Hemorrhagic Transformation of Childhood Arterial Ischemic Stroke

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Background and Purpose—The objective of this study was to describe the occurrence of hemorrhagic transformation (HT) among children with arterial ischemic stroke within 30 days after symptom onset and to describe clinical factors associated with HT.

Methods—Sixty-three children aged 1 month to 18 years with arterial ischemic stroke between January 2005 and November 2008 were identified from a single-center prospective pediatric stroke registry. All neuroimaging studies within 30 days of stroke were reviewed by a study neuroradiologist. Hemorrhage was classified according to the European Cooperative Acute Stroke Study-1 definitions. Association of HT with clinical factors, systemic anticoagulation, stroke volume, and outcome was analyzed.

Results—HT occurred in 19 of 63 children (30%; 95% CI, 19% to 43%), only 2 (3%) of whom were symptomatic. Hemorrhage classification was hemorrhagic infarction (HI)1 in 14, HI2 in 2, parenchymal hematoma (PH)1 in 2, and PH2 in 1. HT was less common in children with vasculopathy (relative risk, 0.27; 95% CI, 0.07 to 1.06; P=0.04) than in those with other stroke mechanisms. HT was not significantly associated with anticoagulation versus antiplatelet therapy (relative risk, 0.6; 95% CI, 0.2 to 1.5; P=0.26) but was associated with larger infarct volumes (P=0.0084). In multivariable analysis, worse Pediatric Stroke Outcome Measure scores were associated with infarct volume ≥5% of total supratentorial brain volume (OR, 4.0; 95% CI, 1.1 to 15; P=0.04), and a trend existed toward association of worse Pediatric Stroke Outcome Measure scores with HT (OR, 4.0; 95% CI, 0.9 to 18; P=0.07).

Conclusions—HT occurred in 30% of children with arterial ischemic stroke within 30 days. Most hemorrhages were petechial and asymptomatic. Infarct volume was associated with HT and worse outcome. (Stroke. 2011;42:00-00.)

Key Words: anticoagulation ■ arterial ischemic stroke ■ hemorrhagic transformation ■ pediatric

Arterial ischemic stroke (AIS) affects 1.2 to 7.9 per 100 000 children per year.1 No clinical trials have characterized the risks and benefits of antiplatelet or anticoagulation therapy in childhood acute stroke. Therefore, notable differences in treatment exist among experienced centers, some starting systemic anticoagulation acutely in most patients and others starting treatment with antiplatelet agents at the same time as using anticoagulation more selectively. In adults, no net benefit has been established for systemic anticoagulation compared with aspirin, even with cardioembolic stroke, mostly because of increased risk of hemorrhagic transformation (HT).2–4 However, because stroke mechanisms and coagulation and fibrinolytic pathways are different in children versus adults, findings from adult clinical trials of antithrombotic therapy cannot be extrapolated to children.5 Similarly, thrombolysis studies for AIS in children are limited, and risk of HT in this context is uncertain.6 Reliable estimates of HT rates obtained from carefully studied cohorts are essential for planning trials of thrombolytic and antithrombotic therapies in children with AIS. The primary goal of this study was to determine the proportion of children with HT in a prospectively identified consecutive cohort of children with AIS. Secondary objectives were to determine whether specific stroke risk factors, infarct volume, or acute antithrombotic treatments were associated with greater risk of HT and to determine whether HT was associated with worse clinical outcome.

Materials and Methods

Study Design
Children 1 month to 18 years of age with acute AIS between January 2005 and November 2008 were prospectively identified and included

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in the stroke registry of a large tertiary care children’s hospital with informed consent from the parent or guardian. With Institutional Review Board approval, retrospective analysis of this cohort was performed.

Case Identification
During acute hospitalization, patients were identified by neurology providers participating in a multidisciplinary neurovascular care program targeting children admitted to the hospital with acute AIS. Acute AIS was defined as acute-onset neurological deficit of any duration consistent with focal brain ischemia in an arterial distribution and confirmed by acute infarction on neuroimaging corresponding to the clinical deficit.

