Angioarchitectural Factors Present in Brain Arteriovenous Malformations Associated With Hemorrhagic Presentation

Marco A. Stefani, MD; Phillip J. Porter; Karel G. terBrugge; Walter Montanera; Robert A. Willinsky; M. Christopher Wallace

Background and Purpose—Associations between clinical presentation of brain arteriovenous malformations (AVMs) and their angioarchitecture have been described. This study aims to identify significant factors related to the initial hemorrhagic event through multivariate statistical methodology.

Methods—The authors studied the initial clinical presentation of 390 consecutive patients with brain AVMs at the University of Toronto Vascular Malformation Study Group. Angiographic features present at that time, such as location, size, and blood supply, were recorded following a standard protocol and associated, through multivariate analysis techniques, with type of presentation.

Results—Patients had hemorrhagic presentation in 146 cases (37.4%). Hemorrhage was the initial presentation in 59.5% of the deep-seated AVMs (odds ratio [OR]=3.26; 95% CI=1.15 to 9.2; P=0.03). A single draining vein was associated with bleeding at presentation in 57.6% AVMs (OR=1.78; 95% CI=1.12 to 2.82; P=0.01), and 72.8% of the patients with venous ectasia had bleeding as initial evidence (OR=3.9; 95% CI=1.63 to 9.28; P=0.002). Hemorrhage was the initial presentation in 47.6% (111/233) of AVMs <3 cm, 22.5% (32/142) in sizes between 3 and 6 cm, and 20% in malformations >6 cm (3/15), but these differences were not significant in multivariate analyses.

Conclusions—For initial hemorrhagic presentation, a small number of draining veins, deep location, and the presence of venous ectasias were significant associated factors. In contrast with many previous reports, AVM size was not associated with hemorrhage at presentation in adjusted analyses. (Stroke. 2002;33:920-924.)

Key Words: angiography • cerebrovascular disorders • intracerebral hemorrhage • vascular malformations

With improved imaging techniques, the angioarchitectural aspects of arteriovenous malformations (AVMs) have been better studied, but their clinical and prognostic significance is not yet fully understood. Although several factors have been associated with hemorrhagic events,1,2 it is not known with certainty whether specific angioarchitectural aspects predispose patients with brain AVMs to any specific clinical presentation.

Some studies attempt to extrapolate the angiographic features present at the first event as determinants of risk for future bleeding. However, little data exist about the relation of these factors for subsequent risk of bleeding from an AVM. Only a prospective analysis of patients with untreated AVMs can establish the significance of the angiographic characteristic to identify any hemorrhagic-prone group.

This study aims to evaluate data from the University of Toronto Brain Vascular Malformation Study group database to correlate clinical presentation with structural aspects of the AVM angioarchitecture.

Subjects and Methods

All patients referred to the University of Toronto Arteriovenous Malformation study group from 1989 to 1997 with a diagnosis of brain AVM were seen by a multidisciplinary team of neurosurgeons, neuroradiologists, and radiotherapists after a diagnostic and therapeutic approach that has already been reported.1 Data on diagnosis, treatment, and follow-up of these patients has been prospectively recorded in a computerized database following standard protocol since 1989. Angiographic characteristics such as size of the AVM, its location, type of arterial feeders, venous morphology, and arterial aneurysms present at the time of the diagnosis of the AVMs were analyzed.

The factors to be analyzed in assessing the relationship to hemorrhagic presentation were chosen from the literature.3-4 These included factors that have previously been variably found to be associated with hemorrhagic presentation, as well as variables that we, based on our experience, thought may be important. The methodology for angiographic interpretation used in the present study is similar to the terminology recently reported by the Joint Writing Group of the Technology Assessment Committee.2

Size was classified according to the Spetzler-Martin criteria5 into small (≤3 cm), medium (>3 cm and ≤6 cm), and large (≥6 cm). The medium and large groups were brought together to form the
group “large” used in the final statistical analyses. Locations were grouped into frontal, temporal, parietal, occipital, corpus callosum, basal ganglia, insular, brain stem, and cerebellum. The location was also grouped into deep (basal ganglia, thalamus, cerebellum, and corpus callosum) and superficial (all other locations). The group was called “deep” based on location of AVM rather than by the presence of deep arterial blood supply or venous drainage.

