Are There Genetic Influences on Sporadic Brain Arteriovenous Malformations?

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Abstract—The genesis of brain arteriovenous malformations remains enigmatic. We reviewed some pathways involving inflammatory and angiogenic signals that are amenable to the study of genetic single-nucleotide polymorphisms associated with the sporadic disease. Such study can yield insights into arteriovenous malformation pathogenesis and suggest possible fruitful approaches to developing medical therapy. Moreover, single-nucleotide polymorphisms identification would provide targets for risk stratification for planning clinical trials and eventually guiding management. (Stroke. 2004;35[supp 1]:2740-2745.)

Key Words: acute care ■ arteriovenous malformations ■ intracranial hemorrhages ■ polymorphism, single nucleotide

Brain arteriovenous malformations (AVMs) represent a relatively infrequent but important source of neurological morbidity in relatively young adults.¹ The basic morphology is of a vascular mass, called the nidus, that directly shunts blood between the arterial and venous circulation without a true capillary bed. There is usually a high flow through the feeding arteries, nidus, and draining veins. The nidus is a complex tangle of abnormal, dilated channels, not clearly artery or vein, with intervening gliosis.

Clinical Behavior
Prevention of new or recurrent intracranial hemorrhage (ICH) is the primary rationale to treat AVMs, although seizures, mass effect, and headache can cause morbidity. Treatment by surgery or radiosurgery, often with adjunctive embolization, can be curative.

The risk of spontaneous ICH has been estimated in retrospective observational studies to range from ~2% to 6% per year, probably higher in the first year, but some recent estimates are higher.¹ Most of the data are from studies of first ICH subsequent to diagnosis; there is a gap in knowledge for rates applicable to ICH after first subsequent hemorrhage.

Although somewhat controversial, there is very strong evidence that clinical presentation with ICH appears to be the strongest risk factor for future hemorrhage (Figure 1), but there are a number of other risk factors proposed, including exclusively deep venous drainage pattern and associated aneurysms; less certain are other factors such as patient age, lesion size, and location.¹²

It is unknown whether increased risk of subsequent hemorrhage in those patients who present initially with ICH represent a different biological subtype. It may be that an AVM nidus "matures" until some critical event or transformation occurs, after which ICH occurs, rendering it more susceptible to rupture. Whether this state of increased risk continues in perpetuity is unclear (Figure 2).

Need for Nonsurgical Management Options
The risk of aggressive interventional therapy may outweigh the risk of nonspecific medical management in certain cases. Definitive treatment is resource intensive and, for many lesions, entails considerable risk.

To balance risk of intervention with natural history risks, current evidence points to a need for identifying which patients have the greatest risk of spontaneous hemorrhage. Not only is the risk of future ICH unclear, but the associated morbidity of AVM hemorrhage is controversial.³

The most valid way to obtain such important data would be a randomized, controlled clinical trial. A large, international multicenter trial has been proposed recently: ARUBA (a randomized trial of unruptured brain AVMs; JP Mohr, personal communication, 2004). ARUBA will randomize patients with unruptured brain AVMs into medical and interventional management if they are deemed eligible for interventional treatment. The null hypothesis of ARUBA is that for unruptured brain AVMs, there is no difference between interventional and conservative management. ARUBA will help settle the issue of treatment for unruptured lesions but will also provide crucial natural history data.

There is also a need to develop specific medical therapies. In current practice, a significant fraction (≈20%) of patients may not be candidates for definitive resection.⁴ Radiosurgical
treatment, useful for smaller lesions, is not highly efficacious for large lesions (≥2 to 3 cm largest dimension). In addition, patients who have received radiosurgical treatment are not protected from hemorrhage risk until the AVM is obliterated, usually after a period of several years.1

Etiology and Pathogenesis of AVM

The genesis of AVMs has been enigmatic. Unlike the association of antecedent head trauma with the pathogenesis of dural arteriovenous fistulae (DAVF), there are no known environmental risk factors for AVMs. The time-honored approach to explaining AVMs is to invoke a congenital or developmental anomaly.5 However, in contradistinction to vein of Galen malformations, a type of DAVF, there is a conspicuous lack of evidence that AVMs are present in the prenatal cerebral circulation, especially when one considers the huge number of prenatal ultrasounds performed annually.

