The Importance of Cerebral Aneurysms in Childhood Hemorrhagic Stroke
A Population-Based Study
Lori C. Jordan, MD; S. Claiborne Johnston, MD, PhD; Yvonne W. Wu, MD, MPH; Stephen Sidney, MD, MPH; Heather J. Fullerton, MD, MAS

Background and Purpose—Prior population-based studies of pediatric hemorrhagic stroke (HS) had too few incident cases to assess predictors of cerebral aneurysms, a HS etiology that requires urgent intervention.

Methods—We performed a retrospective cohort study of HS (intracerebral, subarachnoid [SAH], and intraventricular hemorrhage) using the population of all children <20 years of age enrolled in a large Northern Californian healthcare plan (January 1993 to December 2003). Cases were identified through electronic searches and confirmed through independent chart review by 2 neurologists with adjudication by a third; traumatic hemorraghes were excluded. Logistic regression was used to examine potential predictors of underlying aneurysm.

Results—Within a cohort of 2.3 million children followed for a mean of 3.5 years, we identified 116 cases of spontaneous HS (overall incidence, 1.4 per 100 000 person-years). Cerebral aneurysms were identified in 15 (13%) of HS cases. Among 21 children with pure SAH, 57% were found to have an underlying aneurysm compared with only 2% of 58 children with pure intracerebral hemorrhage and 5% of 37 children with a mixed pattern of hemorrhage (intracerebral hemorrhage and SAH). Independent predictors of an underlying aneurysm included pure SAH (OR, 76; 95% CI, 9 to 657; \(P<0.001\)) and late adolescent age (15 to 19 years versus younger age groups; OR, 6.4; 95% CI, 1.0 to 40; \(P=0.047\)).

Conclusions—Cerebral aneurysms cause the majority of spontaneous SAH in children and account for more than 10% of childhood HS overall. Children, and particularly teenagers, presenting with spontaneous SAH should be promptly evaluated with cerebrovascular imaging. (Stroke. 2009;40:400-405.)

Key Words: aneurysm ■ child ■ hemorrhagic ■ stroke

In hospital series of cerebral aneurysms, 0.5% to 4.6% occur in children, leading to a perception that pediatric aneurysms are rare.\(^1\)\(^-\)\(^6\) A more clinically relevant statistic, however, is the proportion of children with hemorrhagic stroke (HS) who have an underlying aneurysm. Prior population-based studies of pediatric HS had too few incident cases (<10) to accurately assess this proportion.\(^7\)\(^-\)\(^12\) These studies also lacked the statistical power to determine factors that predict the presence of an aneurysm in a child presenting with a HS.

An accurate sense of a child’s risk of an underlying aneurysm is important because these lesions have a high rate of rerupture in the acute phase and therefore require more urgent treatment than other HS etiologies. Such knowledge would guide clinicians in key management decisions such as the importance and urgency of vascular imaging to diagnose or exclude an aneurysm. Using a large population-based cohort of children in Northern California with 116 incident cases of HS, we determined predictors of underlying cerebral aneurysms.

Methods

Study Design and Setting
We performed a retrospective cohort study of HS using the population of Kaiser Permanente Medical Care Program (KPMCP) in Northern California. KPMCP provides medical care to approximately 30% of the population of Northern California with sociodemographic characteristics that are representative of the region except for an underrepresentation of the socioeconomic extremes.\(^13\) The study population included all 2.3 million children <20 years of age enrolled in KPMCP between January 1993 through December 2003. Because membership enrollment and termination dates are recorded, duration of follow-up is known for each individual. The methods of the full cohort study, the Kaiser Pediatric Stroke Study, which includes both ischemic and hemorrhagic stroke, have been described in prior reports.\(^14\)\(^,\)\(^15\) This report focuses only on children with HS.
Institutional Review Boards at the University of California, San Francisco and the KPMCP Division of Research (Oakland, Calif) approved this study.

Case Identification

Potential stroke cases were ascertained through a multiterried process that included electronic searches of hospital discharge databases (coded by medical records abstractors), outpatient diagnosis databases (coded by treating physicians), and radiology databases (using text-string searches of electronic head imaging reports). Cases were confirmed through chart review, including review of formal radiology reports with independent adjudication by 2 neurologists (H.J.F., Y.W.W.) with a third neurologist (S.C.J.) arbitrating disagreements. The criteria for HS were: (1) documented clinical presentation consistent with HS such as a sudden-onset focal neurological deficit, headache, loss of consciousness, or seizure; and (2) CT or MRI showing an intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and/or intraventricular hemorrhage (IVH) of an age consistent with the neurological signs and symptoms. Based on all available head imaging reports, we classified the HS subtypes into 3 groups: (1) pure ICH; (2) pure SAH; and (3) ICH plus SAH. Because the subarachnoid and intraventricular spaces are contiguous, patients with pure IVH were grouped with SAH.

