Inflammatory Biomarkers in Childhood Arterial Ischemic Stroke
Correlates of Stroke Cause and Recurrence

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Background and Purpose—Among children with arterial ischemic stroke (AIS), those with arteriopathy have the highest recurrence risk. We hypothesized that arteriopathy progression is an inflammatory process and that inflammatory biomarkers would predict recurrent AIS.

Methods—In an international study of childhood AIS, we selected cases classified into 1 of the 3 most common childhood AIS causes: definite arteriopathic (n=103), cardioembolic (n=55), or idiopathic (n=78). We measured serum concentrations of high-sensitivity C-reactive protein, serum amyloid A, myeloperoxidase, and tumor necrosis factor-α. We used linear regression to compare analyte concentrations across the subtypes and Cox proportional hazards models to determine predictors of recurrent AIS.

Results—Median age at index stroke was 8.2 years (interquartile range, 3.6–14.3); serum samples were collected at median 5.5 days post stroke (interquartile range, 3–10 days). In adjusted models (including age, infarct volume, and time to sample collection) with idiopathic as the reference, the cardioembolic (but not arteriopathic) group had higher concentrations of high-sensitivity C-reactive protein and myeloperoxidase, whereas both cardioembolic and arteriopathic groups had higher serum amyloid A. In the arteriopathic (but not cardioembolic) group, higher high-sensitivity C-reactive protein and serum amyloid A predicted recurrent AIS. Children with progressive arteriopathies on follow-up imaging had higher recurrence rates, and a trend toward higher high-sensitivity C-reactive protein and serum amyloid A, compared with children with stable or improved arteriopathies.

Conclusions—Among children with AIS, specific inflammatory biomarkers correlate with cause and—in the arteriopathy group—risk of stroke recurrence. Interventions targeting inflammation should be considered for pediatric secondary stroke prevention trials. (Stroke. 2016;47:2221-2228. DOI: 10.1161/STROKEAHA.116.013719.)

Key Words: biomarkers ▶ C-reactive protein ▶ Cox proportional hazards models ▶ inflammation ▶ serum amyloid A protein ▶ stroke

Although childhood arterial ischemic stroke (AIS) is a heterogeneous disorder, most cases fall into 1 of 3 broad pathogenic categories: arteriopathic, cardioembolic, and idiopathic.¹ The presence of an arteriopathy (cervical or cerebral) confers an increased risk of recurrent AIS.²–⁴ In the prospective, multicenter VIPS study (Vascular Effects of Infection in Pediatric Stroke), children with arteriopathic stroke had a 21% (95% confidence interval [CI], 14%–29%) chance of recurrence within 1 year compared with 8% (95% CI, 3–18) with cardioembolic and 5% (95% CI, 2–12) with idiopathic stroke.² Childhood arteriopathies are themselves heterogeneous and poorly understood,⁶ yet mounting evidence suggests that infection and inflammation play a role in their pathogenesis. The VIPS study, and others, provide evidence that acute infection, such as the common cold or herpesviruses, act as triggers for childhood AIS.⁷–¹⁰ Arterial wall imaging...
studies detecting enhancement in the wall of affected vessels in childhood arteriopathies may suggest an acute inflammatory process.\textsuperscript{11,12} Children whose arteriopathies progress after their index stroke have the highest risk of recurrent AIS.\textsuperscript{13,14} We hypothesized that arteriopathy progression is an inflammatory process and that markers of inflammation would predict recurrent AIS in childhood. To explore this hypothesis, we measured serum levels of 4 soluble immune mediators in children with AIS enrolled in the VIPS study: high-sensitivity C-reactive protein (hsCRP), serum amyloid A (SAA), myeloperoxidase, and tumor necrosis factor (TNF)-\textgreek{a}. These 4 analytes were selected because of their published associations with adult stroke and vascular disease.\textsuperscript{15,16}

