Long-Term Hemorrhage Risk in Children Versus Adults With Brain Arteriovenous Malformations

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Background and Purpose—Children with brain arteriovenous malformations (BAVMs) are said to be at higher risk for intracranial hemorrhage (ICH) than adults. Although this notion affects treatment decisions, the evidence to support this claim is limited.

Methods—To compare the risk of ICH in children versus adults with BAVM, we studied all cases of BAVM evaluated at the University of California, San Francisco (January 2000 to December 2004; n = 400) and Kaiser Permanente Northern California (January 1993 to December 2004; n = 819). In Kaplan–Meier survival analyses, the index date was the date of initial BAVM detection; cases were censored at time of subsequent ICH (the primary outcome, defined as ICH after initial presentation), first BAVM treatment, or loss to follow-up. Cox proportional hazards models included childhood presentation (<20 years old), hemorrhagic presentation, and other potential confounders.

Results—Our study included 996 person-years of follow-up in the childhood presentation group and 3260 in the adult presentation group. In the unadjusted survival analysis, the subsequent ICH rates were similar for the 2 age groups (average annual rate 2.0% for children; 2.2% for adults; \( P = 0.82 \) by log-rank test). BAVMs in childhood were more likely to present initially with ICH \( (P < 0.001) \). After adjustment for presentation in the multivariate model, subsequent ICH rates were lower in children (hazard ratio, 0.10; 95% CI, 0.01 to 0.86; \( P = 0.036 \)).

Conclusions—Children with BAVMs do not appear to be at increased risk for a subsequent ICH compared with adults, and may even be relatively protected. Confounding by hemorrhagic presentation should be considered in any study comparing BAVM hemorrhage rates in children versus adults. (Stroke. 2005;36:2099-2104.)

Key Words: cerebral arteriovenous malformations ■ cerebral hemorrhage ■ child

Although stroke in children is relatively rare, hemorrhagic stroke is particularly important: it accounts for half of all childhood strokes compared with <20% of adult strokes.1,2 The majority of childhood hemorrhagic strokes are attributable to underlying brain arteriovenous malformations (BAVMs).3 These malformations can present with intracranial hemorrhage (ICH) or can present unruptured, with seizures, recurrent headaches, progressive neurological deficits, and, in neonates, congestive heart failure.4,5 Although they can be treated by surgical excision, endovascular embolization, or radiotherapy, any treatment is associated with potential risks. Therefore, when faced with the decision of whether to treat a BAVM in a child, one would like to know: what is that child’s risk of future hemorrhage?

Although survival analyses have shown BAVMs to have an overall hemorrhage rate of 2% to 4% per year,6–11 children are often anecdotaly said to have an increased risk of hemorrhage relative to adults. However, the evidence to support this notion is limited. One study that reported this association was small, and because it included patients who had undergone treatment for their BAVM, it was particularly subject to treatment bias.6 Other studies found no association between age (as a continuous variable) and hemorrhage rate in multivariate analyses of potential risk factors for hemorrhage; however, they did not perform a stratified analysis to directly compare children with adults and may have been underpowered to detect a difference.12,13

It is important to note that an association between childhood presentation and risk of a subsequent ICH could potentially be confounded by hemorrhagic presentation (Figure 1). Several studies have reported that compared with adults, children are more likely to present initially with an ICH (Figure 1, arrow A),11,14,15 and that hemorrhagic presentation is a risk factor for a subsequent ICH (Figure 1, arrow B).12,16 Therefore, any apparent increased risk of subsequent ICH in children (Figure 1, arrow C) could simply be because...
of their higher rate of hemorrhagic presentation, a finding that itself may solely be attributable to detection bias.

We hypothesized that at the time of initial BAVM presentation, when treatment decisions are being made, children are not at increased risk of ICH compared with adults. Because children represent a small minority of BAVM cases, and previous studies may have been underpowered to appreciate a difference by age, we chose to combine 2 ongoing cohorts of BAVM cases collected at the University of California, San Francisco (UCSF) and Kaiser Permanente Medical Care Plan (KPMCP).

Methods

UCSF Cohort

After obtaining institutional review board approval, all patients with BAVM evaluated at UCSF from January 2000 through December 2004 were entered into the Hemorrhagic Diseases of the Brain Database, a National Institutes of Health–funded prospective registry maintained by the Center for Cerebrovascular Research, as described previously. The database includes information regarding patient demographics, radiographic features of the BAVM, clinical presentation, treatment, follow-up, and outcome, including hemorrhages. Subsequent ICH (the “failure” event) or censoring. Cases were censored (ie, withdrawn from the survival analysis) at the time of either initiation of BAVM treatment (surgery, embolization, or radiosurgery) or loss to follow-up (using date of last available follow-up). Because few cases had more than a decade of follow-up, only the first 10 years of follow-up were included in the survival analyses.

