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Distribution of Polymorphic Loci of the Interleukin IL1β Gene (T31C) in Duodenal Ulcer Disease and Evaluation of Their Contribution to the Mechanisms of Disease Formation

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Abstract Among human somatic pathologies in the world, a special place belongs to peptic ulcer disease (PUD) and duodenal ulcer disease (DU), which are ubiquitous pathologies detected in 5-10% of the adult population with predominance among men. Introduction of molecular genetic studies allowed to reveal new data on genetic bases and peculiarities of peptic ulcer development. Meanwhile, many aspects of the pathogenesis of the disease remain poorly understood, that additional research in this area is one of the urgent problems of modern medicine.

Keywords Gastric ulcer disease (GUD) and duodenal ulcer disease (DUED), Molecular and genetic features

1. Introduction

Peptic ulcer disease (PUD) is one of the most common diseases of the digestive system characterized by recurrent course and is characterized by damage to the mucosa of the stomach and duodenum by ulcerative process of more than 3-5 mm, reaching the submucosa [1].

According to the estimation of leading gastroenterologists of the world, due to its widespread prevalence and high incidence of serious complications, UD is a national problem in many countries [2]. The results of modern researchers show that the prevalence of peptic ulcer disease (PUD) and duodenal ulcer disease (DU) varies from 5 to 10% [3,7].

The data of world statistics show that the incidence of peptic ulcer disease, annually registered in the population in Western countries in 0.1-0.3% of cases [4,6], while in the structure of digestive diseases duodenal ulcer disease (DU) among the adult population of all countries reaches from 7 to 10% [5].

Purpose of the study: Study of the role of molecular genetic factors in the development and course of duodenal ulcer disease.

2. Material and Research Methods

Molecular genetic methods included four stages: Stage 1 - collection of biological material from the patient; Stage 2 - DNA isolation from peripheral blood lymphocytes; Stage 3 - standard polymerase chain reaction (PCR) and Stage 4 - electrophoresis and visualization of the results obtained by standard PCR.

The research was carried out on the basis of a sample of patients aged from 18 to 84 years, with peptic ulcer disease of the stomach and duodenum who were on inpatient treatment in a multidisciplinary clinic. The number of patients included in the study was 100 patients with peptic ulcer disease.

3. Research Results

Variance analysis of expected (Hexp) and observed (Hobs) genotype frequencies of the studied polymorphism of the interleukin IL1β gene (T31C) in the cohort of patients with gastric and duodenal ulcer disease and healthy controls was performed taking into account the assessment of their concordance at Hardy-Weinberg equilibrium (HWE, $p>0.05$). This analysis showed the absence of significant deviations between the observed Hobs frequencies of genotype variants (T/T, T/C, C/C) and their Hexp frequencies, which corresponded according to RHB in both examined groups.

In the main group of patients with gastric and duodenal ulcer disease according to the polymorphic gene of interleukin IL1B (T31C) Hobs frequencies of t/T, T/C and C/C genotypes were 0.57; 0.33 and 0.1, and their Hexp frequencies at the same time were 0.54; 0.39 and 0.07 with no statistically significant

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differences between them ($\chi 2$ =2.34; P=0.128; df=1).

Among the healthy by polymorphic gene of interleukin IL1β (T31C) Hobs genotype frequencies of T/T, T/C and C/C were 0.72; 0.25 and 0.03, and their Hexp frequencies were 0.71; 0.27 and 0.02, also between which there were no statistically significant differences ($\chi 2$ =0.48; P=0.465; df=1).

In addition, determining the heterozygosity index (D) for the polymorphic gene interleukin il1β (t31c) in the nobs and hexp frequencies of heterozygotes of the proinflammatory gene interleukin IL1B (T31C) in cohorts of patients with duodenal ulcer disease and healthy controls revealed some deviation due to the deficit of observed heterozygosity (d=-0. 15 and d=-0.08) with the lowest expression among healthy controls.

On the basis of follow-up studies on the polymorphic gene of interleukin IL1β (T31C) in the cohort of healthy people we determined the frequencies of the major (T) and attenuated (C) alleles equal to 84.1%/147 and 15.9%/27.

