Abstract—Brain arteriovenous malformations cause intracranial hemorrhage. Molecular characterization of lesional tissue implicates angiogenic (vascular endothelial growth factor, ANG-2, matrix metalloproteinase-9) and inflammatory (cytokines and chemokines) pathways, but the pathogenesis remain obscure and medical therapy is lacking. Macrophage and neutrophil invasion has also been observed in the absence of prior intracranial hemorrhage. Common polymorphisms in interleukin-1β and activin receptor-like kinase-1 are associated with arteriovenous malformation susceptibility, and polymorphisms in interleukin-1β, interleukin-6, tumor necrosis factor-α and APOE are associated with arteriovenous malformation rupture. These observations suggest that even without a complete understanding of the determinants of arteriovenous malformation development, the recent discoveries of downstream derangements in vascular function and integrity may offer potential targets for therapy development. Furthermore, biomarkers can be established for assessing intracranial hemorrhage risk. Finally, these data will aid in development of model systems for mechanistic testing by development of surrogate phenotypes (microvascular dysplasia) and/or models recapitulating the clinical syndrome of recurrent spontaneous intracranial hemorrhage. (Stroke. 2009;40[Suppl 1]:S95-S97.)

Key Words: angiogenesis ■ inflammation ■ vascular malformations

Brain arteriovenous malformations (AVMs) are a cause of intracranial hemorrhage (ICH). The basic morphology is a tangle of abnormal, dilated channels with intervening gliosis, called the nidus, that directly shunts blood between the arterial and venous circulations without a true capillary bed. Prevention of new or recurrent ICH is the primary rationale to treat AVMs. The risk of spontaneous ICH varies widely depending on clinical and angioarchitectural risk factors. Mean estimates are 2% to 4% per year, but range from 1% to 30% per year. Other than nonspecific control of symptoms, eg, headache and seizures, primary medical therapy is lacking.

Etiology and Pathogenesis
There are no known environmental risk factors for AVMs, and, despite direct evidence, they are usually described as congenital. However, there are multiple reports of AVMs that grow or regress, including de novo AVM formation, hinting that an appreciable fraction may in fact have a postnatal genesis. Although unproven, inciting event(s) might include subclinical trauma, tissue hypoxia, infection, inflammation, irradiation, or compression, perhaps involving localized venous hypertension, a potent angiogenic stimulus. Scarce available data on longitudinal assessment of AVM growth suggest that roughly 50% of cases display interval growth.

AVM tissue assays suggest an active angiogenic and inflammatory lesion rather than a static congenital anomaly, eg, increased endothelial proliferation, overexpression of vascular endothelial growth factor-A, ANG-2, myeloperoxidase, interleukin-6, and matrix metalloproteinase-9. Even in unruptured, nonembolized AVMs, neutrophils and macrophages/microglia are evident in both vascular wall and intervening stroma.

Genetic Considerations
Although rare, familial cases of AVM outside the context of hereditary hemorrhagic telangiectasia (HHT) have been reported, but linkage studies are underpowered. Using these reported data, one can derive modest estimates of recurrence risk ratio of disease in siblings, λs, suggesting a genetic influence.

Hereditary hemorrhagic telangiectasia, an autosomal-dominant disorder with a high prevalence of brain AVM, may be a natural model for sporadic disease insofar as it suggests the pathways, if not the genes, involved. The majority of HHT cases involve loss-of-function mutations in 2 genes originally implicated in transforming growth factor-β signaling pathways: (1) endoglin (ENG), encoding an accessory protein of transforming growth factor-β receptor complexes; and (2) activin receptor-like kinase 1 (ALK-1), encoding a transmembrane kinase. In endothelium, ALK-1 may signal through BMP-9 enhanced by ENG; ablation of murine ALK-1 causes embryonic arteriovenous fistula formation.
As a class, AVMs in HHT are characterized by small size, single-hole fistulas, cortical location, and multiplicity but are generally similar to the sporadic lesions and cannot be distinguished individually on the basis of their angioarchitecture. Brain AVMs are approximately 10 times more common in HHT1/ENG (approximately 20%) than HHT2/ALK-1 (approximately 2%). Compared with sporadic lesions, presence of an ENG or ALK-1 mutation results in a 10,000- and 1000-fold increased risk, respectively, of developing a brain AVM. The greatly elevated risk of brain AVM development in HHT raises the hypothesis that germline sequence variants of genes in this pathway may likewise pose a significant risk for sporadic brain AVM development. The growth and behavior of AVMs are likely under genetic influence from modifier pathways, eg, there are multiple genetic loci that control vascular endothelial growth factor-induced angiogenesis.

