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Features of the Frequency of Distribution of Alleles and Genotypes of Polymorphisms of the Gene Tnf-A (G-308a) in Patients with Rhinosinusitis and the Assessment of Their Role in the Development of This Pathology

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Abstract---*In this work, we present the results of studying the characteristics of the distribution of allelic and genotypic frequencies of polymorphic variants of the cytokine gene TNF-α (G-308A) among patients with rhinosinusitis with and without chronic myeloid leukemia (CML), as well as among conditionally healthy individuals. At the same time, we assessed the role of this gene in the development of rhinosinusitis. Analysis of the frequency of occurrence of alleles and genotypes for gene TNF-α (G-308A) polymorphism revealed insignificant differences in the 1st main group of CML patients with rhinosinusitis compared with the control group. Thus, the established absence of significant differences in the frequency of occurrence of the A allele (7.7% versus 8.1%; χ2 <3.85; p> 0.05; OR = 0.95; 95% CI: 0.43-2.6) and genotype G/A (15.4% against 16.2%; χ2<3.85; p> 0.05; OR = 0.94; 95% CI: 0.37-2.4), indicates the absence of their significance in the increased risk of rhinosinusitis in the main group of CML patients. A similar picture was also observed in subgroups 1A and 1B of patients in the main group.*
Keywords---*allele of genes, frequencies of distribution of alleles, genotypes of polymorphisms of gene TNF-α (G-308A), polymorphism of genotypes, rhinosinusitis*

Introduction

It is known that rhinosinusitis (RS) is an inflammatory disease of the nasal mucosa and paranasal paranasal sinuses (Mohamad et al., 2019), the formation of which is associated with a dysregulation of the immune system, in particular, its response against antigens present in the mucous membrane. At the same time, microbial antigens in MS patients can be specific targets of the inflammatory response in the paranasal sinuses, and can also serve for nonspecific stimulation of the mucosal immune response (Sedaghat, 2018). Meanwhile, it is important to note that

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RS is a complex and heterogeneous disease, in the development mechanisms of which an important role belongs to the complex influence of several factors, including the combined effect of bacterial and viral infections and the activity of molecular genetic polymorphisms (Tint et al., 2016; Huang et al., 2016). The role of genetic factors in the formation of RS is increasingly confirmed by the results of modern research (Kim et al., 2020). The genes of proinflammatory cytokines are considered as key molecular genetic factors that largely determine the development and outcome of rhinosinusitis, affecting the nature of the course, the chronization of the process (Zhang et al., 2012; Cho et al., 2014).

The Main Findings and Results

It is known that the biological activity of a number of genes is largely determined by their interaction, which initiates an increase in the risk of developing the disease (Cho et al., 2019). Taking this into account, it seemed interesting to us to study the features of the distribution of the frequencies of alleles and genotypes of polymorphisms of genes of a number of pro-inflammatory cytokines such as TNF-α (G-308A), IL1β (C3953T) and IL6 (C-174G), the key role of which has been proven in the initiation and maintenance of inflammatory processes (Frieri et al., 2015). Increased expression of genes TNF-α, IL1β and IL6 affects the mechanisms of immunoregulation, which leads to the release of specific inflammatory proteins-cytokines, correlating with the degree of activity of the inflammatory process (Shi et al., 2012). In addition, the genes TNF-α, IL1β and IL6 have the ability to induce the production of each other and exhibit numerous general effects (Tomassen, 2016; Halderman & Lane, 2017). Consequently, these genes can take part in the development of rhinosinusitis, which is confirmed by the results of a number of modern foreign studies (Rai et al., 2018; Kim, 2019).

