Predictors of Cerebral Arteriopathy in Children With Arterial Ischemic Stroke

Results of the International Pediatric Stroke Study

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Background—Cerebral arteriopathies, including an idiopathic focal cerebral arteriopathy of childhood (FCA), are common in children with arterial ischemic stroke and strongly predictive of recurrence. To better understand these lesions, we measured predictors of arteriopathy within a large international series of children with arterial ischemic stroke.

Methods and Results—Between January 2003 and July 2007, 30 centers within the International Pediatric Stroke Study enrolled 667 children (age, 29 days to 19 years) with arterial ischemic stroke and abstracted clinical and radiographic data. Cerebral arteriopathy and its subtypes were defined using published definitions; FCA was defined as cerebral arterial stenosis not attributed to specific diagnoses such as moyamoya, arterial dissection, vasculitis, or postvaricella angiopathy. We used multivariate logistic regression techniques to determine predictors of arteriopathy and FCA among those subjects who received vascular imaging. Of 667 subjects, 525 had known vascular imaging results, and 53% of those (n=277) had an arteriopathy. The most common arteriopathies were FCA (n=69, 25%), moyamoya (n=61, 22%), and arterial dissection (n=56, 20%). Predictors of arteriopathy include early school age (5 to 9 years), recent upper respiratory infections, and sickle cell disease, whereas prior cardiac disease and sepsis reduced the risk of arteriopathy. The only predictor of FCA was recent upper respiratory infection.

Conclusions—Arteriopathy is prevalent among children with arterial ischemic stroke, particularly those presenting in early school age, and those with a history of sickle cell disease. Recent upper respiratory infection predicted cerebral arteriopathy and FCA in particular, suggesting a possible role for infection in the pathogenesis of these lesions. (Circulation. 2009;119: 1417-1423.)

Key Words: arteriopathy ■ infection ■ pediatrics ■ stroke

Arteriopathy has been increasingly recognized as a prevalent cause of pediatric arterial ischemic stroke (AIS). As many as 64% of previously healthy children with first AIS have a stenosing arteriopathy.1,2 Although some have better-understood arteriopathies such as arterial dissection and moyamoya, many simply have a focal cerebral arterial stenosis with no apparent cause. The International Pediatric Stroke Study (IPSS) group has coined the term focal cerebral arteriopathy of childhood (FCA) to label these cases. Arterial stenosis on neurovascular imaging is significant in that it confers an increased risk of recurrent childhood stroke, as high as 66% within the first 5 years.1,3,4 Hence, understanding the nature and course of these arteriopathies is critical to the development of primary and secondary stroke prevention strategies.

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Prior estimates of the prevalence of arteriopathy range from 18% to 64% of pediatric AIS cases,1,2,4–6 likely reflecting differences in imaging modalities, classification, and study populations. Often, these studies had too few cases to identify predictors of arteriopathy, particularly FCA. We used
data from the IPSS, a large international series of childhood stroke cases, to determine the prevalence and predictors of cerebral arteriopathy and FCA among children with AIS.

Methods

Setting
The IPSS is an international multicenter registry of children with AIS and cerebral sinus venous thrombosis enrolled between January 2003 and July 2007. The IPSS includes 30 enrolling centers in 5 continents (North America, South America, Europe, Asia, and Australia) that have enrolled 1187 children (age, 0 to 19 years) meeting established clinical and radiographic criteria for AIS and/or cerebral sinus venous thrombosis. The IPSS defines perinatal stroke as stroke occurring between 0 and 28 days of age and childhood stroke as stroke occurring between 29 days and 19 years. This analysis excludes both perinatal strokes and cases of cerebral sinus venous thrombosis. The study was approved by institutional review boards at each enrolling center, and subjects gave informed consent.

