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GENETIC RISK FACTORS OF THROMBOFILIA IN A YOUNG ISCHEMIC STROKE PATIENT (CLINICAL CASE REPORT)

ABSTRACT

Stroke is a multifactorial disease. The stroke pathogenesis is caused by a combination of several risk factors. A determination of the genetic predisposition to stroke is especially important for young patients. Understanding the stroke development mechanisms is extremely useful for adequate treatment and secondary prevention of the disease. We present the case report of ischemic stroke in the young patient with basilar artery thrombosis and severe neurological symptoms. Diagnostics included the clinical, neurological, neuroimaging, ultrasound, immunological, molecular-genetic examination. Genotyping of polymorphisms of hemostasis system's genes *FV, FII, FVII, FXIII, FGB, ITGA2, ITGB3, PAI-I* was conducted. It was found the carrying of the three polymorphisms associated with the thrombosis and ischemic stroke risk: genotype GA polymorphism - 455 G> A gene *FGB*, genotype CT polymorphism 807 C> T *ITGA2* gene, 4G / 4G genotype of polymorphisms 5G> 4G gene *PAI-I*. Thrombophilia due to the carrying of these genetic variants in combination with an antiphospholipid syndrome, altered immune status, were predisposition factors of vertebro-basilar's system ischemic stroke in the young patient.

Keywords: ischemic stroke, vertebro-basilar system, thrombosis, *FV* gene, *FII* gene, *FVII* gene, *FXIII* gene, *FGB* gene, *ITGA2* gene, *ITGB3* gene, *PAI-I* gene

INTRODUCTION

Most strokes are multifactorial diseases, and the combination of several risk factors is important in its pathogenesis, including genetic ones. Despite the significant advances in the diagnostic technologies had been achieved recently, the significant share of strokes is currently regarded as cryptogenic, i.e. a disease of unknown etiology. Determining the possible cause of stroke, especially in young patients, involves conducting a wide range of diagnostic procedures, including genetic examination. Despite the limited using of these molecular genetic studies in clinical practice, the testing for a carriage of known variants of risk gene polymorphisms can be useful for understanding the pathogenic mechanisms of the disease and selecting adequate treatment and effective secondary stroke prevention. In this article, we present the clinical case of ischemic stroke due to basilar artery thrombosis in the young patient, with an interpretation of the alleged genetic risk factors.

Clinical case report. Patient R., female, 21 years old, admitted to Regional Vascular Center (Yakutsk) with diagnosis: Ischemic stroke in the vertebro-basilar system due to basilar artery thrombosis, for the emergency indications, in serious condition. The disease developed acute during physical exercise (training in the gym). Suddenly developed a headache, dizziness, nausea, general weakness. The arterial pressure was 108/60 mm Hg, pulse was 112 per minute. In anamnesis: patient was observed with endemic goiter by endocrinologist, using iodine preparations constantly, there are no other chronic diseases, arterial pressure was with a tendency to hypotension (90/60 mm Hg). The intake of oral contraceptives is denied, there were no pregnancies. Relatives of the first line are healthy; the patient's cousin suffered a subarachnoid hemorrhage due to an arterial aneurysm rupture and was received surgical treatment.

At admission to the hospital, the patient's condition was severe. No pathological abnormalities were detected in the somatic status. Skin and visible mucous membranes were clean with normal color. In neurological status: consciousness's depression to soporus; craniocerebral innervation disorders with the bulbar symptoms (anarthria, dysphagia, aphonia); oculomotor disorders (divergent strabismus); motor disorders (deep tetraparesis with plegia in the lower extremities, bilateral pathological pyramidal signs), moderate meningeal syndrome.

The brain magnetic resonance imaging (MRI) scan determines the acute ischemia zones in the pons 2.3 x 2.6 cm in size, and in the cerebellum left hemisphere 2.1 x 2 cm in size. Screening MR-angiography of Willis Circle determines the total basilar artery occlusion. The blood flow in the posterior cerebral arteries (PCA) on both sides was supported through the posterior connective arteries (PCoA). MRI study conclusion: Total occlusion of the basilar artery. Areas of acute ischemia in the pons and in the left cerebellum hemisphere (Figures 1 and 2).

