Recurrent Hemorrhagic Stroke in Children
A Population-Based Cohort Study

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Background and Purpose—Although hemorrhagic strokes (HS) account for half of all strokes in children, rates and predictors of recurrent HS have not been studied.

Methods—We collected data on all documented cases of HS (intracerebral hemorrhage, subarachnoid hemorrhage, and intraventricular hemorrhage, except neonatal intraventricular hemorrhage), among 2.3 million children (<20 years) enrolled in a Northern Californian health maintenance organization from January 1993 to December 2004. Using Kaplan-Meier survival analyses censoring at death or loss to follow-up, we determined rates of recurrent HS. Log rank tests were used for bivariate comparisons.

Results—Among 116 children with atraumatic incident HS followed for a mean of 4.2 years, 11 had a recurrent HS at a median of 3.1 months (range 7 days to 5.7 years), yielding an overall 5-year cumulative recurrence rate (CRR) of 10% (95% CI, 58% to 18%). Sixty-four percent of recurrences were within the first 6 months. Whereas children with idiopathic HS (n = 29) had no recurrences, children with structural lesions (vascular malformations or tumors) had a 5-year cumulative recurrence rate of 13% (95% CI, 7% to 25%); 9 recurrences among 71 children; P < 0.05 compared with idiopathic). Children with medical etiologies (eg, thrombocytopenia, hypertension) had a 5-year cumulative recurrence rate of 13% (95% CI, 3% to 41%; 2 recurrences among 16 children), but the recurrences were within the first week.

Conclusions—Overall, 1 in 10 children with HS experienced a recurrence within 5 years, despite available therapies. Whereas idiopathic HS rarely recurred, and HS due to medical etiologies tended to recur acutely, children with structural lesions had a high and prolonged risk for recurrence. (Stroke. 2007;38:2658-2662.)

Key Words: child ■ hemorrhagic ■ recurrence ■ stroke

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Cases were confirmed through chart review, with independent adjudication by 2 neurologists (H.J.F., Y.W.W.), with a third neurologist (S.C.J.) arbitrating disputes. 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), or intraventricular hemorrhage (IVH) of a maturity consistent with the neurological signs and symptoms. Because the subarachnoid and intraventricular spaces are contiguous, and because ICH can have subarachnoid or intraventricular extension, we classified the HS subtypes into 3 groups: (1) pure ICH, (2) pure SAH/IVH (blood in either the subarachnoid or ventricular space, or both), and (3) ICH plus SAH/IVH.

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 (IVH 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. We chose not to exclude children with traumatic HS because: (1) HS due to structural lesions might be misclassified as traumatic if, for example, the HS caused a fall, and vascular imaging was not performed; and (2) trauma can predispose to recurrent HS by causing pseudoaneuysms. (There were 3 children in our cohort with a history of trauma who were subsequently diagnosed with aneurysms on conventional angiography; these cases would have been classified as traumatic if the vascular imaging had not been performed.)

Data Abstraction
A single pediatric nurse medical records analyst used a standardized protocol to abstract data from traditional and electronic medical records. All relevant records were rereviewed by a single pediatric stroke neurologist (H.J.F.), who used all available data to categorize the stroke etiology: structural (AVM, aneurysm, cavernous malformation, or tumor), traumatic (directly related to head injury), medical (hemophilia, thrombocytopenia, hypertension, cocaine/amphetamine use, etc), and idiopathic (no identified cause). Within the “idiopathic” group, if vascular imaging was not performed (and therefore the stroke could have been misclassified), the etiology was further subcategorized as “undetermined.”

Recurrent Strokes
KPMCP members receive all routine care within the system, so follow-up data are complete and easily acquired. Because KPMCP covers out-of-plan care for its members, emergent admissions to non-KPMCP hospitals are also captured, and medical records from outside admissions are typically available in outpatient charts. We abstracted data regarding any additional recurrent HS that occurred after the index event, applying the same adjudication procedures. Because children with hemorrhagic stroke may also be at risk for ischemic stroke, we also recorded data on any ischemic strokes that occurred subsequent to the index HS, although these were not included in our recurrence rates.