Case Identification and Confirmation

Potential patients were identified at each IPSS enrolling center in both inpatient and outpatient settings and were enrolled prospectively. Subjects presenting with acute stroke to an outside hospital and subsequently referred to an IPSS center were either transferred or evaluated in clinic as soon as possible. These subjects were then confirmed as stroke cases by the IPSS investigator at that center and were included in the study after informed consent was obtained. Confirmed pediatric AIS was defined by consensus-based, published clinical and radiographic criteria that included neurological deficit of sudden onset and radiographic images (magnetic resonance imaging or computed tomography) showing cerebral parenchymal infarct(s) conforming to known arterial territory(ies) and corresponding to clinical manifestations. We included only those patients with confirmed childhood AIS, excluding transient ischemic attacks without infarction, primary intracerebral hemorrhage, metabolic infarctions, watershed infarctions, and periventricular leukomalacia.

Data Abstraction

Participating centers recorded detailed laboratory data and medical histories from each patient onto standardized IPSS data collection forms, including information about patient demographics (age, gender), stroke origins (including arteriopathy), clinical features at presentation (including the presence of concurrent or preceding illness), radiography, risk factors and comorbidities at presentation (including a description of arteriopathies if present), treatment (antithrombotic, surgical, antibiotic, anticonvulsant), outcome at discharge (normal, death, neurological deficit, and disposition at hospital discharge (home, rehabilitation hospital, other hospital). Race and ethnicity were not on the original data collection form but were added in 2005, so these data were not collected for all subjects. Each subject was given a study number, and deidentified data were collected by the study center in Toronto either by fax or over a secure Web-based data entry system.

Definitions

Vascular imaging was defined as magnetic resonance angiography (MRA; 1.5 T at 73% of centers, 3 T at 27%), computed tomography angiography (CTA), or conventional angiography of the cerebral vessels. Enrolling investigators used the formal clinical interpretation of the imaging and previously published definitions of arteriopathy to classify the results of the vascular imaging into ≥1 categories: normal, occlusion, stenosis, dissection, moyamoya, transient cerebral arteriopathy (TCA), postvaricella arteriopathy, vasculitis, and other. A text box allowed investigators to further specify the “other” diagnosis. Investigators were not asked to specify the vessel(s) involved. Arteriopathy was defined as any abnormality on vascular imaging except isolated vessel occlusion (which may represent an embolus rather than a primary disorder of the blood vessel). Moyamoya included both the primary (idiopathic) form and secondary form (resulting from radiation injury, neurofibromatosis, trisomy 21, etc), except those cases caused by sickle cell disease, which were categorized as sickle cell arteriopathy. For this analysis, we included in the moyamoya category those cases in which the investigator did not specifically indicate moyamoya but entered in the postirradiation vasculopathy text box. Sickle cell arteriopathy was defined as an arteriopathy (as defined above and including moyamoya) in a child with sickle cell disease. FCA was defined as stenosis on vascular imaging not otherwise classified as dissection, moyamoya, sickle cell arteriopathy, postvaricella arteriopathy, vasculitis, or other specific diagnoses (such as postirradiation arteriopathy). FCA included unifocal or multifocal, unilateral or bilateral lesions of the large and/or medium-sized vessels visualized on angiography. TCA is itself a label that does not imply a known origin. In addition, because its definition depends on follow-up imaging, cases that might eventually meet criteria for TCA would initially be classified as stenosis. Hence, we included cases of TCA in our definition of FCA. Recent upper respiratory infection (URI) was defined as parental or patient report of a URI either preceding or contemporaneous with the stroke ictus; a time interval was not specified. Sepsis was defined as a positive blood culture and a clinical diagnosis of sepsis by the treating physician.