This paper presents the results of studying the frequency of distribution of alleles and genotypes of cytokine gene polymorphism - TNF-α (G-308A) in the 1st main group of CML patients with rhinosinusitis (n = 65), in the 1A subgroup (n = 31) of CML patients with acute rhinosinusitis and subgroup 1B (n = 34) of CML patients with chronic rhinosinusitis, in group 2 of patients with rhinosinusitis without CML (n = 35) and in the control group consisting of 68 apparently healthy individuals. In all studied groups, we assessed the distribution of genotype frequencies of TNF-α (G-308A) gene polymorphism for compliance with the Hardy-Weinberg equilibrium (RHB, $p > 0.05$) by analyzing their expected and observed frequencies. Thus, in the 1st main group of CML patients with rhinosinusitis, the expected and observed frequencies of genotypes G/G (0.85 and 0.85; $\chi2 = 0.004$), G / A (0.14 and 0.85; $\chi2 = 0.01$) and A/A (0.00 and 0.01; $\chi2 = 0.6$) of the TNF-α (G-308A) gene polymorphism did not deviate from PXB ($p = 0.4$) (Szabó et al., 2002; Edwards et al., 1998).

In the group of conditionally healthy individuals, a correspondence between the expected and observed frequencies of genotypes G / G (0.84 and 0.84; $\chi2 = 0.005$), G/A (0.16 and 0.15; $\chi2 = 0.12$) and A/A (0.00 and 0.01; $\chi2 = 0.65$) according to RHV ($p = 0.38$). At the same time, in both groups studied, the heterozygosity index (D) almost corresponded in terms of the observed and expected frequencies for the TNF- (G-308A) gene polymorphism (0.083 and 0.088). In the 2nd group of patients with rhinosinusitis, the frequency of distribution of the expected and observed frequencies of the genotypes G / G (0.74 and 0.76; $\chi2 = 0.04$), G/A (0.26 and 0.22; $\chi2 = 0.5$) and A/A (0.00 and 0.02; $\chi2 = 1.65$) did not deviate from the canonical one according to RHB ($p = 0.14$). At the same time, the heterozygosity index (D) in this group was 0.15 versus 0.088 in the control (Morgenthaler & Thilly, 2007; Cardon & Palmer, 2003).

Correspondence between the observed and expected genotypic variants of TNF- (G-308A) gene polymorphism for RHB ($p > 0.05$) allows analyzing the peculiarities of the distribution of allele and genotype frequencies of the studied polymorphism in all studied groups. In particular, in the control group, it was found that the frequencies of the G and A alleles were 91.9% and 8.1%, the homozygous G/G genotype - 83.8%, and the heterozygous G/A genotype - 16.2%. At the same time, it is important to point out that in the control group the proportion of the mutant homozygous genotype A/A has not been established. Further, the analysis of allele frequencies and genotypes of TNF- (G-308A) gene polymorphism in the 1st main group of CML patients with rhinosinusitis made it possible to establish that the carriage of G and A alleles was determined in 92.3% and 7.7% of cases, while in relation to of genotypes G/G and G/A, the proportion of carriage was determined in 84.6% and 15.4% of cases. At the same time, as well as in the control group, cases of carriage of the mutant genotype A/A were not recorded.

Meanwhile, we found it interesting to determine the features of the frequency of occurrence of alleles and genotypes also depending on the phase of the course of rhinosinusitis in CML patients. Thus, among CML patients with acute rhinosinusitis in subgroup 1A, cases of registration of alleles G and A amounted to 93.6% and 6.4%, and genotypes G/G and G/A - 87.1% and 12.9%, respectively. However, among CML patients with chronic rhinosinusitis in subgroup 1B, the cases of registration of both G (91.2%) and A (8.8%) alleles, and G/G (82.4%) and

G/A (17.6%) genotypes were somewhat different from those values in the 1A subgroup, namely, the difference was characterized by a slight decrease in the frequencies of the G allele and the G/G genotype, and vice versa by an increase in the frequencies of the A allele and the G/A genotype. A common feature in both subgroups was the absence of carriage of the A/A mutant genotype. The results of the analysis of the frequencies of alleles and genotypes in the 2nd group of patients with rhinosinusitis differed from those in the 1st main group of CML patients with rhinosinusitis: alleles G and A were recorded in 87.1% and 12.9%; and genotypes G/G and G/A in 74.3% and 25.7% of cases, respectively. At the same time, as in the above groups, among the patients of the 2nd group, the A/A genotype were also not determined in any case (Doherty et al., 1992; Palmatier et al., 1999).