Data Analysis
Incidence rates for the index HS were calculated as the number of HS divided by the total number of person-years at risk. To determine recurrence rates after the index HS, we used Kaplan-Meier survival analysis techniques. The primary outcome variable was time to the first recurrent HS. The “at risk” period began on the date of the index HS, and ended on the date of the first recurrent HS or censoring. Patients were censored at death or loss to follow-up, based on the last visit in the KPMCP system through December 2005. We did not censor at the subject’s 20th birthday. We did not censor at the time of treatment of an underlying structural lesion because this would have led to informative censoring (only those children with a structural etiology would have been subject to censoring for this reason). Although the overall survival curve appeared exponential, this was not true after stratification. In addition, there were important differences in timing of events between subgroups leading to violation of the proportional hazards assumption. Thus, we relied on nonparametric testing. Log rank tests were used to determine the significance of bivariate comparisons (α set at 0.05). We used Stata (version 9.0) to perform all statistical calculations.

Results
Our study cohort included a total of 2,347,982 children followed in KPMCP for a mean of 3.8 years during an 11-year study period. We confirmed a total of 153 incident cases of childhood HS, yielding an average annual incidence rate of 1.7 per 100,000 person-years (95% binomial exact CI, 1.5 to 2.0). The mean age at the time of stroke was 10.9 years (SD 6.9). The stroke cohort was predominantly male (62%), and ethnically diverse (37% non-Hispanic white, 26% Hispanic, 14% Asian, 11% black, 1% Native American, and 11%
other or unknown). Half of the incident HS were pure ICH (n=77, 50%), whereas 34 (22%) were pure SAH/IVH, and 42 (37%) were a combination of ICH and SAH/IVH. Whereas the majority of children were admitted to the hospital, 14 (9%) were never admitted, and had only out-patient diagnostic evaluations. Etiologies of the incident (index) strokes are shown in Figure 1; 37 were traumatic, whereas 116 were spontaneous (atraumatic). Of the 29 children with idiopathic HS, 13 had no vascular imaging, and were therefore of “undetermined” etiology. Of the 71 children with underlying structural lesions, 54 (76%) received treatment after the index HS, before any recurrence (Table 1).

Follow-up data were available for all 153 children. Eight children died in the acute phase, yielding a case fatality rate of 5.2% for the initial hemorrhage. The fatality rate did not vary by stroke subtype. The remaining children were followed for a mean of 3.7 years (median 3.3 years; range 6 days to 12 years). There were 3 deaths during the follow-up period, all in children with cancer (brain tumor, n=1; acute lymphoblastic leukemia, n=2).

Recurrent HS

Among the 37 children with traumatic HS, there was only a single recurrence, yielding a 5-year cumulative recurrence rate of 7% (95% CI, 1% to 41%) in this subgroup. A girl with an initial IVH due to a motor vehicle accident experienced a traumatic SAH 3 years later after falling off a moving vehicle. The remainder of the recurrent HS analysis focuses on the 116 children whose index HS was spontaneous (atraumatic).

Eleven children had a recurrent HS at a median of 3.1 months after the initial event (range 7 days to 5.7 years). Seven of 11 recurrences (64%) occurred within the first 6 months, and 10 of 11 (91%) within the first 3 years. The overall cumulative recurrence rate was 6.3% (95% CI, 3.1% to 13%) at 1 year and 13% (95% CI, 6.9% to 25%) at 6 years (Figure 2A). Only 2 children, both with cavernous malformations, had multiple recurrences; because cases were censored at the time of the first recurrence, these were not included in our calculated recurrence rates. Recurrence rates did not vary significantly by stroke subtype: 1-year cumula-