Statistical Analysis

We calculated binomial exact CIs of proportions. For comparisons of baseline characteristics, we divided subjects into 3 mutually exclusive groups: (1) arteriopathy, (2) no arteriopathy, and (3) no vascular imaging (either not done or results unknown). We made comparisons across all 3 groups and between those with and without vascular imaging results (ie, groups 1 and 2 versus 3). We used χ² tests to compare proportions and the Kruskal-Wallis statistic (nonparametric) to compare continuous variables that were not normally distributed. We set α at 0.05 for our definition of statistical significance. We used logistic regression techniques to identify predictors of arteriopathy and FCA; odds ratios (ORs) and 95% CIs were calculated. We limited the analyses to those children who had received vascular imaging (and had known vascular imaging results) to avoid confounding by that variable. For example, in some centers, children with congenital heart disease may be less likely to get vascular imaging and hence would be less likely to be diagnosed with an arteriopathy. In our primary analysis, predictors of arteriopathy were first assessed through univariate analyses comparing those children with versus without arteriopathy as defined above. To account for possible confounding, we then used univariate screening with a cutoff of P=0.10 to generate a multivariate model. Predictors that met that cutoff were assessed for colinearity before inclusion in the final model. In our secondary analysis, predictors of FCA were similarly assessed, comparing those children with FCA and those without (either no arteriopathy or a defined arteriopathy). We assessed the same covariates used in the primary analysis except a history of head or neck trauma. This was excluded as a predictor because of likely information bias; enrolling investigators would have been aware of a child’s history of trauma and more likely to classify a vascular abnormality as an arterial dissection rather than FCA because of this history. All statistical analyses were done with Stata 9.0 (Stata Corp, College Station, Tex).

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 676 subjects with childhood (nonneonatal) AIS were enrolled at 30 IPSS centers in 10 countries in Asia (4%), Australia (7%), Europe (11%), North America (Canada, 13%; and United States, 58%), and South America (7%). The majority (59%) were boys. Race data were available for only 94 subjects: 64 white (68%), 23 black (24%), and 7 other ethnicity (7%). Median age at stroke ictus was 5.7 years (range,
31 days to 19 years). Most subjects had anterior circulation (n=517, 78%) and unilateral infarcts (n=477, 72%).

Vascular imaging was performed in 545 subjects, and results of that imaging were known in 525 (the Figure). MRA was the most common imaging modality used (n=490), followed by conventional angiography (n=170) and CTA (n=83). The majority (n=362, 66%) had only a single vascular imaging study (MRA, n=314; conventional angiography, n=29; CTA n=19); 168 (31%) had 2 types of studies (MRA/conventional angiography, n=119; MRA/CTA, n=42; CTA/conventional angiography, n=7); 15 (3%) had all 3 types of studies. Compared with subjects with vascular imaging results (groups 1 and 2), those without results (group 3) tended to be younger and less likely to have presented with a focal deficit (Table 1).

An arteriopathy was identified on vascular imaging in 277 different children or 53% (95% CI, 48 to 57) of those with vascular imaging results. FCA was the most common type of arteriopathy observed, followed by moyamoya (Table 2). An additional 7 children were diagnosed with an arteriopathy based on magnetic resonance imaging alone (without vascular imaging): 5 with moyamoya, 1 with FCA, and 1 with arterial dissection. These 7 children were not included in the analyses below.

Table 1. Baseline Characteristics of 676 Children With AIS Enrolled in the IPSS Stratified Into 3 Mutually Exclusive Groups: Arteriopathy, No Arteriopathy, and No Vascular Imaging

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Group 1, Arteriopathy, n/Total (%)‡</th>
<th>Group 2, No Arteriopathy, n/Total (%)‡</th>
<th>Group 3, No Vascular Imaging,† n/Total (%)‡</th>
<th>P, All Groups§</th>
<th>P, Groups 1 and 2 vs 3§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>157/277 (57)</td>
<td>155/248 (63)</td>
<td>87/151 (58)</td>
<td>0.369</td>
</tr>
<tr>
<td></td>
<td>Age, median (IQR), y</td>
<td>7.2 (3.5–12)</td>
<td>5.2 (1.3–12)</td>
<td>2.4 (0.70–11)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presentation</td>
<td>Focal deficit</td>
<td>252/277 (91)</td>
<td>199/248 (80)</td>
<td>45/151 (30)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>59/262 (23)</td>
<td>81/232 (35)</td>
<td>48/149 (32)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>97/221 (44)</td>
<td>69/167 (41)</td>
<td>19/77 (25)</td>
<td>0.011</td>
</tr>
<tr>
<td>Stroke location</td>
<td>Anterior circulation</td>
<td>199/273 (73)</td>
<td>152/245 (62)</td>
<td>94/142 (66)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Posterior circulation</td>
<td>55/273 (20)</td>
<td>65/245 (27)</td>
<td>23/142 (16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>19/273 (7)</td>
<td>28/245 (11)</td>
<td>25/142 (18)</td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
*Unless otherwise indicated.
†Cases with no vascular imaging (n=131) or results of vascular imaging were unknown (n=20).
‡Based on χ² tests for categorical variables and Kruskal-Wallis statistic for continuous data.
§Comparison of those with vascular imaging (groups 1 and 2) to those without (group 3).
Predictors of Arteriopathy

