Arteriopathy Diagnosis in Childhood Arterial Ischemic Stroke

Results of the Vascular Effects of Infection in Pediatric Stroke Study

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Background and Purpose—Although arteriopathies are the most common cause of childhood arterial ischemic stroke, and the strongest predictor of recurrent stroke, they are difficult to diagnose. We studied the role of clinical data and follow-up imaging in diagnosing cerebral and cervical arteriopathy in children with arterial ischemic stroke.

Methods—Vascular effects of infection in pediatric stroke, an international prospective study, enrolled 355 cases of arterial ischemic stroke (age, 29 days to 18 years) at 39 centers. A neuroradiologist and stroke neurologist independently reviewed vascular imaging of the brain (mandatory for inclusion) and neck to establish a diagnosis of arteriopathy (definite, possible, or absent) in 3 steps: (1) baseline imaging alone; (2) plus clinical data; (3) plus follow-up imaging. A 4-person committee, including a second neuroradiologist and stroke neurologist, adjudicated disagreements. Using the final diagnosis as the gold standard, we calculated the sensitivity and specificity of each step.

Results—Cases were aged median 7.6 years (interquartile range, 2.8–14 years); 56% boys. The majority (52%) was previously healthy; 41% had follow-up vascular imaging. Only 56 (16%) required adjudication. The gold standard diagnosis was definite arteriopathy in 127 (36%), possible in 34 (9.6%), and absent in 194 (55%). Sensitivity was 79% at step 1, 90% at step 2, and 94% at step 3; specificity was high throughout (99%, 100%, and 100%), as was agreement between reviewers (κ=0.77, 0.81, and 0.78).

Conclusions—Clinical data and follow-up imaging help, yet uncertainty in the diagnosis of childhood arteriopathy remains. This presents a challenge to better understanding the mechanisms underlying these arteriopathies and designing strategies for prevention of childhood arterial ischemic stroke. *(Stroke. 2014;45:00-00.)*

Key Words: cerebral arterial diseases • pediatrics • stroke • transient ischemic attack

Stroke is among the top 10 causes of death in childhood.1 Population-based estimates of the annual incidence of childhood stroke range from 4.6 to 13 per 100,000 children.2–4 Traditional adult arterial ischemic stroke (AIS) risk factors, such as hypertension, diabetes mellitus, smoking, and hypercholesterolemia, are uncommon in children. Instead, pediatric AIS risk factors include arteriopathy, congenital heart disease, sickle cell disease, and hematologic abnormalities, among others.5–7 Childhood arteriopathies are increasingly recognized as a prevalent cause of childhood AIS, a strong predictor of recurrence and a predictor of poor short-term outcome.8–11 Prior estimates of the prevalence of arteriopathy range from 18% to 64% of pediatric AIS cases.8,12–15 This wide range likely reflects differences in imaging modalities, classification, and
study populations, but primarily the fact that childhood arteriopathies are difficult to diagnose. Challenges to diagnosis include lack of standardized diagnostic criteria, technical limitations of imaging studies, reliance on magnetic resonance angiography (MRA) over conventional angiography, and heterogeneity of childhood arteriopathies.

In the prospective, international, National Institutes of Health–funded Vascular Effects of Infection in Pediatric Stroke (VIPS) study, we enrolled 355 cases of childhood AIS and collected extensive clinical data and imaging studies for central review by study investigators. We sought to determine the role of clinical data, and baseline and follow-up imaging, in diagnosing the presence of childhood arteriopathy.

**Material and Methods**

**Study Design**
The VIPS study was built on the existing infrastructure of the International Pediatric Stroke Study (IPSS). VIPS prospectively enrolled patients at 37 sites: 21 in the United States, 6 in Canada, 5 in Europe (United Kingdom, France, and Serbia), 3 in Asia (Philippines, China, and Hong Kong), and 1 each in Australia and South America (Chile). Ethics committee approvals were obtained at all participating sites. Details of VIPS Methods have been published. Criteria for site participation included MRI scanner with minimum magnet strength of 1.5 Tesla, MRI slice thickness of ≤5 mm, and ability to provide DICOM (Digital Imaging and Communications in Medicine) imaging data. With parental or guardians’ consent, sites enrolled pediatric patients aged 29 days through 18 years with AIS and collected extensive clinical histories, biological samples, and standardized brain and cerebrovascular imaging studies. All imaging was performed on a clinical basis. VIPS cases were initially confirmed by the local investigator using clinical and imaging diagnostic criteria for AIS: (1) a focal neurological deficit of acute onset or a seizure; and (2) a computed tomography or MRI showing a focal brain infarct conforming to an established arterial territory in a location and of a maturity consistent with the neurological signs and symptoms. The clinical and imaging data were then subjected to a centralized review and case confirmation process, described below.