Laboratory blood value showed: potassium level – 3.2 mmol / l, sodium – 146 mmol / l (normal), transient hyperglycemia to 7.6 mmol / l, in complete blood count – leukocytosis 15.9 x 10^9 / l, platelets 289 x 10^9 / l (normal), increased level of blood sedimentation rate in dynamics from 15 to 57 mm / h. The study of blood culture for sterility – there is no growth. It was performed the blood coagulating testing in dynamics. Fibrinogen level was 2.9-4.2 g / l (norm 2-4 g / l); international normalized ratio (INR) in dynamics: 1.12-1.2; activated partial thromboplastin time (APTT) increased with anticoagulant therapy (from 23.3 to 63.2); prothrombin index (PTI): 48.4 – 73.5; thrombin time – 15.7 seconds; protein C (activated Coagulation factor XIV) – 79% (norm 70-130%); protein S (cofactor protein C) – 58% (normal 60-140%); D-dimer – 0.27 ng / ml. The value of lupus anticoagulant was 0.87 (normal 0.8-1.2 conventional units).

Immunological examination data were as follows: no lupus Le cells. In addition, it was detected the disorders in level of blood circulating immune complexes: increased level of anti-streptolysin O (750 IU / ml) and C-reactive protein – 48 mg / l. Enzyme-linked immunosorbent assay (ELISA) were as follows: immunoglobulins G (IgG) of cytomegalovirus, simplex herpes virus – detected; ELISA on ANA (antinuclear antibody, ANA) – not detected; ELISA for antiphospholipid syndrome (APS) – IgG increased.

Data of cardiovascular system examination detected: electrocardiogram - sinus rhythm (with a transient tachycardia to 118 per minute), the heart electric axis is vertical, nonspecific changes in the myocardium in the lower wall. On the 24-

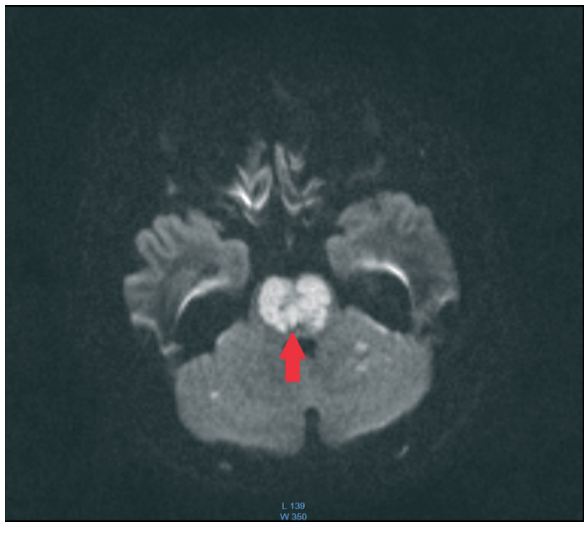

Figure 1. Patient P, 21 years old. Magnetic resonance imaging of the brain, diffuse-weighted image, B-factor 1000. Zone of acute ischemia (arrow) in the pons.

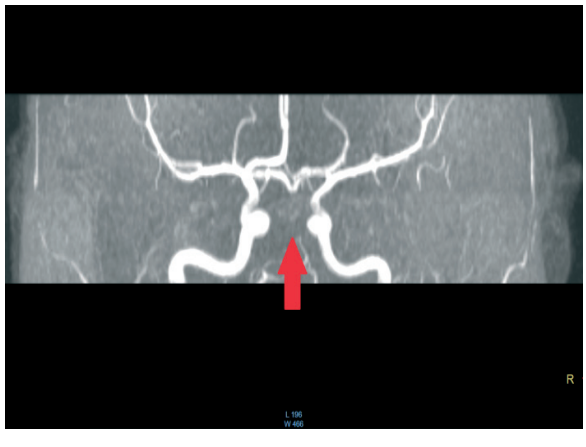

Figure 2. Patient P, 21 years old. Magnetic resonance imaging of the brain. Time-of-flight angiography. There is no MR signal from the basilar artery (arrow)

hour blood pressure monitoring, it was not registered hypertension. Ultrasound examination of the heart detected that the global systolic function of the left ventricle (LV) is normal, the ejection fraction is 66%, LV diastolic function has 1 type, 1st degree mitral regurgitation, the heart cavity is not dilated, the disturbed myocardium zones of the left ventricle are not revealed. Ultrasound examination of brachiocephalic and cerebral arteries revealed a blood flow decrease in the vertebral arteries from both sides. Vertebral artery had small diameter on both sides. Echo graphic signs of functional vasospasm along the right middle cerebral artery. The occlusion of the right posterior cerebral artery it was suspected.

