 Characteristics of Brain Arteriovenous Malformations With Coexisting Aneurysms
A Comparison of Two Referral Centers

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Background—Patients harboring a brain arteriovenous malformation (BAVM) often have coexisting arterial aneurysms. Experts have argued about the clinical significance of these aneurysms, which may be important for risk stratification in patient management and clinical trials. We studied the association between coexisting aneurysms and initial presentation with intracranial hemorrhage (ICH) in patients with BAVM evaluated at two tertiary-care centers.

Methods—Demographic and clinical data were collected from a prospective series of patients evaluated for BAVM at the University of California, San Francisco (UCSF; n = 82), and Columbia-Presbyterian Medical Center, New York (CPMC; n = 254). Using multivariate logistic regression, we examined the independent association between ICH presentation and the presence of a coexisting aneurysm, and compared the association at the two hospitals.

Results—Aneurysms were associated with 28 BAVMs at UCSF (34%; P = 0.39). Initial presentation with ICH was associated with the presence of a coexisting aneurysm at CPMC (odds ratio 1.8, 95% confidence interval 1.0 to 3.0, P = 0.044). The opposite trend was observed at UCSF (odds ratio 0.4, 95% confidence interval 0.2 to 1.1, P = 0.085). We observed an interaction by site involving the association between ICH presentation and aneurysm (P = 0.016).

Conclusion—Although many BAVM characteristics were similar at the referral centers studied, the association between initial presentation with ICH and coexisting aneurysms was not. This heterogeneity between populations undermines the validity of inferences on the role of aneurysms from any single referral series, and emphasizes the complexity in creating BAVM risk-stratification models that incorporate aneurysms. (Stroke. 2002;33:675-679.)

Key Words: cerebrovascular disorders ■ epidemiology ■ intracranial aneurysm ■ intracranial hemorrhages ■ vascular malformations

The association between brain arteriovenous malformation (BAVM) and arterial aneurysms is well examined.1–10 An association between the presence of intracranial aneurysms and initial presentation with intracranial hemorrhage (ICH) has also been described in BAVM patients,1–4 although only one study has examined this question with a longitudinal follow-up.3 The extent of clinical and radiological characterization of the BAVMs in these case series has been inconsistent. Additionally, the validity and reliability of diagnosing aneurysms in BAVM has neither been established nor examined. Nonetheless, given the potential influence of aneurysms on the risk of ICH, it is tempting to incorporate the presence of aneurysms in BAVM risk-stratification models. The vast majority of reported BAVM case series have been derived from patients treated at tertiary medical centers. Studies in these populations may not be generalizable if specific BAVM characteristics are associated with referral. If the apparent association between aneurysm and ICH is modified by referral patterns, then inferences made from any single referral series may not be generalizable to all BAVM cases.

To test the generalizability of findings from referral populations, we compared factors associated with coexisting aneurysms in patients with BAVMs treated at the tertiary medical centers.

To determine whether and how referral patterns might influence the association between coexisting aneurysms and initial presentation of BAVM, we compared the radiographic characteristics and clinical presentation of patients harboring...
BAVMs that were associated with aneurysms in two referral-based populations in California and New York.

**Methods**

**University of California, San Francisco (UCSF), Cohort**

All patients with BAVM evaluated at UCSF from January 2000 through March 2001 were prospectively identified. Those who underwent cerebral angiography at UCSF were included in this study. Patients enrolled in the study were referred from the San Francisco Bay Area and neighboring states. An attending interventional neuroradiologist abstracted all radiographic data.

**BAVM Radiographic Characteristics**

Morphological parameters recorded for this study included BAVM size, venous drainage pattern, and associated arterial aneurysms. Size of the nidus (central mass of densely packed abnormal vessels), defined as the largest diameter, was recorded from both magnetic resonance imaging (MRI) and cerebral angiography. It was measured on the pretreatment MRI in sagittal, coronal, and axial views and the pretreatment angiogram in lateral and anteroposterior projections. MRI size determinations were used when available; otherwise, angiographic dimensions were used.