**Brain and Vascular Imaging**
All clinically obtained brain and vascular imaging were collected for central review. The minimum neuroimaging protocol for patient inclusion in VIPS consisted of the following brain MRI sequences: axial diffusion-weighted images, axial T2-weighted images, axial or coronal fluid-attenuated inversion recovery images, and MRA of the brain. Conventional angiography and computed tomography angiography were also accepted in lieu of MRA. MRA of the neck was collected when performed. Participants were followed up prospectively for a minimum of 1 year, and all follow-up imaging was collected during that time.

**Case Confirmation**
A study neuroradiologist (M.W.) and pediatric stroke neurologist (H.J.F.) centrally reviewed baseline brain MRI scans and clinical data to confirm that each case met clinical and imaging criteria for AIS. Disagreements were resolved by a second neuroradiologist (A.J.B.).

**Initial Descriptive Imaging Review**
Descriptive imaging review was performed centrally by 2 study neuroradiologists; disagreements were resolved by discussion including a third neuroradiologist. In their review of brain parenchymal imaging, the radiologists described infarct size (using ABC/2), location, acuity, and associated hemorrhage. For the vascular imaging review (Figure 1), the neuroradiologists initially classified the vascular imaging as normal or abnormal, and then completely described the vascular findings, including type of abnormality (hypoplasia, irregularity, banding, stenosis, intimal flap, mural hematoma, ectasia, fusiform aneurysm, pseudoaneurysm, and occlusion), vascular segments affected, and degree of collateral flow. This was done for both baseline and all follow-up vascular imaging.

**Arteriopathy Review and Classification**
Images from VIPS patients showing vascular abnormalities during the initial vascular imaging review underwent a subsequent arteriopathy review process (Figure 1) that incorporated clinical data. A pediatric stroke neurologist (H.J.F.) and neuroradiologist (M.W.) independently performed this review in 3 successive steps: step 1, review of baseline imaging studies (and their centralized interpretation); step 2, re-evaluation with addition of clinical information; step 3, reevaluation with addition of follow-up imaging when available.

At each step, the reviewers classified the primary diagnosis: no arteriopathy, possible arteriopathy, or definite arteriopathy. Arteriopathy was defined as the imaging appearance of an in situ arterial abnormality (stenosis, irregularity, occlusion, banding, pseudoaneurysm, dissection flap) not attributable to an exogenous thrombus (eg, cardioembolism) and not considered a normal developmental variant. Patients with an isolated arterial occlusion could be classified as having no arteriopathy (high certainty of occlusion because of thrombus), possible arteriopathy (cause of occlusion unclear), or definite arteriopathy (high certainty of occlusion because of arteriopathy). We used features of both vascular and parenchymal imaging and clinical history (in steps 2 and 3) to distinguish between an occlusion because of arteriopathy versus an occlusion because of thrombus. Features favoring thrombus (no arteriopathy) included the following: abrupt (as opposed to tapering) vessel occlusion, multiple arterial occlusions in a vascular tree (suggestive of an embolus that fragmented and resulted in multiple occlusions), multiple infarcts in a pattern suggestive of cardioembolism, clinical history suggesting high risk of cardioembolism (eg, cardiac thrombus visualized on echocardiogram), and rapid resolution of occlusion on follow-up imaging. Features favoring arteriopathy included a pattern of vascular changes suggestive of moyamoya (distal internal carotid artery occlusion with lenticulostriate collaterals), clinical history of a disorder associated with moyamoya (eg, sickle cell disease, trisomy 21), and changes suggestive of
dissection (eg, dissection flap or tapering occlusion), especially with a history of severe head or neck injury. If the cause of the occlusion was unclear, the reviewers classified these as possible arteriopathy. At each step, for patients with possible and definite arteriopathies, the reviewers also attempted to establish a secondary diagnosis by classifying the arteriopathies into subtypes: arterial dissection, transient cerebral arteriopathy (TCA), primary and secondary moyamoya, genetic or syndromic arteriopathies, such as PHACE (posterior fossa brain malformations, hemangiomas of the face [large or complex], arterial anomalies, cardiac anomalies, and eye abnormalities) syndrome,18,19 primary and secondary vasculitis, fibromuscular dysplasia, iatrogenic, and others. If a single diagnosis could not be made with high certainty, they created a differential diagnosis. The reviewers used pre-established definitions for childhood arteriopathies.20 TCA referred specifically to a focal cerebral arteriopathy involving the distal internal carotid artery and its proximal branches, presumed inflammatory, with a stereotyped, monophasic natural history characterized by frequent early progression (for days to weeks), plateau with nonprogression by 6 months, and subsequent improvement in some with complete resolution in a minority.20,21 Focal cerebral arteriopathy of childhood is a broader label coined to describe intracranial anterior circulation pathology in children at the time of AIS, when TCA may be suspected but cannot be diagnosed with certainty because of lack of follow-up imaging.8 Focal cerebral arteriopathy of childhood has its own differential diagnosis (including TCA and intracranial dissection); hence, we did not include it as an option for secondary diagnosis.

