# THE ROLE OF VASCULAR ABNORMALITIES IN THE DEVELOPMENT OF ARTERIOVENOUS MALFORMATIONS

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***Abstract****. Arteriovenous malformation (AVM) is a congenital abnormality of the blood vessels in the brain, consisting of clusters of various shapes and sizes formed by the disorderly interweaving of pathological vessels. Typical AVMs have three main components: feeding arteries (AVM afferents), a cluster of altered vessels (the core of the malformation), and draining veins (AVM efferents). AVMs usually lack a capillary network, resulting in direct shunting of blood from arterial vessels into the superficial and deep veins of the brain. This vascular abnormality of the brain occurs in 0.01% of the population, more commonly in men, with peak manifestation occurring between the ages of 20 and 40. AVMs are diagnosed based on magnetic resonance imaging (MRI), but selective cerebral angiography is considered the gold standard. Vascular development occurs in two stages: vasculogenesis (the formation of blood vessels de novo in embryogenesis) and angiogenesis. Most genes and genetic risk factors play a role in the development of vasculogenesis, angiogenesis, and vascular remodeling.*
***Keywords****: arteriovenous malformation, vascular anomaly, genes, inflammation.*

Arteriovenous malformation (AVM) is a congenital defect of the cerebral vasculature that manifests as various forms and sizes of tubers caused by the disordered interweaving of weakened veins. The capillary network is often lacking in AVM due to direct blood bypass from the artery channel to the surface and deep veins of the brain. This cerebral vascular abnormality occurs in 0.01% of the population, with men having a higher incidence [1]. The condition can present clinically at any age, although persons aged 20 to 40 [2] are the most commonly affected. The diagnostic complex for the identification of AVM must include magnetic resonance tomography (MRI), computed tomography (CT), and selective cerebral angiography (SCA), which is considered the gold standard [3]. AVM is diagnosed during the acute period of bleeding using multispiral computerized tomography (MSCT) of the brain and cerebral panangiography. A cerebral panangiography is performed when surgical reasons exist. The CT scan allows the identification of the hemorrhage itself by distinguishing liquid blood and its packets. The most informative research was conducted in the first three days following the hemorrhage.

AVM can cause hemorrhagic currents, seizures, and non-specific symptoms including headaches throughout their life. There are five levels of AVM: I, II, III, IV, and V, which indicate the growing complexity of the malformation and the ratio of anatomical structures. The risk of surgery is small at the I grading (1 point). With V grade (5 points), there is a considerable probability of severe disability and death. That instance, the authors (R. Spetzler and N. Martin) emphasize that the degree of ABM increases the surgical risk.

Vessels develop in two stages: vasculogenesis (the creation of new vessels during embryogenesis) and angiogenesis. Vasculogenesis of brain vessels occurs outside the brain, with the creation of the perineural plexus. The capillaries emerge from this plexus and penetrate the neural tube. Angiogenesis then occurs. Angiogenesis is a way of creating new blood vessels from existing ones. These mechanisms have been described in mammals [4, 5].

Inductors (growth factors) and inhibitors (substances that limit the growth and formation of new blood vessels) are distinguished. Inducing agents of angiogenesis include the following:

1. Inducing factors include physical (temperature, radiation), chemical (exposure to chemicals or changes in tissue composition), and biological (hereditary, immunogenic, among others).

2. Stimulating inductors includes hypoxia, tissue edema, inorganic substances, plasminogen activator, heparin, fibrin, and their decomposition products, as well as low molecular and peptide stimulators.

3. Angiogenic Factors

4. Mechanical considerations include intravascular pressure, vascular wall tension, increased viscosity.

Angiogenesis progresses through the following phases:
The first phase of angiogenesis is characterized by the activation, proliferation, and migration of vascular endothelial cells. The neuroectodermal cells and their neuroglial progenitors generate vascular endothelial growth factor (VEGF), which plays an important role in these processes. In reaction to hypoxia, VEGF increases capillary permeability. Growing capillaries have high permeability and low interendothelial connective proteins [6,7,8]. The second phase is vascular stabilization, which involves endothelial cells. They generate capillaries, which then fuse into bigger vessels like arteries and veins. b. Intracellular bonds are enhanced. c. Smooth muscle cells make up the vascular walls. Endothelial cells and pericytes, which are precursors of vascular smooth muscle cells, help to stabilize the vascular wall. Endothelial Platelet Growth Factor B (ENG) and Transforming Growth Factor-β1 (TGF-β1) promote pericyte and extracellular matrix synthesis [8]. Pericytes have the opposite effect on endothelial vessels, decreasing capillary expansion while increasing wall thickness, intercellular bond formation, and cell-matrix adhesion. These processes are influenced by angiopoetin-1 (ANG-1), metalloproteinases (MMP) [9], and ephrine B2 [10]. Reduced pericyte count (e.g., in mice) causes vascular enlargement, endothelial cell hyperplasia, and microaneurysm [11,20].

Recent research indicates that cerebral vascular angiogenesis ceases after birth but can be revived in response to physiological stimuli such as physical overwork [12], brain hypoxia [13], stressors [14], and certain hormones [15,16,19]. Active local angiogenesis is also triggered by pathological alterations such as tumor development, stroke, or traumatic injury [17]. Angiogenesis in adults is governed by the same factors (e.g., VEGF) as in early life, but it also has some distinct mechanisms. Adult capillaries require endothelial reactivation as well as the rupture of stable vascular walls, which is frequently caused by inflammation.

Cerebral vascular abnormalities occur at the junction of arterial and venous endothelium, where capillary endothelium should be normal. AVM is an aberrant tangle of arteries and veins that creates a network of straight arteriovenous bypasses. AVM is a ball with no real capillary bed [18,20,21].

Genes of brain abnormalities and angiogenesis. Most genes and genetic risk factors contribute to the development of vascular genesis, angiogenesis, and remodeling. Hereditary AVM disorders are caused by the loss of function of one copy of the relevant gene in all cells that typically express this gene; nevertheless, these lesions are localized and do not impact the entire vascular network. The second stage of vascular development may be influenced by external influences, either locally physiologically or pathologically.

The most substantial research in recent years has been on genomic investigations of numerous complicated disorders. The genetic determinants of arteriovenous malformations are investigated using the following methods: candidate gene analysis, genomic clutch analysis, and associations. GWA studies have examined the role of genes in the development of AVM, as well as environmental factors, such as the impact of polymorphic variants of inflammatory response genes, angiogenesis, vascular endothelial growth factors, and other genes on AVM pathogenesis.

Polymorphic variations of inflammatory response genes enhance the likelihood of arterial wall damage in vascular diseases. In addition to the harmful agent, inflammation requires the combination of many physiologically active chemicals, specific cells, intercellular and cellular-matrix relationships, the development of local tissue alterations, and overall hemodynamic changes in the body [19].

**Conclusion**

Thus, vascular damage can develop not only as a result of a mutation in one copy of the gene within a specific cell group, but also as a result of other causes commencing the pathological process in the field of future malformation.

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