Unruptured Cerebral Arteriovenous Malformations
To Treat or Not to Treat
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As noninvasive brain imaging for sometimes dubious indications becomes more and more ubiquitous, greater numbers of asymptomatic lesions are being found and management decisions are being required. Cerebral arteriovenous malformations (AVM) represent a particularly challenging subset of these lesions, given their overall low incidence and the high frequency with which some form of multimodality treatment may be required for complete obliteration. In order to make an educated decision regarding therapy, a thorough understanding of the natural history is needed, but not always available. In the case of intracranial AVM, a combination of retrospective and prospective studies have yielded a generally accepted bleed risk of 2% to 4% per year with an associated neurological morbidity of 20% to 30% and mortality of 10% to 30% with each bleed.\(^1\)\(^{–}\)\(^12\) Unfortunately, all of these reports constitute Level V evidence and suffer from the usual methodological problems of case series, including selection bias, treatment bias and inconsistent follow-up.

In this issue of Stroke, Choi et al\(^13\) update these outcome statistics using data prospectively entered into the Columbia AVM Databank from 1989 to 2004. The authors examine the clinical outcome after first and recurrent hemorrhage in patients with untreated cerebral AVM. Rankin Score (RS) and National Institutes of Health Stroke Score (NIHSS), both acutely and after follow-up, were collected. Outcome results were also stratified according to the anatomical location of the initial hemorrhage (nonparenchymatous or parenchymatous). In addition, outcome after parenchymatous hemorrhage was compared with outcome data from survivors of non–AVM-related intracerebral hemorrhage from the Northern Manhattan Study (NOMAS). The study was not designed to provide data regarding the de novo risk of AVM hemorrhage or the risks of treatment.

After their initial hemorrhage, the majority of patients (72%) had an RS of \(\geq 2\) and 61% of patients had NIHSS scores of 0 or 1. In a multivariate analysis, parenchymatous AVM hemorrhage was an independent predictor of an unfavorable outcome (NIHSS score \(\geq 2\)), whereas age, gender, race, and AVM size showed no significant effect. Follow-up data were provided only for untreated patients and for treated patients up to the last available assessment before treatment. A median of 55 days (mean of 657 days) follow-up was achieved. Neurological outcome in terms of NIHSS was similar after a second hemorrhage. However, disability as measured by RS was significantly worse (RS mean 2.7±1.4 versus 2.0±1.4) after a second hemorrhage. One patient died after a recurrent bleed, but 40% demonstrated some clinical improvement. In comparison to NOMAS patients, AVM patients had a significantly better clinical outcome (median NIHSS 1 versus 12). However, AVM patients were also significantly younger and more likely to be white.

Although a valiant effort, Choi et al’s\(^13\) report suffers from many of the same methodological concerns as previously published AVM natural history data, with selection/referral bias and treatment bias being perhaps the most significant. As the authors point out, there was an average delay of 7 days between the index event and first evaluation among the AVM patients. This speaks to the potential for systematic referral bias seen in most case series from tertiary care centers. From the initial RS and NIHSS scores it would appear that those patients considered viable were certainly transferred, but it is quite conceivable that other more devastated patients may not have been referred. Follow-up data were provided only for untreated patients and for treated patients up to the last available assessment before treatment. Because follow-up for treated patients is censored at the time of treatment, it becomes important to know the selection criteria used for treatment. Without this information it is not possible to determine whether treated patients were considered to be at substantially higher risk for rebleeding, whether they were simply the ones with the most treatable/accessible lesions, or both. Depending on the bias in this area, results may be influenced in either direction.

