Pediatric Intracerebral Hemorrhage

Acute Symptomatic Seizures and Epilepsy

Lauren A. Beslow, MD, MSCE; Nicholas S. Abend, MD; Melissa C. Gindville, BS, MS; Rachel A. Bastian, BA; Daniel J. Licht, MD; Sabrina E. Smith, MD, PhD; Argye E. Hillis, MD; Rebecca N. Ichord, MD; Lori C. Jordan, MD, PhD

Importance: Seizures are believed to be common presenting symptoms in neonates and children with spontaneous intracerebral hemorrhage (ICH). However, few data are available on the epidemiology of acute symptomatic seizures or the risk for later epilepsy.

Objective: To define the incidence of and explore risk factors for seizures and epilepsy in children with spontaneous ICH. Our a priori hypotheses were that younger age at presentation, cortical involvement of ICH, acute symptomatic seizures after presentation, ICH due to vascular malformation, and elevated intracranial pressure requiring urgent intervention would predict remote symptomatic seizures and epilepsy.

Design: Prospective cohort study conducted between March 1, 2007, and January 1, 2012.

Setting: Three tertiary care pediatric hospitals.

Participants: Seventy-three pediatric subjects with spontaneous ICH including 20 perinatal (≥37 weeks’ gestation to 28 days) and 53 childhood subjects (>28 days to <18 years at presentation).

Main Outcome Measures: Acute symptomatic seizures (clinically evident and electrographic-only seizures within 7 days), remote symptomatic seizures, and epilepsy.

Results: Acute symptomatic seizures occurred in 35 subjects (48%). Acute symptomatic seizures as a presenting symptom of ICH occurred in 12 perinatal (60%) and 19 childhood (36%) subjects (P = .07). Acute symptomatic seizures after presentation occurred in 7 children. Electrographic-only seizures were present in 9 of 32 subjects (28%) with continuous electroencephalogram monitoring. One-year and 2-year remote symptomatic seizure-free survival rates were 82% (95% CI, 68-90) and 67% (95% CI, 46-82), respectively. One-year and 2-year epilepsy-free survival rates were 96% (95% CI, 83-99) and 87% (95% CI, 65-95), respectively. Elevated intracranial pressure requiring acute intervention was a risk factor for seizures after presentation (P = .01; Fisher exact test), remote symptomatic seizures, and epilepsy (P = .03, and P = .04, respectively; log-rank test).

Conclusions and Relevance: Presenting seizures are common in perinatal and childhood ICH. Continuous electroencephalography may detect electrographic seizures in some subjects. Single remote symptomatic seizures occur in many, and development of epilepsy is estimated to occur in 13% of patients at 2 years. Elevated intracranial pressure requiring acute intervention is a risk factor for acute seizures after presentation, remote symptomatic seizures, and epilepsy.


Original Contributions

Seizures are believed to be a common presenting symptom in neonates and children with spontaneous intracerebral hemorrhage (ICH). However, few data are available regarding the epidemiology of acute symptomatic seizures or the risk for later epilepsy. Estimates of seizures at presentation or in the early or acute period range from 18% to 50%, but definitions of acute symptomatic seizures or early symptomatic seizures vary. Studies have reported epilepsy or recurrent seizures in 10% to 25% of patients at follow-up, but duration of follow-up in these studies was not clearly specified. We aimed to define the incidence of acute symptomatic seizures (within 7 days from presentation) from a large prospective pediatric ICH cohort, both as a presenting symptom and after presentation. We also aimed to define the incidence of remote symptomatic seizures and epilepsy. Potential risk factors for acute symptomatic sei-
Seizures, remote symptomatic seizures, and epilepsy were explored.

METHODS

STUDY DESIGN AND SUBJECTS

This is a prospective cohort study of perinatal subjects (full-term newborns aged ≥37 weeks' gestation to ≤28 days) and childhood subjects (aged ≥28 days of life to 18 years) who presented with spontaneous ICH between March 1, 2007, and January 1, 2012, at 3 tertiary care institutions at which the authors are affiliated. Consent was obtained from subjects' parents and assent from children aged 7 years and older. The institutional review boards of all 3 institutions approved the study. Ascertainment was thought to be near complete because the institutions have clinical protocols for ICH management that include stroke service consultation.

