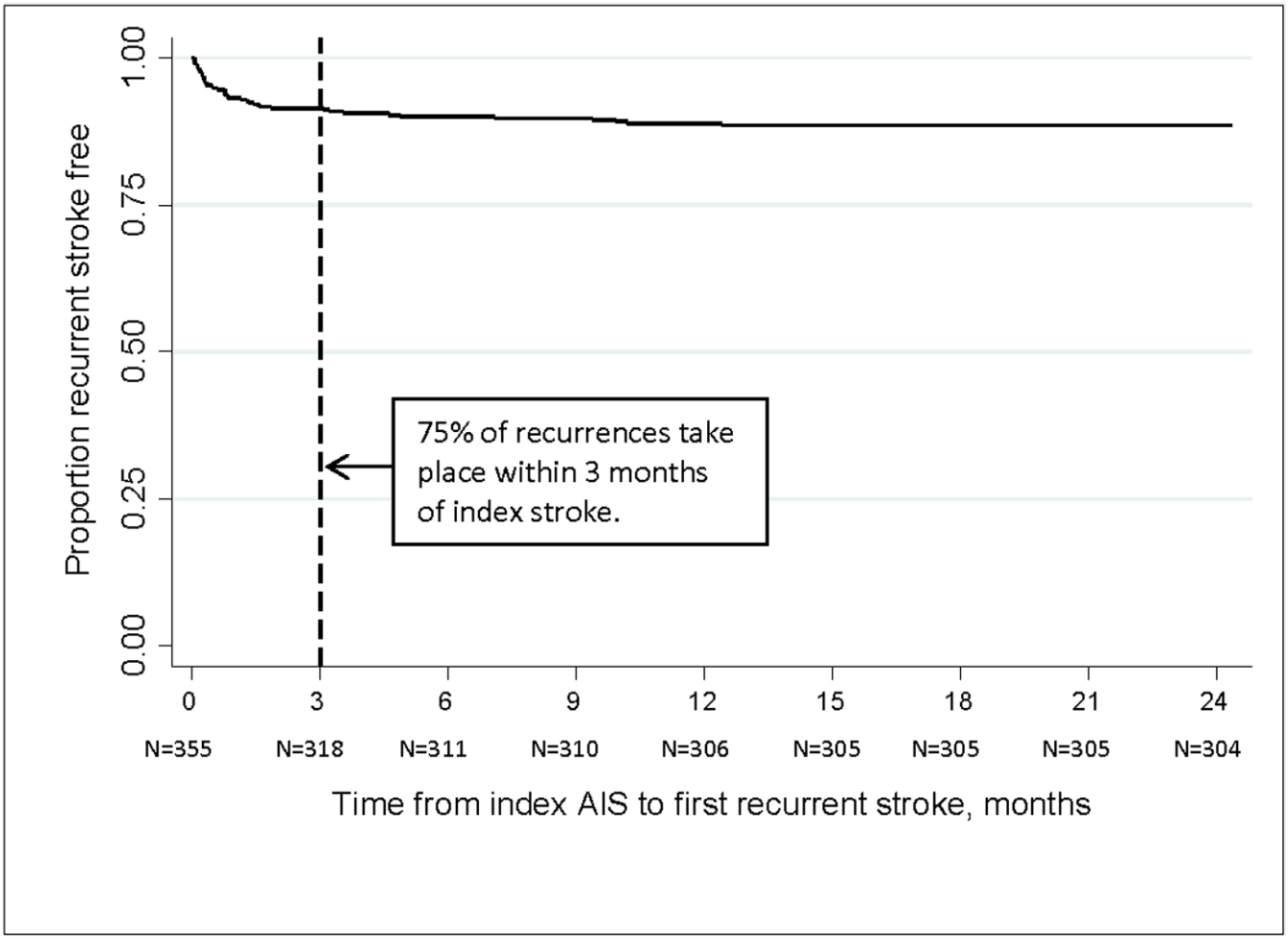


Figure 1.

Flow diagram demonstrating how recurrent strokes were identified and confirmed in the VIPS cohort of 355 children with arterial ischemic stroke (AIS).

A.



