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Hematoma Expansion is Common after Spontaneous Intracerebral Hemorrhage in Children

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Abstract

Importance—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.

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Dr. Beslow and Dr. Jordan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Rebecca Ichord MD, member of Clinical Event Committee for Berlin Heart EXCOR Pediatric IDE trial.

Authors' Contributions:

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Objective—To assess the frequency and extent of hematoma expansion in children with non-traumatic intracerebral hemorrhage.

Design—Prospective cohort study.

Setting—Three tertiary care pediatric hospitals.

Participants—Children (≥37 weeks gestation-18 years) with non-traumatic intracerebral hemorrhage were enrolled in a three-center prospective observational study from 2007–2012 focused on predictors of outcome. For this planned sub-study of hematoma expansion, neonates ≤28 days and participants with isolated intraventricular hemorrhage were excluded. Children with two head CTs within 48 hours were evaluated for hematoma expansion and were compared to children with only one head CT. Consent for the primary cohort was obtained from 73 of 87 eligible subjects (84%); 41 of 73 children enrolled in the primary cohort met all inclusion/exclusion criteria for this sub-study in whom 22 had two head CTs obtained within 48 hours that could be evaluated for hematoma expansion. Within our sub-study cohort, 21/41 (51%) were male, 25/41 (61%) were white, 16/25 (39%) were black, and median age was 7.7 years (interquartile range 2.0–13.4 years).

Main Outcome Measure—Primary outcome was prevalence of hematoma expansion.

Results—Of 73 children, 41 (56%) met inclusion criteria, and 22 (30%) had 2 head CTs to evaluate expansion. Among these 22 children, median time from symptom onset to first CT was two hours (interquartile range 1.3–6.5 hours). Median baseline hemorrhage volume was 19.5mL, 1.6% of brain volume. Hematoma expansion occurred in (7/22) 32%. Median expansion was 4mL (interquartile range 1–11mL). Three children had significant (>33%) expansion; two required urgent hematoma evacuation. Expansion was not associated with poorer outcome. Compared to children with only one head CT within 48 hours, children with two head CTs 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.

Introduction

In a large pediatric study from northern California, intracerebral hemorrhage (ICH) had an incidence of 1.4 per 100,000 person-years.[1] Spontaneous ICH accounts for about 50% of stroke in children compared to 15% in adults. In adults hypertension is the most common cause of ICH while in children, secondary causes, like vascular malformations predominantly cause ICH.[2] Just as in adults, ICH is understudied in children.

In adult ICH, initial hematoma volume is the strongest predictor of mortality and functional outcome.[3] Location is also an important predictor of outcome;[4] 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.[5,6] Moreover, data from the adult INTERACT1 trial[7] 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%).[7,8] For this reason, hematoma expansion[5,9] and its predictors, like the “spot sign,” a marker of active bleeding on CT angiography,[10] and contrast extravasation[11] 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 III randomized clinical trial to assess whether recombinant Factor VIIa would minimize

hematoma expansion and improve outcome[12] 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 one center, in adults with ICH due to brain arteriovenous malformation (AVM), aneurysm, or tumor, significant hematoma expansion (>33%)[8] occurred in 6/30 (20%) within 24 hours.[13] 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.[14,15] 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. ICH volume >2% of TBV in children is approximately equivalent to 30 mL ICH in an adult[3] and is associated with moderate disability[2], while ICH volume ≥4% of TBV (approximately equivalent to 60 mL in an adult)[3] is associated with severe disability.[2,14] Our primary objective was to investigate the prevalence and extent of hematoma expansion in children with non-traumatic ICH. A secondary objective was to assess for associations that predict hematoma expansion.