DEFINITIONS

Spontaneous ICH was defined as intraparenchymal hemorrhage and/or intraventricular hemorrhage not caused by trauma, brain tumor, hemorrhagic transformation of arterial ischemic stroke, or cerebral sinus venous thrombosis. Isolated subarachnoid hemorrhages were excluded. All ICHs were confirmed on head computed tomography or magnetic resonance imaging. Seizures were classified by occurrence time. Acute symptomatic seizures were defined as those occurring from presentation to 7 days after the incident ICH.11 Presenting seizures described those occurring as the first symptom or along with other symptoms immediately at presentation. Acute symptomatic seizures after presentation were those occurring after presenting seizure(s) were controlled or after the subject had come to medical attention but still within 7 days of ICH. Status epilepticus was defined as a continuous seizure lasting more than 30 minutes or recurrent seizures lasting more than 30 minutes in any 1-hour period.12 Remote symptomatic seizures occurred more than 7 days from the incident ICH. Epilepsy was defined as 2 or more unprovoked remote symptomatic seizures more than 24 hours apart.13 Consistent with prior studies, an electrographic seizure was defined as an abnormal paroxysmal event different from the background and lasting longer than 10 seconds (or shorter if associated with clinical change), with a temporal-spatial evolution in morphology, frequency, and amplitude, as well as with an electrographic field.11 Clinically evident seizures and electrographic-only seizures qualified as seizures for all analyses. Elevated intracranial pressure (ICP) requiring urgent intervention was defined as the need for treatment with mannitol, 3% normal saline; drainage of cerebrospinal fluid via intraventricular catheter; urgent hematoma evacuation; or decompressive hemicraniectomy.

CLINICAL AND RADIOGRAPHIC DATA

Data were acquired both prospectively and from abstraction of hospital medical records and stroke clinic follow-up records. These data included seizure occurrence, timing of seizure relative to incident ICH, seizure semiology, and anticonvulsant administration. Radiographic information including intraparenchymal hemorrhage, intraventricular hemorrhage, or both, and cortical involvement of the ICH were recorded. At each follow-up stroke clinic visit, subjects were assessed for seizure occurrence. In those with seizures, seizure date, semiology, and antiseizure medication use were recorded. For this study, all emergency department visits, hospital admissions, and telephone encounters after the incident ICH were reviewed to ensure complete ascertainment of seizures.

STATISTICAL ANALYSIS

STATA version 11.1 (Stata Corporation) was used for all analyses. Fisher exact tests were used to analyze predictors of acute seizures for categorical variables. The Wilcoxon rank-sum test was used to determine whether the age of those presenting with seizures differed from the age of those presenting without seizures among the childhood subjects. The Kaplan-Meier estimate of survival was calculated to determine the remote symptomatic seizure-free survival and epilepsy-free survival of subjects who lived. Survival time was calculated from the date of the incident ICH. The log-rank test was used to explore whether a difference in survival functions existed between subjects with various putative risk factors for development of remote symptomatic seizures and epilepsy. A 2-sided probability value of .05 or less was considered statistically significant. Bonferroni correction for multiple comparisons was made for a priori hypotheses. Our a priori hypotheses were that younger age at presentation, cortical involvement of ICH, acute symptomatic seizures after presentation, ICH due to vascular malformation, and elevated ICP requiring urgent intervention would predict remote symptomatic seizures and epilepsy.

RESULTS

POPULATION

During the study, consent was obtained from 73 of 87 eligible subjects (84%). Intracerebral hemorrhage occurred in 20 perinatal and 53 childhood subjects. For children, the median age was 9 years (interquartile range [IQR], 2-14 years). Racial distribution was 49 white (3 Hispanic) and 24 black subjects. No subject had a history of unprovoked seizures or epilepsy, but 1 childhood subject had a history of a single febrile seizure. Intracerebral hemorrhage locations and etiologies are in Table 1.

ACUTE SYMPTOMATIC SEIZURES

Seizures at Presentation

Seizures as presenting symptoms occurred in 31 subjects (42%; Figure 1). Twelve perinatal (60%; 95% binomial CI, 36-81) and 19 childhood (36%; 95% binomial CI, 23-50) subjects presented with seizures (P = .07; Fisher exact test). For children, the median age of those who presented with seizures was lower than that for those who did not present with seizures (2.0 years; IQR, 0.4-9.0 years, vs 10.8 years; IQR, 6.4-15.2 years; P = .002; Wilcoxon rank-sum test). Seizure semiology was focal in 10 perinatal and 14 childhood subjects. Five children (9%) and 10 perinatal subjects (50%) presented with status epilepticus. Univariable analyses for predictors of seizures at presentation are in Table 2.

