ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

Assessment of the Significance of Polymorphic Allelic Variants of the Genes of the Hemostasis System in the Development of Cerebrovascular Disorders in Metabolic Syndrome

Received: 12 February 2023, **Revised:** 16 March 2023, **Accepted:** 18 April 2023

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Keywords
vasoactive effect and control, atherosclerosis, arteriogenesis, cerebral edema, neuroprotection, neurogenesis

Abstract
The leading cause of cerebrovascular diseases, including stroke, is the pathology of cerebral vessels.

There is evidence of the involvement of VEGFs in the development of atherosclerosis, arteriogenesis, cerebral edema, neuroprotection, neurogenesis, angiogenesis, post ischemic repair of the brain and blood vessels, as well as the effects of transplanted stem cells in experimental stroke [2,5,14]. It has been shown that VEGFs are involved in all phases of vascular, including neurovascular, development [5]. VEGF induces the differentiation of mesenchymal progenitor cells and vasculogenesis, a process that is crucial for the production and repair of blood vessels, as well as neovascularization of ischemic tissues [6,7]. VEGF is involved in hypoxia-induced angiogenesis, or sprouting of new capillaries from existing vessels [16], as well as in arteriogenesis, or expansion of anastomotic arteriolar channels in response to arterial pressure gradients [15]. In addition, VEGFs have a direct trophic and protective effect on neurons [9,18,21].

At the same time, it is known that a high level of VEGF increases vascular permeability [19,20,20] and has inflammatory activity [15,16], which leads to connective tissue damage. Since damage to the vascular endothelium is a trigger for the development of atherosclerosis [4,12], a violation of the vasoreparative function of VEGF contributes to the development of vascular pathology.

Thus, according to the literature data, the vascular and neuronal activity of VEGF, the vector of which is determined by the level of the factor, is related to the pathogenesis of cerebrovascular diseases.

Hyperhomocysteinemia is a metabolic disorder characterized by an increased content of homocysteine in the blood serum of more than 15 mmol/l. The reasons may be genetic defects of folate cycle enzymes, vitamin deficiency (folic acid, B12, B6), as well as some diseases. Hyperhomocysteinemia itself may not have clinical manifestations, but it significantly accelerates the processes of atherosclerosis and increases the risk of thrombosis. As a treatment, preparations of FC, vitamin B12, B6 are used.

Homocysteine is a sulfur-containing amino acid and an intermediate of methionine metabolism. In 1969, American pathologist Kilmer McGill suggested for the first time that homocysteine in high concentrations can have a negative effect on the cardiovascular system. Then, in 1975, a group of British scientists managed to experimentally confirm this theory. Hyperhomocysteinemia is more common among the elderly, more often in men.

Homocysteine metabolism is carried out with the help of several enzymes – methylenetetrahydrofolate reductase (MTGFR), B12-dependent methyltransferase (MT), betaine-homocysteine-methyltransferase (BGMT). With insufficient activity of these enzymes, the processes of metabolic conversion of homocysteine are disrupted and its accumulation occurs in the body. The main causes of hyperhomocysteinemia are listed below:

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Vitamin deficiency. Folic acid, as well as B12 and B6 are coenzymes of the enzymes listed above, therefore, if they are insufficient, hyperhomocysteinemia develops. This is more often observed in vegetarians, vegans, people suffering from malabsorption (celiac disease, Crohn's disease, pancreatitis), alcohol and smoking abusers.

Genetic mutations. Mutations of the MTGFR gene (polymorphisms C677-T, A1298C) are most common. Heterozygous carriers of these mutations are 40-60% of the population of the Russian Federation, Europe and the USA.

Kidney diseases. Homocysteine is excreted from the body with urine, therefore, hyperhomocysteinemia occurs when the excretory function of the kidneys is impaired. 80% of patients with diabetic nephropathy have varying degrees of hyperhomocysteinemia, and among patients with CRF, this indicator reaches 100%.

Some medications, by worsening the absorption of vitamins, can lead to hyperhomocysteinemia. Such drugs include:

Proton pump inhibitors: omeprazole.

Antagonists of H2-histamine receptors: ranitidine.