KPMCP Cohort

KPMCP is a managed-care organization that includes ~3.3 million members, or one third the population of northern California. Its demographics are representative of northern California as a whole except for under-representation of both extremes of the socioeconomic spectrum. After obtaining institutional review board approval, we identified all patients with BAVM who were active members within KPMCP from January 1993 through December 2004 using methods described previously. Demographic and clinical data were collected from electronic databases of inpatient and outpatient services, radiology reports, and chart review. Cases diagnosed before 1998 were identified in a retrospective fashion, whereas those diagnosed from 1998 onward were identified prospectively.

Briefly, case ascertainment included an initial screen of KPMCP inpatient and outpatient databases using International Classification of Diseases 9 code 747.81 to identify all cases with a diagnosis of intracranial vascular malformation, which includes BAVM. Additionally, for the prospectively identified cases, complete text reports for all radiological procedures were searched using CPT-4 codes for various neuroradiological procedures and screened for text strings germane to BAVM. Unique identifiers prevented recounting from multiple patient visits. Cases were confirmed by chart review, and data regarding patient demographics, radiographic features of the BAVM, clinical presentation, treatment, follow-up, and outcome, were abstracted by a trained medical records abstractor. Using the same standardized guidelines as for the UCSF cohort, BAVM characteristics, such as size and venous drainage pattern, were recorded. Cases that were treated at KPMCP and UCSF were excluded from the KPMCP cohort and included only in the UCSF cohort.

Definitions/Cohort Characteristics

Childhood presentation was defined as initial BAVM presentation at <20 years of age; the age cutoff was chosen for consistency with our previous studies. ICH was defined as evidence of hemorrhage on a brain imaging study (computed tomography or MRI) or in the cerebral spinal fluid. Because of the importance of initial presentation with an ICH as a predictor for subsequent ICH, we created a dichotomous variable of hemorrhagic presentation, defined as initial presentation of the BAVM with an ICH. In addition, we created a categorical variable of initial presentation, defined using a hierarchical system of 4 mutually exclusive categories (from most to least important): ICH, seizure, headache, and “other.” The “other” category included presentation with focal neurological deficits, other atypical presentations, and incidental diagnoses. Subsequent ICH was defined as an ICH occurring after the initial presentation, regardless of whether or not the initial presentation was hemorrhagic.

Patient and BAVM characteristics were compared between the UCSF and Kaiser cohorts and between the childhood and adult cohorts using χ² tests. Treatment rates were compared between cohorts using survival analyses in which the primary outcome was time from initial BAVM diagnosis to first treatment (surgery, embolization, or radiosurgery). Log-rank tests and univariate and multivariate Cox proportional hazards regression analyses were used to test the significance of these differences.

Primary Analysis

The primary predictor was childhood presentation, whereas the primary outcome was time from diagnosis to subsequent ICH before any BAVM treatment. The rate of subsequent ICH was assessed using survival analysis. In our primary analysis, the period at risk began on the date of BAVM diagnosis and ended on the date of a subsequent ICH (the “failure” event) or censoring. Cases were censored (ie, withdrawn from the survival analysis) at the time of either initiation of BAVM treatment (surgery, embolization, or radiosurgery) or loss to follow-up (using date of last available follow-up). Because few cases had more than a decade of follow-up, only the first 10 years of follow-up were included in the survival analyses.

Kaplan–Meier survival curves were constructed to compare hemorrhage-free survival rates between children and adults; log-rank tests were used to test significance in this univariate comparison. In addition, multivariate models were created using Cox proportional hazards regression techniques; relative risk was assessed in terms of hazard ratios (HRs) with 95% CIs. We included in the model other predictor variables that could potentially confound an association between childhood presentation and subsequent ICH: gender, ethnicity, cohort (UCSF versus KPMCP), hemorrhagic presentation, exclusively deep venous drainage, and small BAVM size (largest dimension <2.5 cm). Because details regarding morphological characteristics were limited for the KPMCP cohort, deep venous drainage and size, two components of the Spetzler–Martin surgical
risk scoring system,22 were the only morphological predictors used in this analysis. In addition to adjusting for cohort, we tested for an interaction by cohort by entering a cross-product term (cohort × childhood presentation) into the model. Because it was preferable to rule out an interaction, α was set at 0.10 for this interaction term (thereby making it more difficult to obtain the nonsignificant result).

