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Significance of IL28B Gene Polymorphism in the Prediction of Clinical Outcomes of Viral Hepatitis Leading to Liver Cirrhosis

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Abstract Conducted numerous studies about viral hepatitis outcome showed that in most cases the disease proceeds with the formation of liver cirrhosis. The exact mechanisms leading to the development of an unfavorable disease outcome are unknown. A research is conducted for revealing factors that leads chronic viral hepatitis to liver cirrhosis. In recent years, the role of genetic determinants is studied thoroughly to develop systemic diseases regarding liver cirrhosis. There is a need to evaluate the significance of genes polymorphisms in the predictions of the clinical outcome of hepatitis B, D and C. The aim of our study was to investigate the influence of genetic variation of IL28B gene on the risk of developing liver cirrhosis as well as the possibility of disease outcome prognosis of HBV, HDV, HCV infected patients. This article provides information about the influence of IL28B gene polymorphisms on the outcomes of chronic viral hepatitis. The study of genetic markers that influence the formation of liver cirrhosis with HBV, HDV, HCV infection, will allow creating a methodical approach to an individualized assessment of the risk of formation of an unfavorable disease outcome. The presented calculations statistically confirm the evidence that certain alleles of IL28B gene, as well as their adverse combinations have significant differences between the groups of patients with viral hepatitis of various etiologies. Thus, the genetic analysis is a promising method for non-invasive diagnosis of liver cirrhosis risk.

Keywords Liver cirrhosis, HBV infection, HDV infection, HCV infection, Gene polymorphism

1. Introduction

Liver cirrhosis (LC) takes substantial place in the variety of diseases related to the digestive organs. This matter is conditioned by the massive proliferation of etiological factors in the form of persistence of hepatotropic viruses, as well as the high mortality rate [2, 5, 8].

Due to the occurrence of the negative consequences that trouble the current population and the increasing frequency of invalid patients, development of this discipline appeared to be essential so far. Nowadays LC being as a crucial cause of the majority of death cases occupies the 10th place and is included in the list of 6 top reasons leading to the death among people aged 30-35 years [4]. It should be noted that the total mortality rate due to the LC varies in different countries. In Europe this measurement ranges from 4.6 for 100 thousand inhabitants (Norway) [9]. In Asian region, the lethality due to LC indicates 41 cases per 100 thousand inhabitants [13].

Despite all these accounts, neither clinical nor laboratory evidence of disease progression was observed. It is important to note that in more than 50% of patients manifestation of the illness happens only in decompensated stage, which indicates poor prognosis of the disease, when a liver transplantation is offered to more than 70% of patients as the sole method of treatment, conduction of which can be limited for different reasons. [1, 3, 6, 7, 12].

In this regard, one of the most important problems of modern medicine is the study of predictors of progression of chronic viral hepatitis in LC. In the recent years there have been actively carried out studies to identify the determinants that serve as an attribute or sign of the upcoming hazard of LC. It was revealed that the most common changes in gene structure is a single nucleotide polymorphism (SNP), caused by point mutations at certain positions of deoxyribonucleic acid (DNA), for which there are different variants of the sequences in some populations. The gene polymorphism is responsible for the reactions that occur in a particular person under the influence of various factors on the body. At the current time, an overwhelming majority of clinicians have been using the genetic marker SNP in the following positions: rs12979860 and rs8099917 of the gene IL28B to determine the efficiency of proposed treatment. In the recent years the important role of IL28B gene polymorphisms has been proven, which encoded the interferon lambda of the 3rd type

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and located in the 19th chromosome as a predictor of achieving a sustained virological response [10]. There have been unique studies dedicated to the impact of IL28B polymorphism for the purpose of effective treatment of hepatitis B. However, scientists have not uncovered specific links between the polymorphism and procedure of hepatitis B [11].

We have not met any study about the impact of gene polymorphism IL28B to forecast the outcome of hepatitis D. Therefore, it prompted us to analyze the impact of genetic determinants on the outcome of viral hepatitis.

