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THE ROLE OF PLEIOTROPIC CYTOKINE (TGFB) IN THE DEVELOPMENT OF ACUTE CEREBROVASCULAR DISORDERS IN THE PRESENCE OF THE METABOLIC SYNDROME

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Abstract
Metabolic syndrome - a condition that represents a combination of several factors (hyperinsulinemia, hypertension, dyslipidemia, obesity), which greatly increases the risk of cerebrovascular diseases. In our study, we examined patients with ischemic stroke in the acute phase of the disease - 96 people with metabolic syndrome and without it. It was found significant differences in genetic status in patients with metabolic syndrome on the background with acute ischemic stroke. Alleles and genotypes of the rs1800471 (915G> C (Arg25Pro)) polymorphisms of the gene (TGFβ -1) were studied in patients with ischemic stroke with metabolic syndrome and without it;

Keywords: Ischemic stroke, metabolic syndrome, obesity.

Introduction

Metabolic syndrome, as well as its serious consequences - cerebrovascular disorders - belongs to the group of pathological conditions having a multifactorial etiology.
At present, it is known that multifactorial diseases are caused by the combined action of adverse environmental conditions and genetic factors. The likelihood of development and clinical features of most diseases largely depends on the patient's

genotype, which determines the response of endogenous enzymatic and metabolic systems in response to the action of an exogenous damaging factor. Genes are considered as genetic risk factors for multifactorial diseases, the polymorphic alleles of which cause a change in the functional activity of the expression products involved in certain cellular mechanisms or metabolic pathways. Alleles of polymorphic genes, which are functionally unfavorable concerning the mechanisms underlying the pathogenesis of cerebrovascular pathology, can participate in the formation of a hereditary predisposition to the development of acute cerebrovascular disorders (OCS). A certain set of allelic variants of genes in some cases contributes to disease resistance, and in others, it determines a predisposition to the development of a pathological condition. Therefore, an important task in the study of the pathogenesis of such a multifactorial disease as OTsN is the identification of genetic determinants that determine the risk of pathology

TGFβ-1 is a pleiotropic cytokine secreted by regulatory T-lymphocytes [4], which is involved in the regulation of cell proliferation, in the processes of embryonic development, tissue fibrosis, apoptosis, as well as in the regulation of the immune response, modulating the balance of pro-inflammatory and anti-inflammatory T cells through a complex set of interactions [4,11,19,20].

Defects in the function of TGFβ-1 are associated with several pathological conditions, including tumor cell growth, fibrosis, and autoimmune diseases [4,7,12,13,14]. There is evidence in the literature that TGFβ-1 is a tumor suppressor, as well as a powerful factor capable of inhibiting the proliferation of most types of cells, including epithelial, endothelial, hematopoietic cells, lymphocytes [15].

TGFβ-1 plays an important role in the pathogenesis of cardiovascular diseases, including the pathogenesis of atherosclerosis, arterial hypertension, coronary artery disease, myocardial infarction, myocardial hypertrophy, and fibrotic events in the heart [3,5,10,17,18,19, 20.21]. The mechanisms of development of the pathology of the cardiovascular system are mediated by the ability of TGF-β to induce neoangiogenesis, cardiomyocyte hypertrophy, calcification, and fibrosis [6,20]. It is known that high plasma TGFβ-1 level is associated with vascular stenosis and thrombosis, enhances fibrosis, and inhibits endothelial regeneration, which defines it as a pro-atherogenic factor [6]. Studies by several authors have shown that there is a relationship between an increase in the level of circulating TGFβ-1 and arterial hypertension [3,17,18]. Activation of the TGFβ-1 signaling pathway leads to a decrease in the diameter of the arterial lumen with a subsequent increase in vascular resistance and arterial hypertension [3,21]. It is believed that there is an interaction between TGFβ-1 and visceral fat deposition, which plays a central role in the development of

the metabolic syndrome associated with an increase in the frequency of cardiovascular events [19]

The biological effects of TGFβ-1 described in the literature allowed us to consider this pleiotropic cytokine and its polymorphic gene encoding it as a potential genetic factor in the pathogenesis of cerebrovascular complications in the metabolic syndrome. Despite the obvious connection between TGFβ-1 and pathogenetic mechanisms leading to the development of OTsN, a study of the association of the polymorphism of the TGFβ-1 gene with cerebrovascular disorders in the metabolic syndrome has not yet been conducted.

