Study Of Coinfection Of Viral Hepatitis C And Hiv-Infection In Uzbekistan

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Abstract

The aim of this study is to determine the role of IL28B gene polymorphism in the prognosis of fibrosis development. The object of the study were 120 patients with liver cirrhosis of the class. And according to Child-Pugh HCV etiology and 110 patients with coinfection (CHC and HIV). It has been proven for the first time that the IL28B gene polymorphism is the leading a marker of the risk of progression and formation of cirrhosis of the liver of class A according to Child-Pugh HCV etiology in HIV-infected patients. It has been proven for the first time that the non-CC genotype of the rs12979860 polymorphism in HIV-infected patients with HCV Child-Pugh A cirrhosis etiology is the reason for the acceleration of the process of fibrosis in the liver. Liver on the example of patients with coinfection (CVHC+HIV infection).

Keywords: hepatitis C; co-infection, HIV-infection, polymorphism, cirrhosis.

Introduction. A distinctive feature of infection caused by the hepatitis C virus (HCV) is its tendency to a long chronic course. Three quarters of all those infected remain chronically infected and are at risk for severe liver disease (cirrhosis, end-stage liver disease and liver cancer), the remaining 25% self-heal [9; p. 573-575]. There are up to 250 million people worldwide infected with HCV, of which about half are believed to have been infected as a result of unsafe medical practices in third world countries [44; p. 31-41]. Prior to the era of interferon-free therapy, HCV claimed up to 1 million lives annually, becoming one of the leading causes of death worldwide. There are no data on the prevalence of viral hepatitis C in Uzbekistan; large-scale studies on the prevalence of chronic forms of liver diseases have not been conducted.

Due to the common routes of transmission of HCV and human immunodeficiency virus (HIV), co-infections occur in about 5 million people [58; p. 76-79]. The presentation of HIV/HCV coinfection differs from HCV monoinfection in several ways. With coinfection, there is a higher viral load of HCV and a lower likelihood of spontaneous or drug treatment [35; p. 245-2558], while there is a more rapid progression of liver disease [14; p. 172-173.18; p. 371-372, 19; p. 271-273].

It is believed that the acquired immune response plays a significant role in the spontaneous remission of HCV. Spontaneous resolution of HCV is associated with rapid production of neutralizing antibodies and a strong T-cell response. Regarding the effect of neutralizing antibodies on HCV resolution, data are conflicting. Over the past decade, the understanding of the nature of infection and neutralization by antibodies has changed significantly since the development of HCV cell culture (HCVcc) and HCV retroviral particle coat protein (HCVpp) [22; p. 280-284]. A number of studies have shown high titers of neutralizing antibodies induced by HCVcc and HCVpp in the serum of patients with chronic HCV [42; p. 6006-6013.45; p. 966-970, 51; p. 3773-3776. 53; p. 452-463]. However, spontaneous resolution of HCV infection can occur without the induction of neutralizing antibodies [25; p. 40-45, 30; P. 291-296], and, according to many authors, humoral antibodies play an insignificant role in the resolution of HCV [2; p. 601-606].

Some patients with resolved HCV had a broader and stronger T-cell response containing CD4 and CD8 [27; p. 19-23] than in persons with chronic HCV. The detection of fully functional HCV-specific CD4 cells in acute infection is associated with subsequent resolution of HCV. In addition, the temporal relationship between the detection of HCV-

specific CD8 T cells indicates that CD8 cells are also important for HCV resolution. Thus, both CD4 and CD8 T cell responses are required for HCV resolution. The importance of CD4 cells in resolution is underscored by low levels of HIV coinfection, which may be part of the reason for CD4 cell depletion. CD4 cells recognize the target by binding to human leukocyte antigen (HLA) class II and CD8 cells to HLA class I.

Genetic associations with spontaneous resolution of HCV have been investigated at different stages of the human immune response to HCV. Knapp et al. found genetic associations in three main effector mechanisms: IFN-mediated antiviral response, MxA, ribonuclease L controlled by 2'5'-oligoadenylate synthetase (OAS-1), and protein kinase R (PKR) [52; p. 497-502]. Schott et al. pointed to an association between TLR-7 polymorphisms and chronic hepatitis C [37; p. 5]. Haku et al. showed that weak inhibition of NK by their killer ligands (KIRs) affects the effectiveness of protection against chronic hepatitis [16; p. 357-364]. A strong genetic link, reproduced in several independent studies, is associated with a single nucleotide polymorphism (SNP) located at the interleukin 28B locus (IL28B; rs12979860) [13; p. 1329. 33; p. 225-230, 46; p. 4959-4967. 50; p. 988-995, 55; p. 2407-2418, 57; p. 195-204]. Recent results from a genome-wide association study (GWAS) have shown a host genetic influence on HCV resolution in several cohorts. The authors repeated the known association with rs12979860 and identified a new SNP rs4272729 adjacent to the HLA class II gene on chromosome 6, which is associated at the level of statistical significance (p = 10) with spontaneous resolution of HCV. In addition, they tested the role of classical HLA and found that HLA-DQ-0301 can be attributed to the spontaneous resolution factor of HCV at a p = 10 significance level. hepatitis [20; p. 197-203].