Methods

Study Design and Subjects

The current report is a sub-study from a prospective cohort of perinatal (full-term newborns ≥37 weeks gestation to ≤28 days) and childhood subjects (>28 days of life to 18 years) presenting between 2007 and 2012 with non-traumatic ICH at three tertiary care institutions (Vanderbilt, Children's Hospital of Philadelphia, and Johns Hopkins).[16] For the primary cohort, spontaneous ICH was defined as intraparenchymal hemorrhage (IPH) and/or intraventricular hemorrhage (IVH) not caused by trauma, brain tumor, or hemorrhagic transformation of arterial ischemic stroke or cerebral sinus venous thrombosis. Isolated subarachnoid hemorrhages (SAH) were excluded. All ICHs were confirmed on head computed tomography (CT) or magnetic resonance imaging (MRI), but the first image was head CT in all non-perinatal subjects. Additional exclusion criteria for this sub-study included the following: perinatal ICH because repeat head CT is rarely done in this age group, surgical evacuation of hematoma before a second CT was obtained, or isolated IVH. None of the hospitals had a protocol for repeat head CT. Subjects that did not have a second head CT (either had MRI or no additional imaging within 48 hours) were compared to those with 2 head CTs. Subjects with one CT were not included in the group assessed for hematoma expansion for several reasons. First, MRI is part of the standard work-up for ICH etiology in children and does not imply that providers were concerned about hematoma stability versus expansion. A second head CT within 48 hours, which requires radiation, does suggest suspicion of hematoma expansion. Second, hematoma volumes on MRI versus CT are not directly comparable. One adult study found that hematoma volumes on head CT were 80% of those seen on the gradient recalled echo (GRE) sequence MRI.[17] This relationship has not been validated in children.

Clinical and Radiographic Data

Data were acquired from parental interview and abstraction of medical records. Radiographic information including IPH, IVH, or both was recorded. At each follow-up stroke clinic visit, subjects were assessed for neurological outcome via a standardized neurological examination, the pediatric stroke outcome measure (PSOM). The PSOM is a validated outcome score for infants and children with stroke.[18,19] The total PSOM score is

the sum of subscores assigned in five domains: right sensorimotor, left sensorimotor, expressive language, receptive language, and cognition/behavior. PSOM domain subscores are graded based on the examiner's impression of all findings in the full neurologic exam as 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). The total score ranges from 0 to 10. Severe impairment was defined in this study as a total PSOM ≥2.[18,19]

Hemorrhage Volume Assessments

Volumetric analysis of TBV and IPH volume was performed using ImageJ as previously described (http://rsb.info.nih.gov/ij/download.html).[14,15] TBV included the cerebral hemispheres, cerebellum, and brainstem. Ventricular volume was not subtracted from the TBV so that TBV would not vary with hydrocephalus. ICH was expressed both as an absolute value in milliliters and as a percent of TBV.[2,14,15,20]

Significant hematoma expansion was defined as >33% of baseline ICH volume.[7,8]

Statistical Analysis

STATA version 11.1 (StataCorporation, College Station, TX) 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 utilized 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[13] through binomial comparison of proportions. Confidence intervals were calculated by exact methods. A two-sided probability value of ≤.05 was considered statistically significant.

The institutional review boards of all three medical centers approved the study. Written informed consent was obtained from subjects' parents and assent from children ≥7 years. Ascertainment was thought to be near-complete since the institutions have clinical protocols for ICH management that include stroke service consultation.

Results

Consent for the primary cohort was obtained from 73 of 87 eligible subjects (84%). Of 73 children enrolled in the primary cohort, 41 children met all inclusion/exclusion criteria for this sub-study (Figure 1), and 22 children had two head CTs obtained within 48 hours that could be evaluated for hematoma expansion. Within our sub-study cohort, (21/41) (51%) were male, 25/41 (61%) were white, 16/41 (39%) were black, and median age was 7.7 years (IQR 2.0–13.4 years). ICH was due to coagulopathy or vascular cause in 19/22 children (86%) with 2 CTs (Table 1). Median baseline ICH volume among all 41 children without hematoma evacuation regardless of whether a second CT 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 CTs, 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 CTs 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 subjects had ICP monitoring (12 ventriculostomy, 2 subdural bolt).

Hematoma Expansion and Outcome

Hematoma expansion was common, occurring in 7/22 children (32%) undergoing two head CTs, and 7/41 (17%) among all children with intraparenchymal hemorrhage (without urgent

hematoma evacuation). Median ICH volume expansion was 4 mL (IQR 1–11 mL) or 0.3% of TBV (IQR 0.1–1.1% of TBV), 32% of baseline ICH volume (IQR 16–53%). A total of 3/22 children (14%) with two head CTs or 7% of all 41 children without hematoma evacuation had significant expansion (>33% of baseline hematoma volume).

All three children with significant expansion had vascular malformations. Comparisons of demographics, clinical characteristics, ICH volumes, and outcomes in those children with and without hemorrhage expansion are in Table 2.

