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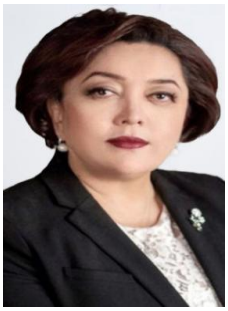
RESEARCH FOR GENETIC DETERMINANTS WHICH MAKE INDIVIDUALS SUSCEPTIBLE TO ARTERIOVENOUS MALFORMATIONS

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ШАХСЛАРНИ АРТЕРИОВЕНОЗ МАЛФОРМАЦИЯЛАРГА МОЙИЛ ҚИЛАДИГАН ГЕНЕТИК ДЕТЕРМИНАНТЛАР БЎЙИЧА ТАДҚИҚОТЛАР

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ИССЛЕДОВАНИЕ ГЕНЕТИЧЕСКИХ ДЕТЕРМИНАНТ У ЛЮДЕЙ, ВОСПРИИМЧИВЫХ К АРТЕРИОВЕНОЗНЫМ МАЛЬФОРМАЦИЯМ

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Резюме. *Артериовеноз малформациялар (АВМ) артериал ва веноз томирлар чегарасидаги аномалиялардир. Улар типик оралиқ паренхимасиз қон томир марказида боғланган диспластик артериялар ва томирларнинг чигаллари шаклланиши билан тавсифланади. "Malus" сўзи "даҳшатли", "ёмон" ва " formation" "шакилланиш" деган маънони англатади. Микрошунт катта АВМга айланмайди, чунки АВМ ҳажми ва меъморий тури генетик жиҳатдан аниқланган ўзига хос фенотипик кўринишни ифодалайди. Артерияларнинг гипертрофияланган деворлари (афферентлар, озиқлантирувчи томирлар), кўп сонли артериовеноз шунтлар, уларнинг ўзаро боғланишидан малформация танаси (фокус) ҳосил бўлади ва кенгайган дренаж томирлари АВМларнинг характерли белгиларидир.*

Калит сўзлар: *артериовеноз малформациялар, мия, қон томир патологияси, генетика.*

Abstract: *Arteriovenous malformations (AVM) are anomalies of the arterial-venous capillary interface. They are marked by the formation of tangles of dysplastic cerebral arteries and veins that connect in a vascular focus without the presence of a typical intermediate parenchyma. The word "malus" means awful, bad, and "formatio" means formation. A tiny microshunt does not develop into a large AVM and a nidus type because AVM size and architectural type represent a genetically established particular phenotypic manifestation. Hypertrophied artery walls (afferents, feeders), a large number of arteriovenous shunts, a tangle of which develops the malformation's body (nidus), and dilated draining veins are characteristics of an AVM.*

Key words*: arteriovenous malformations, brain, vascular pathology, genetics.*

Arteriovenous malformations (AVM) are anomalies of the arterial-venous capillary interface. They characterized by the formation of tubers of dysplastic cerebral arteries and veins that converge in the vascular hearth in the absence of normal intermediate parenchyma. The word "malus" means awful bad and "formatio" means formation.

AVM is a complicated condition that can be affected by the environment as well as the patient's genetic susceptibility. Physical characteristics like blood flow, blood pressure, or tissue tension are examples of damaging factors. Mechanical and electromagnetic aspects, on the other hand, can produce angiogenesis and, for example, cause endothelial cells (EC) to create growth buds and lumens. The area's geographic variety contributes to the growth of AVM as well. It is important to note that although familial observations are rare, the issue is congenital. AVMs are spontaneous gene mutations that occur when an embryo is developing [1]. New arteries start to grow between 6 and 12 weeks of fetal intrauterine development due to a number of gene abnormalities.

Across postmortem studies, the estimated prevalence of AVM varies greatly, from 5 to 613 events per 100,000. The total incidence of AVM varies from 1.10 to 1.42 cases per 100,000 people, based on population studies [3]. The literature has examined two mechanisms of AVM formation: (1) aberrant germinating angiogenesis, which results in the formation of an abnormal direct arterial-venous connection; and (2) progressive capillary channel expansion. The former causes a shunting of high blood flow from the arterial bed to the venous. Although these processes have been explained in animal models [13,14,20], the exact pathophysiology of AVM is still un-

known [10]. AVMs can arise from germline mutations in genes that are known or likely to be involved in angiogenesis and vascular remodeling, such as ENG, ALK1, SMAD4, and RASA1, among others. These mutations can cause AVMs in hereditary syndromes such as hereditary hemorrhagic telangiectasia (HHT) and capillary malformation (CM) [5,19]. Similarly, ALK1 mutations have been linked to the family inheritance of sporadic AVMs.

