Effect of Age on Clinical and Morphological Characteristics in Patients With Brain Arteriovenous Malformation

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Background and Purpose—The goal of this work was to determine the effect of age at initial presentation on clinical and morphological characteristics in patients with brain arteriovenous malformation (AVM).

Methods—The 542 consecutive patients from the prospective Columbia AVM database (mean±SD age, 34±15 years) were analyzed. Univariate statistical models were used to test the effect of age at initial presentation on clinical (AVM hemorrhage, seizures, headaches, neurological deficit, other/asymptomatic) and morphological (AVM size, venous drainage pattern, AVM brain location, concurrent arterial aneurysms) characteristics.

Results—Hemorrhage was the presenting symptom in 46% (n=247); 29% (n=155) presented with seizures, 13% (n=71) with headaches, 7% (n=36) with a neurological deficit, and 6% (n=33) without AVM-related symptoms. Increasing age correlated positively with intracranial hemorrhage (P=0.001), focal neurological deficits (P=0.007), infratentorial AVMs (P<0.001), and concurrent arterial aneurysms (P<0.001); an inverse correlation was found with seizures (P<0.001), AVM size (P=0.001), and lobar (P<0.001), deep (P=0.008), and borderzone (P=0.014) location. No age differences were found for sex, headache, asymptomatic presentation, and venous drainage pattern.

Conclusions—Our data suggest a significant interaction of patient age and clinical and morphological AVM features and argue against uniform AVM characteristics across different age classes at initial presentation. In particular, AVM patients diagnosed at a higher age show a higher fraction of AVM hemorrhage and are more likely to harbor additional risk factors such as concurrent arterial aneurysms and small AVM diameter. Longitudinal population-based AVM data are necessary to confirm these findings. (Stroke. 2003;34:2664-2670.)

Key Words: aneurysm ■ cerebral arteriovenous malformations ■ intracranial hemorrhages ■ seizures ■ stroke

Recent data from international databases1 and prospective population-based studies2–4 suggest that more than half of all arteriovenous malformation (AVM) patients may suffer intracranial hemorrhage. Other complications include epileptic seizures, headaches, and neurological deficits, and only few appear to be asymptomatic.5,6 Brain AVMs most often come to clinical attention in young adults in their mid 30s. Little attention, however, has been paid to the effect of age on AVM-specific characteristics that may influence both the natural course and treatment risk. Earlier reports failed to demonstrate an independent effect of age on the risk of both incident and recurrent AVM hemorrhage.7–10 and the association between age and morphological AVM characteristics has only scarcely been addressed so far.11,12

In this study, we analyzed the effect of patient age at initial presentation on demographic, clinical, and morphological AVM characteristics at the time of initial presentation.

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Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000094824.03372.9B
research reporting terminology.2,14 The initial AVM presentation (or diagnostic event) was defined as the clinical index event that led to the diagnosis of the AVM. Among different modes of initial presentation, incident AVM hemorrhage was defined as any clinically symptomatic event (sudden-onset headache, seizure, and/or focal neurological deficit) with signs of AVM-related bleeding on CT and/or MR brain imaging or in the cerebrospinal fluid at the time of the index event. Nonhemorrhagic modes of AVM presentation were stratified into seizure, focal neurological deficit, headache, or other/ asymptomatic. Morphological variables as used in the present analysis were 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 anatomic AVM location classified as lobar (any frontal, parietal, temporal, and/or occipital location), deep only (the basal ganglia, internal capsule, thalamus, and/or corpus callosum), and infratentorial (brain stem and/or cerebellar location). A borderzone location was coded positive when the AVM 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.15 Arterial aneurysms were defined as saccular dilatations of the lumen ≥2 times the width of the arterial vessel that carried the dilatation. They were further classified as feeding artery aneurysms, intranidal aneurysms (both considered AVM associated), and aneurysms unrelated to blood flow to the AVM (nonassociated aneurysms).16 A feeding artery was defined as any intracranial vessel that angiographically contributed arterial flow to the AVM. The AVM nidus was defined as the vascular mass included in the AVM size measurement. Intranidal aneurysms were coded when visualized early after angiographic injection, eg, before substantial venous filling had occurred. Infundibula, arterial ectasies (ie, dilated feeding vessels), and intranidal aneurysmal dilatations seen during the venous angiographic phase only were not coded as arterial aneurysms. Aneurysm aneurysms were coded as unrelated to the AVM when located on intracranial arteries not contributing blood flow to the AVM.