The 525 children with AIS and vascular imaging results were included in this analysis. In the univariate analysis of predictors of arteriopathy, the predictor with the largest OR was sickle cell disease (OR, 4.0; Table 3). Other predictors positively correlated with arteriopathy included early school age (5 to 9 years) and recent URI. Variables associated with a reduced risk of arteriopathy, on the other hand, included past medical history of cardiac disease, concurrent sepsis, and concurrent meningitis.

In the multivariate model (Table 4), sickle cell disease remained the predictor with the largest OR (OR, 3.1). Early school age and recent URI also were predictors, whereas children with prior history of cardiac disease and sepsis had significantly lower odds of arteriopathy. When subjects with

<table>
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<tr>
<th>Table 2. Arteriopathy Subtypes Among 277 Children With AIS and Arteriopathy Diagnosed on Vascular Imaging</th>
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<tbody>
<tr>
<td>Arteriopathy</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>FCA*</td>
</tr>
<tr>
<td>Moyamoya (primary or secondary)†‡</td>
</tr>
<tr>
<td>Arterial dissection‡</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Sickle cell disease arteriopathy</td>
</tr>
<tr>
<td>Postvaricella angiopathy</td>
</tr>
<tr>
<td>Other§</td>
</tr>
<tr>
<td>Unspecified vasculopathy</td>
</tr>
</tbody>
</table>

*Includes TCA (n=11).
†Excludes children with sickle cell disease.
‡One subject with moyamoya and dissection.
§Fibromuscular dysplasia (n=2), atherosclerosis (n=1), vessel hypoplasia (n=2), HIV vasculopathy (n=1), Sturge Weber (n=1), Susac syndrome (n=1), penetrating trauma (n=1), and cervical artery ligation (n=1).

<table>
<thead>
<tr>
<th>Table 3. Univariate Predictors of Arteriopathy in a Series of 525 Children With AIS and Vascular Imaging Enrolled in the IPSS</th>
</tr>
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<tbody>
<tr>
<td>Arteriopathy, n/Total (%)</td>
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<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age group</td>
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<tr>
<td>29 d–4 y</td>
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<tr>
<td>5–9 y</td>
</tr>
<tr>
<td>10–14 y</td>
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<tr>
<td>15–19 y</td>
</tr>
<tr>
<td>Race, maternal</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Past medical history</td>
</tr>
<tr>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
</tr>
<tr>
<td>Recent infection</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Fever without sepsis</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>URI*</td>
</tr>
<tr>
<td>Head or neck trauma</td>
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</tbody>
</table>

*Includes sinusitis and otitis media.
sickle cell disease were removed from the analysis, the model was essentially unchanged (data not shown).