Short-term outcome assessment revealed that overall, 4/22 children (18%) with 2 head CTs had moderate deficits that interfered with function (total PSOM ≥1). Eleven of these 22 children (50%) had severe impairment (total PSOM ≥2) 3 months after ICH. None of these 22 children with 2 CTs 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 8/19 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 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 SAH (4/5 children) and had both large hematoma size and initially poor or worsening Glasgow Coma Scale scores (5/5 children). PSOMs were median 1.5, mean of 2.7, range (1–6) at 3 months. There were 2 children with 2 head CTs that had significant hematoma expansion and proceeded to have urgent evacuation after the second CT. Both of these subjects had initial ICH volume >2% of TBV with initial GCS of 7 for both children and worsening neurological exam. PSOMs were 2 and 6 at 3 months.

Entire Cohort of Children With and Without Two Head CTs

Comparisons of demographics, clinical characteristics, ICH volumes, and outcomes in those children with and without a second CT within 48 hours are found in Table 3. As expected, children with 2 CTs had a larger baseline median ICH volume than those who did not have 2 head CTs. Children with ICH that was >2% of TBV were more likely to have a second head CT (10/13, 77%) than children with ICH volume ≤2% of TBV (12/28, 43%) (p=.05, Fisher exact). Among children with 2 CTs, the second CT was obtained earlier in children with larger ICH volumes (>2% of TBV) than in those with smaller ICH volumes (≤2% TBV), with a median time to second head CT of 7.7 hours (IQR 3.6–11.5 hours) versus 17.4 hours (IQR 14.1–33.4 hours) (p=.001, Wilcoxon rank-sum). Children with 2 CTs in 48 hours were also more likely to receive treatment for elevated intracranial pressure (ICP). Of the 19 children who did not have 2 CTs in 48 hours, none had clinical deterioration requiring urgent hematoma evacuation. However, the 2 children in the cohort who died were both in the 1 head CT group. They were critically ill. The first child had severe congenital heart disease, fungal sepsis, and required extracorporeal membrane oxygenation. The subject's massive ICH was impetus to withdraw care. The other child also had congenital heart disease and was stable for 10 days after a small ICH but then died suddenly after a presumed cardiac arrhythmia.

Comment

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 7/22 children (32%) with clinical concern for hematoma growth; expansion was significant (>33%)[6–8] in 3/22 (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 percent 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 <5% of children with ICH.[21,22]

The prevalence of hematoma expansion >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% (3/22) (95% CI: 3–35% by exact methods) compared to 20% (6/20) (95% CI: 8–38% by exact methods) in adults with ICH due to brain AVM, aneurysm, or tumor (p=.54).[13]

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 CTs were not performed early enough or at a specified time 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 ICP may have improved the probability of a more favorable outcome.

The present study has several limitations. Despite its prospective design, head CTs were not obtained at prescribed time intervals in this cohort. Performing CTs for research only and without clear benefits is not feasible in children due to the risks of radiation exposure. Therefore, children with two head CTs performed for clinical indications were more likely to have relatively large size ICH volumes at baseline and were more likely to have received treatment for elevated intracranial pressure. Though 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 ICD-9 codes, which misclassify pediatric stroke diagnoses.[23,24] The only previously published large cohort of children with non-traumatic parenchymal hemorrhage is retrospective and images are not available for review.[1] 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,[15,20,25,26] 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.