Statistical Analysis
Several standard statistical models (level of significance, α=0.05) were applied to test the effect of age on demographic (female sex), clinical (mode of presentation), and morphological (AVM size, anatomic location, venous drainage pattern, presence of arterial aneurysm sub- types) characteristics at the time of the diagnostic event.

In a first model, age at presentation was stratified into subsequent age classes in 10-year increments, as illustrated in Figures 1 through 4, and comparisons were made with χ², analysis of variance (ANOVA), and Tukey’s honestly significant difference (HSD) statistics. Based on Spearman’s rank correlation, a second model analyzed age at presentation as a continuous variable and tested for linear correlations with the study variables. A third model tested for nonlinear correlations with squared continuous age values using logistic standardized likelihood estimates. If both linear and nonlinear correlations were found, additional log-linear models (likelihood ratio) and ANOVA statistics were applied to test the goodness of fit for each correlation. All analyses have been considered purely exploratory; therefore, no additional α level downward adjustments or multiple comparison procedures have been undertaken.

Results
Demographic, clinical, and morphological baseline characteristics of the study sample are summarized in Table 1. For the analysis (first statistical model), the 542 AVM patients were further stratified into 7 different age classes: 23 patients <10 years of age, 87 patients 10 to 19 years of age; 116 patients 20 to 29 years of age; 134 patients 30 to 39 years of age; 97 patients 40 to 49 years of age, 55 patients 50 to 59 years of age, and 30 patients ≥60 years of age. The overall mean±SD age of the sample was 34±15 years.

Demographic Characteristics
No significant sex differences were found between the predefined age classes, and no significant linear or nonlinear correlations with increasing age were seen (Table 2).

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Mode of initial clinical presentation in 542 patients presenting with brain AVM stratified by age classes in 10-year increments. Highest bleeding frequencies were detected among patients <10 (n=13, 57%), 50 to 59 (n=55, 58%), and ≥60 (n=19, 63%) years of age vs the numbers found in those 10 to 19 (n=42, 48%), 20 to 29 (n=43, 37%), 30 to 39 (n=53, 40%), and 40 to 49 (n=45, 46%) years of age. Highest proportions of seizures were detected among AVM patients 20 to 29 (n=45, 40%) and 30 to 39 (n=45, 35%) years of age vs those ≤10 (n=5, 22%), 10 to 19 (n=24, 28%), 40 to 49 (n=24, 26%), and 50 to 59 (n=12, 22%) years of age. As to focal neurological deficits (unrelated to hemorrhage), highest relative frequencies were detected in patients 50 to 59 (n=8, 15%) and ≥60 (n=4, 13%) years of age. For the small fraction of those presenting with headaches or asymptomatic AVMs, no significant differences between age classes could be determined.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Mean maximal AVM nidus size measurements in 542 patients stratified into age classes by 10-year increments. Mean±SD maximal AVM nidus diameter in the sample was 33±17 mm, with the largest nidus diameters seen in AVM patients 20 to 29 years of age (mean maximal diameter 37 mm).
Clinical Presentation

Almost half of the patients (247, 46%) initially presented with intracranial hemorrhage. The relative frequency of hemorrhagic AVM presentation differed significantly between age classes (Table 2). Figure 1 illustrates that the highest bleeding frequencies were found among patients in the lowest and highest age groups. As suggested by the shape of the age distribution for AVM hemorrhage, a squared correlation between age and hemorrhagic AVM presentation was found.

The relative frequency of seizures at initial presentation (155, 29%) was significantly different among the age classes (Table 2), with the highest values seen among AVM patients 20 to 29 and 30 to 39 years of age and no seizures detected after 60 years of age (Figure 1). A significant negative correlation between seizure occurrence and increasing age was found for both linear and squared age values (Table 2). The goodness-of-fit analysis was significant for the linear $[\chi^2 (df=1), 8.94; P=0.003]$, squared $[\chi^2 (df=1), 15.90; P<0.001]$, and both effects combined $[\chi^2 (df=2), 22.71; P<0.001]$. Among patients presenting with a sudden or slowly progressing focal neurological deficit (unrelated to hemorrhage), no significant differences across different age groups were found (Table 2). The second statistical model analyzing age as a continuous variable, however, suggested a linear correlation with increasing age. Figure 1 illustrates that the highest relative frequencies were detected in patients 50 to 59 and ≥60 years of age.

As for headache and asymptomatic AVM presentation, neither showed significant differences between age classes or correlations with increasing age (Table 2).

