Abstract of dissertation work
for the degree of Doctor of Philosophy (PhD)
in 8D10102 - Medicine

Title: Evaluation of the influence of clinical and genetic prognostic factors on the course of the arteriovenous malformations in Kazakhstan.

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Relevance of the study.

The scientific work is aimed at studying the influence of clinical and genetic prognostic factors on the course of the disease in arteriovenous malformations of the brain.

Arteriovenous malformation (AVM) is a congenital anomaly of the vascular system characterized by the chaotic interweaving of arteries and veins without the presence of an intervening capillary network. This condition was first described in 1764 by W. Hunter. The frequency of this nosology is 1.3 cases per 100,000 population, with a slight predominance of men (ratio 1.1:1). Thus, according to the study of W.F. McCormick, based on the analysis of autopsies, the frequency of AVM is 0.52%, with surgical activity being 19.7% of all identified cases.

Although many AVMs remain asymptomatic, diagnosis and treatment are essential to prevent serious complications such as hemorrhage and status epilepticus. According to a study by Goldberg (2018), unruptured AVMs are more common than those with intracranial hemorrhage, highlighting the importance of prompt diagnosis and treatment to prevent ruptures. Intracerebral hemorrhage (IC) is the most common complication of AVMs, occurring in 58% of cases. In addition, AVMs trigger seizures in 34% of patients, which are difficult to control with medication.

The exact cause of brain AVMs remains unclear, but they are generally considered to be congenital, developing during embryogenesis. Genetic factors play a key role in the pathogenesis and formation of AVMs, as well as their rupture. Recent studies have identified the importance of somatic and germline mutations, including mutations in the ALK-1, IL-6, TNF-α, and APOE genes, which increase the risk of AVM development and rupture. Mutations in the ENG, ACVRL1, and SMAD4 genes are associated with hereditary hemorrhagic telangiectasia (HHT), an inherited form of AVM. Current genetic research is ongoing to identify new mutations and markers to improve diagnosis and treatment.

The natural history of AVM is associated with a high risk of hemorrhage, which varies from 2.1% to 4.12% per year (Abecassis, A., 2019). There are factors that statistically significantly increase the risk of bleeding. These factors include previous hemorrhage, deep location of AVM, drainage into deep veins, and the presence of

aneurysms. Recurrent hemorrhage occurs in 6-15.8% of cases (Can, A., 2017). These data are extremely important for prognosis and choice of treatment strategy.

The second clinically significant manifestation of brain AVMs are seizures and occur in 29-43% of patients (Garcin, B., 2012). They can be primary or develop against the background of hemorrhage. Studies have shown that seizures are often observed in patients with unruptured AVMs over a long period of time.

Recently, there has been an increased interest in the treatment of patients with cerebral AVMs, including such methods as microsurgical removal, endovascular embolization and radiosurgery. One such study is ARUBA (Mohr, J., 2014), which demonstrated the advantage of conservative treatment over surgery, which led to a significant decrease in the number of surgical procedures for this condition. However, according to Wahood, W. (2021), this was accompanied by a two-fold increase in the incidence of ruptures and a three-fold increase in mortality from this condition. These facts necessitate further research to create an accurate system for assessing surgical risk and determining optimal indications for surgery. Such a system should take into account not only the prevention of hemorrhage but also the improvement of seizure manifestations in drug-resistant epilepsy. This emphasizes the importance of continuing scientific research to optimize treatment and improve the quality of life of patients with cerebral AVMs.

Purpose of the study:

To evaluate the efficacy and safety of surgical interventions (including endovascular and microsurgical methods) in patients with cerebral AVM, considering clinical manifestations associated with hemorrhagic and epileptic symptoms. This evaluation includes an analysis of the dynamics of clinical symptoms, in particular, the dynamics of attacks and hemorrhagic hemorrhages. In addition, this study includes genetic studies among this group of patients, to identify genetic markers associated with the risk of development and rupture of cerebral AVM.

Research objectives:

1. To analyze clinical and demographic factors (age, gender, presence of arterial hypertension, previous hemorrhage, seizure syndrome, surgical intervention) on the course of cerebral AVM in patients in the Republic of Kazakhstan.
2. To analyze the relationship between neuroimaging characteristics (size, localization of AVM, type of drainage) and the course of cerebral AVM.
3. To evaluate key prognostic factors to predict the risk of AVM rupture and select the optimal surgical tactics.
4. To study the course of epileptic syndrome in patients with symptomatic AVMs of the brain after surgical treatment.
5. To conduct a genetic study in patients to search for genes associated with AVM and to study specific associations of gene polymorphisms predisposing to the formation and rupture of AVM in the Republic of Kazakhstan.

Scientific novelty.

In this study, both immediate and remote results of surgical treatment of cerebral AVMs were analyzed for the first time based on a large clinical material covering microsurgical and endovascular methods. The data obtained demonstrate a high level of safety of endovascular and surgical treatment both perioperatively and in the remote postoperative period.