Hypoglycemic drugs: metformin.

Cytostatics: methotrexate, cyclosporine.

Oral contraceptives.

Sulfonamides.

The human VEGF gene is located on chromosome 6 at the 6p21.3 locus [211,198,272]. To date, at least 20 potentially functional single nucleotide DNA polymorphisms (SNPs) of the VEGF gene are known. Among the known VEGF SNPs, gene expression is regulated by such polymorphisms as -2578C>A (rs699947), -634G>C (rs2010963), -1612G/A (rs10434), and -936C>T (rs3025039) [128]. By determining the concentration of the VEGF protein, these polymorphisms affect the process of angiogenesis and can potentially be associated with individual variations in the risk of developing stroke.

Purpose of the study: to determine the significance of polymorphic allelic variants of the vascular endothelial growth factor (VEGFA) gene in the development of ischemic stroke.

The data obtained indicate that the carriage of the C allele increases the risk of stroke, however, the absence of a significant difference between the 1st and 2nd subgroups may indicate that the polymorphism is not associated with the involvement of the metabolic syndrome in the development of cerebrovascular complications.

When analyzing the distribution of genotypic variants of the rs2010963 polymorphism of the VEGF gene, a predominance of the homozygous genotype for the "wild" allele was found in the population control group (75.82%). The

frequency of the G/G genotype in patients of the main group, as well as the 1st and 2nd subgroups, was comparable and significantly differed from the control (control - 75.82%; main group - 56.25%; $\chi 2 = 7.95$; $p = 0.005$; OR=0.41; 95% CI 0.22-0.77; 1st subgroup – 56.25%; $\chi 2=5.64$; $p=0.02$; OR=0.41; 95% CI 0.19-0.86; 2nd subgroup - 56.25%; $\chi 2=5.64$; $p=0.02$; OR=0.41; 95% CI 0.19-0.86) (Fig one).

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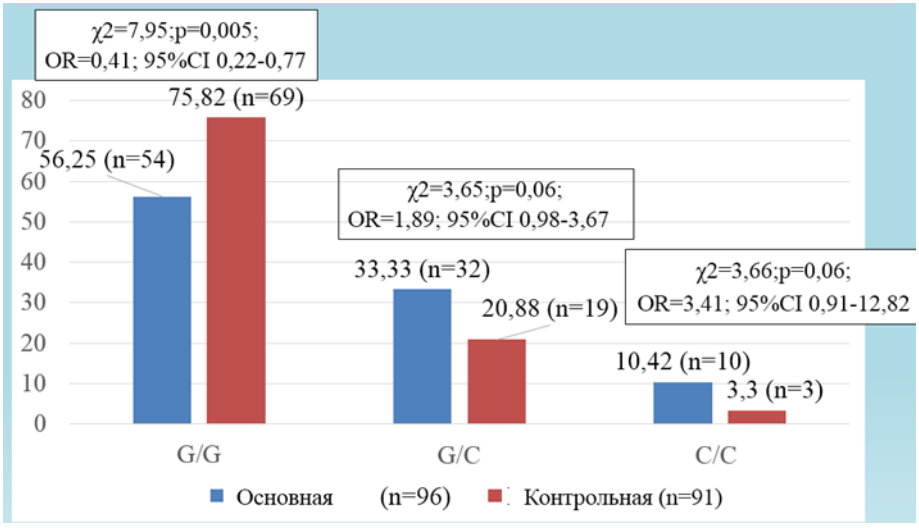

Figure 1.

The data obtained may indicate a protective effect of the genotype homozygous for the "wild" allele in relation to the development of stroke.

The lowest frequency of the heterozygous genotype was registered in the control group (20.88%). The frequency of the G/C genotype in patients with stroke in the main group was not significantly higher than the control (33.33 and 20.88%; $\chi2=3.65$; p=0.06; OR=1.89; 95% CI 0.98-3 .67). In subgroups of patients with stroke, the heterozygous genotype was also more common than in the population control group (1st subgroup - 35.42%; $\chi2=3.46$; p=0.06; OR=2.08; 95% CI 0, 95-4.52; 2nd subgroup - 31.25%; $\chi2=1.83$; p=0.18; OR=1.72; 95% CI 0.78-3.8).

