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Association Of Allelic Polymorphisms Of Pro-Inflammatory Cytokine Genes With The Severity Of Immune Microthrombovasculitis

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Abstract: Purpose of the study: To assess the role of the polymorphic variant of the TNF-α gene (rs1800629) VEGFA (rs2010963) in the development of a severe course of immune microthrombovasculitis.

Material and methods: The study included 75 patients with IMTV (main group) aged 16 to 80 years and 73 conditionally healthy individuals (comparison group) without pathology of the hemostasis system, comparable in age and gender with the main group. Detection of polymorphic variants of genes TNF-α (rs 1800629) and VEGFA (rs2010963) was carried out by SNP-PCR.

Results and discussion: Differences in the frequency of occurrence of the mutant genotype of the mutant genotype G/G ($\chi 2>3.84$; $P<0.05$) of the polymorphic variant of the VEGFA gene (rs2010963) were established depending on the severity of IMTV, which allows clinicians to determine it as a genetic predictor of severe disease.

Keywords: Gene polymorphism, TNF-α (rs1800629), VEGFA (rs2010963), immune microthrombovasculitis (IMTV), allele, genotype, pathogenesis, severity of the course.

Introduction: In everyday practice, doctors of almost all specialties encounter various forms of hemorrhagic diathesis (HD), while their late and late diagnosis leads to the use of long-term unjustified therapeutic tactics in patients, as well as the development of thrombohemorrhagic complications, which significantly

reduce their quality of life [[1, 4, 5, 13].

In terms of the frequency of its occurrence among all populations and age groups of the population, polymorphism and severity of the clinical course in the general structure of HD, a special place is given to immune microthrombovasculitis (IMTV). However, the consequence of insufficient knowledge of the pathogenesis of the disease is the high frequency of its complications and relapses [3, 22, 23, 24].

At the same time, the analysis of the research results of recent years indicates the important role of gene polymorphisms in the mechanisms of the formation of IMTV [2, 7, 8, 9]. In addition, there are data on the influence of functional polymorphisms of a number of genes on the nature of the course, which determine the possibility of predicting the outcome of this disease [11, 12, 14]. Meanwhile, the presence of conflicting results of the currently existing studies on the contribution of various genetic polymorphisms in the genesis of these diseases, and thus the unknown and unresolved many aspects of these major problems determine their relevance [14].

The results of studies by foreign authors have shown an assessment of the relationship of genetic polymorphisms with the development of a severe course of IMTV [10, 17]. In particular, Chinese researchers Liu Desong, Lu Fang, Zhai Songhui, Wei Liu, Ma Shi, Chen Xiuying et al. (2010) found that polymorphisms of the genes of the renin-angiotensin system (ACE-I / D, M235T and T174M) are significantly associated with the severity of the BMI course (p = 0.045 and p = 0.026) [10]. Mahsa M. Amoli et al. (2014) and López-Mejías R. et al. determined that polymorphism of the IL 1 β gene (rs16944) is important in the development of severe renal manifestations in IMTI [16, 17]. Along with this, in recent years, researchers increasingly emphasize the significant role of allelic polymorphisms of the genes for tumor necrosis factor (TNFa) and endothelial vascular growth factor (VEGFA) both in the development and in the severity of the IMTV course [18, 20, 21].

Taking these facts into account, we studied the possible associations of the carriage of unfavorable allelic genotypes with the severity of the clinical course of IMTV.

Purpose of the study. To assess the role of the polymorphic variant of the TNF-α gene (rs1800629) VEGFA (rs2010963) in the development of a severe course of immune microthrombovasculitis.

Methods

The study included 75 adult unrelated patients of the Uzbek ethnic group aged 16 to 80 years (median age 42.1 ± 3.9 years), who constituted the main group with an established diagnosis of immune microthrombovasculitis (Schönlein-Henoch purpura) according to the modern EULAR classification criteria. PRINTO and PreS (2010) [7]. All patients were observed in the consultative and diagnostic polyclinic of the Republican Specialized Scientific and Practical Medical Center of Hematology (RSNPMCG) in the period from 2012 to 2024 yy. The control group consisted of 73 healthy unrelated persons of uzbek nationality, who had no history of inflammatory, allergic, systemic and renal diseases that matched age and sex with the examined group of patients. Written information and consent to participate in the study was obtained from all examined.

Selection and optimization of the operation of oligoprimer systems for the detection of TNF-α (rs 1800629) and VEGFA (rs2010963) gene polymorphisms, the nucleotide sequences of which were selected using the Oligo v.6.31 program (Molecular Biology Insights Inc., USA), were performed. Detection of gene polymorphisms was carried out by SNP-PCR on a programmable thermal cycler from Applied Biosystems 2720 (USA), using test systems from NPF "Litekh" (Russia).