Arterial feeders were classified into deep supply alone, superficial supply alone, and combined deep and superficial blood supply to the AVM. The superficial group included cortical branches of the anterior, middle, and posterior cerebral arteries. The deep included perforating branches and choroidal and posterior fossa arteries.

Venous drainage was categorized as deep or superficial, according to the Spetzler-Martin classification criteria. The number of draining veins was also classified into three groups: single draining vein, two draining veins, or more than two draining veins.

Venous anatomy was described with respect to the presence or absence of ectasias (abnormal dilatations) and outflow obstruction (stenosis) >50%. The presence of arterial aneurysms was noted as well as their locations, which included prenidal, intranidal, or remote aneurysms, as described previously.

A careful analysis of all charts was performed to assure validated information. All imaging tests were interpreted using the criteria mentioned above. Logistic regression was used to statistically assess significant factors associated with hemorrhagic presentation. Independent factors (P<0.05) were chosen from univariate analyses to construct multivariate models by forward stepwise methods. Data were analyzed using the SAS software (SAS Institute).

**Results**

The group was composed of 390 patients with brain AVMs, with an average age of 31.4 years at disease presentation. The average age at presentation for patients with or without bleeding was not significantly different (P=0.18). There were 218 men (55.9%) and 172 women (44.1%). The overall incidence of hemorrhage at presentation was 37.4% (146/390). There were 84 (38.5%) of 218 initial hemorrhages in men and 62 (36%) of 172 in women, which was not significantly different (χ²=0.25, P=0.62).

The association between location and hemorrhage is addressed in Table 1. There was a clear difference in 2 groups: deep-seated AVMs (the first 4 items of the Table 1) had higher frequencies of bleeding than those in superficial locations (P<0.0001). The association of individual locations with hemorrhagic presentation was not significant when controlled for other factors in the multivariate analyses (P>0.1).

There were 233 AVMs with a diameter <3 cm. Of this group, 111 (47%) presented with hemorrhagic events. The lesions with a diameter >3 to ≤6 cm presented with bleeding in 32 (22.5%) of 142 cases. AVMs >6 cm were found in 15 patients, 3 (20%) of whom presented with hemorrhage. In the univariate model, small AVMs (<3 cm) had the tendency to present more frequently with bleeding (odds ratio=2.73; 95% CI=1.8 to 4.15; P<0.0001), but size did not remain significant with multivariate methods.

The univariate analyses for the characteristics associated with hemorrhage are presented on Table 2. Small size, deep venous drainage, venous ectasia, presence of aneurysms,
TABLE 2. Univariate Analyses of Different Angiographic Factors Associated with Hemorrhagic Presentation

<table>
<thead>
<tr>
<th>Feature</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous ectasia</td>
<td>4.48</td>
<td>2.04</td>
<td>9.81</td>
</tr>
<tr>
<td>Deep location</td>
<td>4.21</td>
<td>2.57</td>
<td>6.93</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>2.86</td>
<td>1.35</td>
<td>6.25</td>
</tr>
<tr>
<td>Small size</td>
<td>2.73</td>
<td>1.8</td>
<td>4.15</td>
</tr>
<tr>
<td>Single draining vein</td>
<td>2.5</td>
<td>1.89</td>
<td>3.33</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>2.04</td>
<td>1.32</td>
<td>3.13</td>
</tr>
<tr>
<td>Deep arterial feeder</td>
<td>1.86</td>
<td>1.28</td>
<td>2.73</td>
</tr>
<tr>
<td>Venous stenosis</td>
<td>1.76</td>
<td>0.82</td>
<td>3.80</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.

Discussion

Hemorrhage has been the main clinical event at presentation in the majority of the reported series of AVMs, ranging from 30% to 86% of cases. Since the early works, authors have been trying to find predictors of hemorrhagic episodes. Many of these studies, including a recent series, have reported links between specific features of AVMs and these events.