Methods

Study Subjects and Sample Collection

The VIPS study prospectively enrolled and centrally confirmed 355 children (29 days to 19 years) with AIS at 37 international sites from January 2010 to March 2014. Details of our methods for enrollment, case confirmation, data collection, classification of cause, parental interview, sample collection, and ascertainment and confirmation of recurrent AIS are published.\textsuperscript{2,6,4,7} In brief, a team of pediatric stroke neurologists and neuroradiologists confirmed cases after central review of imaging and clinical features. A single neuroradiologist (M.W.) estimated infarct volume using the ABC/2 method.\textsuperscript{19} A central team similarly reviewed all clinically obtained cerebrovascular imaging and clinical data to classify cases as definite, possible, or no arteriopathy; no arteriopathy cases were further classified into cardioembolic, other specific cause, or idiopathic.\textsuperscript{6} When arteriopathic cases had follow-up imaging, the team classified evolution as stable, improves or resolves, progresses, or progresses then improves or resolves. For analysis, these categories were dichotomized as stable/improving/resolved versus progression (regardless of subsequent improvement). The study protocol included a minimum follow-up of 1 year. Recurrent AIS, defined as a new acute infarction in an arterial territory with corresponding new or worsening clinical signs and symptoms, was centrally confirmed.\textsuperscript{2}

Laboratory Methods

Blood samples were collected locally as soon as possible after enrollment, up to 21 days post stroke. They were centrifuged at 3000 rpm for 10 minutes, with serum samples immediately separated, aliquoted, and stored in 1.2-ml cryovials at \textdegree 70\textdegree C. Samples were then shipped on dry ice to the Center for Advanced Laboratory Medicine at Columbia University and were run in batches by technicians blind to clinical status. hsCRP and SAA concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL). TNF-\textgreek{a} (Invitrogen, Camarillo, CA) and myeloperoxidase (R&D Systems Inc, Minneapolis, MN) concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL). TNF-\textgreek{a} and SAA concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL). TNF-\textgreek{a} and SAA concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL). TNF-\textgreek{a} and SAA concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL). TNF-\textgreek{a} and SAA concentrations were measured using a clinically validated BNII nephelometer (Siemens Dade Behring, Deerfield, IL).

Data Analysis

Analysis focused on cases that could be classified with a high degree of certainty into 1 of the 3 most common pathogenic groups: arteriopathic, cardioembolic, or idiopathic (Figure 1). From the overall VIPS cohort of 355 children, we excluded those with possible arteriopathy (likely a mixture of causes)\textsuperscript{6} or other specific causes not falling into the 3 major categories of interest. We also excluded cases with major infections (sepsis, meningitis/encephalitis, and endocarditis) that would impact serum concentrations of inflammatory biomarkers. We compared analyte concentration levels in the remaining children. Kruskal–Wallis tests were used to make unadjusted compar- isons of each analyte individually across the 3 pathogenic groups; linear regression models examined the associations between individual analytes and stroke cause while adjusting for potential confounders (age, sex, infarct volume, time from stroke to blood sampling, seizures at presentation, and clinical infection in the week preceding stroke). For regression analyses, analyte concentration levels were used as outcomes and log-transformed to reduce the skewness of residuals; our primary predictor was pathogenic group with idiopathic as a reference. To assess variables related to risk of recurrent AIS, we used survival analysis techniques as previously described; the outcome was defined as the time from index AIS to first recurrent AIS and cases were censored at death or loss to follow-up.\textsuperscript{2} To determine whether analyte concentrations correlated with recurrent AIS, we created Cox proportional hazards models. Each analyte was analyzed individually to determine its potential association with recurrence. Analyte concentrations were log-base 2 transformed to yield relative hazards associated with a doubling of concentration. We adjusted for stroke cause, as well as those variables included in the linear regression models above. To investigate potential interactions by stroke cause, we included an interaction term in our Cox models and performed analyses stratified by subtype. Only the arteriopathic and cardioembolic subgroups were assessed in these analyses because of the paucity of outcomes (recurrence) in the idiopathic group. Among the subgroup of children with arteriopathic stroke and follow-up vascular imaging, we analyzed arteriopathy progression as a dichotomous predictor of recurrent AIS; to maintain consistency across models, we adjusted for the potential confounders described above. Our \textgreek{a}-level was set at 0.05. All analyses were conducted using Stata v12 (Stata Corp, College Station, TX).