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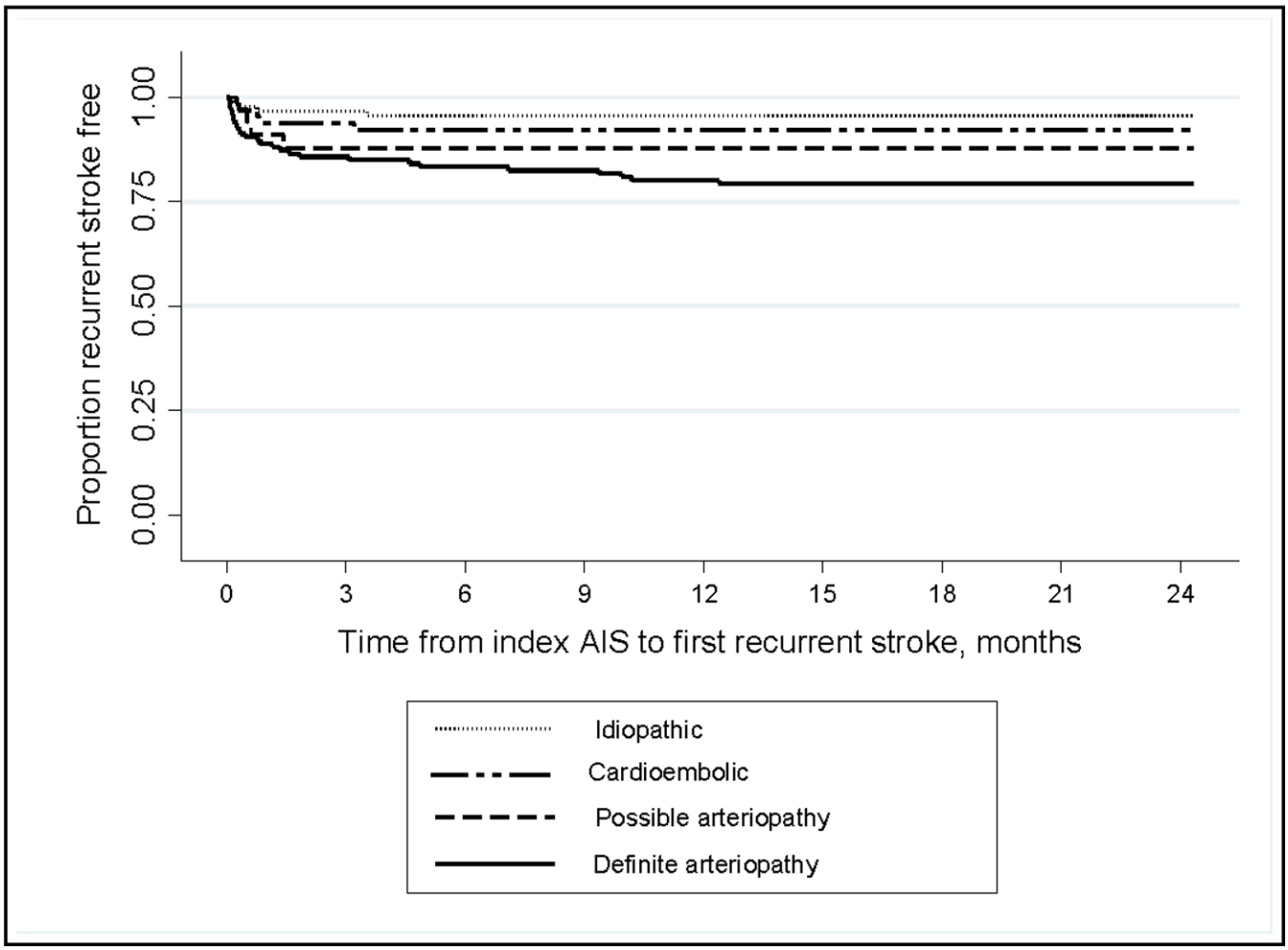

Figure 2.

Kaplan-Meier curves demonstrating recurrent stroke-free survival in (A) all 355 children with AIS, and (B) the same children stratified by stroke subtype.

Table 1

Characteristics of 355 children with arterial ischemic stroke, with versus without recurrent stroke

	Recurrent stroke (N=40)		No recurrent stroke (N=315)				
Characteristic	**n**	**(%)**	**n**	**(%)**	**HR**	**95% CI**	**p-value**
DEMOGRAPHICS							
Age group							
0–3 yrs	10	(25.0)	106	(33.7)	Ref	-	-
4–7 yrs	12	(30.0)	57	(18.1)	2.1	(0.9, 4.9)	0.08
8–11 yrs	6	(15.0)	40	(12.7)	1.6	(0.6, 4.3)	0.38
12–15 yrs	6	(15.0)	67	(21.3)	1.00	(0.4, 2.7)	0.97
16+ yrs	6	(15.0)	45	(14.3)	1.5	(0.6, 4.2)	0.41
Male sex	25	(62.5)	174	(55.2)	1.3	(0.7, 2.4)	0.46
LAMI country	1	(2.5)	24	(7.6)	0.3	(0.1, 2.5)	0.30
Socioeconomic Status							
Residence							
Urban	12	(30.0)	106	(33.7)	Ref	-	-
Suburban	13	(32.5)	140	(44.4)	0.8	(0.4, 1.8)	0.64
Rural	15	(37.5)	67	(21.3)	1.8	(0.8, 3.9)	0.13
Household income (US $)							
<$10,000	1	(2.5)	54	(17.1)	Ref	-	-
$10,000–30,000	6	(15.0)	62	(19.7)	4.9	(0.6, 40.5)	0.14
$31,000–50,000	6	(15.0)	41	(13.0)	7.1	(0.8, 58.6)	0.07
$50,000–100,000	14	(35.0)	76	(24.1)	8.5	(1.1, 65.0)	0.04
>100,000	5	(12.5)	59	(18.7)	4.2	(0.5, 35.9)	0.19
Missing	8	(20.0)	23	(7.3)			
Maternal education, highest level							
Less than high school	6	(15.0)	37	(11.7)	Ref	-	-
High school graduate	9	(22.5)	74	(23.5)	0.7	(0.3, 2.1)	0.58
Some college education	13	(32.5)	96	(30.5)	0.8	(0.3, 2.1)	0.67