At any step, if the reviewers disagreed on the primary diagnosis, or had no overlap in their differentials for the secondary diagnosis,

Table 1. Demographics and Clinical Characteristics of 355 Childhood Arterial Ischemic Stroke Cases

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median (interquartile range), y</strong></td>
<td>7.6 (2.8, 14.3)</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td>199 (56.1)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>230 (64.8)</td>
</tr>
<tr>
<td>Black</td>
<td>39 (11.0)</td>
</tr>
<tr>
<td>Indian/South Asian</td>
<td>26 (7.3)</td>
</tr>
<tr>
<td>East Asian</td>
<td>9 (2.5)</td>
</tr>
<tr>
<td>First Nations/Aboriginal</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Mixed or other</td>
<td>38 (10.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>289 (81.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>47 (13.2)</td>
</tr>
<tr>
<td>Mixed or other</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td><strong>Country</strong></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>223 (62.8)</td>
</tr>
<tr>
<td>Canada</td>
<td>60 (16.9)</td>
</tr>
<tr>
<td>Australia</td>
<td>16 (4.5)</td>
</tr>
<tr>
<td>Philippines</td>
<td>16 (4.5)</td>
</tr>
<tr>
<td>Chile</td>
<td>14 (3.9)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td>France</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Serbia</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>China</td>
<td>4 (1.1)</td>
</tr>
</tbody>
</table>

**Stroke presentation**

| Focal signs |  |
| Hemiaparesis | 283 (80.3) |
| Dysarthria | 97 (27.3) |
| Aphasia | 79 (22.3) |
| Ataxia | 71 (20.0) |
| Visual field deficit | 46 (13.0) |

| Nonfocal signs |  |
| Headache | 126 (35.5) |
| Decreased level of consciousness | 102 (28.7) |
| Nausea/vomiting | 85 (23.9) |
| Seizures at presentation | 84 (23.7) |
| Vertigo | 40 (11.3) |
| Diplopia | 12 (3.4) |
| Papilledema | 4 (1.1) |

**Risk factors or comorbidities (not mutually exclusive)**

| Cardiac disease |  |
| 107 (30.1) |
| Congenital heart disease | 64 (18.0) |
| Acquired heart disease | 21 (5.9) |
| Isolated patent foramen ovale | 21 (5.9) |
| Stroke at cardiac surgery <72 h | 10 (2.8) |

**Other cardiac disease**

| Other chronic disorders |  |
| Sickle cell anemia | 13 (3.7) |
| Downs syndrome | 11 (3.1) |
| Other genetic syndrome | 16 (4.5) |
| Migraine | 12 (3.4) |
| Prothrombotic state | 10 (2.8) |
| Oral contraceptives (girls only) | 10 (6.4) |
| Indwelling catheter | 9 (2.5) |
| Iron deficiency anemia | 6 (1.7) |
| Brain tumor | 5 (1.4) |
| Benign | 2 (0.6) |
| Malignant | 3 (0.8) |
| Aneurysm | 3 (0.8) |
| PHACE syndrome/hemangioma | 3 (0.8) |
| Hematologic malignancy | 2 (0.6) |
| L-asparaginase therapy | 2 (0.6) |
| Connective tissue disease | 2 (0.6) |
| Ventriculoperitoneal shunt | 1 (0.3) |

**Acute systemic illness**

| Fever lasting >48 h | 44 (12.4) |
| Systemic sepsis or bacteremia | 20 (5.6) |
| Dehydration | 18 (5.1) |
| Shock | 9 (2.5) |
| Viral gastroenteritis | 2 (0.6) |

PHACE indicates posterior fossa brain malformations, hemangiomas of the face (large or complex), arterial anomalies, cardiac anomalies, and eye anomalies.
the cases were adjudicated by a 4-person committee, including a second neuroradiologist (A.J.B.) and a second pediatric neurologist (G.D.V.). The adjudication became the gold standard for those cases. If no disagreement, the gold standard was the step 3 interpretation when follow-up imaging was available and the step 2 interpretation when no follow-up imaging was available.

Statistical Analysis
Characteristics were compared across the 3 arteriopathy groups (definite, possible, and none) using the nonparametric Kruskal–Wallis test for continuous variables, and the $\chi^2$ test for categorical variables. When the latter contained cells of <5 observations, $P$ values were calculated using Fisher exact test. For each of the 3 arteriopathy review steps, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of that step’s primary diagnosis (definite arteriopathy as a binary variable) using the gold standard value. Individual reviewer diagnoses at each step were also compared with each other to assess reviewer agreement at each of the 3 steps was represented using simple $\kappa$ (kappa) statistics and their confidence intervals (CI). All analyses were done using Stata version 12 (Stata Corp, College Station, TX).

