IMMUNOLOGICAL AND AUTOIMMUNE REACTIVITY OF THE ORGANISM IN HEPATITIS C

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Abstract*. In recent years, there has been an increase in the number of infectious diseases, including viral hepatitis, which pose a real threat. According to WHO, more than 1/3 of the world's population is infected with the hepatitis B virus. Every year, about 2 million people die from HBV infection worldwide, of which about 700 thousand from cirrhosis and 300 thousand from liver carcinoma [2,5]. About 500 million people in the world suffer from chronic HCV infection; more than 60% of those infected with the virus do not eliminate the virus after the acute phase and develop chronic viral hepatitis C [3,4].*

Keywords*: quasispecies, antiviral treatment, immunological reactivity, autoimmune disorders, chronic hepatitis C.*

The hepatitis C virus is called an “escape virus” that escapes immune surveillance, which is largely due to the high mutational activity of the virus. Currently, six genotypes and several genotypic subtypes of the pathogen have been identified. The hepatitis C virus has 6 main genotypes and 80 subtypes, each of which forms new quasispecies as a result of gene mutations in the body. It is with the genotypes of the hepatitis C virus that many scientists associate the frequency of chronicity of the disease, the development of severe complications, the high level of viremia in the patient’s blood, as well as resistance to antiviral effects in the treatment of chronic viral hepatitis C. Due to the high heterogeneity of the antigenic structure of genotype 1 HCV, the virus avoids the immune response, in As a result, its persistence becomes multi-year in nature, and the stability of the viral response during antiviral treatment is noted [3,5].

In the pathogenesis of viral liver damage, a special place is given to autoimmune disorders, because the high frequency of extrahepatic manifestations in chronic viral hepatitis C, combined with the detection of a wide range of autoantibodies, suggests the role of hepatotropic viruses in the etiology of some autoimmune diseases [2, 3, 10]. At the same time, the question remains open about the significance and place of autoimmune disorders in the pathogenesis of viral liver damage.

The PURPOSE of our study was to study the nature of immunological reactivity and autoimmune disorders in chronic viral hepatitis C (CHC), depending on the immunogenetic characteristics of the virus.

MATERIALS AND METHODS OF RESEARCH.

We examined 162 patients with chronic hepatitis C with an average age of 35.6±2.8 years. The duration of the disease ranged from 1 year to 10 years (average 3.8±1.1 years). The initial examination complex included a traditional set of clinical and biochemical laboratory parameters, ultrasound, and the study of serological markers (anti-HCV-IgG). The diagnosis was verified on the basis of clinical and laboratory data (order of the Ministry of Health of the Republic of Uzbekistan No. 560 dated October 30, 2000).

All patients with chronic hepatitis C had a moderate or minimal degree of activity. When collecting anamnestic data, the vast majority of patients complained of general weakness, fatigue, and slight heaviness in the right hypochondrium.

Among the examined patients, 74% had genotype 1 (1a or 1b), 6% had genotype 2 (2a or 2b), and 21% had genotype 3 of the hepatitis C virus, that is, the most common genotype in our study was 1 genotype.

Immunological and virological studies were carried out in the laboratories of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan using modern and high-precision test systems (ELISA and PCR). Markers of viral hepatitis B and C were identified using the enzyme immunoassay method, and activity was confirmed by polymerase chain reaction (PCR) in the laboratory of molecular diagnostics at the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan. Hepatitis C virus genotypes (1a, 1b, 2a, 2b, 3a) were determined using the PCR method using specific primers. Immunological studies included the study of the main parameters of cellular and humoral immunity using test systems produced by the Institute of Immunology of the Russian Federation and the Institute of Microbiology named after. Gamaleya, were carried out in the laboratory of immunocytokines of the Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan.

The presence of autoimmune disorders in the natural course of chronic viral hepatitis C was determined by identifying autoantibodies to single-stranded (denatured) DNA and interferon-alpha by ELISA. In order to exclude the influence of antiviral therapy on the incidence of autoimmune disorders, none of the examined patients received interferon preparations and/or any interferon inducers during treatment. The lack of complete specific antiviral therapy allows us to discuss the natural course of chronic viral hepatitis C in the examined patients.

RESULTS AND DISCUSSION:

We analyzed the immunological and autoimmune parameters of patients with chronic viral hepatitis C depending on the genotype of the hepatitis C virus.

The cellular component of immunity was assessed by the content of leukocytes, lymphocytes, the total pool of T-lymphocytes (CD3), T-helpers/inducers (CD4) and T-cytotoxic lymphocytes (CD8), the CD4/CD8 ratio (immunoregulatory index - IRI), B-lymphocytes (CD20), as well as activation markers (CD 23, CD25, CD38, CD95).

