Incident Hemorrhage Risk of Brain Arteriovenous Malformations Located in the Arterial Borderzones

C. Stapf, MD; J.P. Mohr, MD; R.R. Sciacca, EngScD; A. Hartmann, MD; B.D. Aagaard, MD; J. Pile-Spellman, MD; H. Mast, MD

Background and Purpose—We sought to assess the relative risk of hemorrhagic presentation of brain arteriovenous malformations (AVMs) located in the arterial borderzone territories.

Methods—The 464 consecutive, prospectively enrolled patients from the New York AVM Databank were analyzed. AVM borderzone location was coded positive when the malformation was supplied by branches of at least 2 of the major circle of Willis arteries (anterior, middle, and/or posterior cerebral arteries). AVMs fed by branches of only 1 major pial or any other single artery served as a comparison group. Clinical presentation (diagnostic event) was categorized as (1) intracranial hemorrhage, proven by brain imaging, or (2) seizure, focal neurological deficit, headache, or other event with no signs of AVM hemorrhage on brain imaging.

Results—In 48% (n=222) of the patients, AVMs were located in the arterial borderzone territories; in 52% (n=242) a non-borderzone location was found. Hemorrhage was the presenting symptom in 44% (n=205); 28% (n=132) presented with seizures, 11% (n=52) with headaches, 7% (n=34) with a neurological deficit, and 9% (n=41) with other or no AVM-related symptoms. The frequency of incident AVM hemorrhage was significantly lower in borderzone AVMs (27%, n=61) than in non-borderzone malformations (60%, n=144; P<0.001). This difference remained significant in a multivariate model controlling for age, sex, AVM size, deep venous drainage, and presence of aneurysms (odds ratio, 0.4; 95% CI, 0.25 to 0.66).

Conclusions—Our findings suggest that borderzone location is an independent determinant for a lower risk of AVM hemorrhage at initial presentation. (*Stroke. 2000;31:2365-2368.*)

Key Words: cerebral arteriovenous malformations ■ cerebral hemorrhage ■ cerebrovascular disorders ■ natural history

Intracranial hemorrhage is the main cause of mortality and persistent morbidity in patients with brain arteriovenous malformations (AVMs). Recent work has helped to define several risk factors associated with AVM bleeds.1–5 Predictors of AVM hemorrhage such as deep venous drainage, high feeding artery pressure, and small AVM size are well established.4–6 The effects of others, such as AVM-associated aneurysms, are currently subject to discussion.7–9 Location in cortical regions with borderzone arterial supply is a distinct anatomic feature of many brain AVMs,10 but scant data exist on the effect of AVM topography on the risk of intracranial hemorrhage. In this study we assessed the relative risk of hemorrhagic presentation of brain AVMs located in the arterial borderzone territories.

Subjects and Methods

The New York AVM Databank is an ongoing prospective database collecting demographic, clinical, morphological, and treatment data on consecutive patients admitted to the New York Presbyterian Hospital with a brain AVM proven by brain imaging and conventional cerebral angiography. Patients enrolled are drawn from both the New York metropolitan area and distant referral sites. Details on the study population, design, variable definitions, and methods have been described in prior publications.3–4 Morphological features evaluated in the present analysis were feeding artery supply (branches of the anterior, middle, and/or posterior cerebral artery; the anterior and/or posterior choroidal artery; the superior, anterior inferior, and/or posterior inferior cerebellar artery; vertebral artery; basilar artery; and/or any dural vascular supply), anatomic location (supratentorial or infratentorial), venous drainage pattern (categorized as drainage into the superficial cortical veins, drainage into the deep venous system, and combined superficial and deep drainage), AVM nidus size (measured as maximum diameter in millimeters), and presence of AVM-associated aneurysms (defined as flow-related feeding artery aneurysms and/or intranidal aneurysms). Border-zone location of an AVM was coded positive when the malformation was supplied by branches of at least 2 of the individual major circle of Willis arteries, ie, the anterior and middle; middle and posterior; anterior and posterior; or anterior, middle,
and posterior cerebral arteries (Figure). Patients with an AVM fed entirely by branches of only 1 major circle of Willis or any other artery served as a comparison group.

The clinical presentation (diagnostic event) was categorized as (1) intracranial hemorrhage (intracerebral, intraventricular, subarachnoid, or any combination of the 3 bleeding types) or (2) nonhemorrhagic presentation, ie, seizure, focal neurological deficit, headache, or any other event that led to the diagnosis of the AVM. Incident AVM hemorrhage (eg, AVM hemorrhage as the initial presenting symptom) was defined as any clinically symptomatic event (sudden-onset headache, seizure, and/or focal neurological deficit) with signs of fresh AVM-related bleeding on CT and/or MR brain imaging or in the cerebrospinal fluid.