Arguing against some unique congenital mechanism, AVMs have been shown occasionally to arise de novo after a normal angiogram and regrow after resection either de novo or from a retained fragment.6,7 They can also regrow after apparent complete obliteration by radiosurgery.8

Although such events are relatively rare in clinical practice, the machinery for such changes strongly suggests that there are active vascular changes taking place in a majority of patients.9 Perhaps these observations are simply extreme cases of a continuum of behaviors reflecting the fact that AVMs are actively growing lesions, albeit slowly. Endothelial proliferation, as suggested by Ki-67 immunohistochemistry in surgically resected AVM tissue, was 7-fold higher than control (structurally normal temporal lobe removed as part of epilepsy surgery).9

Inherited or Acquired Abnormalities?

By all indications, the majority of AVMs are sporadic, making linkage studies impractical. There are only tens of
reports of familial associations in the literature, comprising <50 cases.\textsuperscript{11,12}

Identification of genetic markers such as single-nucleotide polymorphisms (SNPs) would be useful for managing AVM patients. They could yield insights into the pathogenesis of the lesions and suggest possible fruitful approaches to developing medical therapy. Moreover, SNP identification would provide targets for risk stratification for planning clinical trials and eventually guiding management. SNPs are less likely to experience interobserver variations that plague risk factors gleaned traditional radiographic characterizations of AVMs. Such SNPs might be specific to AVMs or may be markers that indicate increased risk of ICH in general.

**Genes Likely to Nonspecifically Increase Risk of ICH**

There are several possibilities for polymorphisms that might generally increase the risk of ICH, but none have been studied in AVMs. A first-degree relative with primary ICH is an independent risk factor for sporadic primary ICH, as well as apolipoprotein E (apoE) genotype.\textsuperscript{13} O’Donnell et al showed increased rebleeding after first lobar (primary) ICH in patients with either the E2 or E4 allele compared with patients homozygous for E3 allele.\textsuperscript{14} The exact influence of apoE on vascular wall stability is unknown at present.

MMPs, a family of zinc-dependent endopeptidases that regulate the extracellular matrix, are associated with various hemorrhagic brain disorders, presumably by excess degradation of the vascular wall.\textsuperscript{15} MMP polymorphisms have been studied in intracranial aneurysms with conflicting results,\textsuperscript{16,17} probably attributable to population stratification, a major challenge to conducting genetic case-control studies.

Other polymorphisms associated with primary ICH involve clotting system proteins such as those that are relatively protective (Factor V Leiden, Prothrombin 20210A) and 2 genotypes that increase risk (Factor XIII V34L, Factor VII-323 Del/Ins).\textsuperscript{18} The mechaneries whereby such alterations influence the occurrence of ICH are not known. Perhaps altered protein function allows “microbleeds,” even at the level undetectable by current imaging methods, to blossom into clinically important events.

**Genes Possibly Specific to AVMs**

Although genetic influences on AVMs are currently unclear, there might there be clues from other Mendelian disorders affecting cerebrovascular circulation. In genes that undergo disease-causing mutations, are there polymorphisms that subtly alter protein function that might contribute to the development of the sporadic AVM phenotype?

An interesting possibility exists in the case of the hereditary hemorrhagic telangiectasias (HHT), an autosomal dominant syndrome of mucocutaneous fragility that is strongly associated with pulmonary and brain AVMs. There are 2 well-characterized types of loss-of-function mutations that result in HHT.\textsuperscript{19} Both are associated with genes related to transforming growth factor-\(\beta\) (TGF-\(\beta\)). TGF-\(\beta\) is a multifunctional cytokine known to modulate several tissue development and repair processes, including cell differentiation, extracellular matrix production. Loss of function for TGF-\(\beta\) signaling proteins appears to result in vascular dysplasia.\textsuperscript{20}

One mutation is in endoglin, an accessory protein of TGF-\(\beta\) receptor complexes. The other is in activin-like kinase-1 (ALK-1), which is a transmembrane kinase. Clinically, brain AVMs in HHT patients are, for the most part, indistinguishable from patients with the sporadic disease, suggesting a common pathway for pathogenesis.

