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Diagnosis and evaluation of intracranial arteriovenous malformations

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Abstract

Background:

Ideal management of intracranial arteriovenous malformations (AVMs) remains poorly defined. Decisions regarding management of AVMs are based on the expected natural history of the lesion and risk prediction for peritreatment morbidity. Microsurgical resection, stereotactic radiosurgery, and endovascular embolization alone or in combination are all viable treatment options, each with different risks. The authors attempt to clarify the existing literature's understanding of the natural history of intracranial AVMs, and risk-assessment grading scales for each of the three treatment modalities.

Methods:

The authors conducted a literature review of the existing AVM natural history studies and studies that clarify the utility of existing grading scales available for the assessment of peritreatment risk for all three treatment modalities.

Results:

The authors systematically outline the diagnosis and evaluation of patients with intracranial AVMs and clarify estimation of the expected natural history and predicted risk of treatment for intracranial AVMs.

Conclusion:

AVMs are a heterogenous pathology with three different options for treatment. Accurate assessment of risk of observation and risk of treatment is essential for achieving the best outcome for each patient.

Keywords: Complications, intracranial arteriovenous malformation, microsurgical resection, technique

INTRODUCTION

Brain arteriovenous malformations (AVMs) present a technical challenge in their management. Despite advances in endovascular, radiosurgical, and microsurgical treatment modalities, these vascular lesions are a heterogeneous pathological entity, varying in their size, shape, location, and hemodynamics, with behavior that is often difficult to predict with or without intervention. The goal of AVM treatment is to alleviate the risk of future hemorrhage without incurring treatment-related morbidity. Microsurgical resection remains the treatment of choice for carefully selected AVMs because it immediately and definitively excludes the AVM. In cases where microsurgical resection is accompanied by a high risk of morbidity, radiosurgery is an option to consider; however, radiosurgical cure takes years, during which risk of rupture remains. Endovascular treatment is available in many centers, but cure is difficult to achieve, so it is most useful as a surgical adjunct. The results of the Randomized Trial of Brain Unruptured AVMs (ARUBA) trial have placed intervention for unruptured AVMs under more intense scrutiny.[48] Therefore, careful patient selection and meticulous and experienced planning and technique are critical for the continuation of any intervention as a viable treatment option. Prudent management of intraoperative and postoperative complications is also imperative for achieving acceptable patient outcomes. In this article, we review our experience in diagnosis and evaluation of AVMs with a specific emphasis on discussion of grading systems used to assess the periprocedural risks associated with intervention.

Diagnosis

Most patients present for neurosurgical evaluation after an acute hemorrhage or after an AVM was found on imaging during the work-up of other complaints such as seizures, focal neurologic deficit, or headaches.[29] Increasingly, AVMs are found incidentally on imaging obtained for other reasons.[50] Once an AVM is identified, all patients receive a thorough preoperative evaluation including history and neurologic exam. Additional imaging is obtained as needed, so each patient has a computed tomography (CT), a magnetic resonance imaging (MRI), and a catheter angiogram. The most important imaging modality for thorough evaluation of an AVM is the preoperative angiogram, which contains a wealth of information about the anatomy and hemodynamics of a given lesion. Once all information is gathered, AVMs at our institution are presented at a multidisciplinary cerebrovascular conference. The AVM is characterized and graded according to both the Spetzler–Martin[71] and supplementary grading scales.[41] The combined grade is used to guide treatment recommendations. In patients who are poor surgical candidates because of comorbidities, or patients who wish to avoid surgery, stereotactic radiosurgery (SRS) is considered and the AVM is graded on the Pittsburgh modified radiosurgery-based AVM grading scale.[57] Selected lesions may be assessed for curative embolization; however, endovascular intervention is more commonly used as an adjunct to microsurgery or SRS. Following review at the cerebrovascular conference, the consensus recommendations are presented to the patient and family, who make the ultimate decision.