A molecular genetic study was conducted at the National Center of Medicine-Republican Hospital No. 1 (Yakutsk). It was performed the genotyping of SNPs of genes of hemostasis system including polymorphism 20210 G> A of gene *FII* (rs1799963), polymorphism 1691 G> A of gene *FV* (rs6025), polymorphism 10976 G> A of gene *FVII*; polymorphism G> A of gene *FXIII* (rs5985), polymorphism - 455 G> A of gene *FGB* (rs1800790), polymorphism 807 C> T of gene *ITGA2* (rs1126643), polymorphism 1565 T> C of gene *ITGB3* (rs5918), polymorphism 675 5G> 4G of gene *PAI-I* (rs34857375). The results of the genetic research: genotype GG of polymorphism 20210 G> A *FII*, genotype GG of polymorphism 1691 G> A *FV*, genotype GA of polymorphism 10976 G> A *FVII*, genotype GG of polymorphism G> A *FXIII*, genotype GA of polymorphism G> A *FGB-455*, genotype CT of polymorphism 807 C> T *ITGA2*, genotype 1565 T> C of polymorphism TT *ITGB3*, genotype 4G4G of polymorphism 675 5G> 4G *PAI-I*. Patient was counseled by hematologist, the diagnosis: Congenital thrombophilia, mutations in genes *FVII*, *FGB*, *ITGA2*, *PAI-I*. Secondary antiphospholipid syndrome, hormone-induced.

The brain MR scan on the 34th day of the disease determined residual the post ischemic gliosis changes in the pons measuring 2 x 2.5 cm. Gliosis changes have small cysts measuring 0.2 cm. Gliosis post ischemic changes in the left hemispheres of the cerebellum measuring 1 x 0.8 cm. There is a restoration of blood flow along the basilar artery. Conclusion: Post ischemic gliosis in the pons and in the left hemisphere of the cerebellum. Restoration of blood flow in the basilar artery.

The patient received the intensive basic stroke therapy, anticoagulant, neuroprotective therapy, nootropics, symptomatic treatment, early neurorehabilitation. Later the patient received a long course of rehabilitation treatment with a good positive dynamics, with regress of focal symptoms to mild tetra paresis, dysarthria. The use of anticoagulant therapy continued for several months.

Discussion. We presented the case report of ischemic stroke (IS) in a young patient. An acute impairment of cerebral circulation developed due to the occlusion (thrombosis) of a large artery of the vertebra-basilar system, which caused ischemia in the brainstem and cerebellum. It was develop the severe cerebral and focal manifestations.

The diagnostic algorithm of the disease included a differential diagnosis between cerebral vascular dissection; cardioembolysm due to the congenital or acquired heart defects, rhythm disturbances, volume formations in the heart cavity, endocarditis; thrombosis due to violations of blood coagulation properties; antiphospholipid syndrome of various genesis; systemic diseases; vasculitis; sepsis; congenital anomalies of cerebral vessels.

According to the survey data, the cardiac, septic cause of the disease, the anomalies of the development of cerebral vessels were excluded. The examination results indicated the blood coagulating impairments, immunologic status disorders. These changes could arise as a nonspecific reaction to a serious acute disease, or be a provoking factor of a stroke. To diagnostics the coagulation system hereditary defects, it was performed the genotyping of eight polymorphisms of genes associated with thrombosis risk. It was genotyped the polymorphism 20210 G> A of gene *FII*, polymorphism 1691 G> A of gene *FV*, polymorphism 10976 G> A of gene *FVII*, polymorphism G> A of gene *FXIII*, polymorphism -455 G> A of gene *FGB*, polymorphism 807 C> T of gene *ITGA2*, polymorphism 1565 T> C of gene *ITGB3*, polymorphism 675 5G> 4G of gene *PAI-I*.

Diagnosis of the pathogenesis type of stroke is extremely important for adequate treatment and secondary prevention of stroke. Nevertheless, according to the literature, 20%-40% of ischemic strokes are cryptogenic, that is, with unidentified (unspecified) etiology [2]. Now most strokes are recognized as multifactorial diseases, several risk factors may be important in pathogenesis, including genetic ones. According to some authors, stroke is a polygenic disease [9]. Carrying out several polymorphisms of the predisposition of certain genes can lead to a higher risk of stroke than the carriage of one such polymorphism [12]. The stroke predisposing candidate genes include genes *FV, FII, FGA / FGB / FGG, FVII, FXIIIA1, vWF, FXII, SERPINE1, ITGB3 / PLA1 / PLA2 / ITGA2B, ITGA2, GP1BA, ACE , AGT, NOS3, APOE, LPL, PON1, PDE4D, ALOX5AP, MTHFR, MTR* and

CBS [9].

