Arteriovenous malformation pathogenesis

The pathogenesis of cerebral arteriovenous malformations (cAVMs) is still not well understood. Generally, cAVMs are thought to be congenital lesions originating prenatally.

AVMs are usually congenital and belong to the RASopathies. The genetic transmission patterns of AVM, if any, are unknown. AVM is not generally thought to be an inherited disorder, unless in the context of a specific hereditary syndrome.

A long-held dogma in neurosurgery is that parenchymal arteriovenous malformations (AVMs) are congenital. However, there is no strong evidence supporting this theory. An increasing number of documented cases of de novo formation of parenchymal AVMs cast doubt on their congenital nature and suggest that indeed the majority may form after birth. Further evidence suggesting the postnatal development of parenchymal AVMs comes from the exceedingly rare diagnosis of these lesions in utero despite the widespread availability of high-resolution imaging modalities such as ultrasound and fetal MRI. The exact mechanism of AVM formation has yet to be elucidated, but most likely involves genetic susceptibility and environmental triggering factors [1)].

Brain pericyte number and coverage are reduced in sporadic bAVMs and are lowest in cases with prior rupture. In unruptured bAVMs, pericyte reductions correlate with the severity of microhemorrhage. A loss of pericytes also correlates with a faster rate of blood flow through the bAVM nidus. This suggests that pericytes are associated with and may contribute to vascular fragility and hemodynamic changes in bAVMs. Future studies in animal models are needed to better characterize the role of pericytes in AVM pathogenesis [2)].

Molecular and cellular biology

A PubMed search was performed using the key words “genetic,” “molecular,” “brain,” “cerebral,” “arteriovenous,” “malformation,” “rupture,” “management,” “embolization,” and “radiosurgery.” Only English-language papers were considered. The reference lists of all papers selected for full-text assessment were reviewed.

Current concepts in genetic polymorphisms, growth factors, angiopoietins, apoptosis, endothelial cells, pathophysiology, clinical syndromes, medical treatment (including tetracycline and microRNA-18a), radiation therapy, endovascular embolization, and surgical treatment as they apply to AVMs are discussed.

Understanding the complex cellular biology, physiology, hemodynamics, and flow-related phenomena of AVMs is critical for defining and predicting their behavior, developing novel drug treatments, and improving endovascular and surgical therapies [3)].

Nikolaev et al. propose that these malformations develop as a result of KRAS-induced activation of the MAPK-ERK signaling pathway in brain endothelial cells [4)].

1)
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2)
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Chang EF, Su H, Kim H, Walcott BP, Lawton MT. Reductions in brain pericytes are associated with arteriovenous malformation vascular instability. J Neurosurg. 2018 Jan 5:1-11. doi: 10.3171/2017.6.JNS17860. [Epub ahead of print] PubMed PMID: 29303444.
3)

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4)

Nikolaev SI, Vetiska S, Bonilla X, Boudreau E, Jauhiainen S, Rezai Jahromi B, Khyzha N, DiStefano PV, Suutarinen S, Kiehl TR, Mendes Pereira V, Herman AM, Krings T, Andrade-Barazarte H, Tung T, Valiante T, Zadeh G, Tymianski M, Rauramaa T, Ylä-Herttuala S, Wythe JD, Antonarakis SE, Frösen J, Fish JE, Radovanovic I. Somatic Activating KRAS Mutations in Arteriovenous Malformations of the Brain. N Engl J Med. 2018 Jan 3. [Epub ahead of print] PubMed PMID: 29298116.