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Etiology, clinical characteristics and prognosis of spontaneous intracerebral hemorrhage in children: A prospective cohort study in China☆

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ABSTRACT

Background and objective: Much is known about spontaneous intracerebral hemorrhage (SICH) in adults, but few studies have examined pediatric SICH, especially in China. The aim of the present study was to describe the etiology, clinical characteristics and prognosis of SICH in children from southwest China.
Method: Consecutive patients aged 1–18 years with SICH at our medical center were prospectively enrolled from January 2012 to June 2014. SICH was defined by WHO criteria and confirmed by CT or MRI findings. Demographic and clinical information was collected at baseline, and follow-up assessments were conducted at 3 and 6 months after SICH, when patients were scored on the modified Rankin Scale (mRS) and events of deaths and recurrent hemorrhagic stroke were recorded.
Results: Among the 70 children (43 males; median age, 12.0 years) in the final analysis, 44 patients (62.9%) had SICH due to arteriovenous malformation, and less frequent etiologies were cavernous malformation (n = 4), aneurysm (n = 2), tumors (n = 2), moyamoya (n = 2), hemophilia (n = 1), hypertension (n = 1), while 14 (20.0%) had SICH of unknown etiology. The mortality rate at 3 months and 6 months was equal, which was both 3%. The rate of disability was 12.1% at 3 months and 9.1% at 6 months.
Conclusion: The most frequent etiology of pediatric SICH in this Chinese cohort was arteriovenous malformation. SICH of unknown etiology occurred much more often in our cohort than in previously published Caucasian patients in the US and Europe.

1. Introduction

Stroke is a major cause of morbidity and mortality throughout the world, and spontaneous intracerebral hemorrhage (SICH) accounts for approximately 15% of all stroke cases [1]. Although the public often associates stroke with old age, stroke occurs in 2–13 children per 100 000 per year [2,3], and SICH accounts for as many as half of these cases [2,4]. Pediatric SICH leads to death in approximately one-third of cases, and in many more cases it leads to long-term disability, including seizures as well as cognitive and motor impairment [5–8]. This poses a substantial burden on the family and society, highlighting the need for a strong understanding of SICH in children.

Despite the devastating effects of SICH in children, much less is known about it than about SICH in adults. The relatively few published studies on pediatric SICH are case series and retrospective chart reviews [4–7,9]. Some prospective cohort studies have been reported, but they involve small samples of 11–22 children [3,10]. This lack of understanding of pediatric SICH poses a serious obstacle to predicting, diagnosing and managing the condition, since its etiology and outcomes appear to be different from those of adult SICH [2,11]. Even this is uncertain, however, since most studies of pediatric SICH have come from the US and Europe, leaving open the question of whether SICH etiology and outcomes are similar in children of other ethnic groups. In China, for example, very little has been published about pediatric SICH [12].

Therefore we prospectively enrolled patients aged 1–18 years with SICH at our medical center in southwest China and analyzed stroke etiology, clinical characteristics and outcomes during 6-month follow-up. We also tried to identify clinico-demographic predictors of poor outcomes.

2. Methods

This research project was carried out under the auspices of the National Key Technology R&D Program of the 12th Five-Year Plan "Study on Etiology and Minimally Invasive Neurosurgery for Hemorrhagic Stroke". The study protocol was approved by the Scientific

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Research Department of West China Hospital, Sichuan University. Written informed consent was obtained from participants or their guardians.

Pediatric patients with spontaneous ICH were prospectively and consecutively enrolled upon being admitted to West China Hospital of Sichuan University in Chengdu, China. The enrollment period was from January 2012 to June 2014. To be enrolled, patients had to be 1–18 years old with a diagnosis of SICH based on World Health Organization stroke criteria [13] and confirmed by neuroimaging, which involved rapid computed tomography scanning or magnetic resonance imaging to distinguish SICH from ischemic stroke [1]. Children were excluded from the study if they had a history of head trauma; if their hemorrhage was restricted to epidural, subdural, intraventricular or subarachnoid compartments; or if patients had both CSVT and hemorrhagic transformation.

A standardized form was used to collect data on patient demographic characteristics, level of consciousness on admission, stroke risk factors, diagnostic tests, treatment, stroke-related complications during hospitalization, and discharge medicine/interventions. Level of consciousness on admission was measured using the Glasgow Coma Score (GCS).

Current medicine use and outcomes (death, disability, combined death or disability, and stroke recurrence) were assessed at 3 and 6 months after stroke onset by telephone interview or letter conducted by experienced stroke neurologists. A different group of stroke neurologists who were blinded to patient clinical data calculated modified Rankin score (mRS) scores. Disability was defined as a score of 3–5 on the modified Rankin Scale (mRS) [14–15]. Recurrence included intracerebral and subarachnoid hemorrhage.

