Association of Infratentorial Brain Arteriovenous Malformations With Hemorrhage at Initial Presentation

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Background and Purpose—The goal of this study was to analyze the association of hemorrhagic presentation with infratentorial brain arteriovenous malformations (AVMs).

Methods—The 623 consecutive, prospectively enrolled patients from the Columbia AVM Databank were analyzed in a cross-sectional study. Clinical presentation (diagnostic event) was categorized as intracranial hemorrhage or nonhemorrhagic presentation. From brain imaging and cerebral angiography, AVM location was classified as either infratentorial or supratentorial. Univariate and multivariate statistical models were applied to test the effect of age, sex, AVM size and location, venous drainage pattern, and associated (ie, feeding artery or intranidal) arterial aneurysms on the likelihood of hemorrhage at initial AVM presentation.

Results—Of the 623 patients, 72 (12%) had an infratentorial and 551 (88%) had a supratentorial AVM. Intracranial hemorrhage was the presenting symptom in 283 patients (45%), and infratentorial AVM location was significantly more frequent (18%) among patients who bled initially (6%; odds ratio [OR], 3.60; 95% confidence interval [CI], 2.09 to 6.20). This difference remained significant (OR, 1.99; 95% CI, 1.07 to 3.69) in the multivariate logistic regression model controlling for age, sex, AVM size, deep venous drainage, and associated arterial aneurysms. In the same model, the effect of other established determinants for AVM hemorrhage—ie, AVM size (in 1-mm increments; OR, 0.95; 95% CI, 0.94 to 0.96), deep venous drainage (OR, 3.09; 95% CI, 1.87 to 5.12), and associated aneurysms (OR, 2.78; 95% CI, 1.76 to 4.40)—remained significant.

Conclusions—Our findings suggest that infratentorial AVM location is independently associated with hemorrhagic AVM presentation. (Stroke. 2004;35:660-663.)

Key Words: cerebral arteriovenous malformations ■ hemorrhage

Intracranial hemorrhage is the most feared complication of brain arteriovenous malformations (AVMs). Established morphological risk factors include small AVM nidus size, deep venous drainage, and presence of AVM-related arterial aneurysms. The impact of AVM location on the risk of rupture, however, remains largely unexplored. We analyzed the effect of infratentorial AVM location on intracranial hemorrhage at initial AVM presentation in a large prospectively enrolled patient sample.

Subjects and Methods

Study Subjects and Data Collection

The Columbia AVM Databank is an ongoing prospective study project collecting demographic, clinical, morphological, and treatment data on consecutive patients with brain AVM admitted to the Columbia-Presbyterian Medical Center since 1989. All AVMs have been diagnosed from brain imaging and cerebral angiography. Other types of intracranial fistulas (such as dural arteriovenous fistulas, vein of Galen malformations) are not included in the data bank. Patients enrolled in the database are drawn from self-referrals and physician referrals from the New York metropolitan area, as well as from distant referral sites. Further details on the Columbia AVM Databank design, variable definitions, and methods have been given in prior publications and conform to the recently proposed consensus recommendations for AVM research reporting terminology.

This study includes patients enrolled in the Columbia AVM Databank until October 31, 2002. The initial AVM presentation (or diagnostic event) was defined as the index clinical event that led to the diagnosis of the AVM. Hemorrhagic presentation was defined as a symptomatic clinical event with signs of fresh intracranial blood on head CT or MRI and/or in the cerebrospinal fluid, leading to the diagnosis of an AVM. Nonhemorrhagic modes of AVM presentation were stratified into seizure, focal neurological deficit, headache, or other/asymptomatic.

Morphological variables tested in the present analysis were anatomic AVM location stratified into supratentorial (any lobar and/or deep cerebral) and infratentorial (brain stem, peduncles,
TABLE 1. Demographic and Morphological Characteristics of 623 AVM Patients With (n=283) and Without (n=340) Hemorrhagic Presentation