Results

The present analysis included 236 children with AIS whose cause was classified into 1 of the 3 major groups (Figure 1): idiopathic (n=78), arteriopathic (n=103), and cardioembolic (n=55). Median age at stroke ictus was 8.2 years overall (interquartile range [IQR], 3.6, 14.3) and was higher in the idiopathic
Among the 103 children with arteriopathic stroke, 62 (60%) had centrally reviewed follow-up vascular imaging (Table I in the online-only Data Supplement). The median time from index stroke to final vascular imaging included in these analyses was 5 months (IQR, 1–12 months). The arteriopathy was classified as progressive in 30 (48%) and nonprogressive (stable or improved) in 32 (52%). In an analysis of these 62 children, arteriopathy progression increased the hazard of recurrent AIS 3-fold (adjusted hazard ratios, 3.1; 95% CI, 1.1–8.7; P=0.036). Among children with progressive arteriopathy, the 1-year cumulative risk of recurrence was 46% (95% CI, 25–84) compared with 25% (95% CI, 12–52) among those with nonprogressive arteriopathy (Figure 3C).

### Discussion

In a large, international study of childhood AIS, serum concentrations of 3 of 4 measured inflammatory biomarkers differed by stroke cause, even after adjusting for potential confounders. Two of these—the acute phase reactants CRP and SAA—predicted risk of recurrent AIS among children with arteriopathic stroke, the subgroup at highest risk for recurrence. Children with progressive arteriopathies had the highest recurrence risk and a trend toward higher hsCRP and SAA concentrations. These findings have important implications for the development of new strategies for secondary stroke prevention in childhood.

Two previous studies of childhood AIS, the Swiss Neuropediatric Stroke Registry Study Group (n=12 cases, n=7 controls) and a single-center US study (n=50 cases), measured serum levels of inflammatory biomarkers; both found elevated hsCRP, whereas other markers, including TNF-α, were not significantly different. Elevations in these serum markers measured poststroke could reflect, in part, downstream effects of the infarct itself related to tissue destruction and breakdown of the blood–brain barrier. Because we could collect only poststroke serum samples, we adjusted our analyses for infarct size, seizures, and timing of the serum sample relative to the stroke. Although residual confounders may exist, several pieces of evidence indicate that these markers also reflect upstream mechanisms underlying the stroke pathogenesis. First, adult studies similarly found that serum levels of soluble immune mediators (TNF-α, interleukin-6, and interleukin-1β) correlate with stroke cause. Second, we observed large variations in biomarker concentrations even among children with low volume infarcts that should have had minimal systemic effects (Figure 1 in the online-only Data Supplement). Third,
the observed associations between biomarkers and recurrence risk in the arteriopathic group suggest that inflammation may be contributing to the pathogenesis of subsequent strokes.

Systemic inflammation could play a complex role in AIS pathogenesis. Circulating immune mediators can activate the coagulation system, promoting thrombosis, and can injure arterial and cardiac endothelium. The different patterns of immune activation we observed across our 3 etiologic subgroups suggest that inflammation may play different roles in different childhood stroke causes. We speculate that systemic inflammation interacts with other pediatric stroke risk factors, like congenital heart disease and trauma. In a child with a structurally abnormal heart, inflammation might trigger intracardiac thrombus formation and cardioembolic stroke. Inflammation might make the cervical arteries more vulnerable to dissection; exposure to trauma after arteries have been primed by inflammation could trigger arteriopathic stroke.

The link between inflammation, arteriopathy, and stroke recurrence in childhood has previously been postulated, but never directly studied. Arterial wall imaging studies suggest that some childhood arteriopathies may be inflammatory in nature. Other studies have reported a correlation between arteriopathy progression and increased risk of recurrence. We confirmed that children with progressive arteriopathy have the highest risk of recurrent AIS: almost half had a recurrence within 1 year, most within the first 30 days, compared with 12% of the VIPS cohort overall. We demonstrated for the first time that higher levels of 2 inflammatory biomarkers (hsCRP and SAA) correlate with higher recurrence risk after arteriopathic stroke, particularly in the first 60 days (Figure 3A and 3B). We observed a trend toward a correlation between those markers and arteriopathy progression (but were likely underpowered because only a subset of cases had follow-up vascular imaging). Although our observational data can demonstrate only correlation, and not causation, we hypothesize that arteriopathy progression results from ongoing inflammation of the affected arteries. This hypothesis could be tested in a randomized controlled trial of anti-inflammatory therapy for secondary stroke prevention in childhood. Such a trial design, however, would need to consider the role of infection and other factors in pathogenesis, and the concern for immunosuppression in the setting of acute infection.