All statistical analyses were performed using SPSS 20.0 (IBM, Chicago, IL, USA). Two-sided P values < 0.05 were considered statistically significant. Results were expressed as odds ratios (ORs) and associated 95% confidence intervals (CIs). Results for categorical variables were compared between different groups using chi-squared or Fisher exact tests. Results for continuous variables were compared using ANOVA or Mann–Whitney U tests. Binary logistic regression was used to identify possible predictors of death or disability in pediatric SICH.

3. Results

3.1. Baseline patient characteristics

A total of 70 patients with childhood SICH (43 males; median age, 12.0 ± 4.6 years) were included in the study. Most were diagnosed with pure ICH (50 patients), while 15 (21.4%) were diagnosed with a combination of intracerebral and intraventricular hemorrhage, and 5 (7.1%) had a combination of intracerebral and subarachnoid hemorrhage. Among the 70 patients, 56 children have undertaken enough imaging examination (eg. MRA, CTA or DSA). Etiology of SICH was undetermined in 14 patients due to lack enough imaging examination. SICH in most patients (n = 44) was caused by arteriovenous malformation; other, much less frequent etiologies were cavernous malformation (n = 4), aneurysm (n = 2), tumors (n = 2)and moyamoya (n = 2) (Table 1). One patient was diagnosed with hemophilia, consistent with the number of patients with hypertension. 46 (65.7%) patients received surgery after SICH (Table 1).

Most patients (54, 77.1%) were transferred to our hospital after being admitted to local hospitals, while the remaining 16 (22.9%) were admitted directly to our tertiary care center. Median time from symptom onset to our hospital was 91 h, with 11 patients (15.7%) arriving at our hospital within 6 h and 49 (70.0%) arriving more than 24 h after symptom onset. SICH was accompanied by altered mental status in 26 patients (37.1%), by headache in 56 (80.0%), and by vomiting in 45 (64.3%). After admission to our medical center, focal deficits were detected upon initial examination in 38 patients (54.3%), seizures occurred in 9 (12.9%), and intracranial hypertension or herniation syndromes occurred in 13 (18.6%). In-hospital complications occurred in 10 patients (14.3%), including respiratory infection (n = 6), electrolyte disturbance (n = 2), urinary infection (n = 1), and acute renal failure (n = 1).

Table 1
Baseline characteristics of Chinese pediatric patients with SICH (n = 70).

Characteristic	Value
Male sex, n (%)	43 (61.4)
Age at index stroke in year, median (range)	12.0 (1–18)
Stroke risk factors, n (%)	
Arteriovenous malformation	44 (62.9)
Unknown	14 (20.0)
Angiocavernoma	4 (5.7)
Moyamoya	2 (2.9)
Tumor	2 (2.9)
Aneurysm	2 (2.9)
Hemophilia	1 (1.4)
Hypertension	1 (1.4)
Localization, n (%)	
Lobe	40 (57.1)
Multiple areas	22 (31.4)
Deep brain	13 (18.6)
Cerebellum	5 (7.1)
Brainstem	4 (5.7)
Laterality, n (%)	
Left	41 (58.6)
Right	22 (31.4)
Both	7 (10.0)
Level of consciousness, n (%)	
Mild (13–15)	53 (75.7)
Moderate (9–12)	6 (8.6)
Severe (3–8)	11 (15.7)
Treatment, n (%)	
Dehydration	59 (83.1)
Surgery	46 (65.7)

3.2. Outcomes at 3 and 6 months

The patient diagnosed with hemophilia died of respiratory failure caused by herniation within 24 h after admission to our hospital; the remaining 69 patients were alive at discharge. Another child was dead within 3 months after ICH, while the cause of the death was unknown. Four patients were lost to follow-up. As a whole, the mortality rate at 3 months among the remaining 66 patients was 3% and the disability rate at 3 months was 12.1% (Table 2). The corresponding rates at 6 months were 3% and 9.1%. The combined rate of mortality or disability was 15.2% at 3 months and 12.1% at 6 months. Among the 66 patients who completed the 6-month follow-up, only 2 experienced recurrence of ICH. Recurrent hemorrhage occurred in one child with unknown etiology of hemorrhage who developed a second ICH 20 days after the initial event. Another child with AVM which was not resected during hospitalization had a secondary hemorrhage within 6 months after first hemorrhage.

3.3. Predictors of disability or death within 6 months of SICH

Univariate analysis identified several variables that were significantly associated with disability or death at 6 months (Table 3): Age 1 (1–4 years old) ($P = 0.04$), focal deficits ($P = 0.01$), GCS on admission [3–8] ($P = 0.03$), deep brain ($P = 0.04$), use of dehydration therapy ($P = 0.02$), surgery ($P = 0.03$), and complications ($P = 0.02$).

Table 2
Rates of mortality and disability [n (%)] at 3 and 6 months after SICH (n = 66).

	3 months	6 months
Mortality	2 (3.0)	2 (3.0)
Disability	8 (12.1)	6 (9.1)
Mortality or disability	10 (15.2)	8 (12.1)
Recurrence of SICH	1 (1.5)	2 (3.0)