The most frequent thromboses predisposing gene variants are the some polymorphisms of genes of factor V (Leyden mutation), prothrombin (factor II), MTHFR [3, 4, 10, 11, 15]. Hereditary thrombophilia with concomitant risk factors, such as surgical operation, trauma, prolonged immobilization, a pregnancy and puerperium, oral contraceptives using, antiphospholipid antibodies and hyperhomocysteinemia may increase the risk of cerebral venous thrombosis. Similarly, the joint inheritance of two or more known mutations also significantly increases the risk [4]. Pathological conditions of the vessel walls (for example, due to atherosclerosis or inflammation) can lead to activation of coagulation through the internal mechanism and increase the likelihood of thrombotic incidents [1, 19].

Factor V is required as a cofactor for activating factor Xa, which in turn activates prothrombin [1]. The "Leiden" mutation is considered as one of the most significant factors of the thrombosis genetic risk [1, 4], the genotypes AA and GA of this polymorphism increase the venous thrombosis risk and ischemic stroke risk, including arterial thrombosis at a young age [20].

Prothrombin (factor II) is the key protein of the coagulation cascade from which thrombin is formed, it converts fibrin into fibrinogen [1]. Polymorphism G20210A of the gene *FII* is associated with an increased prothrombin level in plasma and is a very significant genetic risk factor for venous thrombosis [1]. Variants GA, AA of polymorphism 20210 G> A of gene *FII* are associated with IS risk, venous thrombosis, thromboembolism [20]. "Leiden" mutation, the G20210A prothrombin gene mutation and a deficiency of protein S and C, cause a reduction in the control of thrombin generation. Deficiency of antithrombin causes a decreased neutralization of thrombin. Both these mechanisms are responsible for venous thrombosis [4].

Factor VII (vitamin-K-dependent clotting factor VII) binds to factor III and further activates the "external" coagulation mechanism with significant damage to blood vessels. Increased activity of factor VII is associated with a risk of thrombosis [1]. The study [14] showed that two *FVII* polymorphisms, -670C and IVS7 seven or higher, are independent risk factors for ischemic stroke in young adult patients. Genotypes AA 10976 G> A of *FVII* gene and GA 10976 G> A of *FVII* gene are associated with a decrease in the factor VII level in the blood and with a decrease in the risk of myocardial infarction [20].

Factor XIII (fibrin-stabilizing factor) FXIII A1 forms cross-links of fibrin molecules, thus stabilizing thrombus. The biologically active form consists of globules of two types: alpha and beta. Polymorphism of V34L in the alpha globule was associated with a reduced risk of venous thrombosis, myocardial infarction and stroke [1, 5]. Variants of GT, TT of polymorphism G> A of the gene *FXIII A1* (rs5985) are associated with a decrease in the venous thrombosis risk [20].

Elevated levels of beta-fibrinogen (FGB) in plasma are associated with a risk of cardiovascular disease. Polymorphism -455 G> A gene *FGB* associated with increased fibrinogen levels [1, 7]. Carriage of the genetic variants GA, AA of this polymorphism significantly increases the risk of stroke [20]. The study [12] examined the association between the IS risk and C677T polymorphism of methylenetetrahydrofolate gene (*MTHFR*), polymorphisms 455G and T148C of beta-fibrinogen gene (*β-FGA*), polymorphisms ε2-4 of apolipoprotein E gene (*APOE*), polymorphism I/D of angiotensin converting enzyme gene (*ACE*), polymorphism G894T of endothelial nitric oxide synthase gene (*eNOS*). The results of this study showed that two polymorphisms (*ACE* I/D and *β-FG* T148C) are significant synergistic contributors to the disease risk. For example, the combination of *ACE* DD and *β-FG* 148CC, *ACE* DD and *β-FG* 148CT, *ACE* ID and *β-FG* 148CC resulted in high risk of IS [12].