Confounding by Presentation
We performed an analysis to assess the possible confounding effect of hemorrhagic presentation on the association between childhood presentation and subsequent ICH (Figure 1). We first determined whether children were more likely to present with ICH (Figure 1, arrow A) by comparing initial BAVM presentation between children and adults; χ² tests were performed to test the significance of differences in these proportions. We then determined whether hemorrhagic presentation was associated with higher rates of subsequent ICH (Figure 1, arrow B) by performing a survival analysis stratified by hemorrhagic presentation; a Cox proportional hazards regression analysis was used to determine the significance of this association. To determine whether hemorrhagic presentation was indeed confounding the association between childhood presentation and subsequent ICH (Figure 1, arrow A) by performing a survival analysis stratified by hemorrhagic presentation; a Cox proportional hazards regression analysis was used to determine the significance of this association. This analysis primarily affects cases that were initially diagnosed at a different institution and then received care from UCSF or KPMCP at some later date, such as when they had a subsequent ICH.

Results
We identified a total of 1219 BAVM cases, including 251 (21%) children. The patient demographics, BAVM characteristics, and initial presentation of children compared with adults are shown in the Table. When stratified by age in decades, the relative frequencies of the different categories of initial presentation were similar to a previously published report, except for the lack of an increase in frequency of hemorrhagic presentation in later decades (Figure 2).15

Sensitivity Analysis
Because some patients were enrolled at the time of their subsequent ICH, we were concerned that this could lead to an acquisition bias in that we may have been more likely to enroll patients with a subsequent ICH. To assess for such a bias, we performed an alternate survival analysis in which such cases were excluded. In addition, in this analysis, the time at risk began on the date of first presentation to UCSF or KPMCP rather than the date of initial BAVM detection. This analysis primarily affects cases that were initially diagnosed at a different institution and then received care from UCSF or KPMCP at some later date, such as when they had a subsequent ICH.

Figure 2. Type of initial presentation stratified by decade of age at presentation; total number of cases in each age category shown above the graph.
During the follow-up period, in an unadjusted survival analysis, children had higher rates of treatment for their BAVMs than adults (HR, 1.21; \( P = 0.03 \)). However, the mean and median time to treatment was similar for children and adults (children mean 2.97 years, SD 8.35, median 1.56; adults mean 2.90, SD 5.19, median 1.02). The strongest predictor of time to treatment was hemorrhagic presentation: those presenting with hemorrhage had a higher rate of treatment than those with a nonhemorrhagic presentation (HR 2.21; \( P < 0.001 \)). After adjustment for hemorrhagic presentation, there was no difference in treatment rates between children and adults (HR, 1.05; \( P = 0.52 \); see also Figure 3 for graphical representation). The mean duration of follow-up was similar for children and adults (4.03 years for children; 3.50 for adults), as was the median (0.22 for children; 0.34 for adults).

Of the 1219 cases, 400 (33%) were treated at UCSF and 819 (67%) at KPMCP; 36 cases (31 adults and 5 children) received care at both centers and were included only in the UCSF cohort. The two cohorts were similar in terms of proportion of children (24% at UCSF versus 19% at KPMCP; \( P = 0.06 \)) and gender distribution (49% versus 50% females; \( P = 0.85 \)). At UCSF, there were more Hispanics (24% versus 13% at KPMCP; \( P < 0.001 \)) and Asians (15% versus 9%; \( P < 0.001 \)) and fewer whites (54% versus 69%; \( P < 0.001 \)), whereas the proportion of blacks was similar (6% versus 9%; \( P = 0.08 \)). The BAVMs at UCSF and KPMCP were equally likely to be \( < 2.5 \) cm in size (42% versus 42%; \( P = 0.90 \)) and to have exclusively deep venous drainage (17% versus 21%; \( P = 0.20 \)).

### Primary Analysis

Our primary survival analysis included 857 adults with 3260 person years of follow-up and 47 subsequent ICH events and 214 children with 996 person years of follow-up and 12 events. In the unadjusted analysis \( (n = 1071) \), subsequent ICH rates were similar between children and adults, even when stratified by hemorrhagic presentation (Figure 4). Among those with hemorrhagic presentation, children appeared to have slightly lower rates of subsequent ICH, although this difference was not significant \( (P = 0.17) \). Overall, in the first 10 years of follow-up, the average annual subsequent ICH
However, the major predictor of treatment was hemorrhagic rate of BAVM treatment in children compared with adults. Because cases were subsequent ICH compared with adults. Because cases were adjusting for the higher proportion of hemorrhagic presentation, children actually were at lower risk of a subsequent ICH than adults may be attributable to confounding by presentation, as demonstrated in Figure 1. In our study, after hemorrhagic presentation was associated with an increased risk of subsequent ICH (HR, 2.84; 95% CI, 1.70 to 4.73; \( P<0.01 \)) in a univariate Cox analysis. These data suggest that hemorrhagic presentation could act as a positive confounder on the association between childhood presentation and subsequent ICH. Indeed, when hemorrhagic presentation was removed from the multivariate model described above, the “protective” effect of childhood presentation was diminished (HR, 0.16; 95% CI, 0.02 to 1.26; \( P=0.082 \)), suggesting that the higher rate of hemorrhagic presentation in children was partially masking that “protective” effect in the unadjusted analysis. On visual inspection of the survival curves (Figure 4), hemorrhagic presentation also appeared to modify the association between childhood presentation and subsequent ICH; however, the test for interaction was negative (\( P=0.18 \)).