Univariate ($\chi^2$ test, $t$ test) models and a multivariate logistic regression model controlling for age, sex, AVM size, drainage pattern, and associated aneurysms were applied to assess the relative risk of incident hemorrhage in borderzone AVMs compared with non-borderzone malformations.

Results

A total of 464 AVM patients were evaluated. The mean±SD age at initial presentation was 34±15 years. Of the 464 patients, 222 (48%) had an AVM located in the arterial borderzone territories, and 242 (52%) showed a non-borderzone location. The most frequent mode of AVM presentation was hemorrhage, followed by seizures, headaches, neurological deficits, and other (including not AVM-related) symptoms (Table 1).

Incident hemorrhage was significantly less frequent in borderzone AVM than in non-borderzone malformations (Table 1). This difference retained its statistical significance in the multivariate model (Table 2). In the same model, a significant effect for associated aneurysms, deep venous drainage, and AVM size was found. Supratentorial AVM location alone did not show a statistically significant effect on the risk of hemorrhage when added to the multivariate model.

The univariate analysis (Table 1) and an additional multivariate logistic regression model (again including patient age, sex, AVM size, drainage pattern, and associated aneurysms) also showed a statistically significant association between AVM borderzone location and seizures at initial presentation (relative risk, 2.2; 95% CI, 1.3 to 3.7). No effect was found for other modes of AVM presentation, ie, focal deficit, headache, and other/unrelated symptoms.

Discussion

Our data suggest that an arterial borderzone location of brain AVMs is an independent determinant of lower risk of incident AVM hemorrhage. The additional findings of a close association of intracranial hemorrhage with AVM size and deep venous drainage confirm prior reports and support that our sample is comparable to those from other AVM data sets.5,6,9 Arterial borderzone location has long been suggested to represent a typical morphological feature of many brain AVMs,11 but until the present report it had not been evaluated as a risk factor for hemorrhagic AVM presentation. Several studies have suggested an overall lower hemorrhage risk for supratentorial versus infratentorial AVMs, but the basis for the differences that were found either did not remain significant when controlling for other confounders (such as nidus size or deep venous AVM drainage)4,6 or no multivariate analysis was performed.5,12,13 With the use of our own data set, the multivariate logistic regression model did not show a significant effect on the risk of hemorrhage for supratentorial AVM location per se. Our findings support the notion that the distinct location in the arterial borderzone may account for the trend toward lower supratentorial AVM hemorrhage rates, as shown in prior reports.

The impact of associated aneurysms on AVM hemorrhage is subject to ongoing discussions. Our findings lend support to studies showing a positive association,7,8,13–15 but others were unable to confirm these results.6,9,16,17 Given the large variation in the reported rates of associated aneurysms in AVM series, ranging from 3%18 to 58%,19 interobserver variation in the classification of angiographic AVM studies may be an important factor contributing to the different findings on the effect of aneurysms on AVM hemorrhage.

Cerebral angiography demonstrating an AVM located in the arterial borderzone territory. Top, Early arterial phase showing feeding branches of the middle (x), anterior (y), and posterior (z) cerebral arteries. Bottom, Late arterial phase demonstrating the AVM nidus with both superficial and deep draining veins (arrowheads).
Seizures as an initial AVM presentation occurred with significantly higher frequency in borderzone AVM patients. One likely explanation may be the significantly larger nidus sizes in these patients (mean maximal diameter of 43 versus 27 mm in the comparison group). Differences in seizure frequency between groups, however, remained significant in the multivariate model controlling for the effect of AVM size. The topography of the interarterial borderzone territory commonly involving the cortex of the brain convexities may therefore be another reason for the higher seizure frequency in these patients, supporting prior reports of a positive correlation between seizures and cortical AVM location.20,21

The effect of major determinants for AVM hemorrhage in our sample (ie, size, deep venous drainage) is comparable to data reported in other AVM series. Any hospital-based data set, however, cannot exclude the possibility of local referral bias influencing demographic, morphological, and clinical characteristics of the study sample.22 Additionally, because of known high fatality rates early after intracranial hemorrhage, an AVM referral center cohort may underestimate the overall frequency of hemorrhage in the study population, and the possibility of a systematic error cannot be excluded.23 Finally, our results may be limited by analyzing incident AVM hemorrhage rates only. Other determinants (such as size) strongly associated with the risk of incident hemorrhage failed to show a significant impact on the risk of subsequent hemorrhage.2 Hence, a longitudinal study may be the next step to confirm the effect of borderzone location on the risk of subsequent AVM hemorrhage.