Summary

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

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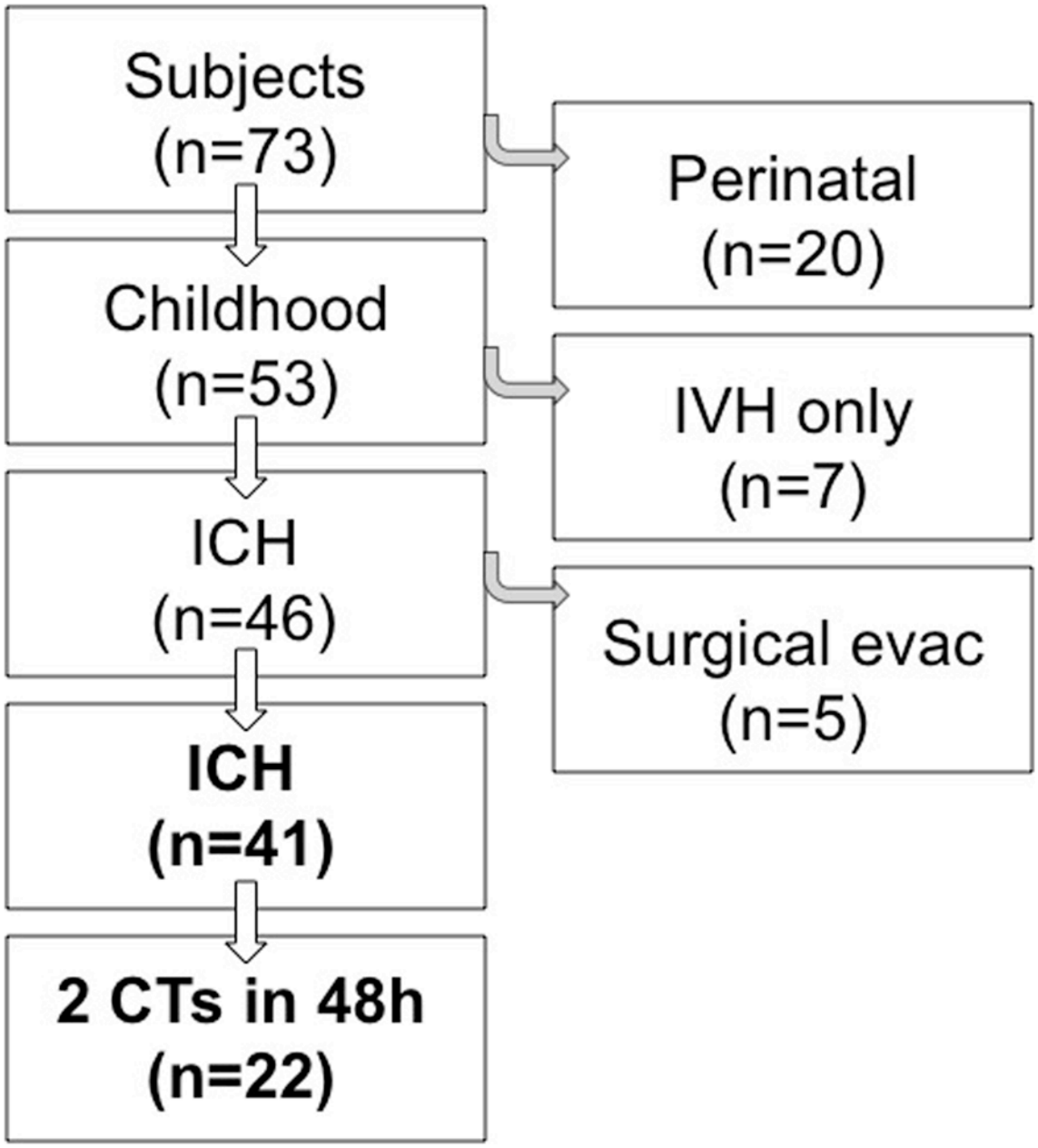

Figure 1. Study subjects

Flow chart of included and excluded children.

Abbreviations for figure 1: n, number; IVH, intraventricular hemorrhage; ICH, intracerebral hemorrhage; evac, evacuation.

