Frequency of Hematoma Expansion After Spontaneous Intracerebral Hemorrhage in Children

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IMPORTANTANCE Hematoma expansion is the only modifiable predictor of outcome in adult intracerebral hemorrhage; however, the frequency and clinical significance of hematoma expansion after childhood intracerebral hemorrhage are unknown.

OBJECTIVE To assess the frequency and extent of hematoma expansion in children with nontraumatic intracerebral hemorrhage.

DESIGN, SETTING, AND PARTICIPANTS Prospective observational cohort study at 3 tertiary care pediatric hospitals. Children (≥37 weeks' gestation to 18 years) with nontraumatic intracerebral hemorrhage were enrolled in a study from 2007 to 2012 focused on predictors of outcome. For this planned substudy of hematoma expansion, neonates 28 days or younger and participants with isolated intraventricular hemorrhage were excluded. Children with 2 head computed tomography (CT) scans within 48 hours were evaluated for hematoma expansion and were compared with children with only 1 head CT scan. Consent for the primary cohort was obtained from 73 of 87 eligible participants (84%); 41 of 73 children enrolled in the primary cohort met all inclusion/exclusion criteria for this substudy, in whom 22 had 2 head CT scans obtained within 48 hours that could be evaluated for hematoma expansion. Within our substudy cohort, 21 of 41 (51%) were male, 25 of 41 (61%) were white, 16 of 41 (39%) were black, and median age was 7.7 years (interquartile range, 2.0-13.4 years).

MAIN OUTCOME AND MEASURE Primary outcome was prevalence of hematoma expansion.

RESULTS Of 73 children, 41 (56%) met inclusion criteria, and 22 (30%) had 2 head CT scans to evaluate expansion. Among these 22 children, median time from symptom onset to first CT was 2 hours (interquartile range, 1.3-6.5 hours). Median baseline hemorrhage volume was 19.5 mL, 1.6% of brain volume. Hematoma expansion occurred in 7 of 22 (32%). Median expansion was 4 mL (interquartile range, 1-11 mL). Three children had significant (>33%) expansion; 2 required urgent hematoma evacuation. Expansion was not associated with poorer outcome. Compared with children with only 1 head CT scan within 48 hours, children with 2 head CT scans had larger baseline hemorrhage volumes ($P = .05$) and were more likely to receive treatment for elevated intracranial pressure ($P < .001$).

CONCLUSIONS AND RELEVANCE Hematoma expansion occurs in children with intracerebral hemorrhage and may require urgent treatment. Repeat CT should be considered in children with either large hemorrhage or increased intracranial pressure.

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Hematoma Expansion in Intracerebral Hemorrhage

In a large pediatric study from northern California, intracerebral hemorrhage (ICH) had an incidence of 1.4 per 100,000 person-years. Spontaneous ICH accounts for about 50% of stroke in children compared with 15% in adults. In adults, hypertension is the most common cause of ICH while in children, secondary factors, like vascular malformations, predominantly cause ICH. Just as in adults, ICH is understudied in children.

In adult ICH, initial hematoma volume is the strongest predictor of mortality and functional outcome. Location is also an important predictor of outcome; however, because both initial ICH volume and location are determined at presentation, hematoma expansion is currently the only modifiable predictor of outcome in adult ICH. Moreover, data from the adult INTERACT1 trial that focused on blood pressure control to prevent ICH expansion suggest a clear dose-response relationship between the magnitude of hematoma expansion and functional outcome and mortality, when using either absolute or proportional definitions of expansion (increase in baseline hematoma volume of ≥12.5 mL or an increase of >33%). For this reason, hematoma expansion5-9 and its predictors, like the “spot sign,” a marker of active bleeding on computed tomography (CT) angiography,10 and contrast extravasation11 on routine head CT, are important research areas in adults with primary (hypertensive) ICH. Attempts to reduce the morbidity caused by hematoma expansion in adult ICH led to a phase 3 randomized clinical trial to assess whether recombinant factor VIIa would minimize hematoma expansion and improve outcome2 as well as to several other ongoing trials focused on preventing hematoma expansion.

