Clinical Features of the Course of Arteriovenous Malformations and Issues of Their Correction

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ABSTRACT

Arteriovenous malformation (AVM) is a congenital vascular disease of the brain, manifested by the connection of arteries, veins and small vessels, randomly intertwined with each other, leading to a violation of blood circulation in the affected organ. Veins and arteries have a specific kind of "tangle" of vessels, which is the core of the malformation, interconnected by shunts or fistulas. The most common are brain arteriovenous malformations.

Keywords: Arteriovenous malformation, genetic predisposition, genes, brain, vessels, pathology.

Arteriovenous malformation is an abnormal connection between arteries and veins, bypassing the capillary system. This vascular anomaly is widely known because of its occurrence in the central nervous system (usually cerebral AVM), but can appear in any location. Although many AVMs are asymptomatic, they can cause intense pain or bleeding or lead to other serious medical problems.

AVMs are usually congenital and belong to the RASopathies. The genetic transmission patterns of AVMs are incomplete, but there are known genetic mutations (for instance in the epithelial line, tumor suppressor PTEN gene) which can lead to an increased occurrence throughout the body.

In the middle of the 19th century, Luschka and Virchow first described the development of AVMs. Angiogenesis of cerebral vessels occurs from 4 to 13 weeks of embryonic development of the fetus. Under the influence of damaging factors in the early stages of vascular development, there is a loss of the ability of the choroid plexus to natural differentiation, which leads to the formation of vascular malformations in the brain.

Among the most common vascular malformations in the brain, arteriovenous malformations (AVMs) and cerebral cavernous malformations (CCMs) are distinguished with an incidence of about 1.1 and 0.6 per 100,000 adults per year [1]. The prevalence of cerebral AVMs according to sectional data is 0 1%, however, there are no exact data [2]. The annual detection rate of AVM is between 0.14 and 0.8%, accounting for approximately 1/10 of the frequency of intracranial aneurysms among the adult population [3]. The survival rate of patients with AVM is 85% in the first 10 years, 65% - 30 years from the date of diagnosis [4]. The disease can manifest itself clinically at any age, however, people of working age from 20 to 40 years old are most often affected, and further prognosis without surgical treatment is unfavorable: death occurs

in 23% of patients, in 48% the disease leads to deep disability, which indicates the social significance of the problem [5,6,7].

Arteries and veins are part of the vascular system. Arteries carry blood away from the heart to the lungs or the rest of the body, where the blood passes through capillaries, and veins return the blood to the heart. An AVM interferes with this process by forming a direct connection of the arteries and veins. AVMs can cause intense pain and lead to serious medical problems. Although AVMs are often associated with the brain and spinal cord, they can develop in other parts of the body.

Normally, the arteries in the vascular system carry oxygen-rich blood, except in the case of the pulmonary artery. Structurally, arteries divide and sub-divide repeatedly, eventually forming a sponge-like capillary bed. Blood moves through the capillaries, giving up oxygen and taking up waste products, including CO2, from the surrounding cells. Capillaries in turn successively join to form veins that carry blood away. The heart acts to pump blood through arteries and uptake the venous blood.

As an AVM lacks the dampening effect of capillaries on the blood flow, the AVM can get progressively larger over time as the amount of blood flowing through it increases, forcing the heart to work harder to keep up with the extra blood flow. It also causes the surrounding area to be deprived of the functions of the capillaries—removal of CO2 and delivery of nutrients to the cells. The resulting tangle of blood vessels, often called a nidus (Latin for "nest"), has no capillaries. It can be extremely fragile and prone to bleeding because of the abnormally direct connections between high-pressure arteries and low-pressure veins. The resultant sign, audible via stethoscope, is a rhythmic, whooshing sound caused by excessively rapid blood flow through the arteries and veins. It has been given the term "bruit", French for noise. On some occasions, a patient with a brain AVM may become aware of the noise, which can compromise hearing and interfere with sleep in addition to causing psychological distress.