Figure 2. A, Nelson-Aalen cumulative hazard plot demonstrating the proportion of children with spontaneous hemorrhagic stroke (n=116) to experience recurrent hemorrhagic stroke. The number of subjects remaining in the analysis over time is shown below the x axis. B, Plot stratified by etiology of index HS: idiopathic (dotted line, n=29, including 13 children with “undetermined” etiology [no vascular imaging]), structural (dashed line, n=71), and medical (solid line, n=16).
relative recurrence rates were 9.1% (95% CI, 3.9% to 21%) for pure ICH, 4.8% (95% CI, 0.7% to 29%) for pure SAH/IVH, and 2.9% (95% CI, 0.4% to 19%) for a combination of ICH with SAH/IVH (P = 0.5 by log-rank test for all 3 pair-wise comparisons).

Recurrence rates did vary by etiology (Figure 2B); most recurrences (9/11) were in children with underlying structural lesions (Table 2). Of the 2 children with recurrences due to medical etiologies, 1 was a teenager with hypertension due to end-stage renal disease of unknown etiology, and the other was a term neonate with idiopathic thrombocytopenia. Both recurrences were within 1 week of the index HS.

Among 9 children with recurrent HS due to an underlying structural lesion, 6 had not received any form of treatment for the underlying lesion at the time of the recurrence (Table 1). In only 1 case was there an active decision not to treat at the time of the initial HS (a child with a left thalamic cavernous malformation). The lack of treatment in the other cases was related to loss to follow-up (n = 1, cavernous malformation), delayed initial presentation to a medical facility (n = 2, cavernous malformations), and delayed diagnosis of the underlying lesion (n = 1, spinal AVM; n = 1, tumor obscured on acute imaging by the initial hematoma, but diagnosed at surgical exploration after the recurrent HS). All 6 subsequently underwent treatment (surgical resection, with preoperative embolization in 1 child with an AVM), with no recurrent HS after treatment. The other 3 children with recurrent HS had received some form of treatment before the recurrence. One child with multiple cavernous malformations underwent surgical resection of the ruptured cavernous malformation, but experienced a recurrent ICH from a different cavernous malformation 2 years later. Another child with a brain stem ICH secondary to a pineal region tumor underwent partial tumor resection and radiosurgery, and experienced a recurrent brain stem ICH 1 year after treatment. The third child had a ruptured left parieto-occipital AVM that was treated with embolization and radiosurgery, and rebled 15 months after the radiosurgery.

### Subsequent Ischemic Stroke
An additional 4 children (3.4%) had subsequent arterial ischemic strokes, 3 in the acute/subacute phase. One was a 3-year-old girl with an arteriovenous malformation who experienced a large frontal ICH with midline shift and herniation, and developed ipsilateral anterior and middle cerebral artery infarctions on post–bleed-day 4. Another was an 18-year-old boy with an aneurysmal SAH in the setting of cocaine use, who had a middle cerebral artery ischemic stroke on post–bleed-day 7, presumably related to either vasospasm or cocaine-vasculopathy. The third was a 12-year-old boy with acute myeloid leukemia with brain parenchymal involvement who had multifocal ICH followed by multifocal ischemic strokes in new locations 16 days later. Only 1 child had delayed ischemic strokes: a 7-year-old boy with moyamoya syndrome secondary to sickle cell disease who experi-