Because IVH in newborns is typically regarded as a distinct entity with a unique pathophysiology, usually related to immaturity of the germinal matrix, we excluded cases of neonatal IVH (pure IVH, without ICH, occurring within the first 28 days of life). We also excluded strokes that occurred before the child’s enrollment in KPMCP or outside of the study period. Children with traumatic HS (n=37)—defined as ICH, SAH, or IVH in the context of a significant head injury—were included in the full study15 but are excluded from the current analysis.

Data Abstraction

A single pediatric registered nurse medical records analyst used a standardized protocol to abstract data from paper and electronic medical records. All relevant records were reviewed by a single pediatric stroke neurologist (H.J.F.) who confirmed all abstracted data. Ethnicity was defined by parental report. Presentation and examination findings were based on the documented reports of the treating physicians. One of the authors (H.J.F.) used all available data to categorize the stroke etiology: traumatic (directly related to head injury; excluded from this analysis), structural (arteriovenous malformation, aneurysm, cavernous malformation, or tumor), medical (hemophilia, thrombocytopenia, hypertension, cocaine/amphetamine use, and so on), and undetermined (no identified cause).

Data Analysis

All comparisons of proportions were analyzed using $\chi^2$ tests or Fisher exact tests when any expected frequency was <5. Logistic regression was used to examine potential predictors of underlying aneurysm in children with HS. Covariates included gender, race, age, presentation, and hemorrhage pattern. Age was treated as both a continuous variable and a categorical variable to allow for a nonlinear (eg, U-shaped) association. For consistency with our prior studies, we divided age into 4 categories: 0 through 4 years; 5 through 9 years, 10 through 14 years, and 15 through 19 years; late adolescence was defined as 15 through 19 years of age.16,17 We addressed potential confounders by first determining whether they were associated with both the predictor and outcome of interest and then adjusting for them through both stratification and inclusion in multivariate models. We used multivariate logistic regression to identify independent predictors of an underlying aneurysm. We selected covariates for the model through univariate screening, including those with alpha <0.10. A probability value of <0.05 was considered statistically significant. STATA (Version 9.0; College Station, Texas) was used to perform all statistical calculations.

Results

The study cohort included a total of 2,347,982 children followed in KPMCP for a mean of 3.5 years during an 11-year study period. There were 116 incident cases of nontraumatic childhood HS yielding an average annual incidence rate of 1.4 per 100,000 person-years (95% binomial exact CI, 1.2 to 1.7). The median age at the time of stroke was 12.1 years (range, 0 to 19.9 years; mean, 10.3 years; SD, 7.0); the incidence rate was highest in the youngest and oldest age groups (Figure 1A; $P<0.0001$ for the overall comparison by $\chi^2$). The stroke cohort was predominantly male but ethnically diverse (Table 1). Half of the incident HS were pure ICH (n=58 [50%]), whereas 37 (32%) were a combination of ICH and SAH, and 21 (18%) were pure SAH. The pure SAH group included 4 children with blood in both the subarachnoid and intraventricular spaces and 2 children with only intraventricular blood. Although the majority of the 116 children with HS were admitted to the hospital, 14 were never admitted and had only outpatient diagnostic evaluations.

Vascular Imaging

Overall, 75 children with HS received vascular imaging: 65 children had conventional angiography, 17 children had a brain MR angiogram, and one child had a neck MR angiogram; no patients had CT angiography. Of 29 children with undetermined etiology, 13 had no vascular imaging. Children with pure SAH received vascular imaging at a median of 1 day after the stroke ictus (range, 0 to 46 days); however, 32% (6 of 19) received such imaging at 3 days or greater, and 10%
(2 of 21) never received vascular imaging. Of the 2 children who did not receive vascular imaging, one was a boy with sickle cell disease who was initially critically ill and had known moyamoya syndrome. The other was a neonate with seizures and hypotonia noted on the second day of life found to have SAH without a history of traumatic delivery. No child with pure SAH or SAH/ICH and initially normal vascular imaging (n=11005) received repeat conventional angiography. One patient had repeat MR angiography at a 2-month interval after SAH.