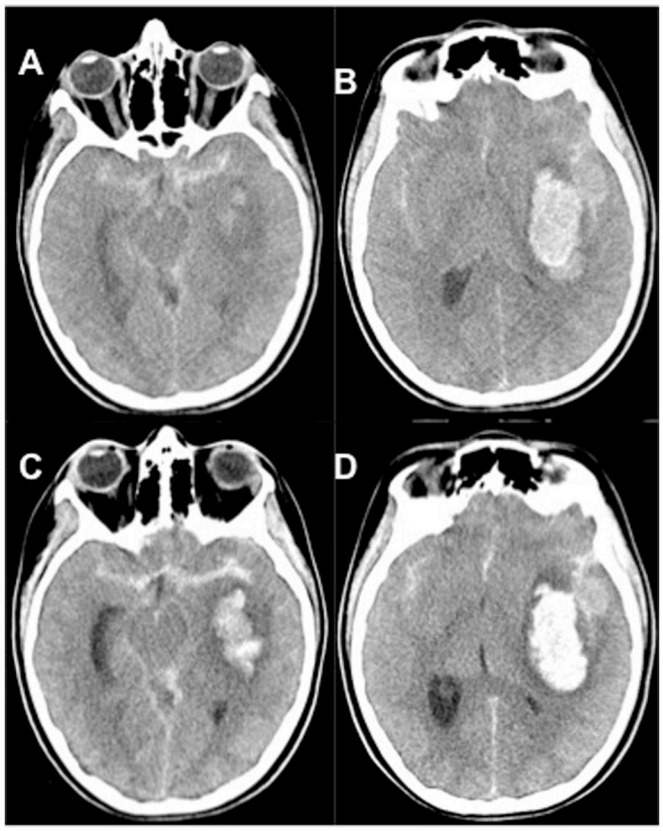

Figure 2. Example of hematoma expansion

Hematoma expansion 40% between first (A–B, 30mL) and second (C–D, 42mL) CT 2.3 hours apart.

Table 1

Intracerebral Hemorrhage Etiology (n=41)

Etiology	Two head CTs performed within 48 hours, N=22 N (%)	One head CT performed within 48 hours, N=19 N (%)
Arteriovenous malformation	9 (40)	6 (32)
Cavernous angioma	4 (18)	4 (21)
Aneurysm[a]	3 (14)	0 (0)
Developmental venous anomaly	0 (0)	1 (5)
Moyamoya	0 (0)	1 (5)
Coagulopathy[a,b]	3 (14)	2 (11)
Anticoagulation	1 (4)	3 (15)
Unknown	3 (14)	2 (11)

Abbreviations: CT, computed tomography; N, number.

[a] one child had both Hemophilia A and Aneurysm.

[b] thrombocytopenia, Vitamin K deficiency, Hemophilia A.

Table 2

Age, ICH volume, ICP, and 3-Month Outcome in Children with and without Hemorrhage Expansion

	With Expansion, N=7 (IQR or %)	Without Expansion, N=15 (IQR or %)	*P* Value
Age (years)	9.0 (1.8–14.2)	6.7 (0.6–10.3)	.65
Baseline ICH volume (mL)[a]	20.8 (2.0–24.7)	17.3 (6.2–30.3)	.65
Baseline ICH as % of total brain volume[a]	1.4 (0.2–2.2)	1.9 (0.6–2.5)	.65
Number with elevated ICP requiring intervention	4 (57%)	9 (60%)	>.99
Time between 1st and 2nd head CT (hours)	9.4 (4.7–15.2)	10.1 (4.5–23.3)	.70
PSOM at 3 months	2 (0.5–3)	1.5 (0.5–3)	.86

Statistics are presented as median (interquartile range) and Wilcoxon rank-sum probability value or as number (%) and Fisher exact test p-value.

Abbreviations: ICH, intracerebral hemorrhage; ICP, intracranial pressure; N, number; IQR, interquartile range; PSOM, pediatric stroke outcome measure.

[a] in expansion group versus group without expansion, absolute ICH volume is larger although ICH as percent of total brain volume is smaller, due to older children with larger brain volumes in expansion group.

Table 3

Age, ICH volume, ICP, and 3-Month Outcome in Children with and without Two Head CTs

	Two head CTs performed within 48 hours, N=22 (IQR or %)	One head CT performed within 48 hours, N=19 (IQR or %)	*P* Value
Age (years)	7.8 (1.8–13.1)	8.2 (2.2–13.9)	.69
Baseline ICH volume (mL)	19.5 (6.2–27.8)	7.0 (2.9–16.2)	.05[a]
Baseline ICH as % of total brain volume	1.6 (0.6–2.5)	0.7 (0.3–1.0)	.06
Number with elevated ICP requiring intervention	13 (59)	1 (5)	<.001[a]
PSOM at 3 months	1.75 (0.5–3)	1 (0.5–2)	.35

Statistics are presented as median (interquartile range) and Wilcoxon rank-sum p-value or as number (%) and Fisher exact test p-value.

Abbreviations: ICH, intracerebral hemorrhage; ICP, intracranial pressure; CT, computed tomography; N, number; IQR, interquartile range; PSOM, pediatric stroke outcome measure.

[a] significant probability value; PSOM, pediatric stroke outcome measure.