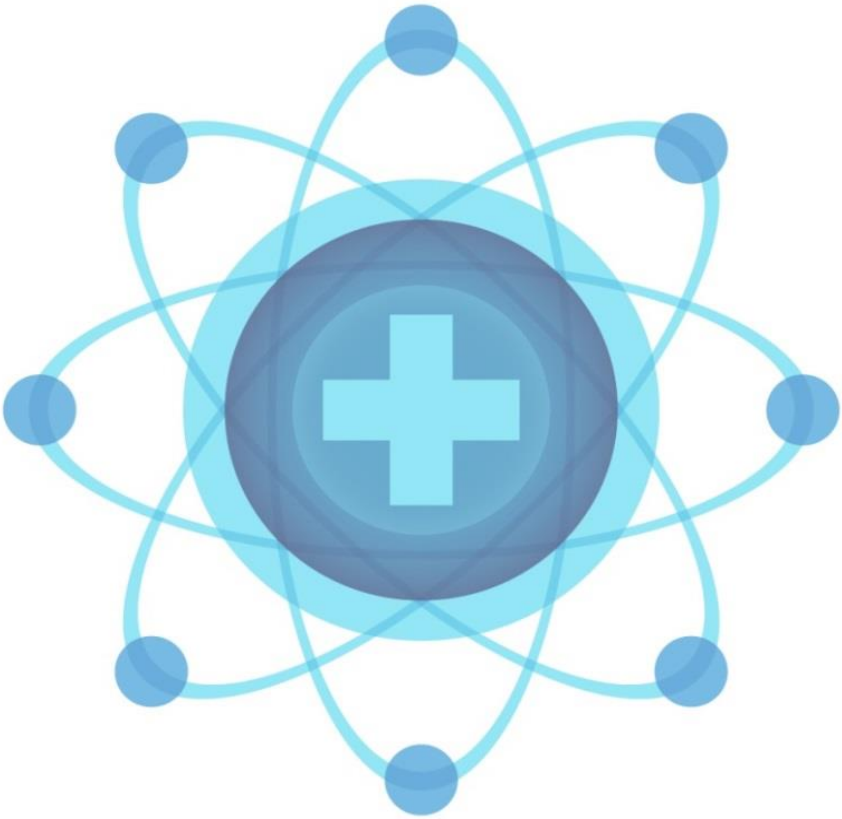

INTERNATIONAL MEDICAL SCIENTIFIC JOURNAL

ART OF MEDICINE

Volume-2
Issue-*3*

Founder and Publisher **North American Academic Publishing Platforms**
Internet address: http://artofmedicineimsj.us
E-mail: info@artofmedicineimsj.us
11931 Barlow Pl Philadelphia, PA 19116, USA +1 (929) 266-0862

Available at https://www.bookwire.com/
ISBN: 978-0-578-26510-0

POLYMORPHISM OF INTERLEUKINS IN MECHANICAL JAUNDICE

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Abstract. The article is devoted to the role of polymorphism of interleukins 2 and 6 in obstructive jaundice. The syndrome of obstructive jaundice, which develops as a result of diseases of the biliary tract, has genetically determined prerequisites. Our study suggests that carriers of the IL-6 C-174G gene allele have a high predisposition to biliary tract diseases, and carriers of the G T 330G allele of IL 2 gene polymorphism are a protective factor in the development of subhepatic cholestasis.

Keywords: obstructive jaundice, interleukins.

The urgency of the problem. The problem of treating patients with obstructive jaundice and liver failure remains an important medical and social problem not only in Uzbekistan, but throughout the world [2, 5-7].

Cytokines (interleukins - IL) play a significant role in the development and course of diseases of the biliary tract. Thus, IL-6 limits the synthesis of pro-inflammatory IL-1β, -6, -8, -12 by macrophages, the formation of highly active metabolites of oxygen and nitrogen. The ability of IL-6 to generate the activity of lymphokine-activated killers and enhance the antitumor activity of macrophages is known [3, 4, 9].

Damage to the extrahepatic bile ducts, which causes blockage of the outflow of bile into the intestine, biliary hypertension and cholemia, leads to endogenous intoxication, which is based on profound violations of the detoxification and synthetic functions of the liver [6, 10]. Experiments have shown that pronounced cholestatic hepatitis develops within 2 weeks after extrahepatic obstruction, and cirrhosis of the liver develops 2 months later [1, 8].