Hematoma expansion has rarely been studied in ICH from secondary causes like vascular malformations. At 1 center, in adults with ICH due to brain arteriovenous malformation, aneurysm, or tumor, significant hematoma expansion (>33%) occurred in 6 of 30 (20%) within 24 hours. In children, the frequency and clinical significance of hematoma expansion, appropriate timing of follow-up neuroimaging to assess for hematoma expansion, and optimal treatment of hematoma expansion are unknown. Hematoma expansion after ICH is concerning because the strongest outcome predictor in pediatric ICH is large hemorrhage volume. Hemorrhage volume may be expressed as an absolute volume or as a percentage of total brain volume (TBV). Expression of ICH as a percentage of TBV is particularly important in children given that children of varying ages have different head sizes. Intracerebral hemorrhage volume greater than 2% of TBV in children is approximately equivalent to 30 mL of ICH in an adult and is associated with moderate disability; while ICH volume greater than or equal to 4% of TBV (approximately equivalent to 60 mL in an adult) is associated with severe disability. Our primary objective was to investigate the prevalence and extent of hematoma expansion in children with nontraumatic ICH. A secondary objective was to assess for associations that predict hematoma expansion.

Methods

The institutional review boards of Vanderbilt, Children’s Hospital of Philadelphia, and Johns Hopkins approved the study.
Hemorrhage Volume Assessments
Volumetric analysis of TBV and intraparenchymal hemorrhage volume was performed using ImageJ as previously described (http://rsb.info.nih.gov/ij/download.html). Total brain volume included the cerebral hemispheres, cerebellum, and brainstem. Intracerebral hemorrhage was expressed both as an absolute value in milliliters and as a percentage of TBV. Significant hematoma expansion was defined as greater than 33% of baseline ICH volume.

Statistical Analysis
STATA version 11.1 (StataCorp) was used for all analyses. Fisher exact tests were used to analyze predictors of hematoma expansion for categorical variables. The Wilcoxon rank sum test was used to determine the difference in time to initial and repeat head CT and difference in outcome for children with and without hematoma expansion. We compared the frequency of significant hematoma expansion in this pediatric ICH cohort with the frequency of significant hematoma expansion in adults with secondary ICH through binomial comparison of proportions. Confidence intervals were calculated by exact methods. A 2-sided probability value of ≤.05 was considered statistically significant.

Results
Consent for the primary cohort was obtained from 73 of 87 eligible participants (84%). Of 73 children enrolled in the primary cohort, 41 children met all inclusion criteria for this substudy (Figure 1), and 22 children had 2 head CT scans obtained within 48 hours that could be evaluated for hematoma expansion. Within our substudy cohort, 21 of 41 (51%) were male, 25 of 41 (61%) were white, 16 of 41 (39%) were black, and median age was 7.7 years (interquartile range [IQR], 2.0-13.4 years). Intracerebral hemorrhage was due to coagulopathy or vascular cause in 19 of 22 children (86%) with 2 CT scans (Table 1). Median baseline ICH volume among all 41 children without hematoma evacuation regardless of whether a second CT scan was obtained was 12 mL (IQR, 4.1-24.0 mL) or 1.0% of TBV (IQR, 0.4%-2.2%). In 22 children with 2 head CT scans, median baseline ICH volume was 19.5 mL (IQR, 6.2-27.8 mL) or 1.6% of TBV (IQR, 0.6%-2.5%). For 17 of 22 children with 2 CT scans in whom time of symptom onset could be determined, the median time from symptom onset to first CT was 2 hours (IQR, 1.3-6.5 hours), and the median time from symptom onset to second CT was 14.1 hours (IQR, 6.5-23.2 hours). Fourteen participants had intracranial pressure monitoring (12 ventriculostomy and 2 subdural bolt).

Hematoma Expansion and Outcome
Hematoma expansion was common, occurring in 7 of 22 children (32%) undergoing 2 head CT scans and 7 of 41 (17%) among all children with intraparenchymal hemorrhage (without urgent hematoma evacuation). Figure 2 shows a participant with hematoma expansion on CT. Median ICH volume expansion was 4 mL (IQR, 1.11 mL) or 0.3% of TBV (IQR, 0.1%-1.1%), 32% of baseline ICH volume (IQR, 16%-53%). A total of 3 of 22 children (14%) with 2 head CT scans or 7% of all 41 children without hematoma evacuation had significant expansion (>33% of baseline hematoma volume).