Results
Between January 2010 and March 2014, VIPS prospectively enrolled 387 pediatric patients. Of these, 355 (92%) were centrally confirmed as meeting study criteria for AIS. Demographics, presentation, and comorbidities are shown in Table 1; 184 (52%) were previously healthy (no chronic or acute illness before their stroke diagnosis).

Arteriopathy Review
In 116 patients (32.7%), there were no abnormalities on the initial vascular imaging review, and the arteriopathy review was not performed (Figure 1). The other 239 underwent arteriopathy review; full committee adjudication was performed in 56 of 239 cases (23%). The source of the gold standard arteriopathy diagnosis is shown in Table 2. Overall, 127 patients (36%) received a gold standard diagnosis of definite arteriopathy, 34 (9.6%) possible arteriopathy, and 194 (55%) no arteriopathy (Table 2). Of the 184 previously healthy children, 42% had a definite arteriopathy, 13% possible arteriopathy, and 45% no arteriopathy compared with 29%, 6%, and 65%, respectively, for the 171 nonhealthy children ($P=0.0005$). Of the 127 with definite arteriopathy, 109 (86%) received a single secondary diagnosis, whereas 18 (14%) could not be further classified with certainty. Demographics were similar among patients with no, possible, and definite arteriopathy although the Filipino site had a high proportion of cases with definite arteriopathy related to cases of secondary vasculitis because of tuberculosis meningitis (Table I in the online-only Data Supplement).

Interobserver agreement on the primary diagnosis yielded a $\kappa$ of 0.77 (95% CI, 0.70–0.84) at step 1. Sensitivity of the step 1 primary diagnosis (for the gold standard primary diagnosis) was 79%, and specificity was 99%. The positive predictive value (PV) of the step 1 primary diagnosis was 97%, and the negative PV was 89%. When clinical data were added (step 2), interobserver agreement yielded a $\kappa$ coefficient of 0.81 (95% CI, 0.74–0.87), and sensitivity and specificity increased to 90% and 100%, respectively. Positive PV rose to 100% and negative PV to 95%. In the 110 patients with follow-up

| Table 2. Gold Standard Arteriopathy Diagnosis in 355 Childhood Arterial Ischemic Stroke Cases |
|---------------------------------|-----------------|
| Source of gold standard arteriopathy classification | n (%) |
| Vascular imaging review (normal, no arteriopathy review) | 116 (32.7) |
| Arteriopathy diagnosis review | 239 (67.3) |
| Baseline with clinical findings (step 2) | 94 (26.5) |
| Follow-up (step 3) | 89 (25.1) |
| Adjudication | 56 (15.8) |
| Definite arteriopathy | 127 (35.5) |
| Secondary diagnosis classified with high certainty* | 109 (30.7) |
| Arterial dissection | 26 (7.3) |
| Transient cerebral arteriopathy | 25 (7.0) |
| Primary moyamoya | 17 (4.8) |
| Secondary moyamoya | 17 (4.8) |
| PHACE | 2 (0.6) |
| Genetic arteriopathy | 4 (1.1) |
| Primary vasculitis | 0 (0) |
| Secondary vasculitis (including meningitis) | 15 (4.2) |
| Iatrogenic | 1 (0.3) |
| Fibromuscular dysplasia | 2 (0.6) |
| Secondary diagnosis not further classified | 18 (5.1) |
| Differential diagnosis includes the following† | |
| Transient cerebral arteriopathy | 9 (2.5) |
| Arterial dissection | 11 (3.1) |
| Primary moyamoya | 4 (1.1) |
| Secondary moyamoya | 0 (0) |
| Genetic arteriopathy | 1 (0.3) |
| Primary vasculitis | 2 (0.6) |
| Secondary vasculitis (including meningitis) | 4 (1.1) |
| Iatrogenic | 0 (0) |
| Possible arteriopathy | 34 (9.6) |
| Differential diagnosis includes the following† | |
| Transient cerebral arteriopathy | 9 (2.5) |
| Arterial dissection | 27 (7.6) |
| Primary moyamoya | 1 (0.3) |
| Secondary moyamoya | 0 (0) |
| Genetic arteriopathy | 0 (0) |
| Primary vasculitis | 1 (0.3) |
| Secondary vasculitis (including meningitis) | 7 (2.0) |
| Iatrogenic | 0 (0) |
| Embolic (not arteriopathy) | 33 (9.3) |
| No arteriopathy | 194 (54.6) |

No abnormalities on vascular imaging (no arteriopathy review) 116 (32.7) |
Arteriopathy review 78 (22.0) |
Classified as no arteriopathy, no embolus 1 (0.3) |
Classified as no arteriopathy, low likelihood embolic 2 (0.6) |
Classified as isolated occlusion, high likelihood embolic 75 (21.1) |

PHACE indicates posterior fossa brain malformations, hemangiomas of the face (large or complex), arterial anomalies, cardiac anomalies, and eye abnormalities.