Given the large number of factors to be analyzed, it is clear that small samples cannot be used. Analyzing very small subgroups may result in misleadings conclusions, like finding a specific feature associated with asymptomatic patients. Also, some of these features are not independent. For example, deep AVMs tend to have deep feeders and drainage. This interaction among variables necessitates multivariate statistical modeling to decide where the strongest associations remain.

TABLE 3. Significant Factors Present in the Final Multivariate Model

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of venous ectasias</td>
<td>3.9</td>
<td>1.63</td>
<td>9.28</td>
</tr>
<tr>
<td>Deep location</td>
<td>3.26</td>
<td>1.15</td>
<td>9.2</td>
</tr>
<tr>
<td>Small number of draining veins</td>
<td>1.78</td>
<td>1.12</td>
<td>2.82</td>
</tr>
</tbody>
</table>

Size

The association between size, especially the group of small AVMs (\(<3\) cm), and clinical presentation with bleeding has been suggested in several large series. Guidetti and Delitala and Graf et al reported a higher incidence of hemorrhage as the first symptoms for small AVMs, but they did not use analyses of presentation features separately from those appearing in patients during follow-up. A similar methodological problem also happened with a more recent report of 100 consecutive prospectively observed patients. Crawford et al. in a series of 343 patients, found excessive bleeding presentation events in the group of small AVMs, but this factor was not controlled for other dependent variables.

In some recent series, these concepts have been reviewed, because the reports have not found a relation between size and hemorrhagic initial event. Although they used a careful statistical evaluation, the small number of cases studied by Marks et al compromised the strength of the conclusions. The report of Turjman et al has some limitations on patient selection bias and lack of multivariate analyses to discriminate dependent variables.

In the present study, AVMs with small size failed to be associated with hemorrhagic presentation, in multivariate models. This goes against most of the classical studies previously mentioned.

Location

Some locations have been associated with hemorrhage as the initial clinical presentation, such as cerebellum, brain stem, temporal lobe, and insular and callosal region. In a retrospective analysis of a series of 32 patients with AVMs of the brain stem and cerebellum at the University of Texas Health Science Center at Dallas, 23 (72%) presented with hemorrhage, which supports the argument that these lesions are at high risk for coming to clinical attention as a result of hemorrhagic events.

Turjman et al. in a series of 100 patients with AVMs treated between 1987 and 1990 found that the basal ganglia was the only significant location associated with hemorrhagic presentation, but the small number of cases compromised the conclusions. This category was not controlled for other related variables, like deep venous drainage and deep arterial feeders.

Temporal and occipital locations have also been identified as risk factors for bleeding, but again hemorrhages after initial presentation are displayed mixed with index hemorrhages. The depth of the malformation was not a significant factor in this particular study; however, only 7% of the group were deep-seated AVMs. Marks et al concluded that there was no preferential location to presentation with bleeding.

Because of the small numbers in subgroups, it is difficult to identify a specific isolated area of the brain that tends to present with bleeding more often. However, when considered as a group, we found that deep AVMs more frequently present initially with bleeding. That remained significant after multivariate analyses adjusting for other important factors.
such as size and deep feeders, which were associated with deep AVM.

Arterial Feeders
The role of deep feeders in hemorrhagic clinical presentation has also previously been emphasized by Turjman et al.\textsuperscript{13} However, deep-seated lesions usually have deep feeders and deep venous drainage. At multivariate analyses, this factor alone failed to be correlated with AVM bleeding at presentation.

Venous Drainage
The association of deep venous drainage alone with hemorrhagic presentation has been presented in several previous reports.\textsuperscript{12,13,17} Turjman et al\textsuperscript{13} found this factor significant, together with 5 others, but as mentioned the analysis failed to control for confounding factors. A series of 340 patients described by Duong et al\textsuperscript{10} had deep venous drainage as a significant factor for hemorrhagic presentation in a multivariate analysis. Unfortunately they did not use the same criteria as used in the present study, with the location variable having only the posterior fossa entry. Deep venous drainage is a variable dependent on deep location, and this could have affected the analysis. In a more recent article, Langer et al\textsuperscript{11} proposed deep venous drainage as a frequent factor present on AVMs that bled.