Venous drainage was defined as superficial if all BAVM drainage was through the cortical venous system, and deep if any or all of the drainage was through deep veins (such as the internal cerebral veins, basal veins, or precentral cerebellar vein). A feeding artery was defined as an arterial structure that demonstrated on angiography a contribution of flow (as evidenced by contrast opacification) to the arteriovenous shunt. Aneurysms were defined as sacculum luminal dilations of the arteries. They were further classified into flow-related aneurysms, intranidal aneurysms, and aneurysms unrelated to the shunt flow to the BAVM. Nidal aneurysms were defined as those with any portion contained in the BAVM nidus.

**Clinical Presentation**

Patients with BAVM were divided into six mutually exclusive, hierarchical symptom categories, as follows: hemorrhage, patients presenting with evidence of hemorrhage as a symptomatic event with signs of new intracranial blood on head CT or MRI, or in the cerebrospinal fluid; seizure, patients presenting with a seizure without any imaging evidence of hemorrhage; focal ischemic deficit, patients presenting with any focal deficit without any evidence of hemorrhage or seizure; headache, patients presenting with a headache without any evidence of hemorrhage, seizure, or focal deficit; other, patients presenting with symptoms attributable to the BAVM but exclusive of the aforementioned symptoms; and incidental, patients in whom BAVM was detected during evaluation of unrelated symptoms.

In this analysis, patients were divided into two groups. The hemorrhagic presentation group was defined as described above. The nonhemorrhagic presentation group was defined as having any clinical event (seizure, focal neurological deficit, headache, or other) not associated with ICH that led to the diagnosis of the BAVM, ie, all other aforementioned initial presentations exclusive of ICH.

**Columbia-Presbyterian Medical Center (CPMC) Cohort**

Under the supervision of the senior author (W.L.Y.), demographic and clinical data were collected from a prospective series of patients with BAVM referred to CPMC (New York, NY) from 1987 through December 1999. Details of the study methodology have been described previously. The data collection protocol was identical to that at UCSF except as follows. Patient demographic characteristics, presenting signs and symptoms (in some cases determined from review of referring physician evaluations), and radiographic characteristics of BAVM were recorded. Until 1994, no information was collected regarding aneurysms. Beginning in 1994, an aneurysm was considered present if luminal dilation was definite or probable in two angiographic views. The aneurysms were also rated as (1) non-BAVM related, (2) proximal to circle of Willis, (3) distal to circle of Willis, and (4) intranidal. Intranidal aneurysms represented discrete focal dilations or sacculations within the conglomerate of tortuous dysplastic vessels near the site of arteriovenous shunting and were considered present when seen on at least one view without vessel overlap.

Beginning in 1997, aneurysms were rated additionally as flow-related on the basis of whether or not they resided on vessels that supplied flow to the BAVM. Radiographic data were abstracted by an interventional neuroradiologist.

**Enrollment Overview**

Cases from CPMC were enrolled no later than December 1999, whereas cases at UCSF were enrolled January 2000 onward. However, all cases from both sites were enrolled using identical case enrollment criteria, and data were collected using identical protocols and instruments under the supervision of the principal investigator of the supporting grant (W.L.Y.).

**Statistical Analysis**

Patient and BAVM characteristics were compared between the two institutions in univariate analysis using the Wilcoxon rank-sum test for continuous variables. For dichotomous variables, the Fisher exact test was used when any cell contained fewer than five observations; Pearson χ² test was used otherwise. The association between these variables and presentation with hemorrhage was computed separately for patients from each institution using logistic regression. Adjusted analyses included all measured patient characteristics. In assessing the association of ICH presentation with coexisting aneurysm, we tested the significance of each aneurysm type in separate multivariate models. To determine whether associations were different at the two sites, we evaluated interactions in the complete multivariate model by sequentially including a single interaction term representing study site and each individual patient characteristic. A P value <0.05 for the interaction term was considered significant.

**Results**

BAVM patients tended to present more frequently with ICH at CPMC (P=0.063; Table 1), and were more likely to have BAVM incidentally discovered at UCSF (P=0.001). Patients at CPMC had significantly larger BAVMs (P=0.016) and were more likely to have exclusively deep venous drainage (P=0.03; Table 1). There was also a trend toward a younger age at diagnosis (P=0.12) and a higher proportion of cases having presented with seizure (P=0.14) and headaches (P=0.15) at CPMC (Table 1).

At both institutions, exclusively deep venous drainage and smaller BAVM lesion size were more frequent in patients who presented with ICH than in those with other presentations (Table 2). There was a trend for patients who presented with ICH to be older than those with other presentations at CPMC (P=0.055) but younger at UCSF (P=0.061; Table 2).