The gene encoding human TGFβ-1 is located at the chromosomal locus 19p13.1–13.3 [8,16,23]. Gene expression depends on the presence of single nucleotide polymorphic variants (SNPs). Unlike genetic mutations, polymorphisms are variations of the natural DNA sequence. The vast majority (90%) (SNPs) are functionally neutral [7], however, certain polymorphisms affect the regulation of gene expression or the function of a protein encoded by a gene. In particular, according to the literature, the "wild" genotype G / G of the rs1800471 polymorphism (915G> C (Arg25Pro)) of the TGFβ-1 gene, which we selected as a potential predictor of cerebrovascular disorders in the metabolic syndrome, determines the enhanced production of TGFβ-1 protein, then as a mutant C / C genotype, in contrast, is associated with decreased expression [18].

Objective: To determine the role of pleiotropic cytokine (TGFβ) in the development of acute cerebrovascular disorders in the presence of the metabolic syndrome.

Material and Research Methods

188 patients with ischemic stroke at the age of 41 to 72 years were examined, 105 of them with metabolic syndrome. To identify genetic predictors of cerebrovascular disorders in the metabolic syndrome, we examined patients with acute cerebrovascular accident (stroke, main group, n = 96), which were divided into two subgroups: 1) subgroup A - patients with stroke, developed against the background of metabolic syndrome (n = 48), 2) subgroup B - patients with stroke, which developed without metabolic syndrome (n = 48). In these samples, a comparative analysis of the frequency of occurrence of polymorphic alleles and genotypes of candidate genes was carried out. As the candidate genes, we have selected: polymorphism rs1800471 (915G> C (Arg25Pro)) of the gene for transforming growth factor beta-1 (TGFβ-1);

To assess the population frequency of these polymorphisms, we studied a sample of conditionally healthy individuals without clinically recorded signs of metabolic

syndrome and episodes of an acute history of cerebrovascular accident (control, n = 91).

Results and its Discussion

Our study of the distribution frequency of alleles of the rs1800471 polymorphism (915G> C (Arg25Pro)) of the TGFβ-1 gene in the sample of patients with stroke and the population sample showed that the mutant C allele was more common in the main group than in the control (8.33% and 5.49%), respectively, the frequency of the "wild" G allele was higher in the control group (91.67% - the main group; 94.51% - the control group), however, the difference in indicators in both cases was statistically insignificant ($\chi 2 = 1.16$; $p = 0.28$; OR = 0.64; 95% CI 0.28-1.45). The data obtained in our study indicate the absence of an association between the "C" allele of the rs1800471 polymorphism of the TGFβ-1 gene and the development of BCH in the metabolic syndrome.

In both studied subgroups of patients with stroke, the variant C allele was more common than in the population control group. It is interesting to note that when compared with the control, the frequency of the "C" allele was higher in the subgroup of patients with stroke on the background of metabolic syndrome (subgroup A) (5.49% - control; 9.38% - subgroup A; $\chi 2 = 1.49$; $p = 0.22$; OR = 0.56; 95% CI 0.22-1.43). In the subgroup of patients with OCH without metabolic syndrome (subgroup B), the C allele was less common than in subgroup A (subgroup B - 7.29%; subgroup A - 9.38%; $\chi 2 = 0.27$; p = 0, 6; OR = 1.32; 95% CI 0.47-3.69) and, despite the fact that the value of this indicator in subgroup B exceeded the control value, the difference with control did not have statistical significance (7.29% and 5 , 49%; $\chi 2 = 0.35$; $p = 0.552$; OR = 0.74; 95% CI 0.27-2.01). Our data on the frequency of occurrence of the studied polymorphic allele in patient samples indicate, however, that the carriage of the "C" allele of the rs1800471 polymorphism of the TGFβ-1 gene does not affect the risk of developing SCN in patients regardless of the presence or absence of MS (Fig. 1).