Clinical Data
Acute hospital records were abstracted. Diagnostic studies were performed as part of a multidisciplinary, consensus-based pediatric acute stroke treatment guidelines following current American Heart Association pediatric stroke treatment guidelines. This protocol typically included MRI brain imaging, cranio cervical vascular imaging, an echocardiogram, and a thrombophilia profile. Cases were classified by primary stroke risk factor as vasculopathoy, cardiac conditions, tumor-related, meningiits, isolated thrombophilia, sickle cell anemia, or other systemic disease. Cases with no stroke risk factor identified after comprehensive evaluation were classified as cryptogenic. Vasculopathy was classified according to methods of Sebire et al and modified by Amlie-Lefond et al and included arterial dissection, moyamoya disease, and autoimmune vasculitis.

Normal ranges for blood pressure based on sex and height were used to classify the first available blood pressure (BP) for each subject as normal, mildly elevated if the systolic or diastolic BP was between the 95th and 99th percentiles for 95th percentile of height, or moderately elevated if the systolic or diastolic BP was >99th percentile for 95% percentile of height. BP at the time of the HT was not available.

Treatment was defined as follows: (1) systemic anticoagulation—received unfractionated heparin, low-molecular-weight heparin, or warfarin; (2) antplatelet therapy—received aspirin but not anticoagulation; (3) both—received anticoagulation and aspirin simultaneously; and (4) neither—did not receive either anticoagulation or antiplalet therapy. The 1 patient treated with both aspirin and anticoagulation simultaneously was pooled with patients receiving anticoagulation alone for analysis as done by Goldenberg et al. Ten children were treated sequentially with aspirin and anticoagulation. Those treated with anticoagulation for >1 day were considered to have been treated with anticoagulation.

Outcome was assessed at routine stroke clinic follow-up. Neurological outcome was classified using a standardized neurological examination scale, the Pediatric Stroke Outcome Measure (PSOM). The examining neurologist classifies findings using the PSOM to characterize deficit type and severity. Subscores are assigned in 5 domains: sensorimotor left, sensorimotor right, expressive language, receptive language, and cognition/behavior. PSOM subscores are graded 0 (no deficit), 0.5 (mild deficit that does not interfere with function), 1 (moderate deficit that interferes with function), and 2 (severe deficit with loss of function). Total PSOM score ranges from 0 to 10. Maximal score (10) was imputed for children who died.

HT Analysis
Neuroimaging studies at admission and within 30 days of stroke onset were reviewed by a board-certified pediatric neuroradiologist (A.V.) blinded to clinical histories and clinical image interpretations. Although head CT was usually the first image performed, and MRI/CT angiography was obtained in most cases, additional follow-up imaging was individualized. Follow-up imaging within 30 days was obtained at the clinicians’ discretion for a clinical change in the patient’s status. Presence of hemorrhage was evaluated on all CT and MRI studies. When obtained at our study site, CT imaging was performed on 16- or 64-detector CT scanners (Siemens, Erlangen, Germany), and MRI was performed on 1.5- or 3-T magnets (Siemens). MRI sequences used T1-weighted, T2-weighted, fluid attenuation inversion recovery, T2* gradient echo susceptibility, echoplanar–spin echo–T2 (B0 images of diffusion-weighted imaging), and susceptibility-weighted imaging.

Hemorrhage was identified on noncontrast head CT as areas of hyperdensity. Effort was made to distinguish calcification and islands of noninfarcted tissue at the margins. On MRI, T1-weighted, T2-weighted, fluid attenuation inversion recovery, T2* gradient echo susceptibility, echoplanar–spin echo–T2 (B0 images of diffusion-weighted imaging), and susceptibility-weighted imaging were also examined for hemorrhage.

HT was classified by the method used in the European Cooperative Acute Stroke Study I (ECASS 1),12 illustrated in Figure 1.

