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Research Article

Physiology and Anatomic Aspects of Brain Arteriovenous Malformations

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Abstract

Brain arteriovenous malformations are dynamic lesions and can be characterized as arteries fistulizing to veins without capillaries interposing them. It leads to abnormalities in these veins that will get dilated and tortuous. They are supposed to be developed during the maturation of fetal vascular nervous system, characterized by a lower degree of cellular maturation and differentiation. The anomalous cellular and anatomic aspects of this entity create a hemodynamic environment prone to hemorrhagic features, which is one of the most common presenting symptoms.

Keywords: *Brain Arteriovenous Malformations; Physiology; Genetic; Hemodynamic; Rupture*

Abbreviations

AVM: Arteriovenous Malformation; BAVM: Brain Arteriovenous Malformations; CVM: Central Venous Malformation; VEGF: Vascular Endothelial Growth Factor; VEGFR: VEGF Receptor; AGN: Angiopoietin; GLUT1: Glucose Transporter Protein Type 1; GGTP: Gamma-Glutamyl Transpeptidase

Introduction

Cerebral arteriovenous malformations (AVMs) can be described as vascular systems in which arteries and veins conjugate without the intersection of capillaries [1-5]. With the ability to regress, advance or even re-emerge after their complete surgical resection (may also receive the designation of de novo BAVM in this case), they are characterized as dynamic lesions [1,4]. It's important to study this pathological entity and review your data because of the risk to spontaneously hemorrhage and the higher rates of patients initially presenting with intracranial hemorrhage and death [2,6,7].

Materials and Methods

We performed a literature review using PubMed for search the following keywords: brain arteriovenous malformations; physiology; genetic; hemodynamic; rupture. We collected data from 18 articles, including review articles, meta-analysis, follow-up and genetic studies.

Results

Development and Physiology

To understand the occurrence of AVMs it is first necessary to know the normal processes of formation of the main involved systems: nervous and vascular. Characteristically, they are the first two systems to be developed in the embryonic process and, in the case of the brain, are systems that develop concomitantly [1,3].

Regarding vascular development, it refers to a two-stage course. The first, called vasculogenesis, is characterized by high levels of vascular endothelial growth factor (VEGF) and growth of new endothelial cells, while the second, named by angiogenesis, refers to the destruction of primeval vessels, maturation of new vessels, elaboration of an immature venous plexus and negative regulation of VEGF [1,3].

Studies concerning the analysis of different AVM's nidus corroborate the deficit in vascular differentiation and maturation, evidencing altered expressions of specific markers for arteries, veins and capillaries (Figure 1) and histoanatomic heterogeneity in the nidus concerned [3]. In addition, a greater expression of receptors capable of elevating endothelial cell proliferation and intensifying this anomalous development has been demonstrated. The most important factors for its development are the fetal brain receptor Flk-1 for a VEGF subtype, AGN-2 which promotes a destabilizing signal increasing vascular remodeling, hypoxia stimulating angiogenesis and microhemorrhage playing an important role in hemorrhagic angiogenic proliferation (Figure 1) [1].

Due to such alterations there is an occurrence of local vascular remodeling, stimulated by the increased venous pressure and tissue hypoxia, both may be caused by the arteriovenous fistulation. These characteristics stimulate angiogenesis by activation of angiogenic factors and their receptors, aggravating the progression of the lesion [8].

Finally, there are studies which suggest that AVMs are fistulized central venous malformations (CVM), with reports of abnormalities in venous drainage present in all major AVMs, which holds the belief that both are transitions forms of the other [9,10].

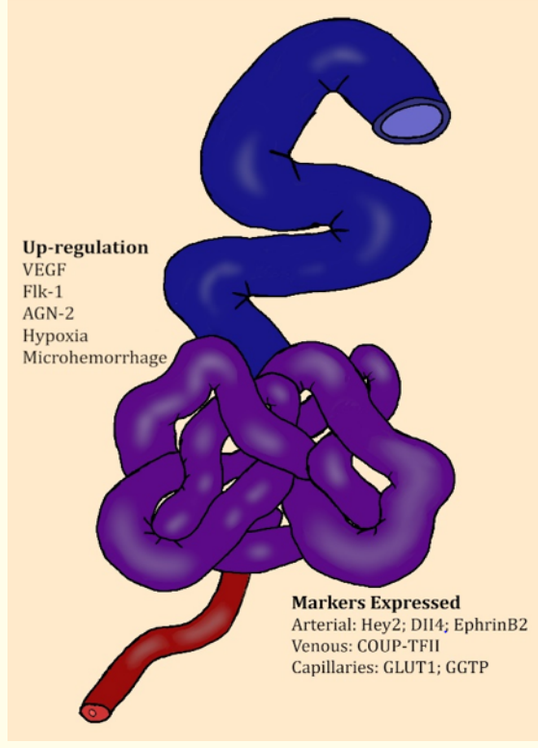

Figure 1: *Representation of basic structure of an AVM with the feeder artery (in red), draining vein (in blue) and the direct communication between them in the nidus, mixing arterial and venous blood (in purple). The image shows the most important markers that are expressed in the AVMs nidus and the up-regulation factors.*

Anatomy and Hemodynamic changes

Hypertension, intranidus aneurysms and obstruction of venous drainage are some of the factors responsible not only for morphological changes but also for the addition of bleeding risk in cases of AVM [8]. Other hemodynamic abnormalities, such as venous or arterial hypertension and changes in flow, are also believed to stimulate the formation of these malformations [8].