All 3 children with significant expansion had vascular malformations. Comparisons of demographics, clinical characteristics, ICH volumes, and outcomes in those children with and without hematoma expansion are in Table 2. Short-term outcome assessment revealed that overall, 4 of 22 children (18%) with 2 head CT scans had moderate deficits that interfered with function (total PSOM score ≥1). Eleven of these 22 children (50%) had severe impairment (total PSOM score ≥2) 3 months after ICH. None of these 22 children with 2 CT scans died. There was no association between hematoma expansion and poor outcome (Table 2). All 3 children (100%) with significant hematoma expansion had severe impairment, and 8 of 19 children (42%) without significant hematoma expansion had severe impairment (P = .23).
**Children With Surgical Hematoma Evacuation**

The 5 children with urgent surgical evacuation before a second CT scan was obtained had hematoma sizes that ranged from 2.4% to 6.2% of TBV. Children who had early evacuation often had both ICH and subarachnoid hemorrhage (4 of 5 children) and had both large hematoma size and initially poor or worsening Glasgow Coma Scale scores (5 of 5 children). At 3 months, the median PSOM score was 1.5; mean, 2.7; and range, 1 to 6. There were 2 children with 2 head CT scans who had significant hematoma expansion and proceeded to have urgent evacuation after the second CT. Both of these participants had initial ICH volume greater than 2% of TBV with an initial Glasgow Coma Scale score of 7 for both children and worsening neurological examination findings. The PSOM scores were 2 and 6 at 3 months.

**Entire Cohort of Children With and Without 2 Head CT Scans**

Comparisons of demographics, clinical characteristics, ICH volumes, and outcomes in those children with and without a sec-

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**Table 1. Intracerebral Hemorrhage Etiology in 41 Children**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
<th>2 Head CT Scans Performed Within 48 h (n = 22)</th>
<th>1 Head CT Scan Performed Within 48 h (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous malformation</td>
<td>9 (40)</td>
<td>6 (32)</td>
<td></td>
</tr>
<tr>
<td>Cavernous angioma</td>
<td>4 (18)</td>
<td>4 (21)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm</td>
<td>3 (14)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Developmental venous anomaly</td>
<td>0</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Moyamoya</td>
<td>0</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy &lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>3 (14)</td>
<td>2 (11)</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>1 (4)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (14)</td>
<td>2 (11)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CT, computed tomography.

<sup>a</sup> One child had both hemophilia A and aneurysm.

<sup>b</sup> Thrombocytopenia, vitamin K deficiency, and hemophilia A.

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**Figure 2. Example of Hematoma Expansion**

Hematoma expansion 40% between first (A-B) (30 mL) and second (C-D) (42 mL) computed tomography scan 2.3 hours apart.
Hematoma Expansion in Intracerebral Hemorrhage

**Discussion**

Understanding the prevalence and sequelae of hematoma expansion in children is a source of uncertainty in their clinical care and represents a potential critical therapeutic target in improving neurological outcome after ICH. We report one of the largest prospective studies of pediatric ICH. Hematoma expansion affected 7 of 22 children (32%) with clinical concern for hematoma growth; expansion was significant (>33)% in 3 of 22 (14%). Among all 41 children in our cohort, hematoma expansion occurred in 17% and was significant in 7%. In our cohort, the median increase in absolute hematoma volume was 4 mL and 0.3% of TBV. It is unknown what amount of hematoma growth in terms of either absolute volume or percentage of TBV will be important in a child.

To our knowledge, other studies have not evaluated hematoma expansion after ICH in children. The adult ICH literature has focused on hematoma expansion after primary (hypertensive) ICH; however, there is scant literature on hematoma expansion in the setting of secondary ICH in adults. Children tend to have “secondary ICH” due to vascular malformations, anticoagulation, or inherited or acquired coagulopathy. No child in this study cohort had ICH related to hypertension, although other studies have reported hypertension as a risk factor in less than 5% of children with ICH.21,22

The prevalence of hematoma expansion greater than 33% from baseline in our cohort of children was not significantly different from the prevalence of hematoma expansion in adults with ICH due to causes other than hypertension. In children, significant hematoma expansion was present in 14% (3 of 22) (95% CI, 3%-35% by exact methods) compared with 20% (6 of 20) (95% CI, 8%-38% by exact methods) in adults with ICH due to brain arteriovenous malformation, aneurysm, or tumor (P = .54).13

