Predictors of Outcome in Childhood Intracerebral Hemorrhage
A Prospective Consecutive Cohort Study

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Background and Purpose—The purposes of this study were to describe features of children with intracerebral hemorrhage (ICH) and to determine predictors of short-term outcome in a single-center prospective cohort study.

Methods—A single-center prospective consecutive cohort study was conducted of spontaneous ICH in children aged 1 to 18 years from January 2006 to June 2008. Exclusion criteria were inciting trauma; intracranial tumor; isolated epidural, subdural, intraventricular, or subarachnoid hemorrhage; hemorrhagic transformation of ischemic stroke; and cerebral sinovenous thrombosis. Hospitalization records were abstracted. Follow-up assessments included outcome scores using the Pediatric Stroke Outcome Measure and King’s Outcome Scale for Childhood Head Injury. ICH volumes and total brain volumes were measured by manual tracing.

Results—Twenty-two patients, median age 10.3 years (range, 4.2 to 16.6 years), had presenting symptoms of headache in 77%, focal deficits 50%, altered mental status 50%, and seizures 41%. Vascular malformations caused hemorrhage in 91%. Surgical treatment (hematoma evacuation, lesion embolization or excision) was performed during acute hospitalization in 50%. One patient died acutely. At a median follow-up of 3.5 months (range, 0.3 to 7.5 months), 71% of survivors had neurological deficits; 55% had clinically significant disability. Outcome based on Pediatric Stroke Outcome Measure and King’s Outcome Scale for Childhood Head Injury scores was worse in patients with ICH volume >2% of total brain volume (P=0.023) and altered mental status at presentation (P=0.005).

Conclusions—Spontaneous childhood ICH was due mostly to vascular malformations. Acute surgical intervention was commonly performed. Although death was rare, 71% of survivors had persisting neurological deficits. Larger ICH volume and altered mental status predicted clinically significant disability. (Stroke. 2010;41:313-318.)

Key Words: childhood ■ intracerebral hemorrhage ■ outcome ■ vascular malformation

S troke occurs in 2 to 13 children per 100 000 per year in developed countries.1,2 Hemorrhagic stroke accounts for as much as half of pediatric stroke, whereas in adults, arterial ischemic stroke is more common.1,3 Intracerebral hemorrhage (ICH) devastates children with death reported in up to 33% and permanent deficits in up to 40%, including seizures, cognitive and motor impairment.4-6 Although this disease is life-threatening, little research has been devoted to pediatric ICH. The few prospective cohort studies have small numbers.2,7 Case series and retrospective chart reviews comprise the remaining literature.7

Much is known about the pathogenesis and outcome predictors of ICH in adults in which hypertension and amyloid angiopathy are among the most common etiologies. Clinical and radiological characteristics influencing adult ICH outcome cannot be applied to children because etiologies of ICH in children differ from those in adults. Additionally, published pediatric ICH outcome studies suggest that the course of recovery in children differs substantially from that in adults. One study reported that pediatric ICH caused by hematoletic abnormalities and infratentorial hemorrhage location is associated with a worse prognosis.8 A recent retrospective series demonstrated that ICH volume predicts poor outcome in children.9 However, this association has not been evaluated in a prospective consecutive cohort. Also, other important factors portending poor recovery in adults such as initial Glasgow Coma Score <9 and intraventricular extension10 have not been assessed prospectively in children. Our study’s primary goals were to describe features of a prospective cohort of children with ICH and to examine

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whether hemorrhage volume and altered mental status predict outcome at short-term follow-up in children with intraparenchymal hemorrhage.

Materials and Methods

Study Design

With Institutional Review Board approval, a prospective consecutive cohort of patients with spontaneous ICH presenting between January 2006 and June 2008 was identified from a large tertiary care children’s hospital stroke registry.