Acute Symptomatic Seizures

After Presentation

Seven childhood subjects (13%) had acute seizures after presentation but within 7 days of ICH (median, 2 days;
range, 1-5 days). Seizure semiology was focal in 6 children. Three of the 7 childhood subjects also presented with seizures, and 4 were taking antiseizure medications at the time of the seizure. Three acute seizures after presentation were electrographic-only seizures and were identified on continuous electroencephalography (cEEG). Univariable predictors of acute seizures after presentation are in Table 3. Only elevated ICP requiring acute intervention was associated with acute seizures after presentation. Six subjects (8%; 3 perinatal and 3 childhood subjects) died during the acute hospitalization. One perinatal subject and 1 childhood subject who died had acute symptomatic seizures.

### EEG

Eletroencephalography was performed at the discretion of the treating neurologist in 15 perinatal (75%) and 31 childhood (58%) subjects (Table 4). An EEG was performed in 30 of 35 subjects with acute symptomatic seizures and in 16 of 38 subjects without acute symptomatic seizures. Use of cEEG monitoring was more frequent in those with perinatal vs childhood ICH (13 of 20 vs 19 of 53, respectively; \(P = .04\); Fisher exact test) and in those with acute symptomatic seizures vs those without acute symptomatic seizure (22 of 35 vs 10 of 38, respectively; \(P = .002\); Fisher exact test).

Five of 13 perinatal subjects (38%) who had cEEG monitoring and 4 of 19 childhood subjects (21%) who had cEEG monitoring had electrographic-only seizures. All 5 perinatal subjects and 3 of 4 childhood subjects with electrographic-only seizures had seizures at presentation of ICH and were taking antiseizure medication at the time of the electrographic-only seizures. Among childhood subjects, elevated ICP requiring acute intervention predicted the use of cEEG (13 of 26 vs 6 of 27; \(P = .05\); Fisher exact test). Three of 4 childhood subjects with electrographic-only seizures had elevated ICP requiring urgent intervention.

### ANTISEIZURE MEDICATIONS

Antiseizure medication use was based on clinical practices and is described in the Table (http://www.jamaneuro.com). Only 4 subjects who did not have acute symptomatic seizures were treated with and discharged taking prophylactic antiseizure medications. All 4 had vascular malformations (2 arteriovenous malformations, 1 aneurysm, and 1 developmental venous anomaly). Two of these malformations were treated (aneurysm clipped and arteriovenous malformation coiled), but the other 2 were untreated at the time of hospital discharge. Eight per-
nental (40%) and 23 childhood (43%) subjects never started treatment with a maintenance antiseizure medication. All 10 perinatal subjects discharged taking antiseizure medications were discharged with a single agent, while 4 of 26 childhood subjects (15%) discharged taking antiseizure medications were treated with dual therapy. Nine perinatal and 12 childhood subjects (58% of all subjects discharged taking antiseizure medications) were weaned from all antiseizure medications in the follow-up period. The median length of treatment in the cohort in those who were weaned in the follow-up period was 84 days (IQR, 63-130 days). One perinatal and 4 childhood subjects not discharged taking antiseizure medications were started on treatment with them during the follow-up period when epilepsy developed. One perinatal and 14 childhood subjects discharged taking antiseizure medications (42% of those discharged taking antiseizure medications) were still taking medication at the time of the last follow-up (median, 885 days; IQR, 221-1247 days).

**FIRST REMOTE SYMPTOMATIC SEIZURE AND EPILEPSY**

Follow-up time was not different between perinatal and childhood subjects. The median number of days to the last follow-up for perinatal subjects was 382 (IQR, 233-987 days) and for childhood subjects was 345 (IQR, 119-596 days) (<i>P</i> = .20; Wilcoxon rank-sum test). Fourteen of 67 surviving subjects had an unprovoked remote symptomatic seizure after 7 days from the incident ICH with 1-year and 2-year seizure-free survival rates of 82% (95% CI, 68-90) and 67% (95% CI, 46-82), respectively (Figure 2A). Of the 14 subjects who had a first unprovoked remote symptomatic seizure, 2 presented with ICH in the perinatal period and 12 in childhood. Nine were still taking antiseizure medications at the time of the first remote symptomatic seizure, and 5 with remote symptomatic seizures had not been discharged taking antiseizure medications. Univariable analyses for risk factors for a first unprovoked remote symptomatic seizure are in Table 5. Only elevated ICP requiring urgent intervention (<i>P</i> = .03; log-rank test) predicted a first unprovoked remote symptomatic seizure. Nine of 67 surviving subjects developed epilepsy with 1-year and 2-year epilepsy-free survival rates of 96% (95% CI, 83-99) and 87% (95% CI, 65-95), respectively (Figure 2B). Univariable analyses for risk factors for epilepsy are in Table 6. Without Bonferroni correction, both elevated ICP requiring urgent intervention during the acute hospitalization (<i>P</i> = .007; log-rank test) and ICH in childhood (<i>P</i> = .04; log-rank test) predicted epilepsy. However, after Bonferroni correction, only elevated ICP requiring urgent intervention predicted epilepsy (<i>P</i> = .04; log-rank test). Of the 9 children with epilepsy, 5 continued taking antiseizure medications after hospital discharge. Eight subjects had a total of 5 or fewer seizures, but 1 child developed medically refractory epilepsy with daily seizures. This child’s epilepsy was
refractory to 5 antiseizure medications and was eventually controlled with the ketogenic diet.