Appropriate patient selection is paramount to maximize desirable outcomes after AVM treatment. Selection of candidates for intervention requires accurate assessments of both the expected natural history of a given AVM and the risk of its treatment. The risk of morbidity and mortality for treatment is tolerable only if matched or exceeded by the AVM's future risk of hemorrhage.

Natural history

Our understanding of the natural history of brain AVMs has been repeatedly refined as larger series with longer follow-up and more nuanced statistical analysis have become available.[10,13,23,24,25,28,53,76,77] Authors of initial series as far back as the middle of the 20th century reported relatively low annual hemorrhage rates (<5%), with morbidity and mortality from AVM hemorrhage reported as high as 40% and 29%, respectively.[10,76,77] As early as 50 years ago, some investigators reported the heterogeneity of the behavior of AVMs, and differences in their risk of hemorrhage.[76,77]

Two recent meta-analyses have looked at composite findings from all existing natural history studies[25] and several large database cohorts.[35] Gross *et al*.[25] evaluated the most reliable existing studies and summarized our current

understanding of the risk of AVM observation, finding an overall annual hemorrhage rate of 3.0%, stratified by hemorrhage status into 2.2% per annum for unruptured AVMs and 4.5% for ruptured lesions. Similarly, Kim *et al*.[35] analyzed the data from four large cohorts of AVM patients and found an overall hemorrhage rate of 2.3% per year, 4.8% per year for ruptured AVMs, and 1.3% per year for unruptured lesions.

As expected, hemorrhagic presentation was the largest risk factor for a subsequent hemorrhage in both meta-analyses. Architectural risk factors differed between the two studies with Gross *et al*. finding increased hemorrhage risk associated with deep AVM location, exclusively deep venous drainage, and associated nidal or feeding artery aneurysms. Kim *et al*.[35] found no increased hemorrhage risk for any of these characteristics, although deep venous drainage trended toward increased risk. Although previous studies have suggested small AVM size may be associated with increased hemorrhage risk, this is an inconsistent finding, and neither study substantiated this claim.[24,25,28,32,33,70,73] Both studies found a trend toward increased hemorrhage risk among women, and Kim *et al*. found a positive correlation between increased hemorrhage risk and age, with each decade of life increasing hemorrhage risk by about one-third. Risks attributable to ethnicity, smoking, family history, and pharmacologic anticoagulation are ambiguous.

This 1–2% annual risk of rupture for unruptured AVMs has been confirmed by both a prospective randomized trial[48] (2.2%) and a prospective population-based cohort study (1.5%).[1] Confirmatory studies of the natural history of ruptured AVMs are more difficult to obtain because observation of these lesions carries a higher risk (6–15% hemorrhage rate during the first year), so fewer such lesions are observed without intervention.[14,25,28,32,70] Combining these annualized rates with individual risk factors and patient life expectancy allows an estimation of lifetime hemorrhage risk. Quantification of lifetime risk has been attempted with the following formula[9,37]:

Rupture risk = 1 – (risk of no hemorrhage)$^{(\text{life expectancy})}$ and Rupture risk = 105 – patient age

There are certain limitations regarding the available natural history studies. First, most studied AVMs were identified because they were symptomatic (about half of them were due to hemorrhage and one-quarter due to seizures). Therefore, the applicability of these studies to the increasing number of truly incidental AVMs discovered via the increased use of neuroimaging is limited and their results may overestimate the risk of hemorrhage for truly asymptomatic lesions. Second, patients who appear to be at higher risk because of the presence of risk factors (e.g., associated aneurysms) would be disproportionately treated compared with patients who have less threatening lesions; this fact would, conversely, underestimate the risk of observation.