Figure 1. Examples of ECASS classification of HT. A, hemorrhagic infarction (HI) on head CT with punctate foci of petechial hemorrhage within the left frontal infarct (white arrows), B, Diffusion-weighted MRI showing left sided infarcts (left panel), HI1 on gradient recalled echo (GRE) T2* susceptibility MRI from the same patient showing punctate foci of petechial hemorrhage within the left occipital infarct (dark arrows; right panel). C, Diffusion-weighted MRI showing left frontal infarct (left panel), HI2 on GRE T2* susceptibility MRI from the same patient as in D showing more confluent small foci of hemorrhage without mass effect (white arrows; right panel), D, parenchymal hematoma (PH)1 on head CT showing a small hematoma with mild surrounding edema within the right basal ganglia infarct (white arrow).
Infarct Volume
Infarct volume measurements were performed on supratentorial strokes. Infarct volume and supratentorial brain volume (SBV) were measured on axial T2 MRI. Stroke volume was expressed as percent of SBV (excluding ventricular volume) to account for varying head size during development. Volumes were measured by manual segmentation tracing using ITK-SNAP (www.itksnap.org). Infratentorial infarcts were not analyzed with these methods because studies have shown infarct volume for strokes involving the brain stem or cerebellum has limited association with symptoms.

Symptomatic HT
Children with HT were considered symptomatic if neurological symptoms were attributable to the HT, including worsening neurological deficits, new neurological deficits, headache, or new-onset seizures.

Statistical Analysis
STATA Version 10.1 (Stata Corporation, College Station, TX) was used for all analyses. Fisher exact test and relative risk with 95% exact CIs were used to evaluate associations of HT with stroke risk factors and treatment. Multivariable logistic regression was not performed due to small sample size. Wilcoxon rank sum test was used to determine whether age and PSOM scores differed between those with and without HT. Analysis of the relationship between outcome (PSOM scores) and HT was adjusted for infarct volume for the subset of children with supratentorial stroke. Generalized ordinal logistic regression was used to evaluate the relationship between PSOM scores (categorized 0 to 1, 1.5 to 3, 3.5 to 6, 6.5 to 10) and infarct volume, HT, age, and duration of follow-up. A 2-sided probability value of <0.05 was considered statistically significant.

Results
Patient Demographics
Sixty-three children (44 males [70%], 19 females [30%]) with AIS met inclusion criteria for this study. Median age at presentation was 5.7 years (interquartile range [IQR], 1.3 to 13.2 years). Race and ethnicity were 43 (68%) white non-Hispanic, 15 (24%) black, 3 (5%) Hispanic, and 2 (3%) mixed race.

Stroke Characteristics and Risk Factors
Stroke location by vascular territory is described in Figure 2. Strokes involved anterior circulation in 37 cases (59%), posterior circulation in 13 cases (21%), middle cerebral artery in 17 cases (27%), and both in 9 cases (14%). The most common primary risk factors for stroke in this cohort were vasculopathy (19 patients [30%]), cardiac conditions (17 patients [27%]), and thrombophilia (18 patients [29%]); (Table 1).

Timing and Modalities of Imaging
Timing and modality of imaging varied widely in this cohort dictated by variations in patient presentation and imaging availability in the facility of initial presentation. Thirty-two of 63 (51%) children presented directly to our tertiary care center. In-hospital stroke occurred in 23 (37%). Median time to the first image was 6.4 hours (IQR, 3.0 to 22.7 hours). The first image was head CT in 49 cases (78%). MRI was performed in 61 children (97%) at a median interval from symptom onset of 26.7 hours (IQR, 13.0 to 53.9 hours). Fifty-eight children (92%) had at least 2 images; the median number of images within 30 days of stroke was 3 (IQR, 2 to 3).

Among 49 children with stroke confined to the supratentorial compartment, median infarct volume, expressed as percent of SBV, was 2.0% (IQR, 0.4% to 11.6%) with a median absolute volume of 22.4 mL (IQR, 4.4 to 106.5 mL). Graphical analysis of infarct volumes showed frequency distribution was bimodal with an apparent threshold between 5% of SBV in 26 (53%) and ≥5% in 18 (47%).