The specificity and the number of amplified fragments were checked by agarose gel electrophoresis. Statistical analysis of the results was carried out using the statistical software package "OpenEpi, Version 9.3".

Results And Discussion

Comprehensive examination of patients with IMTV (n = 75) made it possible to determine the severity of the disease. In particular, the number of patients with mild severity was 29.3%, with moderate severity - 37.4% and with severe severity - 33.3%. At the same time, in the main group of patients with IMTV (n = 75) and in the control group (n = 73), we analyzed the significance of the TNF-α (rs1800629) and VEGFA (rs2010963) genes in the risk of developing a severe course IMTV.

According to our data, the carriage of genotypes G/G and G/A of the polymorphic variant of the TNF-α gene (rs1800629) in patients with IMTV with a mild severity of the disease was 77.3% and 22.7%, respectively, with an average severity of 75.0% and 25.0%, respectively, while with severe severity, their share was 64.0% and 36.0%. These data show the presence of differences between the carriage of genotypes of TNF-α gene

polymorphism (rs1800629), depending on the severity of the disease. However, statistical analysis showed the presence of an insignificant difference in the proportion of G / G and G / A genotypes between patients with mild and moderate severity (for G / G genotype: χ2 = 0.03; P = 0.8; OR = 0.9; 95% CI: 0.24 -3.28; for genotype G / A: χ2 = 0.03; P = 0.8; OR = 1.1; 95% CI: 0.30- 4.22) (table 1).

Table 1

Difference in the frequency distribution of genotypes of TNF-α (rs1800629) gene polymorphism in patients with mild to moderate IMTV

Genotypes	The number of genotypes examined				χ^2	P	RR	OR	95%Cl
	Easy		Average						
	n	%	n	%					
G/G	17	7.3	21	75.0	0.03	0.8	0.9	0.9	0.24- 3.28
G/A	5	22.7	7	25.9	0.03	0.8	1.0	1.1	0.30- 4.22
A/A	-	-	-	-	-	-	-	-	-

Despite the fact that the proportion of carriage of an unfavorable heterozygous G / A genotype of the TNF-α gene (rs1800629) in patients with severe IMTV was almost 2 times higher than its proportion in patients with a mild degree, the difference was not statistically significant (χ2 = 1.0; P = 0.3; OR = 1.9; 95% CI: 0.53-6.93) (table 2).

Table 2

Difference in the distribution of genotype frequencies of TNF-α (rs1800629) gene polymorphism in patients with mild and severe IMTV

Genotypes	The number of genotypes examined				χ^2	P	RR	OR	95% Cl
	Easy		Heavy						
	n	%	n	%					
G/G	17	7.3	16	64.0	1.0	0.3	1.6	1.9	0.53- 6.93
G/A	5	22.7	9	36.0					
A/A	-	-	-	-	-	-	-	-	-

Thus, the study of the association between the carriage of unfavorable genotypes of the TNF-α (rs1800629) gene polymorphism and the severity of IMTV did not reveal the presence of statistically significant differences, which does not allow determining the polymorphic variant of the TNF-α (rs1800629) gene as a prognostic genetic marker of the severity of the persons among the uzbek nationality.

Analysis of the carriage of genotypes of the polymorphic variant of the VEGFA gene (rs2010963) in patients with IMTV, depending on the severity, showed the following: with mild severity of the disease, carriage of C / C and C / G genotypes was detected in 54.5% and 45.5% of cases, respectively. with moderate severity, their values were 53.6% and 46.4%, respectively, and with severe severity - 24.0% and 56.0%, respectively. In addition, it should be noted that only in patients with severe

severity, the carriage of the mutant genotype G / G was recorded, which amounted to 20.0%.

Statistical analysis of the observed differences between the carriage of genotypes of the VEGFA gene polymorphism (rs2010963) depending on the severity of IMTV made it possible to establish the absence of significant differences in the proportion of C / C and C / G genotypes between patients with mild and moderate severity ($\chi 2 < 3.8$; $P > 0.05$) (table 3).

Table 3

Difference in the frequency distribution of genotypes of VEGFA gene polymorphism (rs2010963) in patients with mild to moderate IMTV

Genotypes	The number of genotypes examined				χ^2	P
	Easy		Average			
	n	%	n	%		
C/C	12	54.5	15	53.6	<3.8	>0.05
C/G	10	45.5	13	46.4	<3.8	>0.05
G/G	-	-	-	-	-	-

A significant difference in the frequency of the C / C and G / G genotypes of the VEGFA gene (rs2010963) was found between patients with mild and severe IMTV severity (for the C/C genotype: $\chi 2 = 4.6$; $P = 0.03$; OR = 3.8; 95% CI: 1.1-13.2; for genotype G / G: $\chi 2 = 4.9$; $P = 0.02$), while no significant difference was found in the proportion of heterozygous genotype C / G ($\chi 2 = 0.4$; $P = 0.5$; OR = 0.6; 95% CI: 0.21- 2.07) (table 4).