Incidence of Aneurysmal Hemorrhagic Stroke
Among the 116 cases of incident childhood HS, 15 (13%) were found to have underlying cerebral aneurysms compared with 35 (31%) with brain arteriovenous malformations, 17 (15%) with cavernous malformations, 16 (14%) with medical etiologies, 3 (2.5%) with brain tumors, and 29 (25%) with undetermined etiology. Among children who underwent conventional angiography, 15 of 65 (23%) had cerebral aneurysms. All 15 children with aneurysms were previously healthy with no history of hypertension; 2 older teenagers (aged 18 and 19 years) had urine toxicology screens that were positive for cocaine. The annual incidence of aneurysmal HS in children was 0.18 per 100 000 person-years (95% CI, 0.1 to 0.3 per 100 000 person-years). The incidence was highest in late adolescence: 0.52 per 100 000 person-years in those aged 15 to 19 years compared with 0.06 for age 0 to 4 years, 0.05 for age 5 to 9 years, and 0.09 for age 10 to 14 years (Figure 1B; P=0.001 for the overall comparison by Fisher exact test). Even excluding the 2 cases of cocaine-related aneurysmal SAH, the later teens still had the highest incidence of aneurysmal SAH, 0.43 per 100 000 person-years.

Of the 15 cases of aneurysmal HS, 12 had pure SAH, 2 had a combination of ICH and SAH, and one had pure ICH. Fourteen children had only a single aneurysm; one child had 3 aneurysms. Aneurysm location was known for all 17 aneurysms in 15 children; 15 of 17 were in the anterior circulation. Aneurysm size was documented in 8 children who had a total of 10 aneurysms. Median size was 8.5 mm (range, 3 to 20 mm); 2 children had giant aneurysms (20 mm in size).

Univariate Analysis of Predictors of Underlying Aneurysm
Late adolescent age at presentation (15 years through 19 years) was the only demographic feature predictive of underlying aneurysm with an OR of 7.2 (95% CI, 2.2 to 24.4; P=0.002; Table 1). Syncope and headache were the only presenting features that were predictive, although syncope was present in only a minority of cases (Table 1). The strongest univariate predictor of underlying aneurysm was a hemorrhage pattern of pure SAH (OR, 76; 95% CI, 9 to 657; P<0.001). Among children with pure SAH, 57% (12 of 21) were diagnosed with a cerebral aneurysm compared with only

Table 1. Univariate Predictors of HS in a Population of Children <20 Years Old Enrolled in KPMCP, January 1993 to December 2003

<table>
<thead>
<tr>
<th></th>
<th>Aneurysm (n=15)</th>
<th>Other Etiologies (n=101)</th>
<th>OR (95% CI)</th>
<th>Total (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>11 (73)</td>
<td>57 (56)</td>
<td>2.1 (0.6–7.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Age, years,* mean (SD)</td>
<td>15.5 (5)</td>
<td>9.5 (7)</td>
<td>1.2 (1.1–1.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age 15 to 19 years, n (%)</td>
<td>11 (73)</td>
<td>28 (28)</td>
<td>7.2 (2.1–24.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3 (20)</td>
<td>36 (36)</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>Black</td>
<td>1 (7)</td>
<td>10 (10)</td>
<td>1.2 (0.1–12.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (33)</td>
<td>31 (31)</td>
<td>2.4 (0.4–13.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (20)</td>
<td>15 (15)</td>
<td>1.9 (0.4–8.8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (20)</td>
<td>9 (9)</td>
<td>4.5 (0.8–26.5)</td>
<td>0.097</td>
</tr>
<tr>
<td>Presentation,† n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 (86)</td>
<td>54 (54)</td>
<td>5.1 (1.1–24.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>Seizure</td>
<td>4 (27)</td>
<td>30 (30)</td>
<td>0.9 (0.3–2.9)</td>
<td>0.79</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (15)</td>
<td>2 (2)</td>
<td>8.7 (1.1–68.3)</td>
<td>0.039</td>
</tr>
<tr>
<td>Focal motor deficit</td>
<td>1 (7)</td>
<td>26 (27)</td>
<td>0.2 (0.02–1.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>8 (57)</td>
<td>47 (48)</td>
<td>1.4 (0.5–4.4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Speech deficit</td>
<td>1 (7)</td>
<td>9 (10)</td>
<td>0.7 (0.1–6.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Gait abnormality</td>
<td>0 (0)</td>
<td>8 (9)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Hemorrhage pattern, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>1 (7)</td>
<td>57 (56)</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>SAH</td>
<td>12 (57)</td>
<td>9 (9)</td>
<td>76 (9–657)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAH+ICH</td>
<td>2 (13)</td>
<td>35 (35)</td>
<td>3.3 (0.3–37.3)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Per one advancing year of age.
†Categories are not mutually exclusive.
2% (one of 58) of children with pure ICH and 5% (2 of 37) of children with a mixed pattern of hemorrhage (ICH and SAH; Figure 2). Two children included in the pure SAH category actually had intraventricular blood alone; both had underlying brain arteriovenous malformation. After excluding these cases, 63% (12 of 19) of children with pure SAH had an underlying cerebral aneurysm.