Case Identification

During acute hospitalization, patients were identified for the study by neurosurgery and/or neurology providers participating in a multidisciplinary neurovascular care protocol targeting children admitted to the hospital with spontaneous ICH. Neurosurgery and hematology databases were crossreferenced ensuring complete ascertainment. Inclusion criteria were children aged 1 to 18 years with spontaneous intraparenchymal hemorrhage confirmed by neuroimaging. Exclusion criteria were head trauma; intracranial tumor; hemorrhage isolated to the epidural, subdural, intraventricular, or subarachnoid compartments; hemorrhagic transformation of arterial ischemic stroke; and hemorrhage from cerebral sinovenous thrombosis. Patients with brain tumor, hemorrhagic transformation of arterial ischemic stroke, and hemorrhagic venous infarction related to cerebral sinovenous thrombosis were excluded to avoid potentially confounding effects on outcome from the primary pathological process. Because our primary a priori hypothesis was that ICH volume would be a major predictor of outcome, we excluded isolated intraventricular hemorrhages because they have no measurable ICH volume.

Clinical Data

Acute hospital, neuroimaging, inpatient rehabilitation, pediatric stroke clinic, and neurosurgery clinic follow-up records were abstracted. Patient details are summarized in Supplemental Table I (available at http://stroke.ahajournals.org). Altered mental status (AMS) on admission was defined as present if medical records showed any of these terms/conditions describing the level of consciousness within the first 6 hours of hospitalization: (1) Glasgow Coma Score ≤9; (2) description of the child as comatose, obtunded, or unresponsive; and (3) intubation for deteriorating mental status. AMS was broadly defined because physicians did not uniformly record an initial Glasgow Coma Scale or because record of the first examination was not always available when a child was transferred from another hospital. Diagnostic testing was determined by clinical indications. Short-term outcome was assessed from findings on standard clinical care protocol follow-up examinations 2 to 6 months after initial symptom onset. For children with no follow-up visits during this period, the examination closest to target range midpoint (4 months) was used.

Hemorrhage Analysis

ICH etiology was determined by medical history, neuroimaging, intraoperative observation, and available surgical pathology. Location of hemorrhage (supratentorial or infratentorial) and presence of intraventricular hemorrhage were determined through central review by a study neuroradiologist (R.A.Z.) blinded to clinical history and initial clinical radiographic interpretations. Hemorrhage volume and total brain volume (TBV) were measured on acute CT or MRI by manual segmentation tracing using online software, ITK-SNAP (www.itksnap.org), which has excellent intra- and interoperator reliability for measuring regional brain volumes. Intraventricular hemorrhage was excluded from hemorrhage volume measurements; ventricular volume was excluded from TBV measurements. Supratentorial parenchymal hemorrhages ≤2% of total brain volume were considered small, and those >2% of total brain volume were considered large. Choosing 2% of TBV to define large ICH was based on the observation that hemorrhage >30 mL in adults is associated with functional impairment. In an average adult with brain volume of 1400 mL, an ICH volume of 30 mL approximates 2% of TBV. The predictive significance of hemorrhage volume was evaluated in patients with supratentorial hemorrhage. Because the physiological effects of volume are likely different in the infratentorial compartment, and because only 2 children in our cohort had infratentorial hemorrhage, these patients were excluded from outcome analysis.

Outcome Assessment

Outcome was evaluated and classified using 2 standardized instruments. The Pediatric Stroke Outcome Measure (PSOM) characterizes deficit type and severity on neurological examination and was validated in a cohort of children with ischemic stroke. The PSOM is based entirely on neurological examination with subscores in 5 domains: sensorimotor left, sensorimotor right, expressive language, receptive language, and cognition/behavior. PSOM subscores are graded 0 for no deficit, 0.5 for mild deficit that does not interfere with function, 1 for moderate deficit that interferes with function, and 2 for severe deficit with missing/absent function. The total PSOM score range is 0 to 10. Children who died were not assigned a PSOM score. The King’s Outcome Scale for Childhood Head Injury (KOSCHI) is a pediatric modification of the Glasgow Outcome Scale characterizing global functional status. The KOSCHI incorporates functional impairments plus periodic symptoms like headaches and seizures. It scores 1 for death, 2 for vegetative state, 3a and 3b for severe disability (3a worse), 4a and 4b for moderate disability (4a worse), and 5a and 5b for good recovery (5b full recovery, no residual symptoms). In our study, the KOSCHI was determined from history obtained by parental interview and neurological examination findings. Deficits were considered “clinically significant” for a KOSCHI score ≤4b and/or the PSOM score ≥1 in any category. We chose these scores to ascertain fully all children with functional impairments.