**Predictors of FCA**

In the secondary analysis, we compared the 69 children with FCA and the 456 without FCA (either no arteriopathy or a defined arteriopathy). The only significant univariate predictor of FCA was recent URI (OR, 2.81; 95% CI, 1.28 to 6.12; \( P = 0.003 \)). There was a trend toward an association with early school age (5 to 9 years compared with 28 days to 4 years; OR, 1.74; 95% CI, 0.94 to 3.23; \( P = 0.079 \)). Gender and race; prior history of cardiac disease, systemic lupus erythematosus, and hematologic malignancy; and recent fever, sepsis, and meningitis were not associated with FCA (data not shown). In the multivariate model, including only age group and recent URI, recent URI remained the only predictor of FCA (OR, 2.82; 95% CI, 1.29 to 6.22; \( P = 0.010 \)), whereas there was again a trend toward an association for early school age (1.76; 95% CI, 0.94 to 3.30; \( P = 0.076 \)).

**Discussion**

Within a large international series of children with AIS, we found that arteriopathy is common, occurring in more than half of children who underwent vascular imaging, and that FCA was the most common subtype of arteriopathy observed. Sickle cell disease, early school age, and recent URI were predictors of arteriopathy in general, whereas recent URI was the only predictor of FCA.

Although the association of arteriopathy and stroke in children has been recognized for decades, recent advances in noninvasive neuroimaging have led to the revelation that arteriopathy is a common cause of childhood AIS. We identified an arteriopathy in 53% (95% CI, 48 to 57) of children with AIS who received vascular imaging. Other recent studies have described variables rates of arteriopathy, ranging from as low as 18% (calculated 95% CI, 14 to 23) in a German study to as high as 63% (calculated 95% CI, 56 to 70) in a British study (after exclusion of their occlusion for consistency with our definition of arteriopathy). The lower German rate in a nationwide population-based cohort study may reflect the absence of a referral bias, which could have led to the selection of more severe cases in the British hospital series. However, a nonconcurrent population-based cohort study from California reported arteriopathy in 42% (calculated 95% CI, 29 to 57) of childhood AIS cases.

Our registry study is the first of these childhood AIS studies to attempt to identify predictors of arteriopathy. Not surprisingly, sickle cell disease was associated with arteriopathy, with an adjusted OR of 3.1. More than 10% of patients with sickle cell disease (not receiving primary stroke prevention therapy) will have a clinically overt stroke by 20 years of age. These children typically have a moyamoya-like arteriopathy involving the distal internal carotid arteries and proximal anterior and middle cerebral arteries, with relative sparing of the posterior circulation. This arteriopathy is histologically characterized by intimal hyperplasia and likely caused by multiple pathogenic mechanisms.

Although an association with sickle cell disease was expected, our observed associations with infection are novel: Recent URI was a significant predictor of underlying arteriopathy, whereas children with sepsis were less likely to have an arteriopathy. An association between infection and AIS has been described in adult case-control studies and in a single small pediatric case-control study (OR, 4.0; 95% CI, 1.2 to 15 for the association between AIS and parental report of an infection within 1 month). Infection could contribute to stroke by promoting systemic procoagulant effects and local inflammation (or even direct pathogen invasion) of cervical or cerebral blood vessels. The pathogenesis of stroke in the setting of sepsis may be related primarily to the systemic procoagulant mechanism, which would explain the lack of association between sepsis and arteriopathy in our study. In children with recent URI, on the other hand, the vascular injury mechanism also may be at play. Prior reports have described focal arteriopathies in children with viruses, including varicella, herpes simplex virus type 1, Epstein-Barr virus, and enterovirus. In the adult atherosclerosis literature, the concept of an infectious burden has been proposed whereby the cumulative inflammatory effects of multiple infections over time lead to vascular injury. This concept is a compelling potential explanation for arteriopathy in children, who suffer frequent minor infections yet rarely suffer strokes. Elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) and recent infection have been associated with vascular pathology in children, lending indirect support to this hypothesis.

In our series, early school age (5 to 9 years) also was positively correlated with arteriopathy, but the reason is unclear. It is a predictor even after adjustment for recent URI, suggesting that recent infection is not the explanation for this finding. However, children in this age group could have a greater infectious burden, suffering more frequent infections. Furthermore, although the varicella vaccine has markedly reduced the incidence of varicella infection, children 5 to 9 years of age continue to have the highest incidence. In the absence of specific virological testing, varicella zoster virus may go unrecognized as the cause of the arteriopathy.