A 6-bp insertion polymorphism in an intron 7 of the endoglin gene has shown association with primary ICH.\textsuperscript{21} One study associated the SNP with intracranial aneurysms\textsuperscript{22} but could not be replicated by other groups.\textsuperscript{23,24} The polymorphism in endoglin intron 7 is 26 bp from the splice acceptor site for exon 7; this polymorphism appears to be nonfunctional.\textsuperscript{25} However, the SNP may be in linkage disequilibrium with another endoglin polymorphism that is functionally significant.

Other genes of interest are the angiopoietins (Ang-1 and Ang-2) and their receptor Tie-2 (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains-2, also called TEK), which play a critical role in angiogenesis and vascular stability. Along with VEGF, the Ang–Tie-2 system plays a key role in controlling vascular growth and regression in tumors and in ovaries during the reproductive cycle and shows abnormalities in brain AVMs.\textsuperscript{10} The Tie-2 gene is mutated in the systemic familial venous malformation syndrome.\textsuperscript{26} The venous malformation vascular phenotype shares some similarities with brain AVMs. Ang-2, primarily a Tie-2 antagonist, is a deconstructive signal that promotes vascular remodeling and is minimally present in quiescent, mature vasculature; its expression is greatly increased in AVM tissue.

In a recent study of promoter polymorphisms in inflammatory cytokine genes (Figure 3), AVM patients homozygous for the interleukin-6 (IL-6)-174G allele had a greater risk of ICH presentation (odds ratio, 2.62; \(P=0.003\)) than IL-6 -174C carriers.\textsuperscript{27} IL-6 genotype was an independent predictor of ICH presentation adjusted for race–ethnicity, age, and sex, along with small AVM size and exclusively deep venous
there are some reasonable candidates. For example, there are many conditions that might result in a localized area of microvascular thrombosis, such as minor cranial trauma (either prenatally or postnataley) or a state of relative thrombophilia, DAVF. The inciting event leads to a region of venous hypertension (pathway 1), stimulating hypoxia-inducible factor-1 (HIF-1) elaboration. Downstream from HIF-1 (pathway 2), VEGF stimulation begins a process of focal angiogenesis (pathway 5; 2 other important sources of VEGF are release from leukocytes/macrophages and MMP-9–mediated release from the extracellular matrix). The resultant angiogenesis stimulates multiple cell types to secrete inflammatory cytokines such as IL-6, which in turn could attract leukocytes and macrophages (shaded box); IL-6 and leukocytes may further contribute to MMP expression and activity (pathway 7), accelerating endothelial cell proliferation, migration, and microvessel sprouting. IL-6 may enhance angiogenesis either by stimulation of VEGF (pathway 4) or activation of MMPs (pathway 6).

The angiogenic process might be turned pathological in the presence of some predisposing genetic alteration in TGF-β–signaling function (pathway 8), as suggested by familial genetic disorders, or increased expression or function of Tie-2 and its ligands (eg, Ang-2; not shown). Altered function, perhaps even subtle, in some combination of genes might take otherwise innocuous events and conspire to create the circumstances for development of the human AVM phenotype. Not all gene alterations need be present in a given AVM patient; multiple alterations could converge on a single set of pathways.

Development of a vascular malformation might become self-sustaining through the opening of arteriovenous shunts. Shunting might increase endothelial shear and NO production, thus further driving VEGF stimulation. Downstream activation of MMPs ultimately destabilizes vascular walls and sets the stage for rupture (MMP injection into the brain was an original model for mimicking ICH31).

Conclusions

Much work needs to be done, including: (1) dissecting out pathways in human tissue and laboratory models; (2) further
candidate genes SNP studies and identification of novel SNPs; and (3) using genome-wide SNP arrays to perform detailed haplotype analyses. The International HapMap Consortium is obtaining 9 million genotypes by typing 30,000 SNPs across 300 samples over 3 years.32 Renewed interest in the clinical management of AVMs, coupled with advances in molecular level studies, can lead to real progress in therapy.

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**References**


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