Statistical Analysis

Fisher exact test and relative risk with 95% exact CIs were used to evaluate associations using STATA Version 10.0 (Stata Corporation). Multivariate logistic regression analysis was limited due to small sample size and was therefore only attempted to adjust results from univariate analyses for age. A probability value of <0.05 was considered statistically significant.

Results

Demographics

Twenty-four patients with ICH were identified during the 2.5-year period. Parents of 22 patients (92%) consented to participation, 11 males and 11 females. Mean and median ages at presentation were 10.4 and 10.3 years, respectively (range, 4.2 to 16.6 years). Racial distribution was 73% white and 27% black. All children were neurologically normal before ICH. Two children had medical conditions associated with ICH: one had sickle cell anemia (Supplemental Table I, Case 20), and one had hereditary hemorrhagic telangiectasia (Supplemental Table I, Case 7).

Clinical Presentations

Eighteen patients (82%) presented to local hospitals; 4 presented to our tertiary care center. Median time from symptom onset to presentation to the initial hospital was 70

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minutes: 14 patients (64%) presenting within 3 hours and 5 patients (23%) presenting >24 hours from symptom onset. Symptoms included severe headache in 17 (77%), emesis in 13 (59%), altered mental status in 11 (50%), seizure in 9 (41%), and syncope in 1 (4.5%). Focal deficits were present on admission examination in 11 patients (50%).

Acute life-threatening intracranial hypertension or herniation syndromes requiring intervention occurred in 10 children (45%). Six (27%) received either hypertonic saline or mannitol. Three (14%) were hyperventilated. Moderate therapeutic hypothermia was instituted in 2 (9%). Six (27%) required ventriculostomy. Three (14%) underwent decompressive hemicraniectomy.

Hemorrhage Characteristics
Neuroimaging was performed in all children with median time to the first study of 2.4 hours (range, 30 minutes to 10 days). Eleven children (50%) had their first diagnostic image performed within 3 hours of symptom onset. During their acute hospitalization, 20 children (91%) had head CT, 19 (86%) had MRI, 14 (64%) had MR angiography, 6 (27%) had CT angiography, and 17 (77%) had conventional angiograms. Four had no dedicated vascular imaging: one died before further evaluation and 3 had MRIs diagnostic for cavernoma. All children had a normal platelet count, prothrombin time, international normalized ratio, and partial thromboplastin time. Vascular malformations were detected in 20 patients (91%): arteriovenous malformation in 12 (55%), cavernoma in 7 (32%), and aneurysm in 1 (4.5%). Hemorrhage etiology was not identified in 2 (9%).

Hemorrhage was supratentorial in 20 patients (91%). Two patients had infratentorial hemorrhages, one involving the pons and one the cerebellum. Intraventricular extension occurred in 10 patients (45%), 9 of whom had supratentorial ICH. Additional information on ICH locations is presented in Supplemental Table I.

Surgical Management
Hematoma evacuation, hemicraniectomy, and/or surgical/endovascular management of vascular malformations were performed in 11 patients (50%) during the acute hospitalization. Children with more benign clinical courses or whose malformations were not diagnosed during the acute hospitalization were treated during subsequent hospitalizations. Indication for surgical interventions is presented in Supplemental Table I.

Outcome
Median hospitalization duration was 9 days (range, 2 to 23 days). Median intensive care unit admission was 6.5 days (range, 2 to 23 days). One death occurred on hospital day 2. Care was withdrawn from a patient with a cerebellar hematoma who had already herniated before transfer. Fourteen of 21 survivors (67%) were discharged with a neurological deficit. Eleven (52%) were discharged to inpatient rehabilitation.

Neurological follow-up was available in all patients who survived the acute hospitalization (n=21) at a median of 3.5 months (range, 0.3 to 7.5 months). Recurrent hemorrhage within the short-term follow-up interval occurred in one child with a cavernoma who developed a second ICH 11 days after the initial event. One child (4.5%) with an arteriovenous malformation arising from the middle cerebral artery had a secondary ischemic stroke.