We found that children with a history of cardiac disease were significantly less likely to have an arteriopathy compared with noncardiac patients. Because our analysis included only subjects who received vascular imaging, this finding cannot be explained by lower rates of vascular imaging in cardiac patients. Instead, it likely reflects a cardioembolic, as opposed to vascular, stroke origin in the majority of these children. Although it may appear obvious, it is important to note that cerebrovascular abnormalities may coexist with structural congenital heart disease. Cervical or cerebral arteriopathy has been reported in association with cardiac anomalies in Alagille syndrome, PHACES syndrome, Noonan syndrome, and trisomy 21. Idiopathic structural congenital heart disease also has been associated with arterial dissection and moyamoya syndrome. In our study, one third (45 of 135) of children with a prior history of cardiac disease were found to have an associated arteriopathy, suggesting that vascular imaging is still indicated in such children.

FCA was the most common form of arteriopathy in this series, accounting for one quarter of arteriopathy cases. Other studies have reported a similar proportion of unexplained focal arterial stenosis in children with AIS and have
applied various labels to this entity. Probably the most widely used label is TCA, although serial vascular imaging (demonstrating nonprogression after 6 months) is required to make this diagnosis. The term transient is applied because the arteriopathy is monophasic, meaning that it neither progressed nor recurred after the initial 6 months; however, the arterial stenosis often persists. TCA is alternately called postvaricella angiopathy if there is a history of varicella infection in the prior 12 months. In the pediatric rheumatology literature, unifocal or multifocal symptomatic cerebral arterial stenosis not attributable to other causes has been labeled primary nonprogressive central nervous system vasculitis in children. Except for post-varicella zoster virus arteriopathy, these labels are provisional diagnoses that do not specify an underlying pathophysiology. IPSS investigators coined the term FCA as a descriptive label that could be applied at baseline (unlike TCA) and did not imply an underlying mechanism (unlike vasculitis). The cause of FCA remains unknown. Indeed, FCA may represent the end result of a variety of underlying pathological mechanisms producing the same angiographic appearance, including inflammation, infection, and trauma (arterial dissection). In our multivariate model, the only predictor of FCA was recent URI, suggesting that other viral infections, in addition to varicella zoster virus, may be involved in the pathogenesis of these lesions. However, trauma may also predispose to FCA but could not be assessed in this study.

There were significant limitations to this registry study. Not all children received vascular imaging, and those who did not differed in both age and presentation from those who did. It is difficult to predict whether and in which direction complete vascular imaging results could have altered the observed associations. The lack of centralized imaging review could lead to misclassification of arteriopathy and arteriopathy subtypes. This was compounded by the variability in diagnostic vascular imaging techniques used (MRA, CTA, and/or conventional angiography) with their different sensitivities and specificities for arteriopathy. Cases of arterial dissection, in particular, may have been misclassified as FCA in the absence of specific features of dissection (such as an intimal flap), whereas cases of FCA may have been misclassified as dissection if a history of recent trauma was elicited. Detailed data regarding vascular abnormalities (eg, location, characteristics, number of lesions) were not collected. The study was not population-based; our results may be subject to both referral bias and volunteer bias. Our study included children presenting to enrolling centers in a delayed fashion. Although investigators may have relied more on secondary data (eg, imaging reports rather than primary images) in such cases, we could not assess the effects of this limitation because we did not collect data on the timing from stroke ictus to patient enrollment. Finally, measurement of predictors was based on chart review and/or parental report, not on a formal questionnaire; hence, the rates of recent URI are likely underestimates, and the timing of these infections is unknown.

Despite these limitations, the large sample size of this study allows a first assessment of predictors of arteriopathy, particularly FCA, in children with AIS. Although referral and volunteer biases may affect our estimates of the prevalence of arteriopathy and FCA, these biases are likely nondifferential (equal for children with and without arteriopathy) and therefore unlikely to affect the associations that we observed. For example, we would not expect the association between recent URI and arteriopathy to be biased because there should be equal underreporting for those with and without arteriopathy. Furthermore, although the time interval for recent URI was not explicitly defined, it is unlikely that it would have been differentially interpreted by parents of cases with versus without arteriopathy.