In accordance with such dynamics, the main homozygous genotype T/T (71.8%/61) and the weakened homozygous variant C/C (3.5%/3) were most frequently determined in this group, while the heterozygous form of T/C genotype occupied an intermediate place in this distribution (24.7%/21).

In parallel, among the cohort of patients with the main polymorphic gene of interleukin IL1β (T31C), the shares of the major (T) and impaired (C) alleles were found in 73.5%/147 and 26. 5%/53 cases, respectively, and, of course, as well as among healthy people in this group, the main homozygous genotype T/T (57.0%/57) and the weakened homozygous variant C/C (10.0%/10) were registered most of all, and the heterozygous form of T/C genotype was again in an intermediate position (33.0%/33). However, the frequencies of the major allele and genotype among the patients were markedly decreasing, with simultaneous increase in the frequencies of their weakened forms, which may be associated with the participation of unfavorable allele (C) and genotypes (T/C and C/C) of the polymorphic gene of interleukin IL1β (T31C) in the processes that increase the risk of peptic ulcer formation.

No less important, we studied the distribution of alleles and genotypes for the polymorphic gene of interleukin IL1β (T31C) in groups of patients depending on the absence and presence of complicated course of peptic ulcer disease.

Thus, among the patients without complicated course of peptic ulcer disease the frequencies of the basic (T) and weakened (C) alleles were registered in 80.4%/82 and 19.6%/20 patients, respectively, while the frequencies of similar parameters in the group of patients with complicated course of peptic ulcer disease were found in 66.3%/60 and 33.7%/33 patients, respectively.

As for genotype frequencies, if in the group without complications of peptic ulcer disease variants T/T, T/C and C/C were detected in 66.7%/34; 27.4%/14 and 5.9%/3 cases, then among patients with complications of peptic ulcer disease the cases of their registration were 46.9%/23; 38.7%/19 and 14.3%/7 cases respectively.

Thus, studying the occurrence of alleles and genotypes for the polymorphic gene of interleukin IL1β (T31C) in the groups of patients without and with the presence of complications of peptic ulcer disease we found an increase in the frequencies of unfavorable alleles (T) and genotypes (T/C and C/C) in both cohorts of patients, i.e. both with and without complicated course of peptic ulcer disease. Meanwhile, their highest frequency was determined in the group of patients with complicated course of peptic ulcer disease, which shows a possible relationship between the increased activity of unfavorable alleles and genotypes and increased risk of complications in peptic ulcer disease.

The subsequent statistical analysis allowed us to determine the significance of the established differences between the studied polymorphic loci of the interleukin IL1β gene (T31C) in the groups of patients and healthy individuals.

The differences in the frequency of the weakened allele C in the main group of patients with duodenal ulcer compared to its frequency among healthy people were statistically reliable and were characterized by a significant increase in the risk of ulcer development almost twofold (26.5% vs. 15.9%; $\chi 2$=6.1; P=0.03; OR=1.9; 95%CI: 1.14-3.19).

At the same time, in terms of the frequency of heterozygous variant of T/C genotype, despite its 1.5-fold increase among patients compared to healthy controls (33.0% vs. 24.7%; $\chi 2$=1.5; P=0.3; OR=1.5; 95%CI: 0.79-2.86), the differences between the groups did not reach statistical significance.

However, although the differences between the frequencies of the weakened mutant genotype C/C did not reach statistical significance due to the small number of carriers of this genotype, there was a pronounced tendency among patients to increase its frequency by 3.0 times (10.0% vs. 3.5%; $\chi 2$=2.9; P=0.1; OR=3.0; 95%CI: 0.85-10.8), which shows its possible contribution to the increased risk of peptic ulcer formation.

Thus, according to the above data, we can conclude that the impaired allele C and genotype C/C of the interleukin IL1β (T31C) polymorphic gene are involved in the mechanisms of increasing the risk of peptic ulcer disease formation and can be considered as genetic predictors of the disease.

Studying the nature of differences in the distribution of allele and genotype frequencies of interleukin IL1β (T31C) gene polymorphism among patients without complications of peptic ulcer disease in comparison with the healthy cohort we did not find their statistical significance.