Morphological Characteristics

Overall, the mean±SD maximal AVM nidus diameter in the sample was 33±17 mm. Size measurements differed signifi-
cantly across different age classes (Table 2), with the largest nidus diameters seen in AVM patients 20 to 29 years of age (mean ± SD maximal diameter, 37 ± 17 mm; Figure 2). In the posthoc comparison (Tukey’s HSD procedure; df = 532, α = 0.05), mean maximal size measurements differed significantly between the latter age class and patients 50 to 59 (mean ± SD maximal diameter, 27 ± 15 mm) and those ≥ 60 (mean ± SD maximal diameter, 27 ± 16 mm) years of age. Overall, significant linear and logarithmic correlations were seen between AVM size and increasing age. The goodness-of-fit analysis, however, was significant only for the linear (F(1,535) = 6.19; P = 0.013) not the squared (F(1,535) = 2.74; P < 0.098) trend, suggesting that the linear correlation may suffice to describe the effect of age on AVM size.

The relative frequency of a lobar AVM location showed significant differences across age classes (Table 2), with the highest numbers seen in the 3 median age groups. As suggested by the shape of the age distribution for lobar AVMs (Figure 3), no linear correlation with increasing age was found, but a negative logarithmic correlation with age was seen.

No significant differences between age classes were seen for AVMs in a deep brain location. In the second statistical model, however, a significant negative correlation with increasing age was found (Table 2). Figure 3 illustrates different proportions for deep brain AVMs, ranging from 22% patients in the lowest age group to 4% in those 50 to 59 years of age. No cases with a deeply located AVM were diagnosed in patients > 60 years of age (Figure 3).

The occurrence of infratentorial AVMs showed significant differences between age classes, with the highest proportion seen among patients ≥ 60 years of age (Figure 3). Also, significant linear and logarithmic correlations with increasing age were found (Table 2). The goodness-of-fit analysis was significant for the linear [χ²(df = 1), 12.81; P < 0.001], squared [χ²(df = 1), 28.63; P < 0.001], and both effects combined [χ²(df = 2), 41.00; P < 0.001].

Borderzone AVMs occurred in significantly different proportions across different age groups (Table 2), and significant negative correlations (both linear and logarithmic) with increasing age were found (Table 2). The additional goodness-of-fit analysis was significant for the linear [χ²(df = 1), 6.19; P = 0.013], squared [χ²(df = 1), 7.00; P = 0.008], and both effects combined (χ²(df = 2), 10.73; P = 0.005).

The relative distribution of AVM patients harboring concurrent arterial aneurysms of any subtype showed significant differences between age classes (Table 2). Figure 4 illustrates the proportions, ranging from 3 (13%) in the lowest to 19 (63%) in the highest age group. Accordingly, Spearman’s rho statistics confirmed a significant linear correlation with increasing age. Similarly, robust linear correlations were found for both feeding

### TABLE 2. Univariate Analyses Testing the Effect of Age on the Relative Frequency of Demographic, Clinical, and Morphological Characteristics in 542 Patients With Brain AVM at Initial Presentation

<table>
<thead>
<tr>
<th>Statistical Model</th>
<th>Differences Among Age Classes</th>
<th>Linear Correlation With Age</th>
<th>Squared Correlation With Age</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Test</td>
<td>P</td>
<td>P</td>
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<tr>
<td></td>
<td>Mean maximum AVM size</td>
<td>F(df = 6) 3.13</td>
<td>0.005*</td>
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<tr>
<td></td>
<td>AVM location</td>
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<tr>
<td></td>
<td>Lobar AVM location</td>
<td>χ²(df = 6) 34.025</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Deep AVM location</td>
<td>χ²(df = 6) 10.966</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td>Infratentorial AVM location</td>
<td>χ²(df = 6) 55.495</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Borderzone location</td>
<td>χ²(df = 6) 13.582</td>
<td>0.035*</td>
</tr>
<tr>
<td></td>
<td>Deep venous drainage component</td>
<td>χ²(df = 12) 10.936</td>
<td>0.534</td>
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<tr>
<td></td>
<td>Concurrent arterial aneurysms</td>
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<tr>
<td></td>
<td>Any</td>
<td>χ²(df = 6) 33.211</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Feeding artery</td>
<td>χ²(df = 6) 30.874</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td>Infranidal</td>
<td>χ²(df = 6) 14.614</td>
<td>0.023*</td>
</tr>
<tr>
<td></td>
<td>Unrelated to AVM</td>
<td>χ²(df = 6) 15.597</td>
<td>0.016*</td>
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*Statistically significant (P < 0.05).
†Unrelated to hemorrhage.
artery and unrelated aneurysms, but none was seen for intranidal aneurysms (Table 2). Nonetheless, all 3 subtypes, including intranidal aneurysms, showed significantly different proportions across age classes (Table 2 and Figure 4).