A large role in the development of fibrosis is given to various cytokines that regulate the synthesis of many enzymes and determine the course of the inflammatory process. It is known, for example, that collagenase synthesis is activated by interleukins 6 [1, 2, 10].

All of the above was the reason for conducting a study aimed at a comprehensive study of the polymorphism of interleukin genes that affect the course of liver failure in obstructive jaundice.

The aim of our study was to study the role of IL-2 and IL-6 gene polymorphisms in the prognosis of obstructive jaundice depending on the degree of hepatic dysfunction.

Materials and research methods. The work was performed in 90 patients hospitalized with obstructive jaundice syndrome of various etiologies. For the study, depending on the methods of diagnosis and treatment used, we have formed, standardized by age and gender. The patients were divided into two groups: - the main group (n = 90), patients with obstructive jaundice; - control (n = 60), healthy people in whom the polymorphism of interleukin-2 and interleukin-6 was studied.

The control group consisted of 60 healthy men (n =28) and women (n =32) aged 25 to 66 years (mean age 56.7±8.4). The age of patients in the main group ranged from 29 to 75 years (mean age 57.3±9.3 years) (t=0.048, df=146, p=24.17).

Among them, 47 (52.2%) women and 43 (47.8%) men (χ^2 = 0.018, p=0.89). In 38 patients (42.2%), jaundice was of tumor origin, in 52 patients (57.8%) - non-tumor. The duration of existence of obstructive jaundice ranged from 3 to 51 days. The level of total bilirubin varied from 87 to 526 μmol/l (mean 231.5±28.1 μmol/l).

Results and its discussion. According to our study results, the prevalence of T 330G polymorphism of the IL 2 gene among patients with obstructive jaundice in the Uzbek population is as follows: the T/T genotype of the IL 2 gene was found in 48.3% (29) of individuals, the T/G genotype - in 35% (21) and G/G genotype only in 16.7% (10). Expected T/T -26 (43.3%), T/G -27 (45%) and G/G -7 (11.7%); χ^2 = 2.96, df=2, p=0.086). 65.8% (79) of individuals had the T allele and only 34.2% (41) had the G allele.

These indicators in the main group were also unreliable, i.e. were consistent with the Hardy-Weinberg law (Observed T/T -47 (52.2%), T/G-34 (37.8%), G/G-9 (10%); expected T/T -45.5 (50.1%), T/G -37 (41.1%) and G/G -7.5 (8.3%); χ^2 = 0.58, df=2, p=0.45).

The heterozygous genotype T / T was observed insignificantly more often in persons with obstructive jaundice (47 (52.2%)) than in healthy persons (29 (48.3%)) (χ^2 =0.22; p=0.64). The heterozygous genotype T / G of the main group (34 (37.8%)) also did not differ significantly in comparison with the control (21 (35%)) (χ^2 =0.12; p=0.73.). The homozygous genotype G / G was also not more often detected in obstructive jaundice (9 (10%) versus 10 (16.7%)): χ^2 =1.45; p=0.23. Allele G was the most common in all examined: χ^2 =0.94; p=0.33; odds ratio (OR) -1.28; 95% confidence interval (CI) - 0.78-2.1 (Table 1).

Table 1

Frequencies of genotypes and alleles of T 330G IL 2 among patients with obstructive jaundice and healthy

Comparison groups	T / T	T / G	G / G	T	G
Main group (n= 90)	47 (52.2%)	34 (37.8%)	9 (10%)	128 (71.1%)	52 (28.9%)
Control group (n= 60)	29 (48.3%)	21 (35%)	10 (16.7%)	79 (65.8%)	41 (34.2%)
χ^2	0.22	0.12	1.45	0.94	
p	0.64	0.73	0.23	0.33	
OR (95% CI)	1.17 (0.61-2.25)	1.13 (0.57-2.23)	0.56 (0.21-1.46)	1.28 (0.78-2.1)	

Here, attention is drawn to an unreliable increase in the frequency of occurrence of the G/G genotype of this gene among patients compared with healthy individuals (p>0.05). It should be noted that the frequency of occurrence of this genotype among the healthy individuals of the Uzbek population examined by us practically corresponds to similar results obtained in the examination of residents of other countries of Asian origin [1, 4].