### Table 2. Age, ICH Volume, ICP, and 3-Month Outcome in Children With and Without Hemorrhage Expansion

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>With Expansion (n = 7)</th>
<th>Without Expansion (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>9.0 (1.8-14.2)</td>
<td>6.7 (0.6-10.3)</td>
<td>.65*</td>
</tr>
<tr>
<td>Baseline ICH volume, mLa</td>
<td>20.8 (2.0-24.7)</td>
<td>17.3 (6.2-30.3)</td>
<td>.65*</td>
</tr>
<tr>
<td>Baseline ICH as % of TBVa</td>
<td>1.4 (0.2-2.2)</td>
<td>1.9 (0.6-2.5)</td>
<td>.65*</td>
</tr>
<tr>
<td>No. (%) with elevated ICP requiring intervention</td>
<td>4 (57)</td>
<td>9 (60)</td>
<td>&gt;.99^c</td>
</tr>
<tr>
<td>Time between first and second head CT, h</td>
<td>9.4 (4.7-15.2)</td>
<td>10.1 (4.5-23.3)</td>
<td>.70*</td>
</tr>
<tr>
<td>PSOM score at 3 mo</td>
<td>2 (0.5-3)</td>
<td>1.5 (0.5-3)</td>
<td>.86*</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IQR, interquartile range; PSOM, Pediatric Stroke Outcome Measure; TBV, total brain volume.

* Wilcoxon rank sum.

### Table 3. Age, ICH Volume, ICP, and 3-Month Outcome in Children With and Without 2 Head CT Scans

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>2 Head CTs Performed Within 48 h (n = 22)</th>
<th>1 Head CT Performed Within 48 h (n = 19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>7.8 (1.8-13.1)</td>
<td>8.2 (2.2-13.9)</td>
<td>.69*</td>
</tr>
<tr>
<td>Baseline ICH volume, mL</td>
<td>19.5 (6.2-27.8)</td>
<td>7.0 (2.9-16.2)</td>
<td>.05a,b</td>
</tr>
<tr>
<td>Baseline ICH as % of TBV</td>
<td>1.6 (0.6-2.5)</td>
<td>0.7 (0.3-1.0)</td>
<td>.06*</td>
</tr>
<tr>
<td>No. (%) with elevated ICP requiring intervention</td>
<td>13 (59)</td>
<td>5 (5)</td>
<td>&lt;.001b,c</td>
</tr>
<tr>
<td>PSOM score at 3 mo</td>
<td>1.75 (0.5-3)</td>
<td>1 (0.5-2)</td>
<td>.35*</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IQR, interquartile range; PSOM, Pediatric Stroke Outcome Measure; TBV, total brain volume.

a Wilcoxon rank sum.
b Significant probability value.
c Fisher exact test.
Outcomes in children with hematoma expansion were not significantly worse than in children without hematoma expansion. This comparison may be confounded by the fact that second head CT scans were not performed early enough or at a specified interval such as 6 hours in all children, causing us to miss hematoma expansion in some. While it is possible that hematoma expansion does not affect outcome, a more likely explanation is that our sample size was too small to detect a difference. This is supported by our observation that all 3 children (100%) with significant hematoma expansion had severe impairment, and only 8 of 19 children (42%) without significant hematoma expansion had severe impairment ($P = .23$). Moreover, aggressive neurointensive care and management of intracranial pressure may have improved the probability of a more favorable outcome.

The present study has several limitations. Despite its prospective design, head CT scans were not obtained at prescribed intervals in this cohort. Performing CT scans for research only and without clear benefits is not feasible in children because of the risks of radiation exposure. Therefore, children with 2 head CT scans performed for clinical indications were more likely to have relatively large ICH volumes at baseline and were more likely to have received treatment for elevated intracranial pressure. Although to our knowledge this is the largest prospective study of ICH in children, the sample size is still relatively small. Therefore, the study was unable to identify predictors of ICH expansion or to demonstrate a relationship between an increase in size of the hematoma and clinical outcome. A much larger study is required to determine predictors of expansion and the contribution of hemorrhage expansion to functional outcome.

Despite its limitations, our study has several strengths. The prospective design permits identification of ICH cases without reliance on International Classification of Diseases, Ninth Revision codes, which misclassify pediatric stroke diagnoses. The only previously published large cohort of children with nontraumatic parenchymal hemorrhage is retrospective and images are not available for review. In the current study, images were available and careful volumetric analysis of hemorrhage volume was performed, which is a more accurate method for the assessment of hematoma volume than shorthand or “bedside” methods such as ABC/2, particularly for irregularly shaped hematomas. This study provides clinicians with useful information regarding the risk of hematoma expansion and with information about which children might be most in need of a rapid second head CT scan.

Conclusions

Hematoma expansion occurred in 7 of 22 children (32%) with 2 head CT scans performed for clinical concern for hematoma growth. Hematoma expansion met the definition of significant growth, greater than 33% of initial hematoma volume, in 3 of 22 children (14%) with 2 head CT scans. Repeat head CT should be considered in those with large ICH volume, particularly in children with ICH volume greater than 2% of TBV at baseline, ICH related to vascular malformation or coagulopathy, and increased intracranial pressure.

**REFERENCES**