*Subcategories are mutually exclusive.
†Subcategories are not mutually exclusive.

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Arteriopathies in Childhood Ischemic Stroke

Wintermark et al

Imaging (step 3), the \( \kappa \) coefficient for interobserver agreement was 0.78 (95% CI, 0.66–0.90). Sensitivity for the step 3 primary diagnosis rose to 94%, with a specificity of 100%. Positive PV remained at 100%, whereas negative PV dropped slightly to 91%.

 Imaging Work-Up and Infarct Characteristics
The imaging studies performed were similar across children stratified by primary arteriopathy diagnosis, except that those without arteriopathy were less likely to have conventional angiograms and follow-up vascular imaging (Table II in the online-only Data Supplement). Infarcts in the territory of the middle cerebral artery were the most common location in each stratum. Infarct volume was greatest in those with definite arteriopathy \( (P=0.009; \text{Table 3}) \).

Vascular Imaging Findings
Arterial banding, intimal flap, and intramural hematoma were seen exclusively in patients with definite arteriopathy because these imaging features were used to diagnose arteriopathy (Table 3). One child in the no arteriopathy group had a mycotic aneurysm: because the stroke was the cause of underlying endocarditis, and unrelated to the aneurysm, it was considered cardioembolic. Vascular irregularity and stenosis were observed more often in patients with arteriopathy but were also seen in patients without arteriopathy and attributed to recanalizing thrombus (such as from cardioembolism). Occlusion was a nonspecific finding that was observed frequently in all subgroups, but most commonly in the possible arteriopathy subgroup, reflecting uncertainty about whether the occlusion was because of arterial disease or embolism. When >1 arterial segment was affected, or infarcts were present in >1 vascular territory, definite arteriopathy was more likely. The diagnosis of definite arteriopathy was associated with a higher proportion of vascular imaging findings progressing over time, or progressing then improving.

Discussion
In a large prospective, multicenter, international study, we found that arteriopathy is a common cause of childhood AIS, present in \( \leq 45\% \) of cases (including those with a possible arteriopathy). More than half the cases were previously healthy children at the time of their stroke; among them, arteriopathy was present in \( \leq 58\% \). In our stepwise review process, reviewer agreement was high at each step, and clinical data and follow-up imaging increased the sensitivity for the final gold standard primary diagnosis of definite arteriopathy. However, 10% of all cases could not be definitively classified as having, or not having, arteriopathy—suggesting that even with central review by a panel of pediatric stroke investigators, considerable uncertainty remains around childhood arteriopathy diagnosis.

Arteriopathies are important because they are not only a prevalent cause of childhood AIS but also the strongest predictor of recurrence. In 667 cases enrolled at 30 sites in the IPSS (2003–2007), 53% were classified as having an arteriopathy by the site investigators.\(^6\) In a population-based study of Californian children enrolled in a managed care plan (1993–2004), 52 children had vascular imaging after AIS: 22 (42%) had nonocclusive abnormalities of cerebral or cervical arteries and another 6 (12%) had large-vessel occlusion.\(^8\) Although there were no recurrences among 24 children with normal vascular imaging, the 5-year cumulative recurrence rate among those with abnormalities was 66% (\( P<0.001 \)). A prospective German study of 301 childhood AIS cases (1995–2000) similarly found that arteriopathy was the strongest predictor of recurrence (odds ratio, 3.9; 95% CI, 1.4–10.6).\(^13\) Hence, accurate diagnosis of childhood arteriopathy is important both for understanding an individual child’s risk of recurrent stroke and for the design of secondary stroke prevention trials.

The results of VIPS also demonstrate that childhood arteriopathies remain difficult to diagnose. Standard vascular imaging is currently limited to lumenology—imaging of the arterial lumen, and not the wall of the artery—making it difficult to distinguish a diseased artery from thrombus in a vessel. Imaging features that were particularly suggestive of definite arteriopathy included arterial banding, intimal flap, intramural hematoma, ectasia or aneurysm, and pseudoaneurysm. Vascular irregularity and stenosis were less specific. Occlusion was nonspecific, common in all groups, and most common in the possible arteriopathy group, reflecting uncertainty as to whether the artery was diseased, or occluded by thrombus. In VIPS, we observed cases with arterial stenosis on baseline imaging highly suggestive of arteriopathy, yet a clinical history of cardiac thrombus suggested partially recanalized thrombus (Figure 2). The addition of clinical data increased the sensitivity of the primary diagnosis of arteriopathy (from 79% to 90%) but must be applied with caution because cardiac disease can be coincident with arteriopathy in childhood: Down syndrome, for example, is associated with congenital heart defects, moyamoya syndrome, and arterial dissection because of cervical instability.\(^22–24\) Follow-up vascular imaging was important, increasing the sensitivity to 94%. Rapid resolution of stenosis pointed toward a resolving thrombus, whereas a persistent, or even progressive, stenosis suggested arteriopathy. However, rapid diagnosis of arteriopathy is important if we hope to develop interventions to prevent recurrent stroke in children, most of which occur days to weeks after first AIS.\(^8,13,25\) Improved imaging techniques are needed. Arterial wall imaging, which allows the detection of blood products and enhancement in the vessel walls, may prove to be of benefit to children with AIS by allowing early arteriopathy diagnosis.\(^26,27\)