Stroke Treatment
Aspirin was used in 34 of 63 (54%) children, systemic anticoagulation in 23 (36%), both in 1 (2%), and neither in 5 (8%). Children with stroke due to cardiac conditions or arterial dissection were more likely to receive anticoagulation than those without these diagnoses (65% versus 23%; P=0.0012; relative risk, 2.9; 95% exact CI, 1.5 to 5.5). No child received thrombolysis.
HT of AIS

HT occurred in 19 children (30%; 95% CI, 19% to 43%) within the first 30 days from symptom onset. Median time interval from stroke symptom onset to discovery of HT was 3.7 days (IQR, 1 to 13.7 days). Of the 23 subjects imaged within 4.5 hours of symptom onset, only 1 (4%) had HT on initial scan. HT was discovered in 3 of 35 subjects (9%) imaged at 4.5 to 24 hours from symptom onset, 3 of 27 (11%) imaged at 24 to 48 hours, 1 of 8 (13%) imaged at 48 to 72 hours, 3 of 23 (13%) imaged at 72 hours to 7 days, and 8 of 23 (35%) imaged at >7 days. Two of 19 children with HT were considered symptomatic: 1 had worsened focal deficits (dysarthria and hemiparesis) associated with punctate petechial HT (HI1) in the pons, and 1 had severe refractory headache associated with small parenchymal HT (PH1). Among 3 children with HT on initial scan, all were HI1. Among 16 children with HT on subsequent scans, 11 were classified HI1, 2 as HI2, 2 as PH1, and 1 as PH2. The single patient with PH2 had meningitis, developing petechial hemorrhage outside the stroke area. Three children had worsening HT on subsequent scans, all from HI1 to HI2. The median number of images in children without HT was 2 (IQR, 2 to 3); the median number of images in children with HT was 4 (IQR, 3 to 5; P = 0.0002 rank sum).

Table 2 presents analyses of factors associated with HT. HT was associated with larger infarct volumes. Median infarct volume was 10.8% of SBV (IQR, 5.0 to 17.0%) in children with HT compared with 1.3% (IQR, 0.4 to 6.3%) in those without HT (P = 0.0084, rank sum). In 35 subjects with isolated middle cerebral artery infarction, 0 of 6 with pure subcortical strokes had HT, 3 of 18 (17%) with pure cortical stroke had HT, and 5 of 11 (45%) with strokes affecting the cortical and subcortical structures had HT. However, location was highly correlated with infarct size (P = 0.035). Median age at presentation of children with HT was 2.8 years (IQR, 1.1 to 16.1 years) and without HT was 6.3 years (IQR, 1.8 to 12.6 years), but this difference was not statistically significant (P = 0.82 rank sum). The risk of HT was not associated with antithrombotic treatment group. Ten children in the anticoagulation treatment group were treated sequentially with aspirin and anticoagulation, of whom 2 had HT identified after being on anticoagulation for >10 days. BP data were available at admission in 61 of 63 patients (97%). BP was normal for age and sex in 41 patients (67%), was mildly elevated in 7 (12%), and was moderately elevated in 13 (21%). The highest absolute BP in any patient was 145/97 mm Hg in a 16-year-old. BP at admission was not associated with HT (Table 2).

In bivariable analysis of stroke risk factors, vasculopathy was associated with lower risk of HT (relative risk, 0.27; 95% exact CI, 0.07 to 1.06; P = 0.04). A trend for increased risk of HT in children with cardiac conditions (relative risk, 1.97; 95% CI, 0.96 to 4.05; P = 0.12) and meningitis (relative risk, 2.77; 95% CI, 1.37 to 5.59; P = 0.08) existed, although not statistically significant.