**COMMENT**

In one of the largest prospective studies of pediatric ICH, we found that nearly half of children experience acute symptomatic seizures, and these occurred at presenta-

Figure 2. Kaplan-Meier survival curves by age group (perinatal vs childhood subjects). The graphs demonstrate the time to first remote symptomatic seizure (A) and the time to the development of epilepsy (B).

**Table 5. Risk Factors for First Remote Symptomatic Seizure Among 67 Survivors**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Seizure at presentation</td>
<td>6/29</td>
<td>8/38</td>
<td>.78</td>
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<tr>
<td>Acute seizure after presentation but ≤7 d</td>
<td>0/7</td>
<td>14/60</td>
<td>.32</td>
<td></td>
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<tr>
<td>Any acute symptomatic seizure within 7 d</td>
<td>6/33</td>
<td>8/34</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>Childhood ICH</td>
<td>12/50</td>
<td>2/17</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Cortical involvement</td>
<td>6/31</td>
<td>8/36</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>Parenchymal location</td>
<td>13/60</td>
<td>1/7</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>AED at discharge</td>
<td>9/36</td>
<td>5/31</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Epileptiform discharges</td>
<td>4/22</td>
<td>10/45</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>9/35</td>
<td>5/32</td>
<td>.11</td>
<td></td>
</tr>
<tr>
<td>Elevated ICP requiring urgent intervention</td>
<td>9/26</td>
<td>5/41</td>
<td>.005c</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiseizure medication; EEG, electroencephalography; ICH, intracerebral hemorrhage; ICP, intracranial pressure.

*a Calculated using log-rank test.

*b Correction for a priori hypotheses only.

*c Statistically significant prior to Bonferroni correction for multiple comparisons.

*d Statistically significant after Bonferroni correction for multiple comparisons.
Another important finding in this study was that elevated ICP requiring urgent intervention was associated with acute symptomatic seizures after presentation. Three of 4 children with electrographic-only seizures had elevated ICP requiring urgent intervention. In adults with traumatic brain injury, electrographic seizures have been associated with transient elevations in ICP, which suggests a pathophysiologic mechanism by which seizures could further elevate ICP or make management of elevated ICP more complex. Children with elevated ICP after ICH may derive particular benefit from cEEG monitoring and from more aggressive seizure management in the acute setting.

Surprisingly, cortical involvement of ICH, an important predictor of acute symptomatic seizures in adult ICH, was not related to acute symptomatic seizures in this pediatric cohort. Additionally, acute symptomatic seizures were not associated with remote symptomatic seizures and epilepsy. This lack of statistical significance may be related to the relatively small number of subjects.

This study used survival analysis to estimate the time to remote symptomatic seizures and epilepsy in a prospective cohort of pediatric ICH. Past studies have been limited by small numbers of subjects included and lack of information on follow-up time. In this cohort, while a first remote symptomatic seizure was estimated to occur in about one-third of subjects at 2 years, epilepsy was less common, estimated to develop in less than 15% of the cohort at 2 years. Although not statistically significant, perinatal subjects seem to be at lower risk for remote symptomatic seizures and epilepsy compared with childhood subjects. As with acute symptomatic seizures after presentation, elevated ICP requiring urgent intervention was a risk factor for a first remote symptomatic seizure and for developing epilepsy, which highlights a high-risk group of patients.

More than half of children were taking antiseizure medication at the time of remote symptomatic seizure and epilepsy diagnosis, which indicates that antiseizure medication use does not prevent all remote symptomatic seizures in the follow-up period. However, choice of antiseizure medication was not uniform among subjects because it was based on clinical practices of treating physicians. A randomized controlled trial is required to address properly whether long-term use of antiseizure medications can prevent remote symptomatic seizures and epilepsy. Such a study may benefit from stratification across age groups at incident ICH and across those with elevated ICP.

