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Hemorrhage Rates and Risk Factors in the Natural History Course of Brain Arteriovenous Malformations

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Abstract

Brain arteriovenous malformations (AVMs) are abnormal connections of arteries and veins, resulting in arteriovenous shunting of blood. Primary medical therapy is lacking; treatment options include surgery, radiosurgery, and embolization, often in combination. Judicious selection of AVM patients for treatment requires balancing risk of treatment complications against the risk of hemorrhage in the natural history course. This review focuses on the epidemiology, hemorrhage risk, and factors influencing risk of hemorrhage in the untreated natural course associated with sporadic brain AVM.

Keywords

Arteriovenous malformation; Epidemiology; Intracerebral hemorrhage; Natural history; Risk factor; Survival; Treatment

Introduction

Brain arteriovenous malformations (AVMs) are comprised of a complex tangle of abnormal blood vessels called the nidus, not clearly artery or vein and lacking a true capillary bed. The hallmark feature is shunting of blood directly from the arterial to venous circulations detected by cerebral angiography. There is usually high flow through the feeding arteries, nidus, and draining veins, which may result in rupture and intracranial hemorrhage, the most

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Compliance with Ethics Requirement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from AVM patients included in studies from UCSF and KPNC. All other cited clinical studies describe ethical standards in cited manuscripts.

Conflict of Interest

W. Caleb Rutledge, Nerissa U. Ko, Michael T. Lawton, and Helen Kim declare that they have no conflict of interest.

This review is dedicated in memory of William L. Young, MD, for his unwavering dedication, enthusiastic mentorship, and probing science into understanding the pathogenesis of brain AVMs to ultimately improve the lives of people diagnosed with this disease.

severe complication of an AVM. Patients commonly present with headaches, seizures and focal neurologic deficits. Although patients with AVM rupture and intracranial hemorrhage may have better outcomes than patients with intracerebral hemorrhage from other causes, AVM rupture is still associated with significant morbidity and mortality [1]. In observational studies, the mortality rate after intracranial hemorrhage from AVM rupture ranges from 12%–66.7% [1, 2], and 23%–40% of survivors have significant disability [3]. Current treatment decisions are based on carefully weighing the risk of spontaneous hemorrhage in the natural history course against the risk of invasive treatment. This review focuses on the epidemiology, hemorrhage risk, and factors influencing risk of hemorrhage associated with sporadic brain AVM. We performed a PubMed search using the following keywords: Arteriovenous malformation; Epidemiology; Intracerebral hemorrhage; Natural history; Risk factor; Survival; Treatment.

Epidemiology

Brain AVMs are a leading cause of hemorrhage in children and young adults, although they can cause other morbidities such as seizures, focal neurological deficits, and headaches. Cases present at all ages, with a mean age in the third to fourth decade of life. The population prevalence of brain AVM is estimated to be 10–18 per 100,000 adults [4, 5], with a new detection rate (i.e., incidence) of approximately 1 per 100,000 person-years [6–8]. Overall mortality rates in AVM patients range from 0.7%–2.9% per year [9].

Clinically, brain AVMs are technically challenging and resource-intensive to manage with the available therapeutic modalities (microsurgical resection, stereotactic radiosurgery, or endovascular embolization) and often require multi-modal therapy. Treatment risks (primarily permanent neurological deficits and/or mortality) must be weighed carefully against the risk of spontaneous hemorrhage in the natural history course. There is no primary medical therapy available to treat or slow the progression of the disease. Thus, clinical studies have focused on characterizing hemorrhage rates and identifying the factors that influence these rates in brain AVM patients.

Hemorrhage Rates

The majority of clinical studies determining hemorrhage rates in brain AVM patients come from single referral centers, although there have been a few defined population-based studies [7, 10, 11]. Estimates range from 2% to 4% per year for all AVMs, with generally higher rates in the first year after presentation and in those who initially present with a hemorrhage [3, 10–19]. For unruptured brain AVMs, the hemorrhage rate is around 1%–3% per year [11, 16–18]. A recent meta-analysis of nine natural history studies including 3,923 patients and 18,423 patient-years of follow-up yielded an annual rate of hemorrhage of 3.0% (95% CI=2.7–3.4%) overall, 2.2% (95% CI=1.7–2.7%) for unruptured AVMs, and 4.5% (95% CI=3.7–5.5) for ruptured AVMs [20].

The majority of AVM natural history studies determine hemorrhage rates using Kaplan-Meier survival analysis methods, starting the time-at-risk after diagnosis or study enrollment but before any invasive treatment. This method is the most valid and assumption-free as patients are prospectively followed for hemorrhage events [21]. However, a few studies

have assessed risk beginning at birth, assuming a constant lifetime risk of hemorrhage [22, 23] or using a different statistical model [24]. We quantitatively compared these two approaches for assessing hemorrhage rates in *unruptured* AVM patients using data from 1,581 AVM patients from Northern California, and found that hemorrhage rates were similar for both the traditional diagnosis-to-hemorrhage timeline (1.17%, 95% CI=0.89%–1.53%) and the birth-to-diagnosis timeline (1.27%, 95% CI=1.18%–1.36%), despite differences in survival curve methodology [21]. Interestingly, we achieved virtually identical survival curves by shifting the birth-to-diagnosis timeline by 10 years, suggesting a point at which hemorrhagic behavior changes. Intriguingly, this is the time during childhood when hormonal changes are rampant; others have also noted an increased hemorrhage rate in women of childbearing age who harbor an AVM, again a period of changing hormone levels [24]. Regardless of the analytic approach used, hemorrhage rates from observational studies are fairly consistent across studies and populations, somewhat higher in referral populations and lower in population-based studies.