Another challenge is that childhood AIS is uncommon, so it is difficult for neuroradiologists and neurologists to gain experience in diagnosing childhood arteriopathies. Some arteriopathies are unique to childhood, and only rarely seen in adults with stroke. This includes TCA, a common arteriopathy among previously healthy children; the proximal middle cerebral artery banding seen in the acute phase of this disease can be confused with fibromuscular dysplasia, an arteriopathy with a different natural history (Figure 3).\(^28\) Furthermore to the challenge, the arteriopathies that are more common in adults are rarely seen in children. We made no diagnoses of atherosclerosis in VIPS, even among adolescents, and also no diagnoses of primary central nervous system vasculitis. Finally, the arteriopathies observed in children vary somewhat by geographic location as follows:
Table 3. Infarct Characteristics and Vascular Imaging Findings in 355 Childhood Arterial Ischemic Stroke Cases, Stratified by Primary Arteriopathy Diagnosis

<table>
<thead>
<tr>
<th>Infarct characteristics at baseline</th>
<th>n (%)</th>
<th>Total n=355</th>
<th>Definite Arteriopathy n=127</th>
<th>Possible Arteriopathy n=34</th>
<th>No Arteriopathy n=194</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular distribution of infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial MCA</td>
<td>214 (60.3)</td>
<td>87 (68.5)</td>
<td>15 (44.1)</td>
<td>112 (57.7)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Lenticulostriate</td>
<td>144 (40.6)</td>
<td>59 (46.5)</td>
<td>11 (32.4)</td>
<td>74 (38.1)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>69 (19.4)</td>
<td>15 (11.8)</td>
<td>7 (20.6)</td>
<td>47 (24.2)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>37 (10.4)</td>
<td>13 (10.2)</td>
<td>6 (17.6)</td>
<td>18 (9.3)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>35 (9.9)</td>
<td>17 (13.4)</td>
<td>3 (8.8)</td>
<td>15 (7.7)</td>
<td>0.23*</td>
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<tr>
<td>SCA</td>
<td>27 (7.6)</td>
<td>8 (6.3)</td>
<td>5 (14.7)</td>
<td>14 (7.2)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Anterior choroidal</td>
<td>25 (7.0)</td>
<td>8 (6.3)</td>
<td>2 (5.9)</td>
<td>15 (7.7)</td>
<td>0.91</td>
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<tr>
<td>Basilar</td>
<td>23 (6.5)</td>
<td>3 (2.4)</td>
<td>3 (8.8)</td>
<td>17 (8.8)</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>AICA</td>
<td>8 (2.3)</td>
<td>1 (0.8)</td>
<td>4 (11.8)</td>
<td>3 (1.5)</td>
<td>0.005*</td>
<td></td>
</tr>
<tr>
<td>Other</td>
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<td>121 (34.1)</td>
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<td>58 (29.9)</td>
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<td>52 (40.9)</td>
<td>10 (29.4)</td>
<td>77 (39.7)</td>
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<tr>
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<td>6 (17.6)</td>
<td>58 (29.9)</td>
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<td>Median (interquartile range)</td>
<td>18 (3.2–69.1)</td>
<td>31 (5.8–96.6)</td>
<td>19 (4.7–62.1)</td>
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<td>Occlusion</td>
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<td>74 (58.3)</td>
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<tr>
<td>&gt;1</td>
<td>173 (48.7)</td>
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<td></td>
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<td>162 (45.6)</td>
<td>72 (56.7)</td>
<td>28 (82.4)</td>
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<td>4</td>
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<td>Proximal MCA (M1)</td>
<td>153 (43.1)</td>
<td>101 (79.5)</td>
<td>12 (35.3)</td>
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<td>Supraclinoid ICA</td>
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<td>5 (14.7)</td>
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<td>Vertebrobasilar</td>
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<td>Cervical arteries</td>
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<td>34 (26.8)</td>
<td>11 (32.4)</td>
<td>11 (5.7)</td>
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</table>

(Continued)
of 15 cases of secondary vasculitis in VIPS, 7 were enrolled in the Philippines, where tuberculosis meningitis remains a common cause of childhood AIS.