R. Spetzler and N. Martin, in 1986, developed a convenient and widely used ABM gradation system. The authors sought to create a classification that would be simple, easy to use for all cerebral malformations and would provide a reasonable prognosis of disability and mortality. They described such parameters as: AVM size, which is determined by the maximum size of the tangle in centimeters, the number of afferents, localization, surgical accessibility, blood flow, the degree of steal, the functional significance of the perifocal parenchyma, and the drainage system. But then, the authors simplified the list in an effort to create more user-friendly criteria. These were indicators such as size, drainage system, and functional significance of the area in which the AVM is located. Thus, AVMs of I, II, III, IV and V gradations are distinguished. Venous drainage is assessed as “superficial” if all outflows are carried out into the cortical veins, “deep” if, in addition to cortical drainages, there is an outflow into the internal cerebral, basal veins and precentral cerebellar veins.

There are 5 gradations of AVMs I, II, III, IV and V, reflecting the increasing complexity of the malformation and the relationship of anatomical structures. With grade I (1 point), the risk of surgery is negligible. With grade V (5 points), there is a high risk of profound disability and death. That is, the authors (R. Spetzler and N. Martin) emphasize that the higher the AVM gradation, the higher the surgical risk.

The following risk factors for bleeding from the AVM node are distinguished: young age, a history of hemorrhage, deep and subtentorially located AVMs, a fistula in the AVM, aneurysms, the only draining vein, participation in the blood supply of the branches of the external carotid artery [8,9]. In children, hemorrhage from AVM node as the debut of the disease occurs much more often - in 80% of cases [10]. More often, hemorrhage occurs with small AVM sizes and their deep location. There are parenchymal, subarachnoid, ventricular hemorrhages and combinations of various types. Clinically, hemorrhage is manifested by cerebral and focal symptoms. Cerebral symptoms are characterized by intense headache (sometimes accompanied by vomiting); loss of consciousness, nausea,

lethargy, decreased ability to work. Focal symptoms, depending on the size and location of the arteriovenous malformation in the cranial cavity, may manifest as neurological symptoms associated with impaired function of a particular area of the brain and a particular lobe of the brain (speech, motor, sensory, and others).

The second most common clinical manifestation is epileptic seizures (19–27% of all AVM patients) [12]. In some patients - 20% they develop after seizure, often unrecognized hemorrhages. A relationship was noted between epileptic manifestations and AVM localization in the cortex of the parietal and temporal lobes and blood supply to the branches of the external carotid artery. The key elements of the pathogenesis of the formation of the primary epileptic focus are: cortical localization of the AVM; blood supply by branches of the middle cerebral artery; afferents from the system of cortical arteries; varicose veins of the draining vein, absence of aneurysms in the malformation tangle.

Less common are cephalalgias (1–11%). Cephalgic syndrome most often occurs when the AVM is located in the occipital region, with superficial drainage of the malformation and active participation in the blood supply of the AVM of the branches of the meningeal arteries [13].

Focal neurological deficit is less common (7–15%). Asymptomatic AVMs are mostly incidental findings (0–3%).

Previously, two mechanisms involved in the formation of malformations have been studied: a. abnormal angiogenesis leading to the development of an abnormal direct arterial-venous connection; b. progressive expansion of existing capillary beds leading to shunting of high blood flow from the arterial to the venous bed. These mechanisms have been described in mammals [14,15], but the pathogenesis of AVM has not yet been elucidated.

There are two stages in the development of blood vessels: vasculogenesis and angiogenesis. Vasculogenesis is the process of formation of blood vessels from endothelial progenitor cells in situ. They migrate and fuse with other endothelial progenitor cells into capillaries and differentiate into endothelial cells to form new blood vessels. This process takes place during the embryonic period.

Angiogenesis is the formation of completely new capillaries from existing ones, starting from the 9th day of embryonic development of the fetus [16,17]. Angiogenesis includes activation of endothelial cells, degradation of the extracellular matrix, proliferation and migration of endotheliocytes, and formation of primary highly permeable vascular structures [18,19,20]. Subsequently, another type of cells is recruited: pericytes and smooth muscle cells, as a result of which a complex three-dimensional vascular network is organized. When angiogenesis is modeled, an inflammatory reaction is detected in the surrounding tissues. For the development of inflammation, in addition to the damaging factor, it is necessary to combine various biologically active substances, certain cells, intercellular and cellular-matrix relationships, the development of local tissue changes and general hemodynamic changes in the body.