Assessment of surgical risk

For any patient, determining the potential reduction in hemorrhage risk achieved through intervention requires an evaluation of the risk of treatment-related morbidity. To this end, numerous AVM classification systems have been proposed without gaining widespread usage,[30,55,69,78] and although these earlier grading scales existed, the standard scale for estimation of surgical risk since its publication has become the five-grade Spetzler–Martin system.[71] Using a five-point scale, expected surgical outcomes are stratified based on the size (<3 cm = 1 point, 3–6 cm = 2 points, >6 cm = 3 points), location (in eloquent brain = 1 point, not in eloquent brain = 0 points), and venous drainage pattern (deep venous drainage = 1, no deep venous drainage = 0). This system has since been externally validated,[15] and upon subsequent evaluation of this system, Spetzler and Ponce condensed it into three groups of AVMs[72]: Low surgical risk (Spetzler–Martin grade I-II) for which surgical management is recommended,[49] intermediate risk (Spetzler–Martin grade III) for which multimodality treatment is recommended, and high risk (Spetzler–Martin grade IV-V) for which observation is usually recommended, excepting patients with recurrent hemorrhage, progressive neurological deficit, or medically intractable seizures caused by the AVM.[26]

One of the criticisms of the Spetzler–Martin scale is its assessment of the grade III intermediate risk group. The largest and most heterogeneous of the Spetzler–Martin groupings, grade III consists of four different types of AVMs: small lesions with deep venous drainage in areas of eloquence (S1V1E1), medium-sized lesions with deep venous drainage (S2V1E0), medium-sized lesions in areas of eloquence (S2V0E1), and large noneloquent lesions without deep venous drainage (S3V0E0). Significant effort has been invested in further teasing out a threshold within this grade III population to distinguish low-risk from high-risk subgroups.[42,54] Work by one of our senior authors (MTL) showed

that the S1V1E1 subtype shows risk of surgical morbidity similar to that of Spetzler–Martin grade I and II AVMs, whereas the S2V1E0 subtype shows risk of surgical morbidity similar to traditional aggregate values of surgical risk for Spetzler–Martin grade III AVMs. The S2V0E1 subtype predicts surgical morbidity similar to Spetzler–Martin grade IV and V AVMs, and these lesions are typically treated conservatively. The S3V0E0 subtype is rare and surgical risk associated with these lesions is not well established.[42]

Another criticism of the Spetzler–Martin system is its lack of deference to patient characteristics and hemorrhage status. In 2010, the supplementary grading scale was introduced as an adjunct to the Spetzler–Martin system.[41] This scale allows further refinement and better predictive accuracy, while still accessible and easy to use. In this 10-point system, points are assigned based on age (<15 = 1 point; 15–40 = 2 points; >40 = 3 points), diffuseness of the nidus (diffuse = 1 point; compact = 0 points), and hemorrhage status (hemorrhage = 0; no hemorrhage = 1). These points are then added to the traditional Spetzler–Martin grade (nidus size, eloquence of location, and venous drainage pattern). This supplement incorporates two critical surgical risk factors that were previously not included in Spetzler–Martin grading: the increased risk of morbidity associated with a diffuse nidus and its deep perforating arterial feeders,[20] and the facilitation of surgery and decreased risk of subsequent morbidity following hemorrhagic presentation.[40] This supplement also includes a nonspecific surrogate for overall patient health status by taking the patient's age into account. Subsequent external validation and comparison of Supplementary scale to the traditional Spetzler–Martin scale and Spetzler–Ponce groupings has demonstrated the superiority of the Supplementary scale in surgical risk prediction.[36]

The Supplementary scale quantifies the surgical risk of stable or improved neurologic status versus a neurologic decrement or mortality. Rates of a poor outcome by Spetzler–Martin and Supplementary grade were as follows: Grades 2–3, 0%; grade 4, ~9%; grade 5, ~21%; grade 6, ~27%; and grades 7–10, ~40–60%. Although these grades have not been explicitly assigned a general treatment recommendation as in the three Spetzler–Ponce groupings, the more accurate and nuanced risk assignment allows better comparison with the natural history to determine the best treatment options. A rough division appears between grades 2–6 and 7–10, with the former acceptable for intervention and the latter for observation.[41]

Another grading scale is that of the University of Toronto Brain AVM Study Group. After analyzing their data, they developed a nine-point grading scale assessing three criteria assigned points based on their relative importance (eloquence = 4 points; diffuseness = 3 points; and deep venous drainage = 3 points). This scale discriminates the percentage probability of incurring an early disabling neurologic outcome as follows:

- Low Risk (0–2 points) =1.8%
- Moderate Risk (3–5 points) =17.4%
- High Risk (6–7 points) =31.6%
- Very High Risk (>7 points) =52.9%.[69]

Interestingly, this grading scale has a higher predictive ability (area under receiver operating characteristic [ROC] curve = 0.79) than the 10-point Supplemented Spetzler–Martin scale (area under ROC curve = 0.78), and the original Spetzler–Martin scale (area under ROC curve = 0.69).[41,69] Despite its simplicity and superior predictive ability, the University of Toronto grading scale has failed to become widely used, likely because the use of the Spetzler–Martin scale has become so commonplace.

Assessing risk of stereotactic radiosurgery

In the treatment of brain AVMs, SRS has emerged as an alternative to microsurgery with successful obliteration occurring about 80% of the time[8,11,22,31,43,45,52,60,61,64,66,67,75,84,85] In patients with contraindications to surgery or for AVMs deemed too risky for surgery, SRS may be a safe and effective means of obliterating an AVM.[74] However, unlike the immediate efficacy of microsurgery, the results of SRS evolve over several years, during which a risk of hemorrhage persists. Evaluating the risk of morbidity of SRS in the treatment of AVMs requires analysis of AVM characteristics that influence the ability of SRS to safely obliterate the AVM nidus without adverse effects of radiation such as new neurological deficits or radiation necrosis. Grading scales intended for predicting microsurgical risk such as the Spetzler–Martin scale are not useful predictors of patient outcomes following SRS for the

treatment of AVMs.[58] For example, three-dimensional AVM volume is an important characteristic to consider as it significantly influences obliteration rates when providing treatment with SRS. The Spetzler–Martin scale assesses size, but does not adequately address volume, limiting its utility for predicting outcomes after SRS.

To this end, Pollock and Flickinger published the radiosurgery-based grading system (RBGS) in 2002.[58] Although previous publications reported methods for predicting the likelihood of nidus obliteration after radiosurgery,[34,65] the RBGS predicts the likelihood of both nidus obliteration and treatment-related morbidity after single-session SRS through the use of a formula incorporating patient and AVM variables.[58] The predictive variables are AVM volume, patient age, and AVM location, and they are assigned relative importance as represented in the following equation[58]:

AVM score = (0.1) (AVM volume) + (0.02) (patient age) + (0.3) (AVM location). AVM volume was calculated from MR studies (volume=π/6 (length) (width) (height), and frontal or temporal lesions were assigned a location value of 0, parietal, occipital, cerebellar, intraventricular, or corpus callosal lesions were assigned a location value of 1, and basal ganglia, thalamic, or brain stem lesions were assigned a location value of 2. Applying the formula to a patient series from another institution, this study found that 100% of patients with an AVM score ≤1 had an excellent outcome (defined as complete nidus obliteration without new or worsening neurologic deficit), whereas only 39% of those with an AVM score >2 had an excellent outcome.[58]

The RBGS has subsequently been externally validated with both gamma knife and linear accelerator-based SRS.[4,5,12,46,47,56,59,60,68,86,87] Upon further evaluation of the RBGS, Pollock and Flickinger simplified the location variable of the formula from a three-tiered to a two-tiered variable by assigning 1 point for lesions in the basal ganglia, thalamus, or brainstem and 0 points for all other locations. The formula was slightly modified to appear as follows[57]:

- AVM score = (0.1) (AVM volume) + (0.02) (patient age) + (0.5) (AVM location).