**Conclusions**

Arteriopathy is common in children with AIS and is associated with early school age, sickle cell disease, and recent URI. Although it may represent the end point of a variety of pathogenetic mechanisms, FCA is the most common type of arteriopathy observed and is associated with recent URI. Further studies are needed to explore this relationship between infection and arteriopathy in children, including questions regarding timing, specific infectious agents, inflammatory mediators, and cumulative effects of infections over time. Because recent data suggest that arteriopathy is the strongest predictor of recurrent childhood stroke, a better understanding of the infectious and inflammatory mediators of the vascular injury pathway is critical for the development of rational strategies for secondary stroke prevention in children.

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**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

Cerebral arteriopathy has been increasingly recognized as a prevalent cause of pediatric acute ischemic stroke. However, the pathophysiology of cerebral arteriopathy in childhood is not well understood. Estimates of prevalence range from 18% to 64% and likely reflect differences in imaging modalities and classification. In addition, although sickle cell disease and varicella zoster virus are well associated with vasculopathy, the cause of cerebral vasculopathy in childhood is often unknown. Within a large international series of children with arterial ischemic stroke, we found that over half had cerebral arteriopathy. Focal cerebral arteriopathy was the most common subtype of arteriopathy observed. Sickle cell disease, early school age, and recent upper respiratory infection were predictors of arteriopathy in general, and recent upper respiratory infection was a predictor of focal cerebral arteriopathy. Because recent data suggest that arteriopathy is the strongest predictor of recurrent childhood stroke, this report underscores the importance of careful cerebrovascular imaging. It also emphasizes that understanding of the infectious and inflammatory mediators of vascular injury is critical to the development of secondary stroke prevention strategies in childhood arterial ischemic stroke.
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SUPPLEMENTAL MATERIAL

Appendix

International Pediatric Stroke Study Group

Original Investigators:

1. Steve Ashwal MD, Loma Linda University School of Medicine, Loma Linda, California, USA.
2. Gabrielle deVeber MD MHSc, The Hospital for Sick Children, Toronto, Ontario, Canada.
3. Donna Ferriero MD, University of California, San Francisco, California, USA.
4. Heather Fullerton MD, University of California, San Francisco, California, USA.
5. Rebecca Ichord MD, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.
7. John K. Lynch DO MPH, National Institute of Health/ National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA.
8. Finbar O’Callaghan MBChB, Bristol Royal Hospital for Children, Bristol, UK.
9. Steve Pavlakis MD, Maimonides Medical Center, Brooklyn, New York, USA.
10. Guillaume Sebire MD PhD, Université de Sherbrooke Fleurimont, Sherbrooke, Québec, Canada.
11. Andrew Willan BA MSc PhD, Hospital for Sick Children, Toronto, Ontario, Canada.
Institutions enrolling at least 20 patients (bolded numbers indicate patients enrolled):

1. The Hospital for Sick Children, Toronto, Ontario, Canada, (147), Gabrielle deVeber MD MHSc, Andrew Willan BA MSc PhD, Adam Kirton MD, Mahendra Moharir MD, Rand Askalan MD PhD, Marianne Sofronas MA.

2. Münster University Paediatric Hospital, Münster, Germany, (122), Ulrike Nowak-Göttl MD, Christine Düring MD, Anne Krümpel MD.

3. University of Texas Southwestern Medical Center, Dallas, Texas, USA, (94), Michael M. Dowling MD PhD, Patricia Plumb RN MSN, Janna Journeycake MD, Katrina van de Bruinhorst MA.