### Table 2. Recurrent Spontaneous Hemorrhagic Stroke Stratified by Etiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No.</th>
<th>1-Year Cumulative Recurrence Rate % (95% CI)</th>
<th>5-Years Cumulative Recurrence Rate % (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All etiologies (n=116)</td>
<td>11</td>
<td>6 (3–13)</td>
<td>10 (5–18)</td>
<td>...</td>
</tr>
<tr>
<td>Idiopathic (n=29)</td>
<td>0</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>ref</td>
</tr>
<tr>
<td>Undetermined† (n=13)</td>
<td>0</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>...</td>
</tr>
<tr>
<td>Structural (n=71)</td>
<td>9</td>
<td>7 (3–17)</td>
<td>13 (7–25)</td>
<td>0.05</td>
</tr>
<tr>
<td>AVM (n=36)</td>
<td>2</td>
<td>3 (0.4–19)</td>
<td>7 (2–24)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cav mal (n=17)</td>
<td>5</td>
<td>18 (6–45)</td>
<td>30 (14–58)</td>
<td>0.004</td>
</tr>
<tr>
<td>Aneurysm (n=15)</td>
<td>0</td>
<td>0 (—)</td>
<td>0 (—)</td>
<td>...</td>
</tr>
<tr>
<td>Tumor (n=3)</td>
<td>2</td>
<td>50 (9–99)</td>
<td>100 (—)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical (n=16)</td>
<td>2</td>
<td>13 (3–41)</td>
<td>13 (3–41)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Log-rank test, compared to idiopathic.

†Subset of children in the idiopathic group who did not have vascular imaging.

Cav mal indicates cavernous malformation.
enced ischemic strokes at 8 days and at 6 months after presenting with an SAH/IVH.

Discussion
This study describes recurrence risk in children with HS identified systematically from a well-defined multiethnic population, with a total of 153 incident cases. The number of incident cases in prior population-based studies have ranged from 6 to 31, and these studies did not provide data on recurrent stroke.1,12,13 Overall, we found that >1 in 10 children with a HS will experience a recurrence within 6 years. This rate reflects not the natural history of this disease, as many children received interventions, but rather the rate despite current medical practice. The highest risk period is the first 6 months, although recurrent HS occurred as late as almost 6 years after the index event.

Almost half of children with idiopathic HS received no vascular imaging, and hence could have been misclassified. However, we identified no recurrences among this “undetermined” etiology subgroup. Conversely, children with an identifiable etiology had the highest risk of recurrence. Although their 5-year cumulative recurrence rates were similar, children in the medical etiology group appeared to have a condensed period of risk within the acute phase of their medical illnesses, whereas children with structural abnormalities had a more long-term risk extending over years. These data should provide some reassurance to families of children in whom no source for the hemorrhage is identified despite adequate investigation (eg, acute and convalescent MRI and conventional angiography). They also demonstrate the importance of a thorough diagnostic evaluation to identify underlying structural lesions because this is the major factor determining prognosis.

Once a structural lesion is identified, particularly an AVM, studies specific to such lesions may prove more useful for counseling a family regarding recurrence risk than the data provided here. Recurrence risk in such cases is complicated, and dependent on the specific type of underlying lesion, characteristics of that lesion, whether the lesion was treated, and the success of that treatment. However, it is humbling to note that, despite available therapies, >10% of children with structural lesions will experience a recurrence by 5 years.

Our cohort also demonstrates that children with HS are at increased risk for subsequent ischemic stroke because of a variety of mechanisms. ICH with significant mass effect can compress blood vessels and result in secondary ischemic injury. Children with SAH may develop vasospasm with secondary infarction. In addition, HS may result from an underlying vasculopathy (such a moyamoya, or cocaine-vascularopathy), which can also predispose a child to ischemic stroke.

Despite our relatively large number of incident HS cases compared with previously published reports, the primary limitation of our study is the small sample size, evidenced by the wide confidence intervals around our recurrence rate estimates. In addition, by studying HS in general, we are clearly combining children with strokes due to very different pathophysiologic mechanisms. However, this approach allows us to directly compare children with HS of different etiologies, which can be useful in the clinical setting. In addition, the major strength of our study is its population-based design, which eliminates the referral bias present in hospital series and other studies based on convenience sampling. Our relatively low case fatality rate, for example, may reflect this absence of referral bias which likely inflates such rates in hospital series from tertiary care centers.

In summary, despite available therapies, children with HS have high rates of recurrent stroke. Further research is needed to assess the impact of this cumulative brain injury, and to reduce the burden of recurrent disease in this population.

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Disclosures
None.

References