Norris., *et al.* [11] indicates that hypertension in the artery responsible for nidus nutrition is related to seizures, in addition to hemorrhage, which is linked to increased vascular resistance caused by increased pressure in the local artery. The same research also demonstrated an inverse relationship between food artery pressure and AVM dimensions, corroborated by other studies, showing an association between higher rates of hemorrhage in smaller AVMs [6,11].

As for anatomy, AVMs can be differentiated into two large groups and may involve cerebral parenchyma, which increases surgical risks [4,8]. The monocompartmental are simpler, with only one nidus nourished by only one artery, and therefore of easier regression. Multicompartmentals, however, involve several veins and arteries, and can be divided into hemodynamic, confluent or separated compartments (Figure 2). There are also invisible compartments, not localized to angiography, whose importance is due to edema and hemorrhage caused by their sudden filling [8,12].

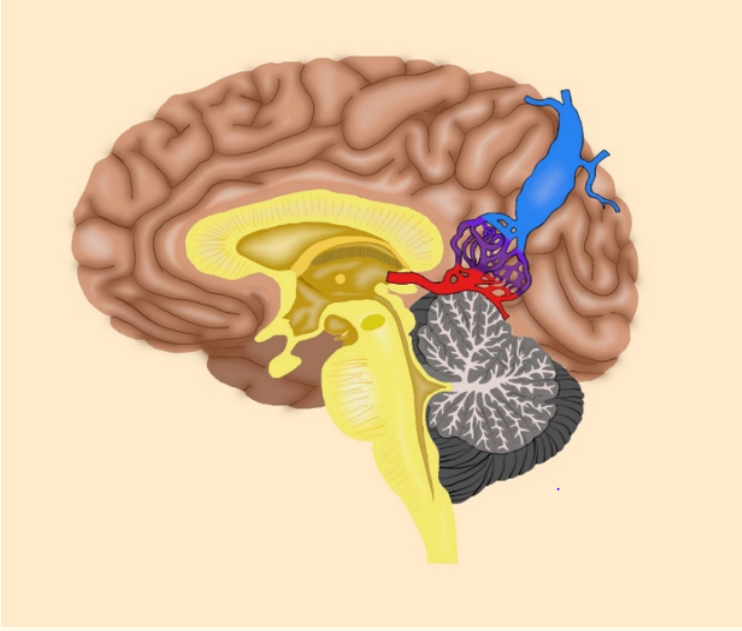

Figure 2: *Representation of a multicompartmental BAVM in which the high pressure in venous drainage made the veins dilated and tortuous.*

Clinical Presentation and Natural Course

Hemorrhage is the most frequently described feature in AVM cases, with emphasis on previous hemorrhage and deep nidus location as the main risk factors [2,13]. As mentioned, studies show its higher prevalence in small AVMs, while in the medium and large ones the occurrence of seizures and other neurological symptoms is prominent than hemorrhage [4,6].

Intracranial aneurysms also have a great association with AVMs [14,15] especially those of smaller size, possibly explained by the greater shear stress present in vessels of smaller diameter. Their risks of rupture and hemorrhage are greater at the first year of presentation and appear to decline in subsequent years [7,14,16].

According to their classification as a form of dynamic injury [1,4] reviews indicate a rate of approximately 2,7% recurrence after surgical excision in adults, with an average time of 4 years for this. In individuals of lower age range their frequency is high and most cases of bleeding occur [17].

Vascular Steal

Studies with computed tomography show reduced flow in near and distant areas caused by malformations, which with AVM regression may lead to an overflow and consequent postoperative intracranial edema. However, other analyzes of the flow in these regions did not make it possible to confirm the theory of the phenomenon of vascular theft, a topic that is divergent among scholars until now [8,18]. The reduced perfusion in vascular territories among the BAVMs was denominated perinidal dip and this might represent the presence of a territorial and a microvascular perfusion injury. The perinidal dip seems to result from lower perfusion pressure in tight arteries and arterioles due to its unequally circulation in a single vascular territory [5].

Discussion

BAVMs are still one of the most challenging entities in medicine and they aren't completely understood. We still have important disagreements about some markable topics as the anatomy implications in hemodynamic flow and the vascular steal phenomenon. Due to its physiology and new researches, probably they are congenital lesions or activated by epigenetics and develop progressively [1,3,4,8].

Conclusion

More studies about these important lesions are necessary due to its dynamic capability to change over the time and we don't understand its mechanisms properly without disagreements. They have an abnormal factors regulations and gene expression, which leads to a lower level of differentiation and maturation of these vessels [1,3]. Other factors involved on its growth is the pressure and shear stress, which is influenced by the size and hemodynamic characteristic of each AVM due to its anatomy, allowing injury to be prone to bleeding [6-8,11,14, 16].

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