The first common genetic polymorphism associated with sporadic AVM susceptibility, thought to result in alternative splicing, is an intronic variant of ALK-1, which was recently replicated. Common promoter polymorphisms in interleukin-1β (−31T>C and −511C>T) also are associated with AVM susceptibility. The GG genotype of the interleukin-6 −174G>C promoter polymorphism was associated with clinical presentation of ICH, and the G allele correlated with interleukin-6 mRNA and protein levels in resected AVM tissue. A promoter polymorphism in tumor necrosis factor-α and APOE ε2 genotype were associated with new ICH after diagnosis. These genetic association studies are in need of replication and large cooperative studies will be needed.

**Experimental Arteriovenous Malformation Models**

A model system for studying AVM is needed. With few exceptions, most “AVM” models are either extradural fistulas, ie, creation of a carotid jugular fistula, or result in morphological microvascular changes that are probably best termed “vascular dysplasia.” A parenchymal nidus is not formed: nidus growth and hemorrhage mimicking the human disease do not occur. An ideal model would feature: (1) a nidus of abnormal vessels of varying sizes, encompassing both micro- and macrocirculatory levels; (2) spontaneous ICH into the brain parenchyma or cerebrospinal fluid spaces; (3) arteriovenous shunting; (4) flow rates sufficient to lower proximal feeding artery pressure; and (5) high angiogenic and inflammatory signal expression consistent with human surgical specimens.

Virally mediated vascular endothelial growth factor gene transfer in ENG-deficient mice enhances vascular abnormalities, suggesting synergy between transforming growth factor-β and vascular endothelial growth factor signaling pathways in development of abnormal or “dysplastic” vessels. Coupled with conditional deletion of ENG or ALK-1, stimulation techniques show promise for development of a true AVM model. Success of this strategy in phenocopying the clinical disorder would lend strength to the approach of controlling pathological angiogenesis and/or inflammation to halt disease progression and decrease risk of spontaneous hemorrhage.

**Figure.** AVM pathogenesis: speculative synthesis of observations. After an inciting event, inflammatory or angiogenic activity (matrix metalloproteinase, vascular endothelial growth factor) initiates microvascular growth and remodeling, which are stabilized through interplay of pathways, including Tie-2/ANG and transforming growth factor-β or BMP-9 signaling through the ALK-1/ENG pathway. Lack of integrin β3 and Hox A5, an antiangiogenic transcription factor, may also play a role. Normal vessels stabilize, but an incipient AVM undergoes a dysplastic response. Arteriovenous shunting and high flow rates synergize with the dysplastic response and with inflammatory signals, causing a vicious cycle in a localized area destined to become the nidus. Eventually, the human disease phenotype emerges. Genetic variation can influence any step of the cycle.

**Conclusions**

The prevailing hypothesis is that AVM pathophysiology is governed to a large extent by chronic hemodynamic derangements imposed on a congenital lesion. Recent findings suggest an alternative hypothesis in which angiogenic and inflammatory pathways synergize with underlying defects or hemodynamic injury to result in the clinical phenotype, perhaps in conjunction with as yet undetermined genetic or environmental influences (Figure). Elucidating these mechanisms offers promise for developing innovative treatments and better risk stratification and may provide insights into mechanisms of vascular biology.

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**References**