Initial presentation with ICH was associated with a coexisting aneurysm at CPMC (odds ratio 1.8, 95% confidence interval 1.0 to 3.0, P=0.044) but not at UCSF, where instead there was an opposite trend (odds ratio 0.4, 95% confidence interval 0.2 to 1.1, P=0.085; Table 2). Interactions with center of treatment were significant for age at diagnosis (P=0.03) and presence of aneurysm (P=0.016; Table 3).
TABLE 1. Characteristics of BAVM Patients at CPMC and UCSF*

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPMC</th>
<th>UCSF</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>254</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>142 (56)</td>
<td>42 (51)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age at diagnosis (mean±SD)</td>
<td>35±15</td>
<td>39±17</td>
<td>0.12</td>
</tr>
<tr>
<td>Initial presentation of BAVM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>126 (50)</td>
<td>31 (38)</td>
<td>0.063</td>
</tr>
<tr>
<td>Seizure</td>
<td>77 (30)</td>
<td>18 (22)</td>
<td>0.14</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>15 (6)</td>
<td>8 (10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (8)</td>
<td>12 (15)</td>
<td>0.15</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Incidental</td>
<td>12 (5)</td>
<td>13 (16)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Venous drainage pattern, n (%)  
- Deep only: 59 (24) vs 11 (13), P=0.03  
- Superficial only: 120 (48) vs 45 (54), P=0.39  
- Deep only: 70 (28) vs 28 (33), P=0.30  

BAVM size in cm (mean±SD)  
- CPMC: 3.4±1.7 vs 3.0±1.4, P=0.016

Aneurysm,‡ n (%)  
- Patients with ≥1 aneurysm: 74 (29) vs 28 (34), P=0.39  
- Flow-related: 35 (16) vs 16 (23), P=0.21  
- Intranidal: 23 (11) vs 11 (17), P=0.24  
- Not flow-related: 10 (5) vs 2 (4), P=1.00

*At CPMC, age at diagnosis was missing in 7 cases, venous drainage pattern in 5 cases, and BAVM size in 17 cases.  
†Wilcoxon rank-sum test for continuous variables and Pearson’s χ² test for dichotomous variables, except when any cell contained <5 observations; then the Fisher’s exact test was used.  
‡Patients with multiple aneurysms are listed more than once by aneurysm type.

**Discussion**

BAVM characteristics of patients treated at two tertiary medical centers studied were remarkably similar in many respects, except for a surprising difference in the distribution of coexisting aneurysms. Although the proportion of BAVM patients who presented with aneurysms was higher at UCSF than at CPMC, this difference was not significant (P=0.39; Table 1). Surprisingly, a coexisting aneurysm was positively associated with ICH presentation at CPMC but not at UCSF (Table 2). Our results are indicative of effect modification by site, whereby the relationship between coexisting aneurysms and ICH presentation differed between the two institutions (P=0.016). This underscores the limitations of drawing sweeping conclusions from referral-based studies, and suggests the potential pitfall of including aneurysm presence in BAVM risk-stratification models for patient management and clinical trials. This is especially germane given that the presence of aneurysms has strongly influenced patient management, primarily on the basis of results from studies of isolated referral populations.

Estimates for the frequency of coexisting aneurysms in BAVM patients have ranged from 4% to 17% in most series.1,4,7,8 However, a higher proportion of BAVMs has been noted to have aneurysms when superselective angiography is performed.3,14,15 A difference in rates of superselective angiography for pretreatment evaluation or therapy between the two sites is unlikely.

There may be differences in the overall prevalence of intracranial arterial aneurysms in the two referral populations. Factors that are associated with increased risk of aneurysmal growth and development, such as tobacco consumption,16 hypertension,17 strong family history, and inherited connective tissue disorders,18,19 might partially account for this difference. However, aneurysm formation in patients harboring AVMs appears to be related to high intravascular flow velocities, rather than to environmental exposures or other comorbidities.4

There were other notable differences in both patient and BAVM characteristics at the two institutions (Table 1). We observed a trend for a higher proportion of patients with BAVM presenting to CPMC with ICH (P=0.063), whereas patients at UCSF were more likely to have their BAVM discovered incidentally (P=0.001). Patients at CPMC had larger BAVMs (P=0.016) with deep venous drainage (P=0.03). There was a trend toward younger age in patients at CPMC (P=0.12; Table 1). The higher proportion of