Brain AVMs are commonly assumed to arise from a developmental derangement during embryonic angiogenesis.10 On the basis of both clinical and morphological features, however, the plausibility of a purely embryologic cause has recently been questioned.24,25 In our series, approximately half of the patients harbor an AVM that is located in the borderzone region shared by the distal anterior, middle, and/or posterior cerebral arteries. This suggests that there might be at least a subgroup of AVMs in which the development may be linked in a time-related manner to the formation of the arterial borderzones starting after the 29th gestational week, ie, during late fetal or early postpartum life.26,27 A lower hemorrhage rate in these patients may imply the existence of developmental factors influencing both AVM maturation and the associated hemorrhage risk—a testable hypothesis for future studies.

**Acknowledgements**

Supported in part by NIH grant RO1-NS-34949, the H.W. Goldsmith Foundation for Cerebrovascular Research, and The Eva and Peter Agoston Fund.

**References**

3. Hartmann A, Mast H, Mohr JP, Koennecke HC, Osipov A, Pile-Spellman J, Duong DH, Young WL. Morbidity of intracranial hemorrhage in

**TABLE 1. Demographic, Clinical, and Morphological Characteristics in 464 AVM Patients**

<table>
<thead>
<tr>
<th></th>
<th>AVM Borderzone Location (n=222)</th>
<th>AVM Non-Borderzone Location (n=242)</th>
<th>Total (n=464)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at presentation, mean±SD, y</td>
<td>32±14</td>
<td>35±15</td>
<td>34±15</td>
</tr>
<tr>
<td>Female sex</td>
<td>122 (55%)</td>
<td>133 (55%)</td>
<td>255 (55%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage*</td>
<td>61 (27%)</td>
<td>144 (60%)</td>
<td>205 (44%)</td>
</tr>
<tr>
<td>Seizures*</td>
<td>98 (44%)</td>
<td>34 (14%)</td>
<td>132 (28%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>27 (12%)</td>
<td>25 (10%)</td>
<td>52 (11%)</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>18 (8%)</td>
<td>16 (7%)</td>
<td>34 (7%)</td>
</tr>
<tr>
<td>Other/unrelated</td>
<td>18 (8%)</td>
<td>23 (10%)</td>
<td>41 (9%)</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVM size, mean±SD maximum diameter, mm</td>
<td>43±15</td>
<td>27±13</td>
<td>35±16</td>
</tr>
<tr>
<td>Deep and superficial venous drainage</td>
<td>87 (39%)</td>
<td>47 (19%)</td>
<td>134 (29%)</td>
</tr>
<tr>
<td>Deep venous drainage only</td>
<td>24 (11%)</td>
<td>71 (29%)</td>
<td>95 (20%)</td>
</tr>
<tr>
<td>Associated aneurysm (intranidal or flow-related)</td>
<td>45 (20%)</td>
<td>54 (22%)</td>
<td>99 (21%)</td>
</tr>
</tbody>
</table>

*Significant (χ² test; P<0.001).
†Significant (t test; P<0.001).

**TABLE 2. Multivariate Logistic Regression Model Testing the Effect of AVM Borderzone Location on Incident Hemorrhage**

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderzone location</td>
<td>0.40</td>
<td>0.25–0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>1.00</td>
<td>0.98–1.02</td>
<td>0.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.65</td>
<td>0.41–1.02</td>
<td>0.06</td>
</tr>
<tr>
<td>AVM size*</td>
<td>0.96</td>
<td>0.95–0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep and superficial venous drainage</td>
<td>1.68</td>
<td>0.97–2.91</td>
<td>0.06</td>
</tr>
<tr>
<td>Deep venous drainage only</td>
<td>3.19</td>
<td>1.78–5.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Associated aneurysm†</td>
<td>2.72</td>
<td>1.52–4.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*In millimeter increments.
†Intranidal or flow-related aneurysm.


Incident Hemorrhage Risk of Brain Arteriovenous Malformations Located in the Arterial Borderzones


*Stroke*. 2000;31:2365-2368
doi: 10.1161/01.STR.31.10.2365

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/10/2365