All above-mentioned data confirm the fact that LC keeps being actual concern and challenge in the field of public health. Besides, these data prove definitely that the LC is considered to be still urgent public health problem; many issues are not solved, including those related to the factors which influence the progression of fibrosis. It prompted us to search the new factors of risk of development of LC.

Purpose of the study was to investigate the distribution of allele frequencies and unfavorable combinations of polymorphisms IL28B gene in patients with a high probability of the LC in the outcome of hepatitis B, D and C.

2. Materials and Methods

The selection of patients for the survey was conducted by the following criteria: studies performed in both sexes between the ages of 17 to 56 years who were on dispensary observation and in-patient treatment in the clinic of Research Institute of Virology Ministry of Health of Uzbekistan. Out of 125 patients in a clinical study 72 were revealed with the liver cirrhosis HDV etiology, 22 - HBV infection and 31 patients with HCV liver cirrhosis. Patients with severe somatic diseases, hematologic, endocrine, cardiovascular, renal, hereditary liver diseases, cryptogenic, malignancies, including HCC, with other infectious diseases were not subjected to the study.

Duration and intensity of the disease were different. All the patients were examined with common biochemical, serological and instrumental methods of examination.

Molecular genetic studies included PCR for detection of DNA HBV, RNA HDV and RNA HCV in the blood.

For genotyping of the SNP, related to IL28B rs8099917, first DNA extraction was carried out from the whole blood using the test-system "DNA-Sorb" (InterLabService, Russia). Genotyping of SNP rs8099917 was performed by TaqMan assay using the reagent kit with universal PCR mix (Applied Biosystems, Foster City, CA) and by combining with a special solution of primers and probes for TaqMan SNP genotyping. The method was adapted for testing by Rotor Gene 6000 (Corbett Research, Australia) and conducted using the following program: 50°C - 2 min; 95°C -10 min; and 40 cycles on the 95°C-15sec; 60°C-1 min. Analysis was made on the endpoint using the Rotor Gene 6000 (Corbett Research, Australia) software.

Statistical analysis was performed by V.I. Oyvina (1960) and V.G. Genesa (1964). To evaluate the statistical significance of differences between the comparable averages it was determined right or wrong response using the Student's criterion (t). The significance level of the response (P) was determined by Student's distribution table (P - coefficient of validity). Differences were considered significant at $P < 0.05$.

3. Results of the Study

LC is one of the variants of the outcome of chronic liver disease. Despite the obvious success in the hepatology, in some patients the disease is imperceptibly into the LC and detected only at this stage. Traditional risk factors of LC (gender, age, viral load, concomitant diseases) had little impact on the outcome chronic viral hepatitis.

Chronic hepatitis D (CHD) is considered to be mainly heavy, liver disease, with high rates of disease progression. In 70-80% of cases there was observed quickly progressive course of chronic hepatitis D, which developed super-infection in HDV patients with chronic hepatitis B or HBV carriers.

Out of the 72 patients with LC associated with HDV infection there were 40 men (55.6%) and 32 women (44.4%). The age of patients ranged from 17 to 56 years, the average age was 31,2±1,6 years. The degree of liver injury was evaluated on the scale of Child-Pugh. According to the severity and intensity of symptoms of the disease class A is defined in 20 (27.8%), B-22 (30.6%), class C in 30 (41.6%) patients.

Among patients there were 12 men (54.5%) and 10 women (45.5%) with LC in the outcome of hepatitis B. An average age of patients was 45,3±2,5 years related to the Class A - 12 (54.5%) to the Class B - 7 (31.8%) and Class C - 3 (13.7%) patients.

The study has shown that there were 16 (51.6%) men and 15 (48.4%) women with liver cirrhosis HCV etiology. An average age of patients comprised 54,5 ± 2,5 years. Patients related to Class A constituted 9 (29.0%), Class B - 19 (61.3%) and Class C - 3 (9.7%).