Lack of a reliable and user-friendly classification system for childhood arteriopathies remains another challenge. Definitions for childhood arteriopathies have been published and were used in our study, but can be difficult to apply for all the reasons mentioned above. The best available system is the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) system for classification of childhood AIS etiology, including arteriopathies. This system has taken a descriptive approach to arteriopathies (including categories such as unilateral focal cerebral arteriopathy of childhood and bilateral cerebral arteriopathy of childhood), and achieved good inter-rater reliability. But further work is needed to link these categories to both underlying mechanisms and prognosis, particularly recurrence risk.

The main limitation of our study was the variability in patient evaluation related to our complete reliance on clinically obtained studies. Research imaging studies would have been prohibitively costly and would have presented ethical issues related to the need for anesthesia in younger children.
Although most baseline vascular imaging studies were MRAs of good quality, their timing with respect to the stroke ictus was variable. Only half of the cases had cervical imaging, and only 14% had conventional angiography, which is still the gold standard for vascular imaging. The timing and frequency of follow-up vascular imaging were also variable; and many patients with normal vascular imaging at baseline did not receive follow-up, precluding an assessment of whether early MRA can be insensitive to acute arteriopathies like TCA. (In 1 VIPS case of TCA, the baseline MRA had been clinically interpreted as normal, then progressed to severe middle cerebral artery stenosis within days.) However, the VIPS study is the first-ever international study of childhood AIS to perform centralized imaging review, which allowed us to apply methods for diagnosis of childhood arteriopathy consistently.

Conclusions
Arteriopathy is common among children with AIS, particularly previously healthy children, but remains difficult to diagnose. Clinical data and follow-up imaging both aid in the diagnosis. More systematic use of follow-up vascular imaging, and advances in techniques such as arterial wall imaging, may prove helpful, and could assist both with prognostication in an individual child, and selection of children for secondary stroke prevention trials. We plan to perform further work with the VIPS cohort to determine predictors of arteriopathy subtypes, with the aim of developing simple algorithms that may assist a clinical neuroradiologist or neurologist in generating a reasonable differential diagnosis for arteriopathy in a child with AIS.

Appendix
M.M. Dowling (University of Texas Southwestern Medical Center, Dallas), S.L. Benedict (Primary Children’s Medical Center, Salt Lake City), T.J. Bernard (Children’s Hospital Colorado), C.K. Fox (University of California at San Francisco), G.A. deVeber (The Hospital for Sick Children, Toronto), N.R. Friedman (Cleveland Clinic Children’s Hospital), W.D. Lo (The Ohio State University and Nationwide Children’s Hospital, Columbus, OH), R.N. Ichord (Children’s Hospital of Philadelphia), M.A. Tan (University of the Philippines-Philippine General Hospital, Manila), M.T. Mackay (Royal Children’s Hospital Melbourne), A. Kirton (Alberta Children’s Hospital), M.I. Hernandez Chavez (Pontificia Universidad Catolica de Chile), P. Humphreys (Children’s Hospital of Eastern Ontario), L.C. Jordan (Vanderbilt University Medical Center, Nashville), S.M. Sultan (Columbia University Medical Center, New York), M.J. Rivkin (Boston Children’s Hospital), M.F. Rafay (Children’s Hospital, Winnipeg, University of Manitoba), L. Titomanlio (L Hôpital Robert Debré-Paris), G.S. Kovacevic (Mother and Child Health Care Institute, Serbia), J.Y. Yager (Stollery Children’s Hospital), C. Amiel-Lefond (Seattle Children’s Hospital), N. Diamini (Evelina London Children’s Hospital), J. Condie (Phoenix Children’s Hospital), A. Yeh (Women and Children’s Hospital of Buffalo), R. Kneen (Alder Hey Children’s Hospital), B.H. Bjornson (British Columbia Children’s Hospital), P. Pergami (West Virginia University), L.P. Zou (Chinese PLA General Hospital, Beijing), J. Elbers (Stanford Children’s Health, Palo Alto), A. Abdalla (Akron Children’s Hospital), A.K. Chan (McMaster University Medical Centre, Hamilton), O. Farooq (Women and Children’s Hospital of Buffalo), M.J. Lim (Evelina London Children’s Hospital), J.L. Carpenter (Children’s National Medical Center, Washington, DC), S. Pavlakis (Maimonides Medical Center, Brooklyn), V.C. Wong (Queen Mary Hospital, Hong Kong), R. Forsyth (Institute of Neuroscience, Newcastle University, United Kingdom).