Of the 21 living children, parents of 13 (62%) reported their child had not fully recovered from the hemorrhage. Six did not attend school due to stroke; 3 others had modified school programs. Five children (24%) had mood alterations, 2 of whom had overt signs of depression. Ten patients (48%) had chronic headaches. Of 3 patients who developed epilepsy, only one had seizures at initial presentation. Five children were readmitted to the hospital due to hemorrhage-related problems, including seizures, re-bleed, or definitive treatment of vascular malformations. Fifteen children (71%) had abnormal neurological examinations (Figure 1). However, all were ambulatory and able to communicate. Twelve (55%) had clinically significant disability, all of whom had a PSOM score ≥1 in at least one category (Supplemental Table I) and a KOSCHI score ≤4b (Figure 2; Supplemental Table I).

Outcome Predictors
Among children with supratentorial ICH, large ICH volume was associated with clinically significant disability in univariate analysis. A diagnostic image performed within the first day of hospitalization was available in 19 of 20 children with supratentorial ICH (16 helical CT, 3 MRI). Median ICH volume expressed as a percent of TBV was 1.68% (range, 0.005% to 6.93%). Median absolute hemorrhage volume was 22.8 mL (range, 0.07 to 92 mL). Children with ICH volumes >2% of TBV had worse outcome compared to children with...
ICH volumes ≤2% (P=0.023; relative risk, 3.9; 95% CI, 1.1 to 14.1). Figure 3 shows examples of small and large hemorrhages.

AMS was associated with clinically significant disability in univariate analysis (P=0.005; relative risk, 7.2; 95% CI, 1.1 to 46.9). Documentation of mental status within 6 hours of hospital arrival was available in 19 of 20 children with supratentorial ICH; 10 of these 19 had AMS. AMS was associated with ICH volume ≥2% of TBV (P=0.005; relative risk, 7.2; 95% CI, 1.1 to 46.9). Only 2 of 10 children with AMS had ICH volume ≥2% of TBV compared with 8 of 9 children without AMS. Given the modest sample size, we were unable to test formally for interaction or to adjust for other potential confounders.

Patients with clinically significant disability were slightly older than those without clinically significant disability in univariate analysis (11.9 ± 3.5 years versus 8.9 ± 3.1 years, P=0.06 by t test). All other univariate analyses performed were post hoc (Table). Although clinically significant disability was numerically more common in patients with intraventricular hemorrhage, seizures, or focal deficit at presentation, these findings were not statistically significant. The 2 children with infratentorial hemorrhage had the worst outcomes: one died and one had severe disability.

Multivariate analysis was performed to determine if age confounded the associations between outcome and either ICH volume or early AMS. Age was not independently associated with outcome in either analysis. However, age modestly impacted the ORs of the covariates described previously but did not alter their significant outcome associations.

**Discussion**

In this study, we described presentations, etiologies, and short-term outcomes of a prospective consecutive cohort of children with spontaneous ICH. More than half of the children had clinically significant disability on the PSOM and/or KOSCHI at follow-up. We considered clinically significant disability to be present in any children with moderate disability or worse because these patients are unable to function normally and require additional care. Children with clinically significant disability face critical difficulties in educational and social arenas. Fourteen percent had epilepsy, 19% were rehospitalized, 43% could not attend regular school programs, >60% had cognitive deficits, and nearly half had chronic headaches. These percentages are similar to retrospective study findings that describe long-term outcomes. One found that nearly 11% of children developed epilepsy and that evidence of cognitive deficits was observed in nearly half of surviving patients at 10-year follow-up. Another reported that patients with good early outcome scores had neuropsychological impairment at 3-year follow-up.

Our finding that hemorrhage volume ≥2% of TBV was associated with worse neurological outcome in childhood ICH confirms the findings of a prior retrospective report. Furthermore, our study demonstrates that AMS within 6 hours of hospitalization was associated with worse outcome. Additionally, AMS within 6 hours of hospitalization was associated with supratentorial ICH volume ≥2% of TBV and therefore may serve as an early clinical indicator of larger, more severe ICH. Larger studies are required to determine the independence of these 2 factors.