More recently, results from a randomized trial of unruptured brain AVM–ARUBA (http://clinicaltrials.gov/ct/show/NCT00389181) have been reported [25], corroborating hemorrhage rates from observational studies. All patients in the ARUBA trial received pharmacologic therapy for existing medical disorders and coexisting vascular risk factors, including diabetes and hypertension. For the 109 unruptured AVM patients randomized to the conservative medical management arm without interventional therapy, the rate of hemorrhage was 2.2% per year (95% CI=0.9%–4.5%) [25]. This rate is exactly the same as reported for unruptured brain AVM cases in a recent meta-analysis of nine cohort studies (2.2%, 95% CI=1.7%–2.7%) [20].

Risk Factors for Hemorrhage

Risk factors for hemorrhage have not been consistent across longitudinal studies, primarily due to small sample sizes and referral or selection biases of cases included. However, identification of risk factors are important as the risk of hemorrhage can vary widely from 0.9% to 34.3%, depending on the number of concomitant risk factors a patient carries [16]. Further, in light of recent ARUBA trial findings demonstrating significantly better stroke and mortality outcomes in unruptured brain AVM patients randomized to conservative management over any interventional therapy (HR=0.27, 95% CI=0.14–0.54) [25], there is an even greater need to identify risk factors to stratify patients who would benefit most from treatment.

The strongest independent risk factor for hemorrhage in the natural history course of AVM patients is previous hemorrhage, with hazard ratios ranging from 2–5 compared to those who have not bled [3, 10, 11, 13, 16–19]. However, this risk factor does not help the approximately 50% of patients that present to medical attention without hemorrhage.

(1) Demographic factors

Some studies have noted an increased risk of hemorrhage in females [17, 24], although the majority of studies have not reported a significant gender effect. Race/ethnicity may play a role in influencing hemorrhage rates associated with AVM, as is the case for other stroke

types. In a large combined cohort from UCSF and Kaiser Permanente-Northern California (KPNC), Hispanic AVM patients were at approximately two-fold increased risk of hemorrhage compared to Caucasians (HR=1.9, 95% CI: 1.1–3.3) [11]. Age has been proposed as a risk factor for hemorrhage, with some studies showing older age [16] and others showing younger age [17] associated with higher risk of hemorrhage. In our UCSF-KPNC series, we demonstrated that children with brain AVMs are more likely to present initially with a bleed, but the risk of subsequent hemorrhage was not increased compared to adults [26]. In a recent individual patient data meta-analysis of four large AVM cohorts participating in the Multicenter AVM Research Study (MARS), increasing age (HR=1.34, 95% CI=1.17–1.53) was found to be an independent risk factor for subsequent hemorrhage (unpublished data).

(2) Angioarchitectural factors

Angiographic characteristics of the AVM lesion are important predictors of outcome after treatment. However, in the natural history course, results have not been as consistent likely due to variability in interpretation of imaging studies or a weaker association of anatomic factors with hemorrhage [11].

Deep venous drainage pattern, deep location, and infratentorial AVM location are typically identified as significant univariate predictors of AVM hemorrhage, although these factors do not necessarily stay significant in multivariable models [15–18]. AVM size is more controversial, with most studies reporting no association with hemorrhage risk in either univariate or multivariable models. Some studies have reported that small AVM size (<3cm) is associated with increased risk of hemorrhagic presentation [17, 27, 28], whereas larger AVM size (>5cm) has been associated with increased risk of subsequent hemorrhage [15, 18, 29].

Coexisting arterial aneurysms are not uncommon in AVM patients, and could additionally increase the risk of intracranial hemorrhage. In our series, 34% of AVM patients had associated aneurysms defined as flow-related aneurysms or intranidal aneurysms [30]. The relationship of aneurysms with hemorrhage is complicated. Several studies have reported an increased risk of hemorrhage in AVMs presenting with associated aneurysms, but the association does not remain significant for hemorrhage during the follow-up period [16, 19, 30, 31]. However, this risk factor bears attention because of the moderate effect size for associated aneurysms (HRs around 2) and the clinical importance of managing aneurysms in the context of AVMs.