In the process of vasculogenesis, the following 3 phases of development are distinguished: In the first phase, blood islands are formed, the inner cells of which are hematopoietic stem cells, and the outer cells are formed from angioblasts, which are precursor cells of blood vesselsDuring the transformation of mesoderm cells into hemangioblasts and angioblasts, the fibroblast FGF2 (Fibroblastgrowthfactor) plays the role of growth factor. In the second phase of vasculogenesis, angioblasts proliferate and differentiate into endothelial cells, which in turn form the lining of blood vessels. In the third phase, endothelial cells form tubes and join to form the primary capillary network. Next, angioblasts grow, migrate and bind, resulting in the formation of blood vessels.

When modeling angiogenesis, in the overwhelming majority of cases, an inflammatory reaction is simultaneously detected in the surrounding tissues. Inflammation occurs as a reaction of the body to a pathogenic stimulus and to the damage it causes. Distinguish the following exo and

endogenous factors of the inflammatory response. Exogenous include: biological factors (microorganisms - bacteria, viruses; animal organisms - worms, parasites, foreign proteins); chemical (alkalis, salts of heavy metals, acids); physical factors: mechanical, stimulating angiogenesis (trauma, foreign body, pressure, rupture), thermal (cold, heat), electromagnetic, for example, a pulsating electromagnetic field causes the formation of growth buds and the formation of a lumen in endothelial cells (EC) and radiation exposure (X-ray rays, ultraviolet rays). Endogenous factors are factors that occur in the body as a result of another disease: blood clots, heart attacks, hemorrhages, gall or urinary stones, and others.

In the last few years, genomic studies of various complex diseases have been most deeply studied. The search for genetic determinants of predisposition to AVM is carried out by such methods as: the method of candidate genes, the method of genome-wide linkage and genome-wide association studies, (GWAS). GWA studies made it possible to evaluate the contribution of genes to the development of AVMs, together with environmental factors, for example, the influence of polymorphic variants of inflammatory response genes, angiogenesis, vascular endothelial growth factors, and others on the pathogenesis of AVMs was shown.

In the vascular wall, inflammatory cytokines enhance and increase the risk of damage to the vascular wall in AVM. For the development of inflammation, in addition to the damaging factor, it is necessary to combine various biologically active substances, certain cells, intercellular and cell-matrix relationships, the development of local tissue changes and general hemodynamic changes in the body [21].

Currently, various biologically active substances are known that are secreted by monocytes and macrophages. These include mediators of inflammation and immunomodulation: interleukin-1α,β (IL-1α and IL-1β), IL-3, IL-6, IL-8, IL-10, IL-12, IL-15, neutrophil activating factor , complement components; interleukin-1 receptor antagonists (IL1RN), tumor necrosis factor (TNF-a), fibroblast growth factor, transforming growth factor; coagulation factors and fibrinolysis inhibitors: V, VII, IX, X, plasminogen inhibitors, plasmin inhibitors; adhesive substances: fibronectin, thrombospondin, proteoglycans. They stimulate the proliferation of leukocytes, angiogenesis, migration of endothelial cells, increase the expression of metalloproteinases that damage the walls of blood vessels and lead to rupture of the AVM node. The main active ingredients are also vascular endothelial growth factors - VEGF. The VEGF family of proteins consists of a number of secreted glycoproteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D, endocrine gland VEGF (EG-VEGF), VEGF-E, VEGF-F, VEGF- placental growth factor (PlGF).VEGF-A participates in angiogenesis. VEGF-C and VEGF-D are involved in the genesis of lymphatic vessels. VEGF-B plays a central role in heart development. Members of the VEGF family interact with three major receptors, VEGFR-1 (Flt-1), VEGFR-2 (KDR in humans and Flk-1 in mice), and VEGFR-3 (Flt-4), all of which are tyrosine kinase receptors and members of the PDGF receptor family. The interaction of VEGFs and VEGFR-2 has been extensively studied and appears to play a central role in promoting endothelial cell migration, differentiation, proliferation and viability.

Thus, AVMs are random sporadic mutations in genes that occur during the formation of the fetus. There are disorders in several genes that lead to the growth of new blood vessels at 6-12 weeks of fetal development.

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