Improvements in HIV treatment during the 1990s led to significant improvements in survival rates for HIV infection. However, as AIDS-related mortality declined, non-AIDS-related diseases began to predominate in the mortality structure [49; p. 560-567]. In HCV/HIV co-infection, the time of illness is strongly related to HCV [4; p. 527-530.5; p. 54-57. 8; p. 121-126. 10; p. 1144-1448. 23; p. 199-200]. In individuals infected with both viruses, there is a rapid progression of liver fibrosis [36; p. 541-548], liver cirrhosis [31; p. 73-82] and death [11; p. 864-870.12; p. 214-215]. In addition, the level of CD4 lymphocytes had an inverse relationship with liver damage [17; p. 235-241, 35; p. 245-258]. Kirk et al. point out that even after adjusting for HCV viral load (VL), chronic HBV, gender, race, and alcohol use, HIV/HCV coinfection was just as significantly associated with the development of liver fibrosis as in those with there was no hepatitis C disease for 10 years more [38; p. 185-190]. Despite the fact that with the introduction of antiretroviral therapy (ART), the risk of complications in the form of liver disease or death from HIV/HCV coinfection has significantly decreased [6; p. 4238-4247. 7; p. 53-62, 21; p. 71-98.29; pp. 681-693.39; p. 441-446, 40; p. 111-115], the adverse effects of HIV and HCV coinfection are not completely reduced by ART [15; p. 639-645, 34; p. 909-912].

Thus, HIV/HCV co-infected patients also require treatment despite many problems (including decompensation of liver disease, substance abuse, socioeconomic status, and treatment adherence) in this group of patients, who are often IDUs. Many guidelines recommend initiating HCV therapy before starting ART if CD4 count > 500/mcL, based on the fact that HCV therapy with CD4 values has not been observed by the authors [3; p. 16. 32; p. 42-48. 48; p. 3924-3929.180; p. 1877-1881, 62; p. 24-30, 48; p. 3924-3929]. The development of steatosis, inflammation, and mortality are associated with genotype 3 [33; p. 213-222. 58; p. 8-17, 47; p. 349-356].

Methods and materials. We studied the role of genetic polymorphism in the clinical and laboratory manifestations of liver cirrhosis in HCV and HIV co-infection. The study included 110 patients co-infected with HCV and HIV. The results of testing for the genotypes of the IL28B gene polymorphism showed that the wild type (TT genotype) of the rs8099917 polymorphism genotype occurs in 68.2% of cases, and genetic mutations were noted in 31.8% of cases. With the rs12979860 polymorphism, this distribution was 80% and 20%, respectively. With such a significant discrepancy in the distribution of genotypes between polymorphisms, the observed difference was not statistically significant. The mean age in all groups was about the same. The age of patients ranged from 20 to 65 years in all groups. The same median distribution indicates a normal distribution and homogeneity of the selected study target group, which allows further research. In the distribution by sex, there is a predominance of men over women, although this predominance is not so significant in groups with mutant genotypes. The clinical stages of HIV are distributed equally, with the exception of the rs8099917 mutant genotype, where there are more patients with the third stage of HIV infection than patients with the fourth stage of HIV infection by one and a half times, but the differences in distribution are not statistically significant. The mean viral load for all genotypes was 2.5 logarithms, with the exception of the group of non-CC genotype of the rs12979860 polymorphism, in this group the mean viral load was more than 3 logarithms. In all study groups, the level of CD4 cells was just under 300 cells. 10% of all patients had cirrhosis of the liver. During the medical examination of the patients included in the study, the patients noted complaints of varying severity.

Results and discussion. So, most often, patients noted weakness (76.4±4.1%), fatigue (70.9±4.4%), headaches (26.4±4.2%), weight loss (22.7±4.0%), fever (20.9±3.9%), memory impairment and loss of appetite (18.2±3.70),

heaviness in the right hypochondrium (17.3±3.6%), plaque on the tongue , irritability and bloating (12.7±3.4%). Pain in the joints (10.0±2.9%), epigastric pain (9.1±2.8%), flies before the eyes and insomnia (7.3±2.5%), dizziness, sweating (6.4±2.3%), nausea, pain in the heart area and heaviness in the epigastrium (5.5±2.2%), decreased performance, heartburn and bitterness in the mouth (4.5±2.0%). Rash, runny nose and vomiting (2.7±1.6%), ascites and belching (1.8±1.3%) were even less common. Complaints of bleeding, constipation, drowsiness, edema, flatulence were noted in less than 1% of cases.