HT and Outcome

Follow-up information was available in 59 of 63 patients (94%) and was missing in 1 child with HT and in 3 without

Table 2. Analysis of Factors Associated With HT

<table>
<thead>
<tr>
<th>Variable (No. of Cases)</th>
<th>Occurrence of HT</th>
<th>RR*</th>
<th>95% Exact CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume (supratentorial stroke)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5% of SBV (26)</td>
<td>3 (12%)</td>
<td>(Reference)</td>
<td>(Reference)</td>
<td>(Reference)</td>
</tr>
<tr>
<td>≥5% of SBV (18)</td>
<td>10 (56%)</td>
<td>4.81</td>
<td>1.54–15.08</td>
<td>0.0026</td>
</tr>
<tr>
<td>Acute antithrombotic treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent alone (34)</td>
<td>12 (35%)</td>
<td>(Reference)</td>
<td>(Reference)</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Systemic anticoagulation (24)</td>
<td>5 (21%)</td>
<td>0.6</td>
<td>0.2–1.5</td>
<td>0.26</td>
</tr>
<tr>
<td>None (5)</td>
<td>2 (40%)</td>
<td>1.1</td>
<td>0.4–3.6</td>
<td>1.00</td>
</tr>
<tr>
<td>BP at presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (41)</td>
<td>12 (29%)</td>
<td>(Reference)</td>
<td>(Reference)</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Mildly elevated (7)</td>
<td>2 (29%)</td>
<td>0.98</td>
<td>0.28–3.46</td>
<td>0.97</td>
</tr>
<tr>
<td>Moderately elevated (13)</td>
<td>5 (38%)</td>
<td>1.31</td>
<td>0.57–3.03</td>
<td>0.73</td>
</tr>
<tr>
<td>Primary stroke risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculopathy (19)</td>
<td>2 (11%)</td>
<td>0.27</td>
<td>0.07–1.06</td>
<td>0.04†</td>
</tr>
<tr>
<td>Cardiac conditions (17)</td>
<td>8 (47%)</td>
<td>1.97</td>
<td>0.96–4.05</td>
<td>0.12</td>
</tr>
<tr>
<td>Cryptogenic (8)</td>
<td>1 (13%)</td>
<td>0.38</td>
<td>0.06–2.48</td>
<td>0.42</td>
</tr>
<tr>
<td>Tumor-related (8)</td>
<td>4 (50%)</td>
<td>1.83</td>
<td>0.81–4.15</td>
<td>0.23</td>
</tr>
<tr>
<td>Meningitis (4)</td>
<td>3 (75%)</td>
<td>2.77</td>
<td>1.37–5.59</td>
<td>0.08</td>
</tr>
<tr>
<td>Isolated thrombophilia (3)</td>
<td>1 (33%)</td>
<td>1.11</td>
<td>0.21–5.76</td>
<td>1.00</td>
</tr>
<tr>
<td>Sickle cell anemia (2)</td>
<td>0 (0%)</td>
<td>. . .</td>
<td>. . .</td>
<td>1.00</td>
</tr>
<tr>
<td>Other systemic disease (2)</td>
<td>0 (0%)</td>
<td>. . .</td>
<td>. . .</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Analysis of RR for primary stroke risk factors reflects comparison of each individual factor to all others in bivariable analysis.
†Although the P value for this association is significant, the 95% CI includes 1 because the CI for the RR is extremely sensitive to small numbers.
RR indicates relative risk.
HT. Median time to follow-up was 13.1 months, (IQR. 7.5 to 21.6 months). In the entire cohort, the median PSOM score in children with HT was 3 (IQR, 1.5 to 6), significantly worse than in those without HT whose median PSOM score was 1 (IQR, 0.5 to 3; P=0.0024 rank sum; Figure 3A). Analyses accounting for infarct volume were performed in 41 of 49 children with supratentorial stroke for whom both PSOM and infarct volume were available. Median PSOM score in children with HT was 3.5 (IQR, 1.5 to 6), significantly worse than in those without HT whose median score was 1.25 (IQR, 0.5 to 3; P=0.0054 rank sum; Figure 3B). Increasing PSOM scores correlated with increasing ECASS grades of HT (OR, 2.0 per grade; 95% CI, 1.0 to 4.0; P=0.04). Median PSOM was 1.5 (IQR, 0.5 to 2.5) in children with infarct volume <5% SBV and 4 (IQR, 1.5 to 6) in those with infarct volume ≥5% SBV (P=0.0027 rank sum). In multivariable analysis adjusted for duration of follow-up, worse PSOM scores were associated with infarct volume ≥5% of total SBV (OR, 4.0; 95% CI, 1.1 to 15; P=0.04). Trends existed toward association of worse PSOM scores with HT of the infarction (OR, 4.0; 95% CI, 0.9 to 18; P=0.07) and with age (OR, 0.90 per year; 95% CI, 0.81 to 1.01; P=0.07).