The study confirmed the scientific validity of endovascular embolization of cerebral AVMs to reduce the frequency of seizures in patients with an epileptic type of clinical course, and also confirmed the dependence of the outcomes of the course of structural epilepsy according to the Engel and ILAE scales on the duration of the seizure syndrome. Also, the available data confirmed the high efficiency of the microsurgical method in the treatment of epileptic syndrome caused by cavernous malformations of the brain.

A retrospective analysis of the endovascular treatment of AVM of the vein of Galen in the pediatric age group was carried out, which made it possible to identify the influence of partial embolization and the age of children on the clinical outcome of surgical intervention.

Genetic analysis of patients with cerebral AVMs was performed, which revealed rare variants of the SIRT gene (g.67884831C>T) associated with congenital arteriovenous malformations (bAVM), as well as a somatic mutation in exon 12 of the KRAS gene (KRAS p.G12D), which is consistent with previous studies and supports the hypothesis of the involvement of somatic KRAS mutations in the formation of cerebral arteriovenous malformations.

Practical significance.

- The data obtained will allow us to predict the risk of AVM rupture and determine clear indications for the choice of treatment tactics.
- Based on the work performed, several risk factors were identified that affect functional outcomes in patients with cerebral AVMs. Among them are AVM localization, type of blood supply, classification according to the SM scale, duration of seizures, and age of patients.
- The use of prognostic markers and specific genetic polymorphisms identified during the study to predict the risk of AVM occurrence and rupture facilitates early diagnosis and prevention of AVM rupture.
- The results of genetic studies of AVMs in the Republic of Kazakhstan will be used to organize a system of medical monitoring and prevention of AVM rupture, as well as to identify pathologies in family members vulnerable to this problem based on genetic information.
- The recommendations being developed are relevant for practical healthcare, since based on genetic testing for polymorphisms it will be possible to assess the risk of developing AVM in the population of the Republic of Kazakhstan and, depending on the risk group, conduct preventive gene and surgical therapy.

• The obtained results of the study are currently used in the protocol of e-treatment applied in the Republican Center for Health Development of the Ministry of Health of the Republic of Kazakhstan in patients with AVM of the brain. In JSC "National Center of Neurosurgery" these protocols are included in the training program for residents and practicing doctors who work with patients suffering from various forms of AVM of the brain.

• The obtained data also served as the basis for a scientific grant provided by the Ministry of Education and Science of the Republic of Kazakhstan. This grant is devoted to the study of new germinal and somatic mutations in brain AVM.

The main provisions submitted for defense

• Endovascular embolization and microsurgical excision of brain AVMs have a positive effect on the dynamics of seizure syndrome in this category of patients. These methods improve control over epileptic seizures and improve the quality of life of patients.

• Endovascular embolization and microsurgical removal in the treatment of cerebral AVM with epileptic manifestations do not increase the risks of severe complications and mortality compared to the natural course of this nosology. This justifies the recommendation to use these treatment methods in this group of patients. Moreover, the risks of complications in the intra- and postoperative periods are higher in patients with AVM who have had a hemorrhage in their anamnesis. This confirms the need for surgical intervention in patients with previous hemorrhages due to rupture of arteriovenous malformations of the brain.

• In the treatment of AVM of the vein of Galen, staged partial embolization, as well as performing surgery in children over 6 months, demonstrate more favorable results of surgical treatment both in the early and late postoperative periods, compared with other intervention methods.

• Identification of rare variants in SIRT genes and mutations in exon 12 of the KRAS gene are important and are associated with a predisposition to the occurrence and rupture of brain AVMs.

Testing the work.

The results of the study were presented at:

- 3rd Congress of Neurosurgeons of Uzbekistan (Samarkand, May 27-28, 2022);
- International Neurosurgical Forum and Neurosurgical Film Festival (Astana, July 01-03, 2022);
- LINNC SEMINAR – ASIA Edition 2022, Interventional Neuroradiology, Neurology & Neurosurgery Course. (Singapore, 6-7 December 2022);
- V Congress of Neurosurgeons of Kazakhstan (Astana, June 29-30, 2023);
- Future of Microsurgery, 3rd International Rhoton Society Meeting, Istanbul, Turkie (Istanbul, Turkey, August 20-26, 2023);

- International neurosurgical Congress “Silk Road” & 7th Congress of International Society of Minimally invasive Neurosurgery (Tashkent, September 15-17, 2023).
- 15th European Epilepsy Congress (Italy, Rome, September 7-11, 2024)

Publication details:

• On the topic of the scientific work, 12 scientific printed works have been published, including 6 in journals included in the Web of Science Core Collection database published in editions included in the first quartile (five articles) and the second quartile (one article) by impact factor according to the Journal Citation Reports of Clarivate Analytics. In four of the articles, the doctoral student is the first author, and in two of them the corresponding author. 2 articles in editions recommended by the Committee for Control in the Sphere of Education and Science. 6 publications in the materials of international conferences (Kazakhstan, Russian Federation, Uzbekistan, UAE, Turkey, Italy).