Table 1. The frequency of genotypes and alleles at SNP rs8099917 IL28B gene in different patients groups

Group	N	Genotype			
		TT	TG	GG	P
Liver cirrhosis HDV	72	62,5%	33,3%	4,2%	<0,05
Liver cirrhosis HBV	22	18,2%	81,8%	-	<0,01
Liver cirrhosis HCV	31	58,1%	41,9%	-	>0,05

Note: P- significance of differences between the indices of TT genotype and TG genotype

The study analysis of SNP rs8099917 IL28B gene showed that, patients with LC in the outcome of hepatitis D, T allele had the major and G - the minor. It was revealed rs8099917

genotype TT in 45 (62.5%) patients, heterozygous genotype TG was detected in 24 (33,3%), genotype GG in 3 patients (4.2%) (Table 1).

At HBV etiology LC genotypes were distributed as follows: rs8099917 genotype TT in the 4 (18.2%), heterozygous genotype TG was determined in 18 (81.8%) cases. There was no detected genotype GG. Indicators of SNP rs8099917 IL28B gene were significantly different in HBV etiology LC and both the HDV etiology LC TT alleles ($P<0.001$), and on the TG allele ($P<0.001$). The results of these studies have shown that TT genotype is more common in LC HDV than TG genotype ($P<0.05$), that is, it can be assumed that the genotype TT is a factor in the progression of the process of HDV infection. In LC associated with HBV infection TG genotype met much more frequently than the TT genotype ($P<0.01$). It is clearly seen that in hepatitis B there is a clear dependence of the outcome of LC from the gene polymorphism. Predictor of adverse outcome of hepatitis B is the presence of a heterozygous genotype TG. Most often (58.1%) patients with LC induced by HCV infection were recorded with carriers of allele TT rs8099917, TG heterozygous genotype was among 41.9% of patients. According to our data, in hepatitis C IL28B gene polymorphism can not serve as a predictor of disease outcome. It should be noted that genetic analysis is a promising method for non-invasive diagnosis of developing LC risk. The advantage of genetic markers is that they carry information about predisposition to the disease and its outcome, regardless of other factors such as the environment and individual characteristics of the organism. We need to continue further study of the significance in the progression of chronic hepatitis B and D rs8099917 IL28B gene as a predictor of the possible formation of the LC.

So the question arises about individual criteria of increased risk of developing LC in chronic viral hepatitis B and D, consequently, about the earliest possible beginning of the preventive measures.

4. Conclusions

Genomic screening of SNP rs8099917 IL28B gene allows to develop a standard approach to predicting individual susceptibility to HDV infection and the risk of developing LC.

On the basis of the data obtained from the studies it is clear that in HDV infection, the TT genotype is more common than the TG genotype, so TT genotype may be a factor in the progression of the process. The study of genetic polymorphisms IL28B gene will allow to predict the predisposition to HDV infection and to evaluate the risk of adverse outcomes of chronic viral hepatitis D.

In LC associated with HBV infection TG genotype met much more frequently - by 4.5 times more than the TT genotype. It is clearly seen that the hepatitis B has a clear dependence of the outcome of the LC from the gene polymorphism. Predictor of adverse outcome of hepatitis B is the presence of a heterozygous genotype TG.

The distribution of IL28B genotypes in LC induced by HDV infection was significantly different from the LC HBV etiology, both rs8099917 TT genotype and TG genotype.

It was not possible to use the gene polymorphism IL28B in hepatitis C as a reliable prognostic marker of disease outcome.

Thus, SNP the genomic screening will develop a standard approach to predicting susceptibility to various diseases, predicting disease outcome. Knowledge of an individual IL28B genetic type may be useful to determine the tactics of patients' treatment considering the possible outcome of the disease. In the future, the model prediction of adverse outcome of any disease can be developed.

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