The present study has several limitations. First, initial Glasgow Coma Scale score was not documented for most subjects; therefore, no standard clinical examination of ICH severity was performed. However, elevated ICP was a risk factor for acute symptomatic seizures, remote symptomatic seizures, and epilepsy; elevated ICP is a likely marker of more severe ICH. Second, because some subjects were lost to follow-up, the true remote symptomatic seizure-free and epilepsy-free survival rates may be underestimated. We believe that most pediatric patients with a remote seizure after ICH would be brought to stroke program physicians because of local referral patterns. Third, EEG monitoring was not performed in all patients, thus the incidence of electrographic seizures is uncertain. Some patients with electrographic seizures may not have undergone EEG monitoring, which leads to underestimation of their frequency. However, EEG monitoring may have already targeted those most at risk.

Despite its limitations, the study has several strengths. The prospective design permitted identification of ICH cases and of seizures without reliance on International Classification of Diseases, Ninth Revision (ICD-9) codes, which misclassify stroke diagnoses. The use of time-to-event analysis to evaluate remote symptomatic seizure-free and epilepsy-free survival rates allowed the most accurate description of the cohort.

This study provides clinicians with useful information for counseling parents of pediatric patients with ICH.

### Table 6. Risk Factors for Symptomatic Epilepsy Among 67 Survivors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Epilepsy/With ICH</th>
<th>Epilepsy/Without ICH</th>
<th>P Value</th>
<th>Bonferroni-Corrected P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure at presentation</td>
<td>4/29</td>
<td>5/38</td>
<td>.82</td>
<td></td>
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<tr>
<td>Acute seizure after presentation</td>
<td>0/7</td>
<td>9/60</td>
<td>.58</td>
<td>&gt; .99</td>
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<tr>
<td>Any acute symptomatic seizure</td>
<td>4/33</td>
<td>5/34</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>Childhood ICH</td>
<td>8/50</td>
<td>1/17</td>
<td>.04c</td>
<td>.20</td>
</tr>
<tr>
<td>Cortical involvement</td>
<td>4/31</td>
<td>5/36</td>
<td>.60</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Parenchymal location</td>
<td>9/60</td>
<td>0/7</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>AED at discharge</td>
<td>5/36</td>
<td>4/31</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>Epileptiform discharges</td>
<td>3/22</td>
<td>6/45</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>6/35</td>
<td>3/32</td>
<td>.11</td>
<td>.55</td>
</tr>
<tr>
<td>Elevated ICP requiring urgent</td>
<td>6/26</td>
<td>3/41</td>
<td>.007c</td>
<td>.04d</td>
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<td>intervention</td>
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</tbody>
</table>

Abbreviations: AED, antiseizure medication; ICH, intracerebral hemorrhage; ICP, intracranial pressure.

a Calculated using log-rank test.
b Correction for a priori hypotheses only.
c Statistically significant after Bonferroni correction for multiple comparisons.
d Statistically significant after Bonferroni correction for multiple comparisons.
who present in the perinatal and childhood periods regarding the risk for remote seizures and epilepsy. Additionally, we identified a subset of subjects with elevated ICP requiring urgent intervention who appear to be at the greatest risk for acute seizures after presentation, remote symptomatic seizures, and epilepsy. Further study is needed to determine the incidence of remote symptomatic seizures and epilepsy with longer follow-up.

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Author Affiliations: Section of Child Neurology, Departments of Pediatrics and Neurology, Yale University School of Medicine, New Haven, Connecticut (Dr Beslow); Division of Neurology, The Children’s Hospital of Philadelphia, Pennsylvania (Dr Abend, Licht, Smith, and Ichord, and Ms Bastian); Division of Child Neurology, Department of Neurology, Vanderbilt University Medical Center, Nashville, Tennessee (Ms Gindville and Dr Jordan); and Division of Cerebrovascular Neurology, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland (Dr Hillis).

Correspondence: Lauren A. Beslow, MD, MSCE, Section of Child Neurology, Departments of Pediatrics and Neurology, Yale University School of Medicine, PO Box 208064, New Haven, CT 06520 (lauren.beslow@yale.edu).

Author Contributions: All authors 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. Study concept and design: Beslow, Abend, and Jordan. Acquisition of data: Beslow, Abend, Gindville, Bastian, Licht, Smith, Ichord, and Jordan. Analysis and interpretation of data: Beslow, Abend, Licht, Hillis, Ichord, and Jordan. Drafting of the manuscript: Beslow, Abend, and Jordan. Critical revision of the manuscript for important intellectual content: Beslow, Abend, Gindville, Bastian, Licht, Smith, Hillis, Ichord, and Jordan. Statistical analysis: Beslow. Obtained funding: Jordan. Administrative, technical, and material support: Abend, Gindville, Bastian, Licht, and Ichord. Study supervision: Jordan.

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Online-Only Material: The eTable is available at http://www.jamaneuro.com.

REFERENCES