TABLE 2. Patient Characteristics in BAVM Patients With and Without ICH Presentation: CPMC Versus UCSF

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPMC</th>
<th>UCSF</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>n=126</td>
<td>n=128</td>
<td>0.060</td>
</tr>
<tr>
<td>Age at diagnosis (mean±SD)</td>
<td>247</td>
<td>32±16</td>
<td>0.055</td>
</tr>
<tr>
<td>Venous drainage, deep only vs other; n (%)</td>
<td>249</td>
<td>44 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BAVM size (mean±SD)</td>
<td>237</td>
<td>2.9±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any aneurysm vs none;† n (%)</td>
<td>254</td>
<td>44 (35)</td>
<td>0.044</td>
</tr>
<tr>
<td>Flow-related</td>
<td>215</td>
<td>22 (21)</td>
<td>0.061</td>
</tr>
<tr>
<td>Intranidal</td>
<td>203</td>
<td>15 (16)</td>
<td>0.075</td>
</tr>
<tr>
<td>Not flow-related</td>
<td>190</td>
<td>6 (7)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*Wilcoxon rank-sum test for continuous variables and Pearson’s χ² test for dichotomous variables, except when any cell contained <5 observations; then the Fisher’s exact test was used.  
†In the analysis involving a specific aneurysm subtype, patients with other subtypes were excluded; eg, patients with intranidal aneurysms only were excluded from the analysis of flow-related aneurysms vs none.
patients with exclusively deep venous drainage at CPMC may have resulted from the fact that the highest-volume neurosurgeon represented in the CPMC data set had particular interest in the treatment of deep BAVMs.\textsuperscript{20–22} Despite the discrepancy in sample size between the two sites, we were able to demonstrate the presence of statistical interaction. A larger UCSF patient sample will narrow the confidence intervals of our point estimates, although we do not expect the relationships between sites to change (Table 3).

Several factors, such as deep venous drainage and increasing feeding (mean) artery pressure, have been demonstrated to be associated with ICH presentation in BAVM.\textsuperscript{12,23} The role of aneurysms is less certain. We found a distinct difference between the two institutions with regard to the association between the presence of aneurysms and presentation with ICH. At CPMC, BAVM patients who initially presented with ICH were more likely to be detected with a coexisting aneurysm than were BAVM patients whose initial presentation was exclusive of ICH. This association was not observed at UCSF; rather, the opposite trend was found. At UCSF, BAVM patients who initially presented with ICH were less likely to be detected as having a coexisting aneurysm than were BAVM patients whose initial presentation was exclusive of ICH. This finding is likely due to referral bias or differences in detection, and does not imply an underlying physiological difference. Several studies have suggested that coexisting aneurysms are associated with ICH presentation, including one longitudinal population-based study by Brown et al\textsuperscript{1} that showed increased hemorrhagic risk of cohaboring an aneurysm. However, a recent cross-sectional study did not detect an association in a cohort of 662 patients,\textsuperscript{24} similar to our findings in the UCSF cohort. The differences in these study results underline the importance of standardized definitions\textsuperscript{13} and the limitations of referral populations in cross-sectional analyses. There are other limitations to the analyses we have presented here. For example, time of data acquisition was not simultaneous. Although the study patients were not ascertained contemporaneously, patients at both sites were subjected to an identical case ascertainment and data acquisition protocol. Our findings therefore cannot be due to differential enrollment criteria or study methodology; rather they demonstrate the effect of differential referral. For example, changes in treatment philosophy (eg, the acquisition of radiosurgery units in the community) may have affected the referral patterns. Stereotactic radiosurgery using linear accelerator or gamma knife technology is now available at many smaller hospitals and may have altered referral patterns. Also, there may be a differential referral of patients with aneurysms to UCSF because of a perceived increased availability of endovascular coil embolization.