Other etiologies of pure SAH included arteriovenous malformation (one additional child), moyamoya syndrome (n = 1), hemophilia (n = 1), and undetermined (n = 4). One case of undetermined etiology was a neonate who never received vascular imaging, whereas the other 3 were older children with negative conventional angiography (n = 2) or MR angiography (n = 1). The SAH location was perimesencephalic in one, over the vertex in another, and in the right sylvian fissure extending to the suprasellar cistern in the third.

Confounding by Vascular Imaging and Age

Children with pure SAH had 2.7 times the odds of having vascular imaging than children with ICH alone (95% CI, 1.9 to 41.6; P = 0.006). In addition, vascular imaging predicted underlying aneurysm (OR, 9.2; 95% CI, 1.2 to 72.6; P = 0.036). Because vascular imaging could serve as a confounder, we stratified by this variable. Among patients who received vascular imaging, pure SAH still predicted the presence of aneurysm with an OR of 50 (95% CI, 5 to 449; P = 0.001). Age could also serve as a confounder, because late adolescent age predicted undergoing vascular imaging (OR, 5.9; 95% CI, 2.1 to 16.9; P = 0.001). Therefore, we also stratified by age. For the late adolescents, pure SAH still predicted the presence of aneurysm (OR, 67; 95% CI, 5 to 854; P = 0.001).

Multivariate Analysis of Predictors of Underlying Aneurysm

Using univariate screening to create our multivariate logistic regression model, we included the following variables in our model: adolescent age at presentation, hemorrhage pattern of pure SAH, headache, syncope, and vascular imaging (as a confounder). Neither headache nor syncope remained significant predictors (Table 2). However, both pure SAH and adolescent age were independent predictors of an underlying aneurysm.

Discussion

In the management of a child with a HS, clinicians need to know the likelihood that this child has an underlying aneurysm. This likelihood of aneurysm cannot be reliably determined from hospital-based case series due to referral bias. Prior population-based studies, although free of referral bias, had too few incident cases of HS (ranging from 3 to 9) to measure the prevalence of aneurysms.7,10,12 We now present a substantially larger population-based study of childhood HS with 116 incident cases. We found that at least 13% of children with HS, and 63% of children with pure SAH (exclusive of pure IVH), had an underlying cerebral aneurysm. A hemorrhage pattern of pure SAH and adolescent age at presentation were independent predictors of underlying aneurysm in multivariate analysis.

Our observation of a high proportion of aneurysms in children with HS, particularly pure SAH, is likely generalizable. Our study population included an unselected cohort of children enrolled in a large health maintenance organization over an 11-year time period. Hence, unlike estimates generated from hospital series, our results are not affected by referral bias. The study population was ethnically and socioeconomically diverse with demographics similar to that of Northern California except for underrepresentation of the very rich and the very poor.13

Table 2. Multivariate ORs for Predictors of Aneurysm in a Cohort of Children With HS

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage pattern</td>
<td>Reference</td>
<td>...</td>
</tr>
<tr>
<td>SAH</td>
<td>55</td>
<td>(5–602)</td>
</tr>
<tr>
<td>ICH + SAH</td>
<td>2.6</td>
<td>(0.2–33)</td>
</tr>
<tr>
<td>Late adolescence†</td>
<td>6.4</td>
<td>(1.0–40)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Syncope</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Vascular imaging</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Variables included in the multivariate logistic regression model were selected by univariate screening with alpha = 0.10. All variables included in the model are shown.
†Age 15 to 19 years.
The high proportion of aneurysms in children with HS is also clinically relevant. Clinicians should have a high index of suspicion for an underlying aneurysm in children presenting with pure SAH, particularly teenagers. Although less likely, other patterns of hemorrhage can also be caused by aneurysm rupture. If an aneurysm is suspected, the child should have vascular imaging performed promptly. Cerebral aneurysms have a high rate of rerupture in the acute phase—15% within the first 24 hours. In comparison, rerupture of cerebral arteriovenous malformations (without high-risk features like nidal aneurysms) tends to occur weeks to months after the index event. Hence, children at high risk for an underlying aneurysm should be investigated rapidly to minimize delays in treatment and risk of stroke recurrence.