The plasminogen activator inhibitor-1 gene (*PAI-1*) is associated with the stroke pathogenesis [18]. Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of fibrinolysis, as well as a marker of inflammation. Polymorphism 4G / 5G gene *PAI-1* is associated with PAI-1 levels in plasma in different ethnic populations [18] and thromboembolism [1]. Carriage of genetic variants of 5G / 4G and 4G / 4G of this polymorphism increases the level of PAI-I in the blood, reduces fibrinolytic activity and increases the risk of cardiovascular diseases [20]. The aim of the study [18] was to determine the possible potential relationship between 4G / 5G polymorphism of gene *PAI-1* and the PAI-1 level, IS risk in young Asian Indians. The PAI-1 level was significantly higher in patients than in the control group (p = 0.03). The variant involving 4G allele showed both genotypic (p = 0.0013, $\chi 2$ = 10.303; odds ratio [OR] = 3.75) as well as allelic association (p = 0.0004, $\chi 2$ = 12.273; OR = 1.99) with IS. It was also found that the homozygous variant 4G / 4G is associated with higher levels of PAI-1 (p = 0.005) [18]. However, the study [16] did not establish the association between insertion/deletion (4G/5G) polymorphism of plasminogen activator inhibitor *PAI-1* gene and IS in German child population. The distribution of the 4G/5G genotypes was no different in childhood stroke patients and controls [16]. The same results were established in study [17] which suggests that the 4 G/5 G polymorphism of the *PAI-I* gene is not a risk factor of ischemic stroke in Polish children.

Integrin alpha-2 platelets (glycoprotein IIa) ITGA2 is the main platelet receptor of collagen. *ITGA2* polymorphisms are associated with coronary heart disease and myocardial infarction [1, 6]. In several studies, the relationship between the -GA807T polymorphism of the gene *ITGA2* (rs1126643) and IS were studied, but the results were inconsistent [8]. It was performed a meta-analysis of studies on the association of polymorphism -C807T *ITGA2* (rs1126643) with IS, a total 15 studies with stroke cases (n=2242) and control groups (n=2408). The authors suggest that the polymorphism C807T of gene *ITGA2* may be a susceptible predictor of the IS risk [8]. Variants CT, TT of polymorphism 807 C> T *ITGA2* are associated with IS risk and thromboembolism [20]. It was established the cardiovascular disease risk and thromboembolism are associated with polymorphism 1565 T> C *ITGB3* (genotypes CT and CC) [20].

Study [13] investigated the association between polymorphisms of the two integrin genes (C807T of *ITGA2* gene and T176C of *ITGB3* gene) and IS risk, plasma lipid and lipoprotein levels. As expected, total cholesterol, triglycerides and low-density lipoprotein were significantly higher in the patient's group compared with the control group (p<0.05). The genotype and alleles frequencies of -C807T *ITGA2* were significantly different between patients and the control group (p <0.05), but no differences were found between groups in the frequencies of genotypes and alleles of T176C *ITGA3*. Allele T *ITGA-2* had a relative IS risk higher in 1.266 times (OR = 1.226, CI 95%: 1.053-1.428) than allele C. In addition, the total cholesterol level was higher in T-allele carriers compared with non-carriers (p <0.05). Thus, the T allele of polymorphism C807T *ITGA2* is associated with ischemic stroke [13].

As follows from the above, the most studied genetic factors of thrombophilia can contribute to the development of both venous and arterial strokes. In the devel-

opment of the disease, in most cases, a number of factors are important. Hereditary predisposition to defects of thrombus formation, especially in young patients, can become a key link in the pathogenesis of a stroke.

Thus, the patient R., 21 years old, with ischemic stroke in the background of basilar artery thrombosis was genotyped on the most significant polymorphisms of genes that affect the hemostatic system. The carriage of three variants of polymorphisms associated with the risk of thrombosis and ischemic stroke (GA genotype of the polymorphism -455G> A *FGB*, the CT genotype of the polymorphism 807 C> T *ITGA2*, the 4G / 4G genotype of the polymorphism 5G> 4G *PAI-I*). In the presented clinical case, the participation of the products of these genes in the disease pathogenesis manifested the hyperactivation of thrombus formation on the probably altered endothelial site of the large artery of the vertebrobasilar system. The contribution to the disease development included the genetically determined thrombophilia in combination with the altered immune status, antiphospholipid syndrome. In this clinical case, the observation of the patient for the long period with the monitoring of the blood coagulation, immune status, blood lipid spectrum, general clinical trials continued anticoagulant therapy for secondary stroke prevention is expedient.

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