Regardless of one’s view of the study biases, the documented rebleed rate and clinical outcome remain concerning. In the short follow-up period examined (average 1.8 years), the crude annual rebleed rate was 7% and disability was significantly increased after subsequent hemorrhage. If one takes the average age of the AVM population from this study of 37 years of age and uses a life expectancy of 39 additional years (Period Life Table, Actuarial Publications, http://www.ssa.gov/OACT/STATS/table4c6.html), the cumulative risk of rehemorrhage is 94%. Even if one assumes the risk of rebleeding stabilizes at 4% per year, the cumulative risk of rehemorrhage over 39 years is 78%. Clearly, this does not suggest a benign future for patients with a history of AVM-related intracranial hemorrhage. In terms of clinical status, a careful examination of the outcome information provided is crucial. Of the 2 “outcome” measures provided, it is the RS that provides the most critical information. After all, it is the patient’s disability, or lack thereof, which will determine their functional status, not their neurological deficit per se. As
such, a good outcome (RS ≥2) in 72% of patients after incident hemorrhage translates into moderate to severe disability in 28% of patients. This number increases to 33% at 30 days and 45% after recurrent hemorrhage. These numbers are well in line with previously published studies and suggest a significant proportion of patients will experience a pronounced reduction in their functional status.

Finally, the comparison of AVM hemorrhage morbidity and mortality with that of intraparenchymal hemorrhage is troublesome. As the authors mention, patients in the NOMAS group were considerably older and of a different racial make-up. Obviously, age is a well-known risk factor for poor outcome from just about any disease, and cerebrovascular disorders are no exception. With age also comes medical comorbidities, and unfortunately no data regarding medical comorbidities was available. Although controversial and sometimes of doubtful clinical significance, various studies have also reported a worse outcome among blacks and Hispanics (a large segment of the NOMAS population) after ischemic and/or hemorrhagic outcome among blacks and Hispanics (a large segment of the NOMAS population) after ischemic and/or hemorrhagic stroke.\(^\text{14}\) As the authors correctly emphasize, any difference in outcome may be explained solely on the basis of non–AVM-related factors. In the end, the use of univariate analysis, which does not control for potentially significant covariates, such as age, gender, medical comorbidities and race, does not yield a meaningful result.

Although the risks of intervention and the natural history of asymptomatic AVM are beyond the scope of the current report, these are the critical and contentious variables that must be included in the continuing debate regarding the treatment of asymptomatic cerebral AVM. The A Randomized Trial of Unruptured Brain AVMs (ARUBA) study purports to promise a definitive answer to these questions. The study plans to randomize patients with unruptured AVM between medical management and “best” intervention. However, although a prospective, randomized, controlled trial (PRCT), it is unlikely that this study will provide an adequate answer. As designed, ARUBA is subject to many of the same methodological issues common to most PRCTs. Selection bias remains a major challenge, and in a disease such as cerebral AVM with a long history of established treatment patterns, the inclusion of high-volume, high-success treatment centers and the randomization of an adequate representation of lesions with various risk profiles will be difficult. Without such representation, the external validity of this trial is threatened. The heterogeneity of cerebral AVM leads to further difficulties, especially when combined with the various multimorbidity treatment combinations that may be used as the “best” intervention. Adequately controlling for all the necessary covariates will likely render the study underpowered to detect a significant difference at only 5 years. While the use of a 5-year end point is typical of PRCTs of this type, the relevance of such a short time period to clinical decision-making in a disease that may play out over 20-plus years is at best unclear and at worst nonexistent. Undoubtedly, ARUBA will provide clinicians with new information, but the scope and applicability of this information will likely be much more limited than first anticipated.

Ultimately, as with any disease, and most certainly with one in which the patient is asymptomatic and future morbidity is uncertain, whenever intervention is contemplated the risks and benefits of treatment must be carefully weighed against those of observation alone. For cerebral AVM a considerable body of evidence exists to support treatment in many patients, even when asymptomatic.\(^\text{15}\) That this evidence is not prospective and not randomized does not support the conclusion that the treatment of asymptomatic AVM is “experimental.”\(^\text{16}\) Unfortunately, not all clinical questions can be answered by PRCTs, and the lack of such trials in established areas of therapy simply serves to illustrate the complexity of the disease process being evaluated. In the case of intracranial AVM, the results presented here by Choi et al.\(^\text{13}\) add to this ongoing debate. However, even though the mortality of AVM hemorrhage reported is relatively low, a one-third incidence of moderate-to-severe disability at 30 days should not lead anyone to conclude that intracranial AVM are clinically benign entities.

References

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