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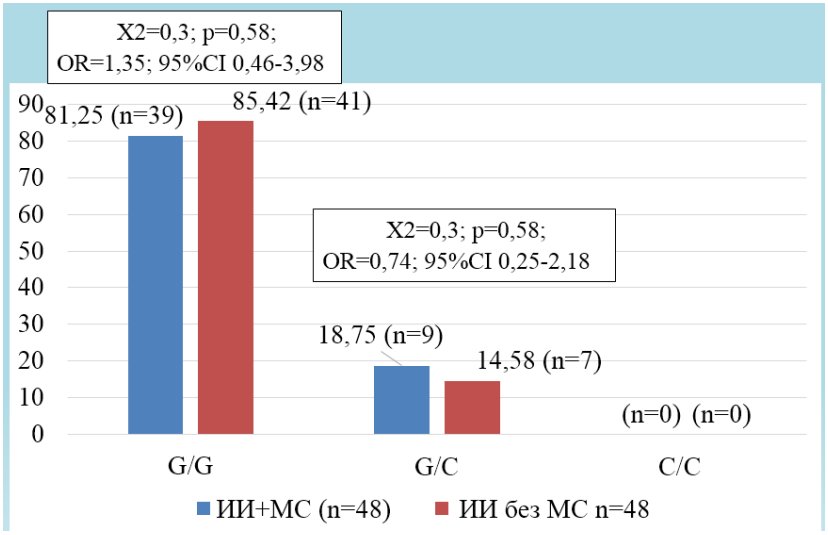

Fig. 1. The frequency of occurrence of polymorphism of the rs1800471 genotype of the TGFβ-1 gene in AI groups with MS and II without MS.

An analysis of the distribution of the genotypic variants of the rs1800471 polymorphism of the TGFβ-1 gene revealed the predominance of the homozygous genotype for the "wild" allele in the population group of individuals without SCI (89.01%). The frequency of the G / G genotype in the main group of patients, as well as in subgroups A and B, was within close values; however, in no group of patients the difference between the indicator and the control had statistical significance (control - 89.01%; the main group - 83.33%; $\chi 2 = 1.26$; $p = 0.26$; OR = 0.62; 95 % CI 0.26-1.44; subgroup A - 81.25%; $\chi 2 = 1.6$; $p = 0.21$; OR = 0.53; 95% CI 0.2-1.42; subgroup B - 85.42%; $\chi 2 = 0.38$; $p = 0.54$; OR = 0.72; 95% CI 0.26-2.04) (Fig. 2)

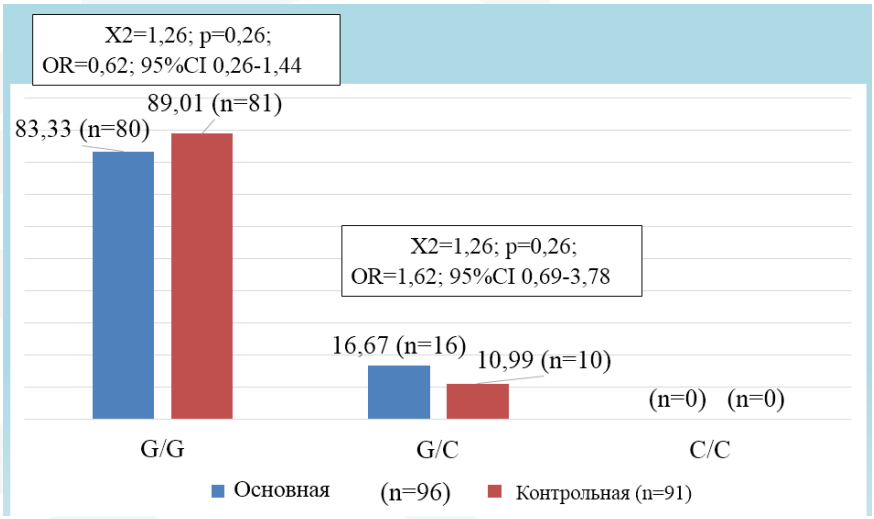

Fig. 2. The frequency of occurrence of polymorphism of the rs1800471 genotype of the TGFβ-1 gene of patients in the main and control groups.