<table>
<thead>
<tr>
<th></th>
<th>Hemorrhagic AVM Presentation (n=283)</th>
<th>Nonhemorrhagic AVM Presentation (n=340)</th>
<th>All Patients</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (mean±SE), y</td>
<td>34.8 (±1.0)</td>
<td>33.0 (±0.7)</td>
<td>34 (±15)†</td>
<td>0.14</td>
<td>1.01 (1.00–1.02)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>138 (49)</td>
<td>186 (55)</td>
<td>324 (52)</td>
<td>0.14</td>
<td>0.79 (0.57–1.08)</td>
</tr>
<tr>
<td>Infratentorial AVM location, n (%)</td>
<td>52 (18)</td>
<td>20 (6)</td>
<td>72 (12)</td>
<td>&lt;0.001</td>
<td>3.60 (2.09–6.20)</td>
</tr>
<tr>
<td>AVM size (mean±SE maximum diameter), mm</td>
<td>26.6 (±0.9)</td>
<td>38.5 (±0.8)</td>
<td>33 (±16)‡</td>
<td>&lt;0.001</td>
<td>0.95 (0.94–0.96)</td>
</tr>
<tr>
<td>Deep venous drainage, n (%)</td>
<td>90 (32)</td>
<td>32 (9)</td>
<td>122 (20)</td>
<td>0.001</td>
<td>4.49 (2.89–6.98)</td>
</tr>
<tr>
<td>Deep and superficial venous drainage, n (%)</td>
<td>157 (55)</td>
<td>150 (44)</td>
<td>307 (49)</td>
<td>0.005</td>
<td>1.58 (1.15–2.17)</td>
</tr>
<tr>
<td>Any associated arterial aneurysm, n (%)</td>
<td>85 (30)</td>
<td>56 (16)</td>
<td>141 (23)</td>
<td>&lt;0.001</td>
<td>2.23 (1.52–3.28)</td>
</tr>
<tr>
<td>Feeding artery aneurysm*</td>
<td>59 (22)</td>
<td>47 (15)</td>
<td>106 (18)</td>
<td>0.017</td>
<td>1.67 (1.09–2.54)</td>
</tr>
<tr>
<td>Infranidal aneurysm*</td>
<td>31 (12)</td>
<td>21 (7)</td>
<td>52 (9)</td>
<td>0.029</td>
<td>1.89 (1.06–3.38)</td>
</tr>
</tbody>
</table>

*Because of multiple aneurysm types in 37 patients, the total number of patients in the 2 groups of aneurysm subtypes exceeds the total number of 141 patients with concurrent arterial aneurysms.
†Values in parentheses represent SD.

vermis, cerebellar hemisphere, deep cerebellar nuclei, and any combination), AVM size (measured as maximum nidus diameter in millimeters on pretreatment angiography or MR brain imaging), venous drainage pattern (categorized as angiographic drainage into the superficial cortical veins, drainage into the deep venous system, and combined superficial and deep drainage), and presence of associated arterial aneurysms. Arterial aneurysms were defined as saccular dilatations of the lumen ≥2 times the width of the arterial vessel that carried the dilatation. A feeding artery was defined as any intracranial vessel that angiographically contributed arterial flow to the malformation. Feeding artery and intranidal aneurysms were considered associated aneurysms with blood flow related to the AVM. The AVM nidus was defined as the vascular mass included in the AVM size measurement. Infranidal aneurysms were coded when visualized early after angiographic injection, eg, before substantial venous filling. Infundibula, arterial ectasias (ie, dilated feeding vessels), and intranidal aneurysmal dilatations seen during the venous angiographic phase only were not coded as arterial aneurysms. Arterial aneurysms located on intracranial arteries not contributing blood flow to the AVM were considered unrelated to the AVM and were not included in the analysis.

Statistical Analysis
Univariate tests (χ² test, t test) and a multivariate logistic regression model including age, sex, AVM location, size, venous drainage pattern, and associated arterial aneurysms were applied to assess the effect of an infratentorial AVM location on hemorrhagic AVM presentation. The attributable risk of infratentorial AVMs for hemorrhagic presentation was determined as described by Fleiss10; the attributable risk (etiologic fraction) measures the relative decrease in the proportion of hemorrhages expected from the elimination of all infratentorial AVMs in the patient sample.