Although differences in BAVM referral patterns are not surprising, our findings nonetheless show that the influence of BAVM case referral needs to be addressed and carefully examined. Future studies should be population-based or should focus on those patient and BAVM characteristics that may be indicators of referral patterns. This latter point would be pertinent to multicenter studies. Studies should also examine the validity and reliability of diagnosing coexisting aneurysms in patients with BAVM. The complexities involved in such a diagnosis may influence the validity of studies examining the significance of coexisting aneurysms. Our conclusions do not necessarily undermine the probative value of data involving the presence of aneurysms and ICH presentation in BAVM from any isolated referral populations. However, they emphasize the need to exercise caution when generalizing results of individual studies from isolated referral populations.

Further data on this general topic may be forthcoming from the cohort of patients harboring BAVMs detected by the

### TABLE 3. Comparison of Odds Ratios for the Association Between Patient Characteristics and ICH Presentation, Between CPMC and UCSF

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPMC</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.6</td>
<td>1.0–2.7</td>
<td>1.9</td>
<td>1.0–3.4§</td>
<td>0.8</td>
<td>0.3–1.9</td>
<td>0.6</td>
<td>0.2–1.7</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (per decade)</td>
<td>1.2</td>
<td>1.0–1.4</td>
<td>1.1</td>
<td>0.9–1.4</td>
<td>0.8</td>
<td>0.6–1.0</td>
<td>0.8</td>
<td>0.5–1.1</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous drainage: deep only vs other</td>
<td>4.1</td>
<td>2.1–7.9§</td>
<td>3.5</td>
<td>1.7–7.3§</td>
<td>8.5</td>
<td>1.7–43.4§</td>
<td>7.0</td>
<td>1.2–39.2§</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAVM size (per cm)</td>
<td>0.7</td>
<td>0.6–0.8§</td>
<td>0.8</td>
<td>0.6–0.9§</td>
<td>0.8</td>
<td>0.5–1.1</td>
<td>0.8</td>
<td>0.5–1.2</td>
<td>0.56</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any aneurysm vs none</td>
<td>1.8</td>
<td>1.0–3.0§</td>
<td>1.8</td>
<td>0.9–3.3</td>
<td>0.4</td>
<td>0.2–1.1</td>
<td>0.4</td>
<td>0.1–1.3</td>
<td>0.016</td>
<td></td>
<td></td>
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<tr>
<td>Flow-related</td>
<td>2.0</td>
<td>1.0–4.3</td>
<td>2.1</td>
<td>0.7–6.6</td>
<td>0.1</td>
<td>0.01–0.7§</td>
<td>0.0</td>
<td>NA</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranidal</td>
<td>2.2</td>
<td>0.9–5.5</td>
<td>2.4</td>
<td>0.9–6.5</td>
<td>0.7</td>
<td>0.2–2.7</td>
<td>0.6</td>
<td>0.1–2.3</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not flow-related</td>
<td>1.8</td>
<td>0.5–6.6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tbody>
</table>
International Study of Unruptured Intracranial Aneurysms,25 a large multicenter study of hemorrhage risk. Such information will be required to determine whether coexisting aneurysms and other BAVM characteristics are truly risk factors for subsequent hemorrhage to improve current treatment selection algorithms.26

Acknowledgments
This work was supported in part by US Public Health Service Grants RO1 NS34949 (to W.L.Y.), K24 NS02091 (to W.L.Y.), and K08 NS02042 (to S.C.J.).

The following members of the UCSF BAVM Study Project also directly contributed to this work: Nancy J. Quinnine, RN; Louis P. Caragine, MD, PhD; James E. Leffler, MD; John Bennett, BS; Brad Dispensa, BFA; Elizabeth Hewlett, RN; Michael McDermott, MD; and Penny Sneed, MD. Other members of the UCSF Brain Arteriovenous Malformation Study Project and Center for Cerebrovascular Research who contribute patient referrals or technical assistance in data processing and analysis are listed at http://avm.ucsf.edu.

We thank the Stroke Service, Department of Neurology, Division of Interventional Neuroradiology, Department of Radiology, and Department of Neurosurgery, Columbia-Presbyterian Medical Center, for their respective contributions to the Columbia arteriovenous malformation (AVM) registry project, which was supported in part by US Public Health Service Grant RO1 NS34949 (to W.L.Y.). A complete listing of the Columbia University AVM Study Group members who contributed to the Columbia University data registry can be found at http://avm.ucsf.edu/research/prior.html.

References
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Stroke. 2002;33:675-679
doi: 10.1161/hs0302.104104

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