Although the presence of the G/C genotype increases the risk of developing cerebrovascular complications against the background of the metabolic syndrome by 2.1 times, and without the metabolic syndrome by 1.7 times, the difference in the frequency of occurrence of the heterozygous genotype with the control in all studied samples was not significant. (Fig. 6). We also failed to identify a significant difference in the frequency of the heterozygous genotype when comparing the studied subgroups (1st subgroup - 35.42%; 2nd subgroup - 31.25%; $\chi2=0.19$; p=0.67; OR=0 .83; 95% CI 0.35-1.94), which does not confirm the association of the studied polymorphism with stroke developing against the background of MS.

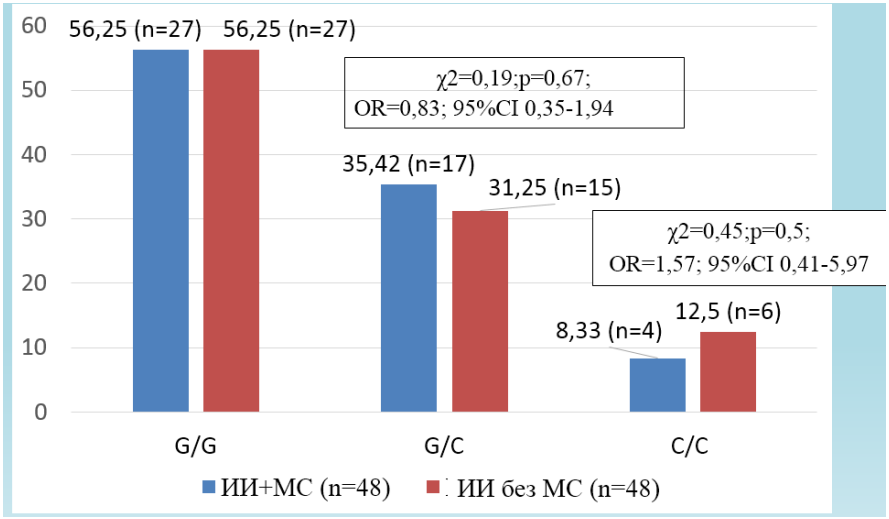

Figure 2

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Homozygous for the mutant allele, the C/C genotype of the rs2010963 polymorphism of the VEGF gene in the population control sample was found in 3.3% of cases, while among patients with stroke in the main group - in 10.42% ($\chi2$=3.66; p=0.06; OR=3.41; 95% CI 0.91-12.82). The study showed that the carriage of a genotype homozygous for the altered allele slightly increases the risk of developing cerebrovascular complications by 3,4 times. It was noted that in the subgroup of patients with stroke on the background of MS, the frequency of the C/C genotype was lower than in patients without MS (subgroup 1 - 8.33%; subgroup 2 - 12.50%; $\chi2$=0, 45; p=0.5; OR=1.57; 95% CI 0.41-5.97). At the same time, the frequency of the homozygous genotype in subgroup A did not have a significant difference with the control (subgroup 1 - 8.33%; control - 3.3%; $\chi2$=1.67; p=0.2; OR=2.67; 95% CI 0.57-12.44), while the difference between this indicator and the control in the 2nd subgroup was significant (2nd subgroup - 12.50%; control - 3.3%; $\chi2$=4.4; p=0.04; OR=4.19; 95% CI 1-17.58). The odds ratio indicator indicates an increase in the risk of developing stroke without MS in the carriage of the C/C genotype by 4.2 times, however, there is no significant difference in the frequency of occurrence of this marker between subgroups of patients ($\chi2$=0.45; p=0.5; OR= 1.57; 95% CI 0.41-5.97) does not confirm its association with MS.

Thus, the data obtained indicate an association of the rs 2010963 polymorphism cerebrovascular disorders. At the same time, the associative relationship can be traced about both heterozygous and homozygous genotypes. However, we failed to identify the relationship between this genetic marker and the metabolic syndrome in the pathogenesis of stroke.

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