According to our data, the content of leukocytes in the peripheral blood with chronic viral C on average differed from the control data ($p < 0.05$), leukopenia was observed with genotype 1 of the virus, and leukocytosis was observed with genotypes 2 and 3. The relative content of lymphocytes in patients with chronic viral hepatitis C and controls did not reveal a significant difference ($p>0.05$), however, there is a tendency towards lymphopenia, which is also noted in absolute indicators, for which there is a significant difference between the values of patients with chronic hepatitis C and controls data. And it should be noted that lymphopenia is more pronounced with genotype 1 of the virus compared to genotypes 2 and 3. Thus, in patients with chronic hepatitis C, the absolute content of lymphocytes for virus genotype 1 was 1776.3±120.9 cells/μl; with virus genotype 2 - 2092.5±117.8 cells/μl; at 3 - 2010.7±140.7 cells/μL, whereas in the control group – 2238.1±89.1 cells/μL ($p<0.05$).

It is known that the degree of surface expression of CD3+ receptors on the membrane of T-lymphocytes reflects its transmissible function and makes it possible to identify the total number of T-lymphocytes. Analysis of the immunophenotype of T-lymphocytes in patients with chronic

hepatitis C showed the presence of a significant suppression of CD3+ expression on T-lymphocytes both in relative and absolute value in comparison with the control group ($p < 0.05$), which was observed to varying degrees in all genotypes of the hepatitis C virus .

The CD4+ T cell response to viral proteins is an important defense mechanism for the host, and suppression of this mechanism reduces the effectiveness of combating the viral agent. Thus, in patients with chronic hepatitis C of all genotypes of the virus, a significant suppression of CD4+ expression on T-lymphocytes was observed compared with the values of the control group ($p < 0.001$), which was manifested in both the relative and absolute content of CD4+ T-helper cells in the study groups.

It is known that cytotoxic CD8+ T lymphocytes play an important role in the pathogenesis of viral diseases, which is due, on the one hand, to their ability to cause the death of infected cells expressing the corresponding peptides presented by MHC class 1 molecules, and on the other hand, to their ability to secrete antiviral factors (pro-inflammatory cytokines – IFN-α, TNF-α and many others) [5,9]. Analysis of the content of CD8+ T-lymphocytes between the studied groups of patients with chronic viral hepatitis C; in the studied groups of patients, a significant increase in the relative and absolute content of CD8+ T-lymphocytes was observed for all genotypes of the virus when compared with data from the control group ($p < 0.01$). Thus, in the group of CHCV patients, the relative value of CD8+ expression on T lymphocytes was 25.4±1.1% for genotype 1; with genotype 2 -24.4±1.3%; with genotype 3 - 24.3±1.5%; in the control group this figure was 18.4±0.5%.

During chronic viral hepatitis, the immunoregulatory index (IRI), which is the ratio of the number of CD4+ T helper cells/inducers to the number of CD8+ T lymphocytes, is of significant importance. It should be noted that in CHCV patients, regardless of the genotype of the virus, the IRI was 0.9 with genotype 1; whereas for genotypes 2 and 3 it was 1.0 and 1.3, respectively, and in the control group – 1.5±0.05 ($p<0.05$). It is obvious that suppression of CD4+ T helper cells/inducers against the background of an increase in the number of CD8+ T lymphocytes leads to a decrease in IRI in groups of patients with chronic hepatitis C, and is an important criterion for the depth of the T cell immunodeficiency state in chronic liver lesions, which, as we see, more pronounced with genotype 1 of the hepatitis C virus.

Natural killer cells (NKCs) are a major effector of natural or innate immunity that are capable of lysing target cells or mediating antibody-dependent cellular cytotoxicity and are involved in antiviral, antibacterial, and antiprotozoal defense. It is they who are inherent in performing the functions of the first line of defense before immune T-lymphocytes and specific antibodies arise [1,5]. A study of NK cells with CD16+ phenotypes revealed an increase in the relative number of CD16+ NK cells in groups of CHCV patients with different genotypes of the virus. A significant difference in the content of CD16+ NK was detected between the values of patients with 1 genotype of the virus and the values of CHCV controls ($p<0.01$). Whereas in groups with other genotypes of the hepatitis C virus, there was a tendency to increase the relative number of CD16+ NK.

It is known that, along with T-lymphocytes, B-lymphocytes are the main effectors of immunity. Considering that the main function of B lymphocytes in the body's fight against infection is the production of antibodies, changes in the expression of surface receptors of B lymphocytes indicate their active participation in the antiviral response [8]. We studied the content of B-lymphocytes based on the expression of CD20+ receptors, which revealed a significant

increase in CHCV patients for all genotypes of the virus in comparison with the values of the control group ($p < 0.01$). Thus, the relative number of CD20+ B-lymphocytes in CHCV patients with hepatitis C virus genotype 1 was 23.2±0.6%; with genotype 2 - 25.5±1.1%; with genotype 3 - 24.3±0.9%; whereas the relative content of CD20+ B lymphocytes in the control group averaged 18.6 ± 0.6%. As we see, with genotype 1 of the hepatitis C virus, the least active participation of the B-cell component of immunity in the antiviral response is noted.