During an objective examination, almost all patients had a general condition of moderate severity, clear consciousness, respiratory rate was recorded within 20 per minute, pulse 75 beats/min, vesicular respiration, blood pressure within normal limits. Palpation revealed an enlarged liver and most had an enlarged spleen.

The distribution and frequency of some patient complaints differed depending on the polymorphism genotype. Thus, in the mutant genotypes of both polymorphisms, weakness 50.0±10.9 was statistically less common in the non-CC genotype versus 83.0±4.0 in the CC genotype of the rs12979860 polymorphism (p=0.02). Plaque on the tongue also had differences between wild and mutant genotypes for both polymorphisms. So, with the CC genotype, as well as with the TT genotype, this complaint was statistically significantly less common: 9.1±3.1% versus 27.3±11.7 and 6.7±2.9 versus 25.7±8, 5 respectively. Other complaints arose to varying degrees depending on the polymorphism. Thus, with the rs12979860 polymorphism, a statistically significant difference was noted in the frequency of fatigue, diarrhea, and weight loss. These complaints were statistically significantly (p>0.05) more common in individuals with the wild genotype (77.3±4.5%, 33.0±5.0 and 27.3±4.8, respectively). Among the average laboratory indicators below the norm were noted: hemoglobin 95.7±1.5 g/l, erythrocytes 3.2±0.03 1012/l, PTI 70.3±5.5%, albumin 27.9±0.9 g/l; within the normal range: leukocytes 4.8±0.17 109/l, AST 27.6 U/l, total bilirubin 19.2±3.8 μmol/l, direct 17.6±4.4 μmol/l, indirect 1.6±2.1 μmol/l, creatinine 73.7±7.9 μmol/l. , glucose 5.4±0.3 mmol/l, total protein 69.7±0.3 g/l, alkaline phosphatase 153.1±7.1 U/l; ALT 70.0±12.9 U/l and ESR 22.02±1.3 mm/h were above normal. Significantly increased GGTP index 131.9±57.6 U/l.

When analyzing the distribution of laboratory parameters depending on the polymorphism of the IL28B gene, it was found that laboratory parameters practically did not differ in polymorphism types and genotypes, with the exception of the total protein index in the rs12979860 polymorphism, however, the difference between genotypes has no clinical significance and this indicator can be neglected. The probability of the outcome of liver cirrhosis depending on the genotype of polymorphism in both types of polymorphism indicates that the development of cirrhosis does not depend on the genotype. Thus, the relative probability of occurrence (OR) of liver cirrhosis with point polymorphism rs12979860 was OR 0.87 - 95% CI 0.17-4.38, and with polymorphism rs8099917 OR 0.44 - 95% CI 0.09-2.1 .

The aim of the study was to determine the association between the CC genotype and the TT polymorphisms rs12979860 and rs8099917 of the IL28B gene and an increased risk of HCV-associated liver cirrhosis in HIV-infected patients. This group of patients is of particular interest in light of the accelerated natural course of liver disease associated with HCV infection [2; pp. 76-79,145; pp. 1467-1471, 213; pp. 706-717.224; P. 247-252] It is believed that liver fibrosis in patients with chronic hepatitis C is the result of immune-mediated events, and not a direct consequence of the cytopathic effect of HCV replication [179; pp. 1-6] Increased intrahepatic mRNA expression of pro-inflammatory cytokines (i.e., IFN-ɣ regulated by normal T-cell activation, macrophage inflammatory protein-1a, and interferon-inducible protein-10) has been found in co-infection with HIV and HCV. compared with patients with HCV - monoinfection [59; p. 103-106. 60; p. 46-49, 63; p. 22-28. 24; S. 203-210]. Interestingly, most patients with CC genotype IL28B have a more intense inflammatory process in the liver compared to non-CC genotypes [1; p. 439-443], which ultimately accelerates liver damage and fibrogenesis [61; p. 65-67, 26; p. 829-841].

Conclusion. Viral hepatitis is endemic in Uzbekistan, annually causing a large number of diseases and a burden on the economy. Viral hepatitis is characterized by a long, chronic and asymptomatic course, which leads to their detection at the stage of development of complications. Cirrhosis of the liver is the most formidable and most frequent complication of viral hepatitis, developing in 20-30% of those infected. In the advanced stages of cirrhosis, treatment tactics are significantly limited up to liver transplantation, but in the early stages the process can be stopped, and in some cases reverse processes are observed. Thus, based on the above analysis of literary sources, it has been shown that, in the epidemiological and pathogenetic terms, the formation of liver cirrhosis in patients with hepatitis C has not undergone any special changes at the present stage; Despite the existing gold standard for diagnosing cirrhosis using liver biopsy, the modern development of medical science and technology dictates the need to expand the possibilities and approaches to diagnosing this pathology using non-invasive highly informative methods that allow screening the dynamics of cirrhosis at the stages of therapy and predicting their results.

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