4. Ohio Stroke Registry, (94), Akron Children's Hospital, Akron, Ohio, USA, Abdalla Abdalla MD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, Tonya Phillips MD, Cleveland Clinic, Cleveland, Ohio, USA, Neil Friedman MD, MetroHealth Medical Center, Cleveland, Ohio, USA, Elie Rizkallah MD, Nationwide Children's Hospital, Columbus, Ohio, USA, Warren Lo MD, Khaled Zamel MD, Rainbow Babies and Children’s Hospital, Cleveland, Ohio, USA, Max Wiznitzer MD, Karen Lidsky MD.

5. Pontificia Universidad Catolica de Chile, Santiago, Chile, (78), Marta Isabel Hernandez Chavez MD.

6. Royal Children’s Hospital, Melbourne, Victoria, Australia, (75), Professor Paul Monagle, Mark MacKay MD, Chris Barnes MD, Janine Furmedge RN BSc, Anne Gordon MSc BAppSc.

7. The University of Utah and Primary Children's Medical Center, Salt Lake City, Utah, USA, (70), Susan L. Benedict MD, James F. Bale Jr. MD.
8. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, (63), Rebecca Ichord MD, Daniel Licht MD, Sabrina Smith MD.

9. Loma Linda University School of Medicine, Loma Linda, California, USA, (54), Steve Ashwal MD, Chalmer McClure MD PhD.

10. Schneider Children's Hospital, New Hyde Park, New York, USA, (46), Li Kan MD MS, Robin Smith MD, Joseph Maytal MD, Rosemarie Sy-Kho MD.


12. University of California San Francisco, San Francisco, California, USA, (37), Donna Ferriero MD, Heather Fullerton MD.

13. Maimonides Medical Center, Brooklyn, New York, USA, (26), Steve Pavlakis MD, Sharon Goodman PNP, Kim Levinson PNP

14. Riley Hospital, Indianapolis, Indiana, USA, (26), Meredith Golomb MD MSc.

15. Winnipeg Children’s Hospital, Winnipeg, Manitoba, Canada, (24), Mubeen Rafay MB.BS, MSc, Frances Booth, MD, Michael Salman MD, Charuta Joshi MD, Namrata Shah MD, Monica Nash RN.

16. Children’s Hospital of New York, New York, New York, USA, (22), Geoffrey Heyer MD.

17. Great Ormond Street Hospital, London, United Kingdom, (21), Vijeya Ganesan MBChB MD.

18. Stollery Children’s Hospital, Edmonton, Alberta, Canada, (21), Jerome Y. Jager MD

19. Paediatric Institute Hospital, Kuala Lumpur, Malaysia, (20), Hussain Imam MBBS FRCP DCH
Institutions enrolling less than 20 patients:

1. Bangkok Hospital Medical Center, Bangkok, Thailand, Montri Saengpatrachai MD.
2. British Columbia Children’s Hospital, Vancouver, British Columbia, Canada, Bruce Bjornson MD.
3. Children’s Central Hospital, Tbilisi, Georgia, Nana Tatishvili MD.
4. Children’s Hospital of Buffalo, Buffalo, New York, USA, E. Ann Yeh MD.
5. Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada, Peter Humpheries MD.
6. Children’s Hospital of Wisconsin, Milwaukee, Wisconsin, USA, Catherine Amlie-Lefond MD, Harry T. Whelan MD.
7. Denver Children’s Hospital, Denver, Colorado, USA, Timothy Bernard MD, Neil Goldenberg MD.
8. Hospital Dr. Sotero del Rio, Puente Alto, Chile, Manuel Arriaza Ortiz MD.
9. McMaster University Medical Centre, Hamilton, Ontario, Canada, Anthony Chan MBBS.
10. Miami Children's Hospital, Miami, Florida, USA, Marcel Deray MD, Zaid Khatib MD.
11. Queen Mary Hospital, Hong Kong, China, Virginia Wong MD.
12. Université de Sherbrooke Fleurimont, Sherbrooke, Quebec, Canada, Guillaume Sebire MD PhD.
13. University of Rochester Medical Center, Rochester, New York, USA, Jill M. Cholette MD, Shalu Narang MD, Norma B. Lerner MD MPH.