One of the most important biological functions of immunoglobulins is antigen binding and the formation of an immune complex (CIC). An important characteristic of CECs is their size. Thus, in patients with chronic hepatitis C there was an increase in the average CEC values of 3% and 4% by 3.4 and 4.5 times, respectively, relative to control values. Depending on the genotypic characteristics of the virus, the humoral link of the immune system was characterized by a high level of small CECs with genotype 1 of the virus than with genotypes 2 and 3. Small CECs are poorly eliminated from the body, can be deposited subendothelially, and are not able to activate the complement system, and indicate the progression of the process .

According to many researchers, HCV viral replication occurs not only in liver cells, but also in peripheral mononuclear cells, lymph nodes, and to a lesser extent in the bone marrow, spleen, thyroid gland and adrenal glands, which allows HCV to remain invisible to the human immune system for a long time and determine both the development of extrahepatic manifestations of HCV infection, including autoimmune ones, resistance to ongoing antiviral therapy, and the high frequency of relapses of HCV infection after treatment [11,12]. Based on this, we decided to study the relationship between the persistence of HCV infection in mononuclear cells and the risk of developing autoimmune disorders in chronic HCV.

According to the data obtained, persistence of HCV infection in the blood serum was detected in 67.3% of patients, and no HCV RNA was detected in the serum in 32.7%. When studying the persistence of HCV infection in peripheral blood mononuclear cells, viral RNA was detected in 69.3% of cases, and in 22.3% of these cases, no viral RNA was detected in the blood serum.

When calculating the risks of developing autoimmune disorders, it was revealed that the incidence of autoimmune disorders was 1.52 times higher among patients in whom HCV RNA infection was detected in blood mononuclear cells compared to patients in whom HCV RNA infection was not detected in mononuclear cells.

RESULTS:

1. In chronic viral hepatitis C, there is a pronounced imbalance in the cellular and humoral components of the immune system, which is more pronounced in genotype 1 of the virus. The identified changes in the state of immunoreactivity of CHCV patients indicate the influence of the immunogenetic characteristics of the virus on the formation of the immune response and the course of the infectious process.

2. Persistence of HCV infection in mononuclear cells is a prognostically unfavorable factor for the development of autoimmune disorders in chronic hepatitis C.

REFERENCES

1. Akhmedova M.D., Gulyamov D.G., Faizullaeva D.B., Akhmedova Kh.Yu. On the lymphotropic properties of HBV, HCV and HDV: significance for the pathogenesis, clinical picture and ELISA diagnosis of chronic viral hepatitis. // Materials. international conference

"Viral hepatitis: successes and problems" – Journal. Theoretical and wedge. medicine. – 2002. – 2. – P. 6-10.

2. Astakhin A.V., Efimova E.E., Zverev V.V., Levitan B.N., Afanasyev S.S. Concentration of natural autoantibodies to interferon-alpha and indicators of interferon status in chronic hepatitis and liver cirrhosis. // Journal of Microbiol. - 2007. - No. 4. - P. 65-68.
3. Bueverov A.O. Immunological mechanisms of liver damage // Ross. and. gastroenterol., hepatol., coloproctol. - 1998. - No. 5. - pp. 18-21.
4. Ignatova T.M. Natural course of chronic HCV infection // Ros. magazine gastroent., hepatol., coloproctol. – 2002. – No. 2. – P.20-29.
5. Ignatova T.M., Serov V.V. Pathogenesis of chronic hepatitis C. // Pathology Archives. – 2001. – 3. – P. 54-57.
6. Karev V.E., Tsinzerling V.A., Komarova D.V., Yakovlev A.A. The relationship between chronic viral hepatitis and hepatocellular cancer. // Issues of oncology. – 2000. – T. 46. – 4. – P. 427-432.
7. Niyazmatov B.I., Matkarimov B.D., Atabekov N.S. On the epidemiology of viral hepatitis in the Republic of Uzbekistan // Journal. theory and wedge. medicine. – 2001. – 4. – P.129-131.
8. Semenenko T.A. Cellular immunity in hepatitis C // Viral hepatitis. Achievements and prospects: Inform. bulletin - 2002.- No. 1. P. 3-10.
9. Khazanov A.I., Ivlev A.S., Vasiliev A.P. Relationship between liver cirrhosis and infection with hepatitis B and C viruses. // Ros. journal gastroen., hepatol., coloproctol. – 2004. – 2. – P. 16-19.
10. Ray Kim.W. Global epidemiology and burden of hepatitis C. Microbes. Infect. – 2012 -No. 4, -R.1219-1225.
11. Clifford B.D., Donahue D., Smith L. et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C // Hepatology.- 1995.- Vol. 21,- pp. 613-619.
12. Manns M.P. Hepatotropic viruses and autoimmunity // J. Viral Hepat. -2007. N 4. - Suppl.l. - P.7-10.