Results
Demographic and morphological baseline characteristics of the total patient sample are given in Table 1. The 72 patients harboring an infratentorial AVM showed the following distribution: 42 affecting the cerebellar hemisphere only; 8 affecting the cerebellar hemisphere and either brain stem, vermis, or peduncle; 6 affecting solely the vermis; 7 in the brain stem only; 7 involving the deep cerebellar nuclei in various combinations; and 1 in the brain stem and peduncles; 1 patient had a large, complex AVM extending from the brain stem through the peduncle and the deep nuclei to the hemispheric surface. From the 623 patients, 283 (45%) were diagnosed because of intracranial hemorrhage. The remaining 340 patients (55%) had a nonhemorrhagic diagnostic event, ie, a seizure (n=182, 29%), headache (n=74, 12%), focal neurological deficit (n=43, 7%), or other clinical events, including incidental AVM diagnoses (n=41, 7%).

In the univariate comparison, infratentorial AVM location was significantly more frequent among patients with compared with those without hemorrhagic presentation (Table 1). Furthermore, a significant association with AVM hemorrhage was found for decreasing AVM size, deep venous drainage (either exclusively or combined with superficial venous drainage), and associated arterial aneurysms (Table 1).

In the multivariate model, an independent effect of infratentorial AVM location on presentation with a hemorrhage was found (Table 2). In the same model, AVM size, deep venous drainage, and the presence of AVM-associated arterial aneurysms were significantly associated with hemorrhagic AVM presentation.

Compared with supratentorial AVM patients presenting with hemorrhage, infratentorial AVM hemorrhage patients were older and had a higher frequency of feeding artery aneurysms and deep venous drainage component (Table 3).

The attributable risk (etiologic fraction) of infratentorial AVMs on presentation with intracranial hemorrhage was 7.7% (95% confidence interval [CI], 4.3 to 11.0).

TABLE 2. Multivariate Logistic Regression Model Testing the Effect of Infratentorial AVM Location, Age, Sex, AVM Size, Deep Venous Drainage, and Associated Aneurysms on Hemorrhagic Presentation in 623 AVM Patients

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial AVM location</td>
<td>1.99 (1.07–3.69)</td>
</tr>
<tr>
<td>Patient age</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.73 (0.51–1.06)</td>
</tr>
<tr>
<td>AVM size*</td>
<td>0.95 (0.94–0.96)</td>
</tr>
<tr>
<td>Deep venous drainage only</td>
<td>3.09 (1.87–5.12)</td>
</tr>
<tr>
<td>Associated aneurysm</td>
<td>2.78 (1.76–4.40)</td>
</tr>
</tbody>
</table>

*Maximum diameter in 1-mm increments.
TABLE 3. Demographic and Morphological Characteristics of 52 Patients With Infratentorial and 231 Patients With Supratentorial AVM Location Presenting With Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>Infratentorial AVM (n=52)</th>
<th>Supratentorial AVM (n=231)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation (mean±SE), y</td>
<td>42.3 (±2.7)</td>
<td>33.1 (±1.0)</td>
<td>0.0003</td>
<td>1.03 (1.02–1.05)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>25 (48)</td>
<td>113 (48)</td>
<td>0.91</td>
<td>0.97 (0.53–1.77)</td>
</tr>
<tr>
<td>AVM size (mean±SE maximum diameter), mm</td>
<td>22.4 (±1.9)</td>
<td>27.6 (±1.1)</td>
<td>0.04</td>
<td>0.98 (0.96–1.00)</td>
</tr>
<tr>
<td>Venous drainage pattern, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous drainage only</td>
<td>22 (42)</td>
<td>68 (29)</td>
<td>0.07</td>
<td>1.76 (0.95–3.26)</td>
</tr>
<tr>
<td>Any deep venous drainage</td>
<td>37 (71)</td>
<td>120 (52)</td>
<td>0.01</td>
<td>2.28 (1.19–4.38)</td>
</tr>
<tr>
<td>Any associated arterial aneurysm,* n (%)</td>
<td>21 (42)</td>
<td>64 (30)</td>
<td>0.09</td>
<td>1.72 (0.91–3.24)</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeding artery aneurysm*</td>
<td>18 (36)</td>
<td>41 (19)</td>
<td>0.01</td>
<td>2.4 (1.23–4.69)</td>
</tr>
<tr>
<td>Intranidal aneurysm*</td>
<td>5 (10)</td>
<td>26 (12)</td>
<td>0.68</td>
<td>0.81 (0.29–2.23)</td>
</tr>
</tbody>
</table>

*Because of multiple aneurysm types in some patients, the total number of patients in the 2 groups of aneurysm subtypes exceeds the total number of 85 patients with concurrent arterial aneurysms.