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References


Arteriopathy Diagnosis in Childhood Arterial Ischemic Stroke: Results of the Vascular Effects of Infection in Pediatric Stroke Study


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### Supplemental Table I. Demographics and clinical characteristics of 355 childhood arterial ischemic stroke cases, stratified by primary arteriopathy diagnosis

<table>
<thead>
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<th>Characteristic</th>
<th>Definite Arteriopathy N=127</th>
<th>Possible Arteriopathy N=34</th>
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<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<td>Demographics</td>
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Nausea/vomiting 31 (24.4) 9 (26.5) 45 (23.2) 0.96
Seizures at presentation 32 (25.2) 6 (17.6) 46 (23.7) 0.02
Vertigo 13 (10.2) 5 (14.7) 22 (11.3) 0.93
Diplopia 2 (1.6) 2 (5.9) 8 (4.1) 0.66
Papilledema 3 (2.4) 0 (0) 1 (0.5) 0.55

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<tr>
<td>Ventriculoperitoneal shunt 1 (0.8) 0 (0) 0 (0) 0.45*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute systemic illness by chart review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever lasting &gt;48 hours 18 (14.2) 2 (5.9) 24 (12.4) 0.47*</td>
</tr>
<tr>
<td>Systemic sepsis or bacteremia 9 (7.1) 2 (5.9) 9 (4.6) 0.65*</td>
</tr>
<tr>
<td>Dehydration 6 (4.7) 1 (2.9) 11 (5.7) 0.94*</td>
</tr>
<tr>
<td>Shock 0 (0) 1 (2.9) 8 (4.1) 0.04*</td>
</tr>
<tr>
<td>Viral gastroenteritis 0 (0) 0 (0) 2 (1.0) 0.61*</td>
</tr>
</tbody>
</table>

*P-value calculated using Fishers exact test (indicated by *); otherwise, chi-square tests were used

** Kruskal-Wallis test

***females only: N=59 (definite), 12 (possible), 85 (no arteriopathy)
## Supplemental Table II

Imaging modality and timing of vascular imaging in 355 childhood arterial ischemic stroke cases, stratified by primary arteriopathy diagnosis

<table>
<thead>
<tr>
<th>Imaging modality at baseline</th>
<th>Total N=355</th>
<th>Definite Arteriopathy</th>
<th>Possible Arteriopathy</th>
<th>No Arteriopathy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Brain parenchyma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>MRI only</td>
<td>216 (60.8)</td>
<td>72 (56.7)</td>
<td>20 (58.8)</td>
<td>124 (63.9)</td>
<td></td>
</tr>
<tr>
<td>CT only</td>
<td>5 (1.4)</td>
<td>1 (0.8)</td>
<td>1 (2.9)</td>
<td>3 (1.5)</td>
<td></td>
</tr>
<tr>
<td>MRI and CT</td>
<td>134 (37.7)</td>
<td>54 (42.5)</td>
<td>13 (38.2)</td>
<td>67 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Intracranial vascular imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA brain</td>
<td>323 (91.0)</td>
<td>116 (91.3)</td>
<td>30 (88.2)</td>
<td>177 (91.2)</td>
<td>0.76*</td>
</tr>
<tr>
<td>CTA brain</td>
<td>84 (23.7)</td>
<td>34 (26.8)</td>
<td>10 (29.4)</td>
<td>38 (19.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>Conventional angiography, brain</td>
<td>51 (14.4)</td>
<td>28 (22.0)</td>
<td>8 (23.5)</td>
<td>15 (7.7)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cervical vascular imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRA neck</td>
<td>154 (43.4)</td>
<td>49 (38.6)</td>
<td>17 (50.0)</td>
<td>88 (45.4)</td>
<td>0.35</td>
</tr>
<tr>
<td>CTA neck</td>
<td>45 (12.7)</td>
<td>17 (13.4)</td>
<td>7 (20.6)</td>
<td>21 (10.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Conventional angiography, neck</td>
<td>14 (3.9)</td>
<td>6 (4.7)</td>
<td>3 (8.8)</td>
<td>5 (2.6)</td>
<td>0.13*</td>
</tr>
<tr>
<td>Follow-up vascular imaging (any modality)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one follow-up study</td>
<td>147 (41.4)</td>
<td>68 (53.5)</td>
<td>15 (44.1)</td>
<td>64 (33.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;1 follow-up study</td>
<td>68 (19.2)</td>
<td>39 (30.7)</td>
<td>6 (17.6)</td>
<td>23 (11.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time to vascular imaging, days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke to baseline imaging, median (IQR)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
<td>0.81**</td>
</tr>
<tr>
<td>Stroke to 1st follow-up, median (IQR) (n=147)</td>
<td>79 (18, 128)</td>
<td>39 (12, 111)</td>
<td>70 (24, 105)</td>
<td>99 (44, 155)</td>
<td>0.002**</td>
</tr>
<tr>
<td>Stroke to last follow-up, median (IQR) (n=68)</td>
<td>277 (172, 408)</td>
<td>257 (106, 397)</td>
<td>212 (172, 355)</td>
<td>372 (219, 448)</td>
<td>0.15**</td>
</tr>
</tbody>
</table>

* Fisher’s exact  
**Kruskal-Wallis