Genetic research on complicated medical conditions has grown enormously in the last few years. A variety of techniques were used to investigate the genetic determinants of AVM predisposition, which are necessary to build an entire picture of the disease's pathogenesis. These techniques included the use of candidate genes and genomic analysis of chaining and associations (GWAS, genome-wide association studies, and GWA study). The role of environmental factors, such as the influence of polymorphic variants of inflammatory response genes, angiogenesis, and other factors on AVM pathogenesis, together with the contribution of genes to AVM development has been determined through GWA research. Nevertheless, more ethnic group confirmation of the findings is necessary for these data.Hemorrhagic telangiectasia and Sturge-Weber syndrome are illustrations of hereditary disorders that have provided some insight into the critical signaling pathways that promote the advancement of AVM. Studies reveal that 28 AVM morphologies are brought on by interruption of the TGF-β signal and activation of the MAPK pathway [8,15]. Sporadic AVM has been linked to polymorphisms in the following genes: metal peptidase 3 (MMP3), integrin β8 (ITGB8), endoglin (ENG), receptor-growth factor of vascular (VEF), and VEG-growth factor 124-factor of VEF (VEG), angiopoietin-like protein 4 (PTL4) [11]. It has been revealed that the overexpression of the signaling protein family VEGF, which controls angiogenesis, in the AVM core and surrounding astroglia in response to hypoxia-induced stimuli aids in the development of AVMs. The stability of the AVM vascular bed has been associated with the differential expression of angiopoietins (ANG), and the advancement of AVM may be influenced by the interactions between ANG and VEGF [17].

Given that vascular problems are focused, it is possible that AVM creation might come from a combination of events, including a mutation in one copy of a gene inside a particular cell group, which could trigger a pathological process leading to future malformation. These could include mechanical elements that encourage angiogenesis, angiogenic agents, inflammatory cytokines, and environmental variables [6]. Hemodynamic elements include intracorporeal pressure, vascular wall strain and tension, and high blood flow cause a blood stream to form, which in turn triggers molecular pathways in the brain's endothelial cells and smooth lung, resulting in vascular remodeling and proliferation [16,18]. O. Hudlicka states that the interactions between angiogenic factors like VEGF, TGF-b, fibroblast growth factors, intercellular matrix components, etc., and mechanical factors—such as blood flow—is what causes AVM. EC damage happens in the vessel wall, when the vessels are at their most curved. They cause the proteolysis of collagen 4, 5, and fibromylenes, as well as the death of MB, by killing and releasing the fibrinogen's activator, which is then converted into plasmid-protease. Then, damaged ECs may move outside of the vessel wall. In the cytoplasm, the formation of pseudopods and current splitting result in the breakdown of microtubules and microfilaments. It serves as a warning indication for the development of vascular kidneys, further growth, and mitotic division [2].

AVM usually is not hereditary, despite the identification of genetic risk markers. Genetic guidance is typically not necessary for family members of AVM patients. The development and rupture of AVM was related to extracellular matrix remodeling and inflammation. Genetic modifiers linked to bleeding AVM include polymorphisms in interleukin-6 (IL6), IL1, type B receptor 4 ephrine (EPHB4), allele ε2 apolipoprotein E (APOE), and an allele of tumor necrosis factor α (TNF- α) - 238G>A [9]. Vascular network instability may be caused in part by neutrophils and a protein that inhibits macrophage migration [12,17]. Metalloproteinases also seem to be involved in the growth and stability of AVM, since alterations in angiogenesis and vascular instability result from proteolytic enzymes breaking down pericellular materials.

AVM grading was developed in 1986 by R. Spetzler and N. Martin. It is a simple and widely used method. The authors' goal was to create a classification for all cerebral anomalies that is easy to comprehend and that offers a reliable estimate of disability and death. AVM size, affinity number, localization, surgical availability, blood sweat, degree of robbing, functional value of perifocal parenchyma, and drainage system were among the factors they recorded. The list was then condensed by the writers in an effort to provide more approachable standards. These elements included the AVM area's parameters, drainage setup, and functional importance. AVM I, II, III, IV, and V are therefore unique [4].

The AVM size is decided by the nidus maximum size in centimeters. Essentially significant parts of the brain include the respiratory and vasomotor centers, which are more likely to be damaged and result in a severe permanent neurological deficiency. Venous drainage is classified as "superficial" if all outflows occur in the cortical veins, and "deep" if, in addition to cortical drainage, there is an outflow into the internal cerebral, basal, and precentral cerebellar veins [7].

We can determine the degree of grading by adding the scores. The five AVM levels—I, II, III, IV, and V—indicate the increasing intricacy of the deformity and the proportion of anatomical structures. At the I grade, there is little chance of surgery (1 point). A V grade of five points carries a significant risk of death and serious disability. For example, the authors (R. Spetzler and N. Martin) stress that the surgical risk is higher the higher the degree of ABM.

Conclusion. Therefore, vascular damage can arise from various sources initiating the pathological process in the field of future malformation, in addition to a mutation in one copy of the gene throughout an individual cell group.

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ИССЛЕДОВАНИЕ ГЕНЕТИЧЕСКИХ ДЕТЕРМИНАНТ У ЛЮДЕЙ, ВОСПРИИМЧИВЫХ К АРТЕРИОВЕНОЗНЫМ МАЛЬФОРМАЦИЯМ

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Резюме. *Артериовенозные мальформации (АВМ) - это аномалии на границе между артериальными и венозными сосудами. Они характеризуются образованием клубков диспластических артерий и вен, которые соединяются в сосудистом центре без наличия типичной промежуточной паренхимы. Слово "malus" означает "ужасный", "плохой", а "formation" - "образование". Микрошунт не развивается в крупную АВМ, потому что размер АВМ и архитектурный тип представляют собой генетически установленное специфическое фенотипическое проявление. Гипертрофированные стенки артерий (афферентов, питающих сосудов), большое количество артериовенозных шунтов, из переплетения которых образуется тело мальформации (очаг), и расширенные дренажные вены являются характерными признаками АВМ.*

Ключевые слова*: артериовенозные мальформации, головной мозг, сосудистая патология, генетика.*