The 4 specific immune mediators we measured provide a window into a complex immune response. SAA concentrations were elevated in both our arteriopathic and cardioembolic cases and correlated with recurrence in the arteriopathic group. SAA is not only a biomarker but also a participant in the innate immune response. It promotes adhesion, migration, and infiltration of lymphocytes and monocytes; regulates production of cytokines by inflammatory cells; and increases generation of extracellular matrix metalloproteinases. Through these effects, SAA plausibly participates in damage to arterial or cardiac endothelium that may be relevant to childhood stroke. SAA is elevated in adults with both Takayasu arteritis and giant cell arteritis and correlates with disease activity of inflammatory arteriopathies.

### Table 1. Levels of Inflammatory Markers in Children With Idiopathic, Arteriopathic, and Cardioembolic Arterial Ischemic Stroke

<table>
<thead>
<tr>
<th>Marker†</th>
<th>Idiopathic</th>
<th>Arteriopathic</th>
<th>Cardioembolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>78 (0.18–2.5)</td>
<td>100 (2.8–6.1)</td>
<td>54 (1.3–14)</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>77 (1.3–8.4)</td>
<td>97 (1.8–33)</td>
<td>52 (7.2–32)</td>
</tr>
<tr>
<td>MPO, ng/mL</td>
<td>78 (158–342)</td>
<td>103 (158–73)</td>
<td>54 (327–532)</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>78 (2.6–4.1)</td>
<td>103 (2.4–2.9)</td>
<td>55 (3.3–4.5)</td>
</tr>
</tbody>
</table>

hsCRP indicates high-sensitivity C-reactive protein; IQR, interquartile range; MPO, myeloperoxidase; SAA, serum amyloid A; and TNF, tumor necrosis factor.

*From linear regression models using log-transformed outcomes and adjusted for age, sex, infarct volume, time from stroke to blood sample, seizure, and clinical infection in preceding week.

†Kruskal–Wallis tests across all 3 groups.

### Table 2. Adjusted HR* for Inflammatory Markers as a Predictor of Recurrent Arterial Ischemic Stroke in Children With Arterial Ischemic Stroke

<table>
<thead>
<tr>
<th>Marker†</th>
<th>Overall (29 Recurrences)</th>
<th>Arteriopathic (24 Recurrences)</th>
<th>Cardioembolic (5 Recurrences)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>HR (95% CI)</td>
<td>Adjusted P Value*</td>
<td>n</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>151 (0.99–1.28)</td>
<td>0.06</td>
<td>98</td>
</tr>
<tr>
<td>SAA, mg/L</td>
<td>147 (0.96–1.28)</td>
<td>0.15</td>
<td>97</td>
</tr>
<tr>
<td>MPO, ng/mL</td>
<td>155 (0.81–1.43)</td>
<td>0.58</td>
<td>101</td>
</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>155 (0.96–1.49)</td>
<td>0.12</td>
<td>101</td>
</tr>
</tbody>
</table>

HRs are interpreted as the relative hazard of recurrence risk associated with a doubling of the marker.

*From Cox proportional hazards models adjusted for age, sex, infarct volume, time to blood sample, seizure, and clinical infection in preceding week. Overall models include, and are adjusted for, cardioembolic and arteriopathic stroke subtype; idiopathic strokes were excluded because of the extremely low rate of recurrence in this group.

†All marker concentrations were converted to log-base 2 for analysis.
hsCRP was significantly elevated only in our cardioembolic cases although there was a trend toward higher levels in arteriopathic cases. Levels also correlated with recurrence risk in the arteriopathic group. CRP is an acute phase reactant used clinically as a nonspecific marker of inflammation; it predicts a broad variety of cardiovascular and noncardiovascular causes of morbidity and mortality, including adult AIS, prognosis after stroke, and atherosclerosis. Mounting evidence indicates that CRP, like SAA, is not only a biomarker but also a participant in the innate immune response. The aforementioned Swiss study reported higher median hsCRP levels in their 12 cases of childhood AIS (median, 5.9 μg/mL; range, 0.13–98) than 7 age-matched control children (median, 0.12 μg/mL; range 0.003, 4.1; P=0.007). The single-center US study of childhood AIS reported similar median CRP concentrations for cardioembolic (n=11) and arteriopathic (n=26) subtypes compared with our study, but was underpowered to detect a significant difference. Regardless, the nonspecificity of CRP may limit its utility in distinguishing among mechanisms of stroke subtype, whereas it may still be useful as a marker of recurrent stroke risk among children with arteriopathic stroke.