The lowest frequency of the heterozygous genotype of rs1800471 polymorphism of the TGFβ-1 gene was noted in the control group (10.99%). The frequency of the G / C genotype in the main group of patients with OTsN was higher than the control value (16.67% and 10.99%; χ2 = 1.26; p = 0.26; OR = 1.62; 95% CI 0.69 -3.78). In the subgroups of patients with OTsN against the background of MS and without MS, the heterozygous genotype was also more common than in the population control group (control - 10.99%; subgroup A - 18.75%; χ2 = 1.6; p = 0.21; OR = 1.87; 95% CI 0.7-4.97; subgroup B - 14.58%; χ2 = 0.38; p = 0.54; OR = 1.38; 95% CI 0.49- 3.9). However, despite the fact that the carriage of a heterozygous genotype increased the chance of developing OTsN with MS by 1.9 times and without MS by 1.4 times, the revealed difference in frequency in the patient subgroups and control had no statistical significance, as well as the difference in the frequency of occurrence of the genotype G / C between both subgroups (subgroup A - 18.75%; subgroup B - 14.58%; χ2 = 0.3; p = 0.58; OR = 0.74; 95% CI 0.25-2, 18) (Fig. 1.).

Thus, the data of our study showed the absence of an associative relationship between the heterozygous genotype G / C of the rs1800471 polymorphism of the TGFβ-1 gene and the development of OTsN in patients regardless of the presence or absence of MS. This suggests that the studied polymorphism does not contribute to the development of OTsN in any of the studied categories of patients and is not associated with the development of cerebrovascular disorders.

It should be noted that the C / C genotype homozygous for the mutant allele was not found in any of the studied samples, which did not allow us to estimate its frequency both in the population control group and among patients with OST. This fact is associated with a rare frequency of occurrence of this genotypic variant. Considering that the product of the TGFβ-1 gene plays an important role in the pathogenesis of cardiovascular diseases and in the processes that can take place in the development of cerebrovascular disorders, it is possibly the functionally unfavorable homozygous C / C genotype that is associated with BCH. Confirmation of this hypothesis requires additional studies with a significant increase in the sample size of the subjects

Thus, the data obtained in the study of the distribution frequency of alleles and genotypes of rs1800471 polymorphism of the TGFβ-1 gene among patients with stroke and in the population sample may indicate the absence of a reliable association of the mutant “C” allele and the heterozygous G / C genotype with the development of BCH. The connection with the development of cerebrovascular disorders of a functionally unfavorable C / C genotype requires additional studies.

conclusions

For the first time, the frequency of alleles and genotypes of rs1800471 polymorphisms of the TGFβ-1 gene was studied in patients with II on the background of metabolic syndrome and without MS;

The rs1800471 polymorphism of the TGFβ-1 gene is not associated with AI and does not independently contribute to an increased risk of developing cerebrovascular disorders (AUC = 0.53).

Literature

1. Gusev E.I., Skvortsova V.I., Stakhovskaya L.V. Epidemiology of stroke in Russia. - Journal. neurology and psychiatry. S.S. Korsakova. 2003.9 (stroke), S. 114-118.
2. Orlova A.Yu., Artyushkova EB, Sukovatykh BS, et al. Relation of the C-509T polymorphism of the TGFB1 gene to the risk of developing atherosclerosis obliterans of the lower limb arteries // Clinical Medicine. 2016. - 94 (12). -FROM. 924-927.
3. Aihara K., Ikeda Y., Yagi S., et al. Transforming Growth Factor-β1 as a Common Target Molecule for Development of Cardiovascular Diseases, Renal Insufficiency and Metabolic Syndrome // Cardiol Res Pract. –2010 Dec 28. –2011. -175381. (doi: 10.4061 / 2011/175381.)
4. Annes J.P., Munger J.S., Rifkin D. B. Making sense of latent TGFbeta activation // J Cell Sci. –2003 Jan 15. –116 (Pt 2). –P.217-224.
5. Auer J., Weber T., Berent R., et al. Genetic polymorphisms in cytokine and adhesion molecule genes in coronary artery disease // Am J Pharmacogenomics. –2003. –3 (5). –P.317-328.
6. Clark-Greuel J.N., Connolly J.M., Sorichillo E., et al. Transforming growth factor-beta1 mechanisms in aortic valve calcification: increased alkaline phosphatase and related events // Ann ThoracSurg. –2007 Mar. - 83 (3). - R. 946-953.
7. Drabsch Y., ten Dijke P. TGF-β signaling and its role in cancer progression and metastasis // Cancer Metastasis Rev. –2012 Dec. –31 (3-4). –P.553-68. (doi: 10.1007 / s10555-012-9375-7.)
8. Fujii D., Brissenden J.E., Derynck R., Francke U. Transforming growth factor-beta gene maps to human chromosome 19 long arm and to mouse chromosome 7 // Somat Cell Mol. –1986 May. –12 (3). –P.281-288.
9. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. JAMA. 2003; 289: 187-193.
10. Hilbers F.S., Boekel N.B., van den Broek A.J., et al. Genetic options in TGFβ-1 and PAI-1 as possible risk factors for cardiovascular disease after radiotherapy for breast cancer // RadiotherOncol. –2012 Jan. –102 (1). –P.115-121. (doi: 10.1016 / j.radonc.2011.10.01.01.)