This simplification has also been externally validated and did not significantly detract from the accuracy of the grading system in predicting morbidity after SRS for the treatment of brain AVMs.[57,81,83]

An alternate grading system, the Virginia radiosurgery AVM scale, was introduced by Starke *et al*. in 2013. This scale was developed based on a series of 1012 patients treated at the University of Virginia and was intended to address the mathematical complexity of the RBGS. It consists of three variables assessed on a 0–4 scale. AVM volume (<2 cm^3 = 0 points; 2–4 cm^3 = 1 point; >4 cm^3 = 2 points), eloquent location (eloquent location = 1 point; noneloquent location = 0 points), and history of hemorrhage (hemorrhage = 1, no hemorrhage = 0) were found to be the predictive variables; 83% of patients with a cumulative score of 0 experienced a favorable outcome, defined as complete AVM obliteration without posttreatment hemorrhage or permanent SRS-associated symptoms. Among patients with a score of 1, 2, 3, or 4, a total of 79%, 70%, 48%, and 39%, respectively, experienced a favorable outcome. This scale was determined by its developers to be a better predictor of outcome than the RBGS.[74] The group at the University of Virginia has since confirmed these findings in subsequent studies,[17,18,19] but this scale has yet to be externally validated.

Assessing risk of endovascular embolization

Due to its traditionally low rates of obliteration as the sole treatment modality, endovascular embolization has occupied an adjunctive role in the treatment of brain AVMs, often used to make microsurgery or SRS easier or safer. In 2011, a meta-analysis of treatment modalities for brain AVMs reported an obliteration rate of 13% for embolization.[79] In a more recent report, long-term curative embolization was achieved in 50.3% of patients (mean follow-up was 47 months).[62] A smaller series of highly selected lesions reported an even higher rate of successful curative embolization (96%).[80] In the study by van Rooij *et al*., small and medium, superficially located AVMs with a small number of accessible feeding arteries from the same vascular territory, a compact nidus, and easily delineated draining veins were selected for curative embolization performed in one procedure. Although the results of this report were quite good, the highly selective nature of this series renders the results less applicable to AVMs in general, and suggests a subset of AVMs amenable to curative embolization.[80] This study also discusses the technique of nidal embolization in which the microcatheter is positioned just beyond the most distal aspect of the feeding artery so the embolisate is deposited into the AVM nidus rather than the feeding artery. This technique was previously described by others[2,6,16,38,51] and deserves mention as it allows for obliteration of nidal compartments rather than feeding

arteries. This allows the systematic reduction of nidal size without the risk of subsequent recruitment of additional feeding arteries and persistence of the AVM.[38] This technique makes possible the staged treatment of high-grade AVMs, potentially resulting in cure. Reducing the AVM grade also makes it amenable to surgical resection or radiosurgery. Unfortunately this technique is difficult to master, and even in very skilled hands is not always possible due to distal location of the nidus or tortuosity of the vessels.[16] In practical terms, nidus embolization is not reliably available in our centers, so in our experience, embolization primarily serves as an adjunct to microsurgical resection or SRS.

Evaluating the risk of endovascular embolization for brain AVMs has traditionally been based on Spetzler–Martin grading; however, as with SRS, the applicability of the microsurgically oriented Spetzler–Martin scale to risk-assessment for endovascular embolization has been drawn into question.[27] In 2001, Willinsky *et al*.[82] outlined a grading scale (0–6 points) for small AVMs based on angioarchitecture. The type of nidus (fistula = 0 points, <1 cm nidus = 1 point, 1–3 cm nidus = 2 points), type of feeding arteries (cortical = 0, perforator or choroidal = 1), number of feeding arteries (single = 0, multiple = 1), and number of draining veins (single = 0, multiple = 1) were all assessed, and a score was calculated for each AVM. They found that the AVMs with the most simple angioarchitecture (0–2 points) were most likely to achieve obliteration through curative embolization with low permanent morbidity (2.5%). In 2010, Feliciano *et al*.[21] published a proposal for a new five-point grading scale based on variables they determined through analysis of existing literature to increase the risk of morbidity during and after embolization.[21] These variables include the number of feeding vessels (<3 vessels = 1 point; 3–5 vessels = 2 points; >5 vessels = 3 points), eloquent location (eloquent = 1 point; noneloquent = 0 points), and presence of arteriovenous fistula (no AVF = 0 points; AVF = 1 point). Although this scale is based on a thorough review of existing literature, its applicability is unclear as it has not yet been validated by further studies.