Sensitivity Analysis

In the sensitivity analysis excluding follow-up time before first presentation at UCSF or KPMCP, designed to assess ascertainment bias, there were no meaningful changes in the survival curves (data not shown; \( P=0.97 \) for the log-rank test comparing children with adults) or average annual subsequent hemorrhage rates (2.0% for children and 2.1% for adults). There were too few events to perform multivariate analysis.

Discussion

Although children with BAVMs are more likely to present with hemorrhage, we found that they are not at increased risk for a subsequent ICH. Although differences in presentation are of interest, the risk of future hemorrhage is of greater importance when facing treatment decisions for a child with a BAVM. Our findings suggest that BAVMs in children do not necessarily need to be treated more aggressively than those in adults. However, it is worth noting that although their annualized risk is similar to adults, their cumulative risk is greater given their greater number of years left to live.

Previous impressions that children have a higher risk of ICH than adults may be attributable to confounding by presentation, as demonstrated in Figure 1. In our study, after adjusting for the higher proportion of hemorrhagic presentation in children, children actually were at lower risk of a subsequent ICH compared with adults. Because cases were censored from the survival analysis at the time of treatment, this relative “protection” could be related in part to the higher rate of BAVM treatment in children compared with adults. However, the major predictor of treatment was hemorrhagic presentation, and after adjusting for this confounder, treatment rates were actually similar between adults and children; this argues against informative censoring as the etiology of this finding. On the other hand, this finding could represent a biological difference in the BAVMs presenting at a younger age. Regardless, it highlights the importance of adjusting for presentation in any comparison of subsequent ICH risk between children and adults.

The meaning of the higher rates of hemorrhagic initial presentation in children compared with adults is also unclear. It may again reflect a biological difference in the BAVMs presenting at a younger age; that is, we may be observing a more “malignant” type of BAVM that hemorrhages at a younger age and is therefore more likely to present during childhood. However, if this were the case, although the biological relationship between a presenting hemorrhage and a subsequent hemorrhage is not precisely known, one might also expect BAVMs presenting during childhood to be at higher risk for subsequent hemorrhage; we observed the opposite. Alternatively, the difference in presentation may be attributable to an acquisition bias. That is, BAVMs in children may be less likely to present in a nonhemorrhagic fashion simply because children may be less likely to get head imaging when they present with either a headache or other symptoms that could lead to an incidental diagnosis. This would cause the relative frequency of hemorrhagic presentation to be higher in children simply because unruptured BAVMs in children were less often detected. Indeed, in our study, children were less likely to present incidentally or atypically (the “other” presentation) or with headache (although the latter was a nonsignificant trend).

The absolute subsequent hemorrhage rates reported in this study, as with any survival analysis of BAVMs, should be interpreted with caution. Our study may be more likely to include BAVMs that are prone to hemorrhage because more “benign” BAVMs may not come to medical attention; therefore, these rates may be an overestimation of the true hemorrhage rates. However, if high-risk BAVMs are more likely to be treated and therefore censored from our survival analysis, then our rates may actually be an underestimation of the true natural history.

In addition to the limitations alluded to above, our study was potentially problematic in that it combined two study cohorts. This is particularly a concern in light of previous observations of heterogeneity in BAVM characteristics between different populations. We did indeed find differences in ethnic distribution and BAVM size between the two cohorts, although other features were similar. However, by adjusting for cohort in our multivariate model, we eliminated any direct effect (ie, confounding) of cohort on the primary association of interest. In addition, a test for interaction was negative, suggesting that the association did not differ significantly by cohort.

In summary, our data suggest that although children with BAVMs are more likely to present with hemorrhage, they are not at increased risk for a subsequent ICH and may even be relatively “protected” from future hemorrhage after adjusting for presentation. Whether these differences reflect biases...
versus biological differences in the BAVMs that present at younger ages deserves further study.

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