Discussion
In this cohort, 30% (95% CI, 19% to 43%) of children with acute AIS had evidence of HT within 30 days. In ECASS II, 39.6% of adult patients with AIS in the placebo arm had HT within 7 days, but they were imaged using a standardized protocol. Since our study was retrospective and observational, it is possible additional children who were not reimaged had asymptomatic HT. This limitation is highlighted by the finding that children with HT had more images than children without HT, although only 2 had symptomatic hemorrhage. However, our systematic, blinded review of all available imaging minimized bias in detection of HT. In our patients, 84% of HT was petechial, comparable to the 92% found in ECASS II placebo patients. Only PH2 hemorrhage is associated with worse outcome in adults, and most symptomatic adult HT is PH2. However, with only 2 symptomatic HTs in our cohort, it was not possible to determine risk factors for symptomatic HT. Even with only 3 PHs, a trend (P=0.07) existed toward worse outcome in patients with HT in multivariable analysis, suggesting that even clinically silent HTs may impact long-term recovery and function in children. Similarly, asymptomatic hemorrhage has been associated with worse outcome in adults after thrombolysis.

We analyzed factors predicting timing and occurrence of HT in children because these have not been previously evaluated. Of 23 children imaged within 4.5 hours of symptom onset, only 1 had HT on initial scan, suggesting that few patients would be excluded from thrombolysis and antithrombotic treatment trials due to hemorrhage. We identified 40% of the HT at >72 hours from stroke symptom onset. However, we cannot ascertain the exact timing of occurrence of HT due to the observational nature of our study. Information about prevalence of different ECASS HT grades will be important when examining potential adverse effects in any antithrombotic or thrombolysis trial. Systemic anticoagulation was not significantly associated with HT in this study, although we had limited power to detect associations or to adjust for potential confounders. For example, children with arterial dissection or a cardioembolic source were more likely to receive anticoagulation, potentially confounding any treatment association with HT. Moreover, in this selected population, clinicians may have made treatment choices with antithrombotic or thrombolysis trial. Systemic anticoagulation is needed to identify treatment associations with HT definitively. BP on admission was also not associated with the risk of HT. Reduced risk for HT was seen with vasculopathy compared with other stroke risk factors, but the strength of this association is uncertain due to the small size and observational nature of our study. These preliminary findings warrant further investigation to clarify the role of stroke subtype as a risk factor in the course and pathogenesis of HT. A limitation of our study is inability to control for initial clinical stroke severity, a risk factor for HT in adults. Presently, no validated method exists to estimate the Pediatric National Institutes of Health Stroke Scale score retrospectively.
tively from narrative neurological examinations. Additional studies evaluating this variable are needed.

This is the first pediatric cohort in which a relationship between supratentorial stroke volume and HT has been established, a well-known finding in adult stroke.\(^{16,18}\) Although the ECASS classification for HT has not been previously used in children, in unadjusted analysis, increasing HT grade was associated with worse outcome on a validated measurement tool (PSOM) in the current study. In multivariable analysis, HT was not an independent risk factor for worse outcome. However, the study sample was small, and the probability value of 0.07 suggests further study of HT as an independent predictor of neurological outcome should be investigated in a larger cohort. Furthermore, infarct volume \(\geq5\%\) SBV was associated with worse outcome in children with supratentorial strokes. This expands the findings of Ganesan et al who demonstrated that infarct volume \(>10\%\) supratentorial intracranial volume is associated with worse outcome in children with middle cerebral artery stroke.\(^{13}\) This study provides hypothesis-generating information on risk factors for HT in children and on the relationship of HT to neurological outcome that should be explored in larger cohorts.

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Disclosures

R.N.I. is on the Clinical Event Committee for the Pediatric Berlin Heart Trial (industry-sponsored).

References

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