Our observed overall HS incidence rate of 1.4 per 100 000 person-years (95% CI, 1.2 to 1.7) is comparable to prior estimates in the United States. A study from Minnesota identified 3 incident cases of HS between 1965 and 1974, yielding an incidence of 1.9 per 100 000 person-years (calculated 95% CI, 0.4 to 5.5). A study from Cincinnati with 9 incident cases occurring between 1988 and 1989 reported an incidence of 1.5 per 100 000 person-years (95% CI, 0.3 to 2.0). The most recent estimate, based on 6 incident cases in Corpus Christi in 2000, was 3.2 per 100 000 person-years (calculated 95% CI, 1.1 to 7.1). Finally, a study using California-wide administrative data identified 1111 childhood admissions with diagnostic codes for HS between 1991 and 2000, suggesting an incidence of 1.12 per 100 000 person-years (95% CI, 1.06 to 1.19). Although the first 3 studies were limited by small sample sizes, and the last by the lack of case confirmation through chart review, all provided similar estimates with overlapping CIs, suggesting that there are no major geographic differences or recent temporal changes in childhood HS incidence in the United States.

In adults, the incidence of SAH related to ruptured aneurysm in the Greater Cincinnati stroke study was 6 per 100 000 person-years. In contrast, we found an annual incidence of aneurysmal HS of 0.18 per 100 000 children. Although these estimates represent different populations and time periods, these data suggest that adults are 35 times more likely to experience an aneurysmal SAH than children. However, the pediatric incidence rate may be an underestimate for a number of reasons. Not all children received vascular imaging, and some were only imaged with MR angiography and not catheter angiography (the gold standard). Vascular imaging was not rereviewed by the study investigators to identify abnormalities that may have been missed by the clinical radiologist. Catheter angiography was not repeated among children with angiogram-negative SAH, and hence some underlying aneurysms may have been missed. However, there were no recurrent hemorrhages among the children with undetermined HS etiology.

Among children, we found that the incidence of aneurysmal HS varied by age with rates more than 5-fold higher in the older teenagers compared with the younger age groups (Figure 1). This may suggest a greater role for acquired aneurysm risk factors with advancing age in childhood. Notably, 2 of the older teenagers with aneurysmal SAH tested positive for cocaine, which likely played a role in the pathogenesis of their lesions. However, even after excluding those cases, the incidence was highest in the late adolescent age group: 0.43 per 100 000 person-years.

Despite the large size of our cohort (2.3 million children), the small number of incident hemorrhagic strokes and aneurysms limited our ability to detect all but strong predictors of underlying aneurysm. For example, for covariates prevalent in approximately 50% of the overall cohort (such as headache), we had 80% power to detect a minimum OR of 6.5 for the association with aneurysm. The results of our multivariate analyses must be interpreted with caution given the small number of subjects with the outcome of interest (aneurysm). Another limitation is that we did not review actual imaging studies and therefore were limited in our ability to describe the aneurysms in more detail. Finally, only 65% of children with atraumatic HS underwent vascular imaging. This means that the prevalence of aneurysms and other vascular etiologies reported here could be underestimated. However, despite these limitations, these data represent the largest population-based study of children with HS and the first report of the incidence of aneurysmal SAH and predictors of underlying aneurysms in these children.

In summary, our data support the commonly held perception that the incidence of aneurysmal rupture is low in a population of children. However, when faced with a child with a HS, clinicians should not be falsely reassured by this low incidence. In our cohort, cerebral aneurysms caused the majority of spontaneous pure SAHs and accounted for more than 10% of childhood HS overall. Children, particularly teenagers, presenting with spontaneous SAH should be emergently evaluated with cerebrovascular imaging to avoid delays in the treatment of an underlying aneurysm.

Sources of Funding
This work was supported by an American Heart Association Scientific Development grant, Neurological Sciences Academic Development Award (K12 NS01692), and Independent Scientist Award (K02 NS053883; to H.J.F.); and K12 NCRR 017627 (to L.C.J.).

Disclosures
None.

References


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*Stroke*. 2009;40:400-405; originally published online November 20, 2008; doi: 10.1161/STROKEAHA.108.518761

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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