Mortality in our cohort, 4.5% at 30 days, was low compared with rates of nearly 25% reported in other studies. Furthermore, mortality in our cohort was far lower than that in adult studies in which 6-month mortality ranges from 23% to 58%. Several possible explanations exist for our low mortality. First, our cohort included only one hemorrhage

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. With Clinically Significant Disability/No. With Variable</th>
<th>No. With Clinically Significant Disability/No. Without Variable</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Hemorrhage volume ≥2% TBV*</td>
<td>7/9</td>
<td>2/10</td>
<td>3.9</td>
<td>1.1–14.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Altered mental status*</td>
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<td>1/9</td>
<td>7.2</td>
<td>1.1–46.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>6/9</td>
<td>4/11</td>
<td>1.8</td>
<td>0.7–4.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Seizure</td>
<td>6/9</td>
<td>4/11</td>
<td>1.8</td>
<td>0.7–4.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>7/10</td>
<td>3/10</td>
<td>2.3</td>
<td>0.8–6.5</td>
<td>0.18</td>
</tr>
<tr>
<td>Surgery during acute hospitalization</td>
<td>7/11</td>
<td>3/9</td>
<td>1.9</td>
<td>0.7–5.3</td>
<td>0.37</td>
</tr>
<tr>
<td>Male gender</td>
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<td>5/10</td>
<td>1.0</td>
<td>0.4–2.4</td>
<td>1.00</td>
</tr>
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<td>7/14</td>
<td>1.0</td>
<td>0.4–2.6</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*One patient did not have imaging available for hemorrhage volume measurement or documentation of mental status and was not included in these analyses.
≥4% of TBV, whereas a previously published report with more deaths included 8 children with hemorrhage volume ≥4% of TBV. Furthermore, we excluded patients with brain tumor and with hemorrhage associated with cerebral venous sinus thrombosis, primary conditions that may portend poor prognosis. No child in our cohort had ICH resulting from coagulopathy, an etiology associated with poor outcome in a retrospective study. Referral bias may exist such that some patients may have died before transfer to our tertiary care center. Finally, children in our study who rapidly deteriorated were treated aggressively with hemorrhage evacuation and/or hemicraniectomy and maximal medical therapy for intracranial hypertension.

The association of poor outcome and intraventricular hemorrhage reported in adult ICH was not definitively demonstrated in our study. In this cohort, intraventricular hemorrhage was not statistically associated with clinically significant disability in children with supratentorial ICH. Due to the small numbers, it is possible that the added negative effect of intraventricular hemorrhage was too small to detect. Infratentorial ICH is also associated with poor outcome in adults. Only 2 patients presented with infratentorial ICH, so this study could not adequately evaluate infratentorial location as an outcome predictor. Note that these 2 patients had severe outcomes: death in one and severe disability in the other.

Another study limitation is that no validated standard outcome measure exists in pediatric ICH. The 2 measures used here have been used in other related disease processes: the PSOM for pediatric ischemic stroke and the KOSCHI for childhood head injury. Other studies have used nonvalidated tools such as the Glasgow Outcome Scale and the modified Rankin Scale. In a head trauma study, the KOSCHI had limited use predicting long-term outcome, so the implications for long-term outcome in our study should be interpreted cautiously. Some children in this cohort with clinically significant disability on short-term KOSCHIs and PSOMs may continue to improve, so early outcomes may overestimate long-term deficits. However, some children may manifest neurocognitive problems as they mature. The benefit of using the KOSCHI plus the PSOM is that the former accounts for seizures and headaches, thereby separating children with no sequelae from the injury from those with no deficit but with other repercussions. Larger studies with greater follow-up duration should be performed to elucidate the relationships between hemorrhage volume and long-term outcomes and that between early altered mental status and long-term outcomes.

The strength of our findings is enhanced by the prospective design, by the high rate of inclusion and ascertainment, and by our use of objective standardized outcome measures. The prospective design particularly eliminates the selection and ascertainment bias that often plagues retrospective studies based on International Classification of Diseases, 9th Revision code searches, which have been inadequate in identifying children with stroke diagnoses. The prospective design and use of objective standardized outcome measures further strengthen our conclusions by minimizing recall bias for patient presentations and for interpretation of clinical examinations and outcomes.

Summary and Future Directions

In this single-center prospective cohort of children with ICH, hemorrhage volume >2% of TBV and altered mental status within 6 hours of hospital presentation were associated with clinically significant disability at short-term follow-up. Seventy percent of children had neurological deficits and 55% had clinically significant disability. Enhanced understanding of factors affecting outcome for children with ICH is needed to provide better prognostic counseling for families and to design clinical trials for management strategies. Validating our results in a larger prospective cohort and identifying other potentially modifiable factors associated with outcome may lead to significant improvements in the care of children with ICH.

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Disclosures

None.

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