(3) Genetic factors

Our group and others have had an interest in identifying genetic risk factors for both susceptibility and progression of AVM disease phenotypes. Even if the mechanism of AVM formation is unknown, the subsequent growth and behavior of the lesion may still be influenced by genetic variation and the genes affected can provide clues to the pathogenesis of the disease. Genetic factors for hemorrhage in AVM patients has been reported in three settings: presentation with hemorrhage [32, 33], new hemorrhage after diagnosis [34–36], and hemorrhage after treatment [37]. A promoter polymorphism in the interleukin-6 gene

(*IL-6* −174G>C) was associated with greater risk of clinical presentation with a bleed (OR=2.4, 95% CI=1.0–5.7), independent of small BAVM size, exclusively deep venous drainage, and demographic characteristics [32]. The high risk *IL-6* −174 GG genotype was later shown to be associated with the highest IL-6 mRNA and protein levels in AVM tissue [38]. Polymorphisms in the *EPHB4* gene, encoding a tyrosine kinase receptor involved in embryogenic arterial-venous determination, are also associated with increased risk of hemorrhage at initial presentation [33].

TNF-α −238G>A (HR=4.0; 95% CI=1.3–12.3; P=0.015) and *APOE* ε2 (HR=5.1, 95% CI=1.5–17.7, P=0.01) have been associated with increased risk of new hemorrhage in the natural history course of AVM cases [34, 35]. When examined together in a multivariate model, both the APOE ε2 and *TNF-α* −238 A alleles were independent predictors of hemorrhage risk [35]. In addition to their association with spontaneous hemorrhage in the natural, untreated course, both APOE ε2 and *TNF-α* −238 A alleles appear to confer greater risk for post-radiosurgical and post-surgical hemorrhage [37]. Finally, promoter variants in the proinflammatory cytokine gene, *IL-1β,* also appear to be associated with increased risk of new hemorrhage after diagnosis [36].

These findings suggest that variants in genes involved in inflammation or in structural integrity of blood vessels play a role in AVM rupture. The genetic findings are supported by expression studies in AVM-resected tissue [38–41] or in blood from AVM patients [42], and in animal models [43, 44]. Even in unruptured, previously un-embolized or untreated bAVMs, there is prominent infiltration of inflammatory cells and cytokine elaboration.

However, the majority of these genetic association results await replication in independent AVM cohorts. Because AVMs are rare, this poses considerable challenges for accruing sufficiently large sample sizes for replication that will require international collaboration. Further study is needed to clarify the importance of genetic findings, which may be explained by socio-economic and environmental factors, or a complex combination of these influences with genetics. It is interesting that no specific environmental or epidemiological risk factors have been identified in published AVM series, with the possible exception of essential hypertension [27].

(4) Novel risk factors

Silent microhemorrhages in *unruptured* brain AVM patients have been proposed as a novel risk factor for symptomatic hemorrhage [45]. Evidence of old hemorrhage on CT or MR (T1- or T2-weighted sequences) prior to diagnosis but unrelated to any hemorrhage at presentation was present in 6.5% of patients, was highly predictive of hemorrhagic presentation (OR=3.97; 95% CI: 2.1–7.5, P<0.001), and was an independent predictor of new hemorrhage in the natural history course of AVM patients (HR= 3.53, 95% CI=1.35–9.23, P=0.010). Furthermore, hemosiderin positivity in AVM tissue was found in 36.2% (29.6% in unruptured; 47.8% in ruptured; P=0.04) and was independently associated with hemorrhagic presentation (OR=3.64, 95% CI=1.11–12.00, P=0.034) in 79 AVM patients with both tissue and longitudinal data available. These results suggest that a subgroup of AVMs may be at higher risk of subsequent hemorrhage. In this regard, several groups have recently reported using ferumoxytol-enhanced MRI to non-invasively assess cellular

inflammation in cerebrovascular malformations; ferumoxytol is a superparamagnetic iron oxide nanoparticle ingested by macrophages [46]. Preliminary results in brain AVM patients are promising for identifying “unstable” lesions or those that are more prone to rupture [47]. Further studies are needed to clarify whether microhemorrhages can serve as a biomarker signaling increased risk of future hemorrhage.

Summary

In conclusion, AVMs are complex lesions that often require multi-modal therapy. Judicious selection of patients for treatment requires carefully balancing treatment complications against the risk of hemorrhage in the natural history course. The overall risk of hemorrhage is 2%–4% per year, but varies widely depending on the number of risk factors a patient carries. The rate of hemorrhage in unruptured patients is around 2% per year. Previous hemorrhage is the strongest and most reproducible risk factor for subsequent hemorrhage in almost all AVM natural history studies, whereas angiographic factors, such as deep venous drainage pattern, and deep or infratentorial AVM location, have not been consistently replicated. Novel risk factors, including genetics and presence of silent microlesional hemorrhage, have been proposed but require further studies. Individual patient data meta-analysis of existing longitudinal cohorts, such as that proposed in MARS, would provide an opportunity to obtain better estimates of risk factors for hemorrhage in the natural untreated course. Ultimately, development of a risk prediction tool for predicting natural history risk would aid clinical decision-making for AVM patients, similar to efforts that have been made for determining outcomes after AVM surgery, e.g., Spetzler-Martin grade [48, 49] and Spetzler-Martin-Supplemented score [50, 51].

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