A parallel slight increase among patients and the frequency of the G/G genotype leads to a compensatory decrease in the frequency of the T/T genotype ($p>0.05$), which indicates the association of this genotype with the state of relative resistance to the development of the disease. From the results, it follows that this is probably associated with the IL-2-330G allelic variant, the frequency of which is moderately higher among infected patients compared with healthy individuals (1.28; 95% confidence interval (CI) - 0.78-2 ,1).

Given our data on the association of genotypes containing the IL-2-330G allele with a reduced ability of activated cells to produce interleukin-2, it can be assumed that one of the mechanisms for the predisposition of carriers of this allele to the development of obstructive jaundice is their low ability to develop full-fledged cellular reactions. immunity under the control of this particular cytokine.

The value of the prognostic coefficient for carriers of the IL-2-30G allele is not too significant, 3.3, which confirms the well-known position on the polygenic nature of the genetic control of the state of predisposition and resistance to the development of multifactorial diseases and suggests the need to study a significantly larger number of polymorphic points of genes immune response regulators.

As mentioned above, one of the key mediators of the inflammatory response with pro-inflammatory properties is IL-6. Checking the distribution of genotypes for C-174G of the IL-6 gene in healthy people for compliance with the Hardy-Weinberg equilibrium showed that the distribution of genotypes did not significantly differ from the theoretically expected (Observed C/C -11 (18.3%), C/G- 34 (56.7%), G/G-15 (25%), expected C/C -13.1 (21.8%), C/G -29.9 (49.8%) and G/G -17.1 (28.4%); $\chi^2 = 1.15$, df=2, p=0.28). These indicators in the main group were also unreliable, i.e. were consistent with the Hardy-Weinberg law (Observed C/C -7 (7.8%), C/G-45 (50%), G/G-38 (42.2%); expected C/C -9.7 (10.7%), C/G -39.7 (44.1%) and G/G -40.7 (45.2%); $\chi^2 = 1.63$, df=2, p=0.2).

In patients with cholestasis on the background of obstructive jaundice, the heterozygous C /G genotype (45 (50%)) and the G allele of the C-174G polymorphic locus (67.2%) of the IL-6 gene predominated. A positive association of MF development with the G allele ($\chi^2 =5.87$, p = 0.015; OR = 0.56 , CI = (0.35-0.9);) and the G/G genotype ($\chi^2 =4.67$, p = 0.031; OR = 2.19); CI = (1.07-4.5)), while the genotypes C/G ($\chi^2 =0.64$, p = 0.42; OR = 0.76 , CI = (0.4-1.47)) and C/C ($\chi^2 =3.8$, p = 0.051; OR = 0.38 , CI = (0.14-1.03)) proved to be a protective genetic factor.

The study of the diagnostic and prognostic possibilities of T 330G polymorphisms of the IL 2 gene and C-174G polymorphism of the IL-6 gene showed that the sensitivity was 61.8% and 65.4%, the specificity was 44.1% and 48.4%.

At the same time, the predictive value of a positive result, which reflects the probability of being sick with a positive indicator, was 71.1% and 67.2%. The predictive value of a negative result is 34.2% and 46.7%. The accuracy index was 56.3% and 59%. The likelihood ratio of a positive result is 1.1 and 1.3; the likelihood ratio of a negative result is 0.9 and 0.7, respectively.

The relationship of the A allele of the TNF-α G-308A gene ($\chi^2 = 9.45$, p = 0.002; OR= 3.2 (1.48-6.89) T 330G polymorphism of the IL 2 gene ($\chi^2 = 0.22$, p = 0.64) and C-174G of the IL-6 gene ($\chi^2 = 5.87$, p = 0.015) with increased risk the

development of obstructive jaundice due to choledocholithiasis and tumor lesions of the hepatopancreatoduodenal zone, which is consistent with modern literary sources.

Thus, obstructive jaundice syndrome, which develops as a result of diseases of the biliary tract, has genetically determined prerequisites, which the study helped to partially establish. Our study suggests that carriers of the C allele of the IL-6 gene of the C-174G gene have a high predisposition to diseases of the biliary tract, and carriers of the A allele of the TNF-α G-308A gene have a high probability of complicating the course of obstructive jaundice. While the G allele T 330G polymorphism of the IL 2 gene is a protective factor in the development of subhepatic cholestasis.

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