11. Itoh S., Itoh F. Inhibitory machinery for the TGF-β family signaling pathway // Growth Factors. –2011 Oct. –29 (5). -R. 163-173. (doi: 10.3109 / 08977194. 2011.614236.)
12. Katsuno Y., Lamoille S., Derynck R. TGF-β signaling and epithelial-mesenchymal transition in cancer progression // CurrOpinOncol. –2013 Jan. –25 (1). –P.76-84. (doi: 10.1097 / CCO.0b013e32835b6371.)
13. Liu G., Ding W., Liu X., Mulder K.M. c - Fos is required for TGFbeta1 production and the associated paracrine migratory effects of human colon carcinoma cells // Mol Carcinog. –2006 Aug. –45 (8). –P.582-593.
14. Meulmeester E., Ten Dijke P. The dynamic roles of TGF-β in cancer // J Pathol. – 2011 Jan. –223 (2). –P.205-218. (doi: 10.1002 / path.2785.)
15. Miyazono K., Ehata S., Koinuma D. Tumor-promoting functions of transforming growth factor-β in the progression of cancer // Ups J Med Sci. 2012 May. –117 (2). –R.143-152. (doi: 10.3109 / 03009734.2011.638729.)
16. Raju G.T., Lakkakula B.V.K.S., Murthy J., et al. Transmission analysis of TGFB1 gene polymorphisms in non-syndromic cleft lip with or without cleft palate // Int J PediatrOtorhinolaryngol. –2017 Sep. -100. –R.14-17. (doi: 10.1016 / j.ijporl.2017.06.01.01.)
17. Raman M., Cobb M.H. TGF-beta regulation by Emilin1: new links in the etiology of hypertension // Cell. –2006 Mar 10. –124 (5). –P.893-895.
18. Randell A., Daneshtalab N. Elastin microfibril interface-located protein 1, transforming growth factor-beta, and implications on cardiovascular complications // J Am SocHypertens. –2017 Jul. –11 (7). –P.437-448. doi: 10.1016 /j.jash.2017.04.010. Epub 2017 May 3.
19. Santibañez J.F., Quintanilla M., Bernabeu C. TGF-β / TGF-β receptor system and its role in physiological and pathological conditions // Clin Sci (Lond). –2011 Sep. –121 (6). –P.233-251. (doi: 10.1042 / CS20110086.)
20. Shimizu C., Jain S., Davila S., et al. Transforming growth factor-beta signaling pathway in patients with Kawasaki disease // CircCardiovasc Genet. –2011 Feb. – 4 (1). –R.16-25. (doi 10.1161 // CIRCGENETICS. 110.940858)
21. Zacchigna L., Vecchione C., Notte A., et al. Emilin1 links TGF-beta maturation to blood pressure homeostasis // Cell. –2006 Mar 10. –124 (5). –P.929–942.
22. Zachary I. Neuroprotective role of vascular endothelial growth factor: signaling mechanisms, biological function, and therapeutic potential // Neurosignals. 2005 14 (5): 207-21.
23. Zheng W., Yan C., Wang X., et al. TheTGFB1 functional polymorphism rs1800469 and susceptibility to atrial fibrillation in two Chinese Han populations // PLoS One. –2013 Dec 12. –8 (12). –E83033. (doi: 10.1371 / journal.pone.0083033.)