Characteristic	Recurrent stroke (N=40) n	(%)	No recurrent stroke (N=315) n	(%)	HR	95% CI	p-value
Bachelor's degree	6	(15.0)	62	(19.7)	0.6	(0.2, 1.9)	0.4
Graduate education	4	(10.0)	34	(10.8)	0.8	(0.2, 2.7)	0.68
Missing	2	(5.0)	12	(3.8)			
STROKE CLASSIFICATION*							
No arteriopathy	10	(25.0)	184	(58.4)			
Idiopathic	4	(10.0)	86	(27.3)	Ref	-	-
Cardioembolic†	5	(12.5)	60	(19.0)	1.8	(0.5, 6.8)	0.37
Other	1	(2.5)	38	(12.1)	0.6	(0.1, 5.1)	0.61
Possible arteriopathy	4	(10.0)	30	(9.5)	2.9	(0.7, 11.6)	0.13
Definite arteriopathy	26	(65.0)	101	(32.1)	5.0	(1.8, 14.4)	0.003
Transient cerebral arteriopathy	6	(15.0)	19	(6.0)	6.3	(1.8, 22.4)	0.004
Arterial dissection	5	(12.5)	21	(6.7)	5.0	(1.3, 18.5)	0.02
Moyamoya	10	(25.0)	24	(7.6)	7.4	(2.3, 23.5)	0.001
Secondary vasculitis	1	(2.5)	14	(4.4)	1.5	(0.2, 13.8)	0.7
Other	4	(10.0)	23	(7.3)	3.3	(0.8, 13.2)	0.09
MARKERS OF INFECTION							
Infection in the week prior to index stroke	6	(15.0)	58	(18.4)	0.8	(0.3, 1.9)	0.59
Poorly vaccinated‡ (some/few/none routine vaccines)	2	(5.1)	25	(8.3)	0.6	(0.2, 2.6)	0.54
TREATMENT							
Antithrombotic treatment after index stroke							
Anti-platelets	15	(37.5)	132	(41.9)	0.98	(0.4, 2.7)	0.98
Anticoagulation	13	(32.5)	85	(27.0)	1.3	(0.5, 3.7)	0.58
Both	7	(17.5)	56	(17.8)	1.1	(0.3, 3.4)	0.91
Neither	5	(12.5)	42	(13.3)	Ref	-	-
Antithrombotic treatment at the time of recurrence							
Anti-platelets	15	(37.5)	-		-		-
Anticoagulation	14	(35.0)	-		-		-

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Characteristic	Recurrent stroke (N=40) n	(%)	No recurrent stroke (N=315) n	(%)	HR	95% CI	p-value
Both	5	(12.5)	-		-		-
Neither	6	(15.0)	-		-		-

HR=hazard ratio (univariate Cox model); CI=confidence interval

*reference group is idiopathic stroke for all HRs shown

†Spontaneous (as opposed to iatrogenic, procedure-related) cardioembolic strokes

‡Excludes any who answered "unknown"; N=39 for recurrent stroke, N=303 for no recurrent stroke

Table 2

Multivariable Cox Proportional Hazards model showing predictors of recurrent stroke among 355 children with arterial ischemic stroke

Characteristic	HR	95% CI	p-value
Age group			
0–3 years	Ref	-	-
4-7 years	1.5	(0.7, 3.6)	0.32
8-11 years	1.4	(0.5, 3.9)	0.52
12–15 years	1.1	(0.4, 3.1)	0.82
16+ years	1.6	(0.6, 4.5)	0.35
Male sex	1.4	(0.7, 2.6)	0.36
Stroke Classification			
No arteriopathy			
Idiopathic	Ref	-	-
Cardioembolic	2.0	(0.5, 7.4)	0.32
Other	0.6	(0.1, 5.7)	0.68
Possible arteriopathy	2.7	(0.7, 11.0)	0.16
Definite arteriopathy	4.9	(1.7, 14.5)	0.004

HR=hazard ratio; CI=confidence interval; Ref=reference