In addition to attempted cure, embolization may be utilized preoperatively to decrease blood flow through the AVM and subsequent blood loss during surgery or to occlude deep arterial feeders that may be difficult to control during surgery. Embolization can facilitate SRS by decreasing the volume of the nidus and is thought to increase the likelihood of obliteration after SRS. Embolization can also be used to treat a vascular steal phenomenon caused by an AVM with a high-flow shunt, potentially alleviating a progressive neurologic deficit.[7,26,39,44,63] It is our opinion that in order to maximize outcomes, the goal of a specific endovascular intervention for AVMs must be clearly stated. Furthermore, the overall outcomes of embolization, including achievement of the predetermined goals of treatment as well as complications, must be analyzed in future studies. Only then can a true risk–benefit ratio be estimated for embolization of a given AVM. We avoid overembolization of AVM feeding arteries as this maneuver leads to hypertrophy of deep white matter feeders that cause a significant increase in technical complexity of microsurgical intervention. This issue is further discussed in part 2 of this series (unpublished manuscript submitted as companion to this manuscript).

DISCUSSION

Microsurgical resection remains the gold standard for AVM treatment, providing immediate angiographic cure and protection from future AVM rupture. Evidence in favor of SRS as an effective alternative to surgery continues to mount. Endovascular embolization is not typically used for AVM cure, but as techniques and selection criteria improve, reported nidus obliteration rates are improving as well. Multimodality and mulitidisciplinary approaches involving all the latter options to AVM management is ideal. Despite three available treatment modalities, correct decision-making regarding AVM treatment in certain AVMs often remains dubious. Occasionally, the decision is straightforward. At one end of the spectrum, patients with low-grade AVMs have low treatment-associated risk, and given a long life expectancy, a significant lifetime risk of hemorrhage. For these patients, the low risk of periprocedural morbidity is outweighed by the high lifetime risk of hemorrhage, and curative treatment is most appropriate. Conversely, patients with high-grade AVMs have a high risk of treatment-related morbidity. In a patient with a relatively short life expectancy, these AVMs harbor a low natural history risk of hemorrhage, and observation is clearly a better option.

The difficult decisions lie between the above extremes. For patients with lesions predicting a moderate lifetime risk of hemorrhage and a moderate risk of treatment-related morbidity, the appropriate management is not clear-cut, and in light of the ARUBA trial,[48] decision-making regarding these lesions is likely to be increasingly scrutinized for unruptured AVMs. Although the ARUBA investigators stated that the risk of morbidity from treatment outweighs the

natural history of unruptured AVMs, this conclusion was based on only 2 years of follow-up and may not adequately assess the risk of AVM rupture. Longer follow-up is needed to truly evaluate this assertion. Many lesions are Spetzler–Martin grade III AVMs with a supplementary scale grade of 6 or 7, falling near the estimated threshold for safe surgical resection.[41] Likewise, these lesions fall between 1 and 2 on the RBGS.[58] For these lesions in the middle range, treatments are often multimodality therapies and individually tailored treatment plans devised by a team of specialists in conjunction with the patient. Unfortunately, the only randomized trial for AVM treatment did little to provide a standard course of management for patients at any level of risk.[3,48]

It should be noted that this is a disease of the relatively young as the average age at diagnosis of an AVM in a recent natural history meta-analysis was 33.7 years,[25] imparting a life expectancy of 45–49 years (per U.S. Social Security Administration Actuarial Life Table available at http://www.ssa.gov/OACT/STATS/table4c6.html), or a lifetime hemorrhage risk of ~60%. More intervention risk is acceptable following rupture: That same 33-year-old patient now has a >87% hemorrhage risk with 6–15% of that risk in the first year, and a 60-year-old patient now has a 61% lifetime risk of rupture.[40] Appropriate surgical patient selection therefore involves the evaluation of each individual's vascular and clinical risk factors, both for treatment and for observation by an experienced team of cerebrovascular specialists with access to multimodality treatment, including endovascular and radiosurgical options. Often the decision to not operate is the most difficult decision to make.

Footnotes

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