Angioarchitecture Abnormalities
The studies that analyzed venous ectasia did not demonstrate any association with hemorrhagic events at the initial clinical presentation.\textsuperscript{12,13,15} One has to consider that the exact criteria for the presence or absence of a venous ectasia are not completely clear. Venous ectasia has variably been defined as "a markedly ectatic vein"\textsuperscript{13} or as "pouches," usually associated with a stenotic draining vein.\textsuperscript{15} Those features are sometimes well seen only in high-quality nonselective or superselective catheterization, which makes it difficult to apply in the whole AVM population, considering that not all patients are subjected to such investigation. This feature was significantly associated with hemorrhagic presentation in our study, but this finding must be interpreted with caution. The series describing this characteristic used superselective angiography in a large proportion of the patients. Usually those were cases considered for embolization, eg, AVMs with deep feeders in deep or surgically inaccessible locations.

The relation between venous stenosis and small number of draining veins with bleeding due to AVM rupture was theoretically studied by Hademenos and Massoud\textsuperscript{18} with special relation to high-flow draining veins. A Japanese series of 108 patients stated the importance of the venous side for risk of bleeding.\textsuperscript{17} In a simple analysis, venous stenosis was reported as a significant factor for initial AVM bleeding in a small subset of young females in the third decade.\textsuperscript{18} The report of Turjman et al\textsuperscript{13} describes selective investigation in all of the 100 patients seen. They found no association between venous stenosis and initial bleeding, defining a venous stenosis as reduction of 50% or more of the vein diameter. In our multivariate analyses it did not present as a significant feature.

Aneurysms
Intranidal aneurysms have been reported to be significantly associated with hemorrhage at presentation.\textsuperscript{12,13} The risk of intracranial hemorrhage among patients with a coexisting saccular aneurysm and unruptured AVM was reported by Brown et al\textsuperscript{19} to be 7% per year at 5 years after diagnosis, compared with 1.7% per year for the group of patients with AVM alone. The same study found that typically aneurysms are located on the feeding vessels of the AVM. Okamoto et al,\textsuperscript{20} in their series of 154 patients, also found a higher incidence of hemorrhage when aneurysms are associated with AVMs, but they had only 5 identified aneurysms in their study.

Pollock et al\textsuperscript{11} also could not identify any relation between aneurysms and hemorrhagic presentation in a series of 313 patients. This finding was also seen in another large series recently reported.\textsuperscript{6} In the same set of patients used in the present study, Redekop et al\textsuperscript{4} found the occurrence of hemorrhage in 22 (63%) of 35 patients with intranidal aneurysms and in 29 (41%) of 71 patients with flow-related aneurysms. In our study, however, multivariate analyses in this group of patients failed to demonstrate any significant association with hemorrhagic presentation.

The remaining controversy is still whether specific angioarchitecture aspects predispose patients with brain AVMs to any subsequent clinical course, specifically a higher hemorrhage risk. When analyzed at initial presentation, these factors reflect only features present in one moment of the AVM’s natural history and provide unclear information in terms of outcome. Many of the previous reports either simply extrapolate the angiographic features present at the first event as determinants of risk for future bleeding,\textsuperscript{6,12,17,20} or mix those aspects with subsequent bleeding risk.\textsuperscript{7,8,22,23} The influence of these factors present at the first presentation on the natural history requires prospective follow-up to assess.

Thus, our study is also limited in that it reports clinical presentation aspects of AVMs and the angiographic features found at that time. It is not a report on risk factor or prognosis, but it may contribute to epidemiological data on AVM presentation for patients surviving initial events who are referred to neurosurgical centers.

Conclusions
In this large series of patients, a number of factors were found to be associated with hemorrhage at the initial presentation. A small number of draining veins, deep locations (brain stem, thalamus, corpus callosum, and cerebellum), and the presence of venous ectasies were significant features in multivariate analysis. Analyses of the clinical behavior of brain AVMs with these characteristics is necessary to demonstrate clear associations with subsequent risk of hemorrhage.

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