Thus, in the group of patients impaired carriage of C allele was 1.3 times higher than in the healthy cohort (19.6% vs. 15.9%; $\chi 2$=0.6; P=0.5; OR=1.3; 95% CI: 0.68-2.44). At the same time, unfavorable variants of T/C and C/C genotypes among patients were statistically insignificant in 1.2 (27.5% vs. 24.7%; $\chi 2$=0.1; P=0.8; OR=1.1; 95% CI: 0.52-2.54) and 1.7 (5.9% vs. 3.5%; $\chi 2$=0.4; P=0.6; OR=1. 7; 95% CI: 0.34-8.65) times were determined more often in comparison with those among healthy people, indicating their absence in the formation of uncomplicated course of peptic ulcer disease.

However, in the distribution of allele and genotype frequencies of the interleukin IL1β gene polymorphism

(T31C) polymorphism among patients with complications compared to the healthy cohort, we found a statistically significant increase in carriage of the impaired C allele and the C/C genotype, the activity of which was highly significantly associated with an increased risk of a complicated course of peptic ulcer disease by 2. 7 (33.7% vs. 15.9%; $\chi2$=11.3; P=0.01; OR=2.7; 95% CI: 1.51-4.78) and 4.6-fold (14.3% vs. 3.5%; $\chi2$=5.2; P=0.03; OR=4.6; 95% CI: 1.24-16.76), respectively.

Moreover, in the group of patients among T/C heterozygote carriers, there was a tendency to increase the risk of complicated course of peptic ulcer disease almost twofold (38.8% vs. 24.7%; $\chi2$=2.9; P=0.1; OR=1.9; 95% CI: 0.91-4.09).

Thus, the above results show that polymorphic loci of the interleukin IL1β gene (T31C) do not participate in the mechanisms that increase the chance of uncomplicated course of peptic ulcer disease, with their significant association with an increased chance of complicated course of peptic ulcer disease.

These results are confirmed by the data of comparative analysis of differences in allele and genotype frequencies of the polymorphic gene of interleukin IL1β (T31C) between groups with complicated and uncomplicated course of peptic ulcer disease.

In particular, a statistically significant association with an increased chance of developing a complicated course of peptic ulcer disease was found among carriers of the impaired C allele 2.1-fold (33.7% vs. 19.6%; $\chi2$=5.1; P=0.03; OR=2.1; 95% CI: 1.1-3. 94), while among carriers of the attenuated mutant genotype C/C there was a clear tendency to increase the risk of complicated course of peptic ulcer disease by 2.7 times (14.3% vs. 5.9%; $\chi2$=2.0; P=0.2; OR=2.7; 95% CI: 0.68-10.52).

4. Conclusions

Thus, the analysis of the prevalence of polymorphic gene of interleukin IL1β (T31C) carried out among the cohort of patients with gastric and duodenal ulcer disease in a comparative aspect with healthy individuals showed the presence of its contribution to the increase in the chance of disease development when carrying the weakened allele C statistically significantly almost twice ($\chi2$=6.1; P=00.3) and a clear tendency of increased chance of gastric and duodenal ulcer development at carrying the weakened mutant genotype C/C by 3.0 times ($\chi2$=2.9; P=0.1).

Moreover, the obtained results prove a statistically significant association between the increased chance of developing a complicated course of duodenal ulcer when carrying the weakened C allele and C/C genotype by 2.7 ($\chi2$=11.3; P=0.01) and 4.6 times ($\chi2$=5.2; P=0.03), respectively, as well as the presence of a tendency to increase the risk of forming a complicated course of peptic ulcer disease almost twofold ($\chi2$=2.9; P=0.1) when carrying the heterozygous T/C variant genotype for the polymorphic gene of interleukin IL1β (T31C).

Consequently, polymorphic loci of the interleukin IL1β gene (T31C) are associated both with a high risk of gastric and duodenal ulcer development and with the formation of a complicated course of this disease, which directly proves their role as genetic predictors of gastric and duodenal ulcer and its complicated course.

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