No age effect was found for relative frequencies of different venous drainage pattern; neither could a correlation with increasing age be determined.

**Discussion**

Our findings suggest a significant effect of age on several clinical and morphological AVM variables at the time of the initial diagnosis, including associations with established risk factors that may influence both the natural history and the risk of invasive AVM treatment.

The clinically most relevant mode of AVM presentation, intracranial hemorrhage, occurred at significantly different proportions across age classes. In addition, the observed frequency of factors favoring the risk of AVM rupture such as AVM size and the presence of associated aneurysms showed significant differences relative to age. For other modes of AVM presentation, the occurrence of symptomatic seizures also showed a significant association with age. The additional association of age with AVM size and borderzone location, both known predictors for AVM-related seizures, further supports the plausibility of these findings.

As for invasive treatment modalities, AVM size and deep venous drainage are recognized morphological risk predictors for surgical therapy outcome and are the basis for the well-established Spetzler-Martin grading scale. Both factors may also play a role in risk prediction for endovascular treatment. Although in our study venous drainage pattern did not show significant differences across different age classes, the mean maximal nidus size was significantly associated with age, trending toward lower AVM diameters with increasing age at presentation. One recent series already suggested an independent effect of age on the risk of AVM surgery, but further studies are necessary to confirm these findings.

Patients presenting after 60 years of age assembled several clinical and morphological features that may be unique to this subgroup. Clinically, no case presenting with AVM-related seizures was detected in these patients, but the highest proportion of hemorrhagic presentation (73%) was seen. None had been diagnosed with a deeply located AVM, but this group harbored the highest proportion of concurrent arterial aneurysms. Most surprisingly, this age class showed the smallest mean AVM diameter in the entire study cohort. This observation challenges the widely accepted notion that AVMs represent an embryonic disorder that, once it emerges, grows steadily over time. The significantly smaller nidus diameters in patients ≥60 years of age support the idea of late-onset AVMs, which may develop after birth and even during adulthood. The possibility of spontaneous AVM regression may add to the trend toward smaller nidus diameters at higher age, but because evidence for common AVM regression is lacking, its overall impact on the size curve may be limited. The relatively large nidus diameters seen in children <10 years of age may indicate relatively rapid AVM enlargement after the initial lesion has emerged. Whether the possibility of fast AVM growth is limited to young patients (as described for AVM recurrence after complete removal or may also occur in adults remains to be determined.

Patient age characteristics are a factor illustrating the limited comparability between referral center studies. A recently published comparison of 1289 AVM patients from 4 international treatment centers demonstrated significant age differences between the samples, most likely a result of local referral bias. The overall mean age of patients included in this meta-analysis (31 years; 95% confidence interval [CI], 30 to 32) is significantly different from the figure found in our own sample (34 years; 95% CI, 33 to 35) and clearly differs from prospective population-based estimates in the ongoing New York Islands AVM Study (35 years; 95% CI, 33 to 37; 2-tailed t test, P<0.001). These comparisons emphasize that in AVM natural history and treatment studies, only limited inferences on the total population of AVM patients can be made on the basis of single-center experience alone.

This is also true for our own analysis to which some additional methodological limitations may apply. All variables investigated were coded at the time of the diagnostic event and do not include follow-up data on possible changes in AVM characteristics. Hence, this cross-sectional study is merely observational and does not provide a longitudinal risk analysis. The patient sample is drawn from a large prospective data set, but because of as-yet-unknown population-based case fatality rates after AVM hemorrhage, referral center cohorts such as ours may underestimate the overall frequency of incident AVM hemorrhage and associated risk factors. Finally, referral bias to specialized treatment centers may significantly influence demographic, clinical, and morphological characteristics of the local patient cohort. The possibility of a systematic error in the data analysis can therefore not be excluded.

Overall, our data argue against the assumption of uniform AVM characteristics across different age classes at initial presentation. In particular, AVM patients diagnosed at a higher age seem to bear a higher proportion of AVM hemorrhage and are more likely to show additional risk factors (ie, concurrent arterial aneurysms and small AVM size). These findings suggest a “dynamic” risk exposure at different ages and may caution against stable annual risk predictions in patient counseling. Slowly accumulating data from prospective longitudinal and population-based surveys will allow more adequate risk predictions regarding AVM-related morbidity and mortality.

**Acknowledgments**

This work was supported by NIH grant R01 NS 40792–01 (principal investigator, Dr Mohr). We thank S. Marshall for his reliable help and W.L. Young, MD, for his effort during the data collection process.

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Editorial Comment

Age-Dependent Brain AVM Characteristics: What is the Evidence?