Figure 3. (Continued)
Myeloperoxidase was elevated in our cardiac cases and did not seem important in our arteriopathic cases. Myeloperoxidase levels correlate with active coronary artery disease, predicting risk of myocardial infarction. Atherosclerosis and coronary artery disease are unlikely to be contributors to stroke risk in children, but other childhood cardiac disorders are associated with stroke risk and could explain some of the association with myeloperoxidase. TNF-α, which has been associated with cardioembolic stroke in adults, neither correlate with either stroke cause or recurrence in our pediatric study nor is it elevated in the cases of childhood AIS in the Swiss study. TNF-α is a less stable marker in stored specimens, however, and associations may thus be limited by measurement error.

In addition to the limitation of having only poststroke serum samples available for analysis, our study has many other limitations. Although VIPS is the largest-ever prospective study of childhood AIS, some of our analyses may have been underpowered to detect actual differences between groups. Because we had only clinically obtained imaging, our analyses of arteriopathy progression were likely biased as children are more likely to get follow-up imaging if they have a recurrent stroke. Hence, our estimates of stroke recurrence among children with arteriopathy progression and nonprogression were likely overestimates. For feasibility of enrollment, our blood samples were collected alongside clinical phlebotomy over a 3-week window after the stroke; late samples may have been less likely to reflect prestroke inflammatory processes. Published pediatric normative values for most of our analytes are not available, and we did not have serum samples from healthy control children. The VIPS study collected blood samples only from trauma controls (for antibody titers), and the trauma would likely have affected the inflammatory biomarker concentrations. Finally, we measured only 4 biomarkers; since our study began, more immune mediators have been linked to stroke and vascular injury. The renewal of the VIPS study proposes to address many of these limitations by collecting serum samples in a shorter time window (72 hours post stroke), using multiplex technology to analyze a large number of inflammatory markers and collecting serum samples from well children undergoing elective procedures.

Conclusions

Different inflammatory responses may underlie the heterogeneity in childhood stroke pathogenesis and recurrent stroke risk. Because children with progressive arteriopathies have the highest risk of recurrent AIS, a better understanding of the inflammatory processes underlying their arteriopathies will guide the development of secondary stroke prevention strategies.

Appendix

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Disclosures

None.

References


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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/08/16/STROKEAHA.116.013719.DC1

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Supplemental Table:

Table I. Arteriopathy progression, stratified by arteriopathy subtype, for the 103 cases with definite arteriopathy included in the immune marker analysis.

<table>
<thead>
<tr>
<th>Arteriopathy Subtype</th>
<th>Stable/Resolved</th>
<th>Progressed</th>
<th>No Follow-up Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Transient cerebral arteriopathy (N=23)</td>
<td>8 (35%)</td>
<td>10 (43%)</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Moyamoya (N=31)</td>
<td>5 (16%)</td>
<td>8 (26%)</td>
<td>18 (58%)</td>
</tr>
<tr>
<td>Dissection (N=25)</td>
<td>9 (36%)</td>
<td>7 (28%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>Other/not further classified (N=24)</td>
<td>10 (42%)</td>
<td>5 (21%)</td>
<td>9 (38%)</td>
</tr>
<tr>
<td>Total (N=103)</td>
<td>32 (31%)</td>
<td>30 (29%)</td>
<td>41 (40%)</td>
</tr>
</tbody>
</table>

Supplemental Figure and Figure Legend:

Figure I. Scatter plots demonstrating the relationship between infarct volume (mL; x axis) and the log-transformed (log base 2) serum concentration of (A) hsCRP, (B) SAA, (C) MPO, and (D) TNF-α. A.
B. Spearman's rho = 0.26, p < 0.0001

C. Spearman's rho = 0.09, p = 0.11
Scatter plot of TNF-alpha level by stroke volume

Spearman's rho = -0.05, p = 0.43