Table 4

Difference in the frequency distribution of genotypes of VEGFA gene polymorphism (rs2010963) in patients with mild and severe IMTV

Genotypes	The number of genotypes examined				χ^2	P	RR	OR	95% CI
	Easy		Heavy						
	n	%	n	%					
C/C	12	54.5	6	24.0	4.6	0.03	2.3	3.8	1.1- 13.2
C/G	10	45.5	14	56.0	0.4	0.5	0.8	0.6	0.21- 2.07
G/G	-	-	5	20.0	4.9	0.02	-	-	-

The frequency of the C / C and C / G genotypes of the VEGFA gene (rs2010963) in patients with IMTV with moderate and severe severity did not differ in statistical significance (for the C / C genotype: $\chi 2 = 4.8$; $P = 0.03$; OR = 0.3; 95% CI: 0.084-0.89; for genotype C / G: $\chi 2 = 0.5$; $P = 0.5$; OR = 1.5; 95% CI: 0.5-4.34). A significant difference was found in relation to the proportion of the mutant genotype G/G ($\chi 2 = 6.2$; $P = 0.01$) (Table 5).

Table 5

Difference in the distribution of genotype frequencies of the VEGFA gene polymorphism (rs2010963) in patients with moderate and severe IMTV

Genotypes	The number of genotypes examined				χ^2	P	RR	OR	95%CI
	Average		Heavy						
	n	%	n	%					
C/C	15	53.6	6	24.0	4.8	0.03	0.4	0.3	0.084-0.89
C/G	13	46.4	14	56.0	0.5	0.5	1.2	1.5	0.5- 4.34
G/G	-	-	5	20.0	6.2	0.01	-	-	-

Thus, the study of the correlation between the carriage of unfavorable genotypes of the VEGFA gene polymorphism (rs2010963) and the severity of IMTV did not reveal the presence of statistically significant differences in relation to the heterozygous C / G genotype ($\chi 2 < 3.8$; $P > 0.05$). However, in relation to the mutant genotype G / G ($\chi 2 = 6.2$; $P = 0.01$), an association was established with the risk of developing a severe course of IMTV. Therefore, the G / G genotype of the VEGFA gene polymorphism (rs2010963) is a prognostic marker for the development of a severe course of IMTIV among the uzbek nationality.

Conclusion

Clinical manifestations of immune microthrombovasculitis (IMTV) are characterized by their polymorphism, the severity of which depends on the nature and severity of the disease [1, 4]. At the same time, it is known that genetic polymorphisms are of great importance in the realization of the severity of the pathological process [2, 6]. This is evidenced by the results of studies by a number of foreign authors to assess the relationship of genetic polymorphisms with the development of a severe course of IMTV [9, 12, 14]. In this regard, the analysis of the distribution of allelic and genotypic variants of genes of proinflammatory cytokines in patients with immune microthrombovasculitis, determination of the role of the carriage of unfavorable genotypes of polymorphisms of these genes in the formation of the severity of the course, their association with the severity of clinical manifestations of IMTV is of particular importance.

We have studied the correlation between the carriage of unfavorable genotypes of polymorphic variants of the TNF-α (rs1800629) and VEGFA (rs2010963) genes with the severity of the IMTV course. At the same time, the presence of the prognostic significance of the mutant genotype G / G ($\chi 2 = 6.2$; $P = 0.01$) of the VEGFA gene polymorphism (rs2010963) as a predictor of a severe course of IMTV was established, while the significance of the unfavorable genotype G / A ($\chi 2 = 1.0$; $P = 0.3$) the TNF-α gene (rs1800629) was not detected in the development of severe course in IMTV. Consequently, the established differences in the frequency of occurrence of the mutant genotype G/G of the VEGFA gene (rs2010963) in IMTV, depending on the severity, allows clinicians to determine it as a genetic predictor of a severe course of the disease.

The data obtained suggest that polymorphism of the VEGFA gene (rs2010963) can participate in the processes of damage to endothelial cells, as well as in the modulation of inflammation. Together with other risk factors, this polymorphism can determine the development of a severe course of the disease, and, from a clinical point of view, contribute to predicting the clinical course and development of complications in patients with IMTV of the Uzbek ethnic group, which allows targeted planning of therapeutic strategies.

Concluding the discussion, it should be noted that the obtained results of the study allow us to expand the modern understanding of the mechanisms of the formation of a severe course of IMTV. Analysis of genetic polymorphisms, the frequency of their allelic and genotypic variants, taking into account ethnic characteristics, allows monitoring among the population to identify a predisposition to the development of an unfavorable course of the disease,

assessing the prognosis, and a differential approach in the management and prevention of complications in patients with IMTV.

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