Discussion

Prior studies already found higher frequencies of AVM rupture in patients with malformations in the brain stem or cerebellum. However, results on statistically independent associations of infratentorial AVM location and hemorrhagic presentation were inconsistent, probably because of methodological limitations. Particularly, studies derived from patient samples before the era of noninvasive brain imaging may overestimate the frequency of intracranial hemorrhage when diagnosed solely on the basis of clinical criteria. Although nonuniform results among smaller series on the association of AVM location and presentation with hemorrhage are readily explained by subgroup sizes that are insufficient for computing multivariate models, even larger-scale registries show contradictory findings from multivariate analyses despite the repeatedly significant association of infratentorial location for hemorrhagic presentation in univariate tests. In a recent study by the Toronto Study Group, the rate of hemorrhage among patients with infratentorial AVM (60%) was similar to our findings and roughly twice as high as in supratentorial AVM cases (35%). The positive association of deep location with hemorrhagic presentation in multivariate analysis, however, may not be directly comparable to our results because most of the patients in this subgroup had supratentorial deep AVMs (callosal and thalamic). Finally, in a cross-sectional study of 662 consecutive patients from 3 centers, Mansmann et al also found a higher frequency of posterior fossa AVMs among patients with initial hemorrhage. Their finding, however, did not sustain significance in multivariate models. Therefore, this study is the first to elicit a statistically independent association of infratentorial AVM location with hemorrhage at initial presentation in a large, prospective data set.

Most other studies reported rates of infratentorial AVM location comparable to our sample. Possible limitations of our findings arising from tertiary referral center bias are therefore less likely but need to be elucidated in population-based datasets. Furthermore, by corroborating the effects of other determinants for hemorrhagic AVM presentation such as small AVM size, deep venous drainage pattern, and associated arterial aneurysms, the findings from our study sample lend support to prior work from other investigators. However, population-based fatality rates after AVM hemorrhage are as yet unknown, and referral center patient cohorts may generally underestimate the overall frequency of AVM hemorrhage. The possibility of a systematic error in the analyses can therefore not be excluded entirely. Also, our study was performed on the basis of data referring to initial AVM presentation and does not allow direct linear extensions to the risk of future hemorrhage. Some currently available data on the effect of morphological characteristics on recurrent AVM hemorrhage were unable to confirm the risk models for initial hemorrhage.

Infratentorial AVMs are conceivably less likely to induce seizures. Thus, a relative increase in hemorrhagic presentation compared with supratentorial AVMs may be expected. In an exploratory model eliminating all patients presenting with seizure, the proportion of hemorrhagic presentation among patients with infratentorial AVMs (72%) still exceeded the frequency among those with supratentorial AVMs (231 of 369 patients, 63%), but the difference did not reach statistical significance ($\chi^2; P=0.12$). The actual effect size of infratentorial location for the risk of hemorrhagic AVM presentation may therefore be low. This is reflected in the small etiologic fraction of $\approx 8\%$, ie, only 1 of 13 initial AVM hemorrhages would have been avoided if all infratentorial AVMs had been eliminated. The etiologic fraction (attributable risk) and the modest odds ratio (OR) and its lower CI value close to unity suggest a significant but small effect size on hemorrhagic AVM presentation.

In conclusion, our data suggest that infratentorial AVM location is independently associated with hemorrhagic AVM presentation. The significant age difference between the supratentorial and infratentorial hemorrhage groups as seen in the univariate model did not sustain multivariate analysis, suggesting that age at presentation may interact with infratentorial AVM diagnosis but not with hemorrhagic presentation. Because our cross-sectional study did not analyze the effect of infratentorial AVM location on the risk of future hemorrhage, no immediate treatment recommendations can be derived from our data. The results, however, emphasize the need for prospective data on natural history and risk...
predictors from population-based studies.\textsuperscript{21,22} Definite treatment recommendations may be drawn only from a clinical trial testing the long-term benefit of “invasive” treatment compared with best medical therapy in a cohort that also includes infratentorial AVMs. Our findings may provide additional information for prespecified subgroup analyses in the planning of future prospective AVM studies.

Acknowledgments
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References
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