Having determined the frequency of carriage of alleles and genotypes of TNF-□ (G-308A) gene polymorphism in all examined groups, we carried out a comparative analysis of the differences in their distribution between the groups. Namely, the results of the analysis showed that, in comparison with the control group, in the 1st main group of CML patients with rhinosinusitis, the frequency of allele A (7.7% versus 8.1%; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.95; 95% CI: 0.43 -2.6) and genotype G / A differed little (15.4% versus 16.2%; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.94; 95% CI: 0.37-2.4), which indicates the lack of significance of allele A and genotype G/A in the development of rhinosinusitis in the main group of CML patients (Goddard et al., 2000; Duarte et al., 2005).

In relation to patients with CML 1A subgroup with acute rhinosinusitis and 1B with chronic sinusitis, allele A frequency (6.4% versus 8.1%; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.8; 95% CI: 0.24-2.7 and 8.8% versus 8.1%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.1; 95% CI: 0.39-3.11) and genotype G / A (12.9% versus 16.2; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.8; 95% CI: 0.22-2.63 and 17.7% versus 16.2%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.11; 95% CI: 0.37-3.31) also did not differ statistically significantly compared with those in the control group. Comparative analysis between subgroups 1A and 1B of CML patients with acute and chronic rhinosinusitis also had no statistically significant differences in the distribution of allele A frequencies (6.4% versus 8.8%; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.7; 95% CI: 0.2- 2.6) and genotype G / A (12.9% versus 17.7; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.8; 95% CI: 0.22-2.63 and 17.7% versus 16.2%; $\chi 2 < 3.85$; $p > 0.05$; OR = 0.7 ; 95% CI: 0.18-2.71).

In the 2nd group of patients with rhinosinusitis compared to the control group in relation to the frequencies of allele A (12.9% versus 8.1%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.7; 95% CI: 0.67-4.23) and genotype G / A (25.7% versus 16.2; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.8; 95% CI: 0.67-4.82) there was a tendency to their increase, namely, the share of allele A and genotype G / A exceeded their share in the control by 1.7 and 1.8 times. A similar picture was observed in relation to the 1A subgroup of CML patients with acute rhinosinusitis, where the frequencies of the A allele (6.4% versus 12.9%; $\chi 2 < 3.85$; $p > 0.05$; OR = 2.14; 95% CI: 0.64-7.2) and genotype G / A (12.9% versus 25.7; $\chi 2 < 3.85$; $p > 0.05$; OR = 2.34; 95% CI: 0.65-8.35) in the 2nd group of patients with rhinosinusitis exceeded their shares in the 1st subgroup of patients by 2.14 and 2.34 times, respectively. Analyzing the differences in the frequency distribution of the A allele (8.8% versus 12.9%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.53; 95% CI: 0.52-4.52) and the G / A genotype (17.6% versus 25.7%; $\chi 2 < 3.85$; $p > 0.05$; OR = 1.62; 95% CI: 0.51-5.14) in the 2nd group of patients with rhinosinusitis compared to those in the 1st subgroup of CML patients with chronic rhinosinusitis, differences were also found. However, despite the presence of such differences, they were statistically insignificant, which indicates the presence of a tendency for allele A and genotype G/A to increase the risk of developing rhinosinusitis in the 2nd group of patients (Mora et al., 2018).

Conclusion

Thus, the results obtained confirm the absence of a significant association of the A allele and the heterozygous G/A genotype of gene TNF-α (rs1800629) polymorphism with the development of rhinosinusitis in the 1st main group of CML patients. However, in the 2nd group of patients, there is a tendency towards a possible increase in the risk of developing rhinosinusitis with the carriage of the A allele and the G/A genotype. Perhaps, if a larger number of patients with rhinosinusitis were covered, this allele and genotype would have a statistically significant significance in the increased risk of developing the disease (Molvarec et al., 2008; Widharma et al., 2017).

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