Cerebral arteriovenous malformations (AVMs) came to clinical attention more than a century ago, and since that time, they have been recognized as lesions that can cause serious neurological deficits or death. Although AVMs can present mostly with hemorrhage or seizure, the advent of contemporary brain imaging techniques has allowed an
increasing number of AVMs to be detected before rupture. Over the last decade, there has been a growing interest in knowing more about the incidence, frequency, and clinical course of these vascular lesions; thus, both retrospective and prospective-based studies offering new insights have accumulated.

Population-based studies have reported that half of the adults with a first presentation of brain AVM have intracranial hemorrhage.\(^2\) Other important presenting symptoms include seizures, headaches, progressive neurological deficit, pulsatile tinnitus, and other unrelated symptoms that lead to a fortuitous diagnosis.\(^3\) Finally, an AVM can be suggested by a distinctive combination of these features.

An understanding of the different modes of presentation and their relative frequencies is important to raise the clinical suspicion of an AVM, so that clinical management is undertaken appropriately. The study by Stapf and colleagues\(^4\) provides seminal findings in this issue by reporting preliminary results of the Columbia AVM Data Bank, an ongoing prospective study.\(^5,6\) By collecting demographic, clinical, and morphological data on 542 consecutive patients with brain AVM, the authors assessed the effect of age at the time of the diagnostic event on clinical and morphological characteristics of brain AVM.

To define precise criteria of analysis, patients were stratified into 7 different age classes (\(<10, 10 \text{ to } 19, 20 \text{ to } 29, 30 \text{ to } 39, 40 \text{ to } 49, 50 \text{ to } 59, \text{ and } \geq 60 \text{ years}). As far as the clinical characteristics are concerned, the authors found that hemorrhage was the presenting symptom in 46% of the cases. Interestingly, the highest bleeding frequencies were found among patients in the lowest and highest age groups. Increasing age correlated well with hemorrhage, focal neurological deficits, infratentorial AVM location, and concurrent arterial aneurysm. On the other hand, an inverse correlation was found with seizure, AVM size, and lobar, deep, and borderzone location. No significant differences were detected across different age groups for sex, headache, asymptomatic presentation, or venous drainage pattern.

These data are unique in that they provide an excellent characterization of AVMs with respect to patient age at the time of initial presentation. Important differences among patients mainly between 2 different classes of age, younger and older, are suggested. From the data reported, intracranial hemorrhage is the clinically most relevant mode of AVM presentation, especially in patients presenting after 60 years of age. This is in agreement with the data reported by Karlsson et al\(^7\) that increasing age confers an increased risk of AVM rupture. Furthermore, in this class of patients, no case with AVM-related seizures and deeply located AVM was detected.

A few points, however, are worthy of note. By age stratification, older patient were found to have the smallest mean AVM diameter in the analyzed cohort study. This finding, as the authors state, differs with the widely accepted notion of AVM representing a congenital malformation that grows over time. However, a spontaneous AVM regression could be a hazardous explanation for such an observation because, to date, strong evidence does not exist. In this regard, spontaneous AVM regression is considered to be a rare occurrence. In a series of 700 cerebral AVMs treated for 20 years,\(^8\) just 6 cases of angiographically documented lesions that disappeared on follow-up angiograms were identified, and 24 similar cases from the preexisting literature were reviewed. The common threads of such cases were modest size, a limited number of arterial feeders, isolated venous drainage, and a history of hemorrhage.

Finally, on the basis of their data, the authors provide an estimate of the probability of hemorrhage as a presenting symptom, because, in this study, the older AVM patients have the maximum risk of bleeding compared with the other age classes. Unfortunately, this type of study cannot completely address this issue. Because this study is merely observational and does not provide a longitudinal risk analysis, it may underestimate the overall frequency of incident AVM hemorrhage and associated risk factors. Hence, although Stapf and collaborators\(^4\) provide a reasonable argument linking age with AVM variables, they appropriately caution that referral bias to specialized treatment centers may significantly influence the analysis of the local patient cohort. Despite this inherent limitation of epidemiologically based observations, the authors’ findings provide a compelling argument against the assumption of uniform AVM characteristics across different age of presentation.

In summary, the findings reported by Stapf and collaborators, especially the notion that a “dynamic” risk exposure at different ages may caution against stable annual risk predictions in AVM patient, even if deserving further population-based AVM data, add an important contribution to our existing knowledge that could be helpful in our decision-making process when treating patients with cerebral AVM.

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Stroke. 2003;34:2664-2669; originally published online October 23, 2003;
doi: 10.1161/01.STR.0000094824.03372.9B

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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