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THE IMPORTANCE OF CYTOKINES IN PATIENTS WITH CIRRHOSIS OF THE LIVER OF VIRAL ETIOLOGY.

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Abstract. Liver cirrhosis is currently a pressing medical problem and is considered the terminal stage of all chronic liver diseases. According to the World Health Organization, about two million people die from liver disease every year. Liver disease accounts for 4% of all deaths worldwide, meaning 1 in 25 deaths is due to this disease. In many cases, the etiological factor of acute hepatitis is hepatotropic viruses [1]. In recent years, in our region there has been a significant increase in liver cirrhosis due to viral hepatitis.

Objective: study of serum concentration of pro- (IL-17A) and anti-inflammatory (IL-10) mediators of immune response in CPU. Material and methods: Serum of 72 patients with CPU. The control group consisted of 28 practically healthy persons of similar age. Serum IL-17A concentration was determined by solid-phase enzyme immunoassay using CYTOKINE CJSC test systems (Russia, Saint Petersburg). Results: Results suggest that IL-17A and IL-10 overexpression are strongly associated with the progression of chronic HBV and HCV infection and therefore severe liver cirrhosis.

KEYWORDS: cirrhosis, viral hepatitis, cytokines, serum, imbalance.

INTRODUCTION. When HCV and HBV infections interact with the immune system, both adaptive humoral reactions with the formation of virus-specific antibodies and T-cell reactions with the participation of cytokines are activated. At the same time, the leading factor in the development of chronic viral hepatitis HBV, HCV is insufficient production of cytokines or a decrease in the sensitivity of viruses and body cells to them, which may be due to the influence of allelic variants of cytokine gene polymorphism. Chronic viral hepatitis determines a significant incidence rate, causes a deterioration in the quality of life and economic damage. According to modern concepts, liver damage in chronic hepatitis depends on the intensity of inflammatory processes, the level of viremia and the genotype of the virus, while the activity of the immune system plays a leading role *[3,4]*. A large number of cytokines play a role in the regulation of fibrogenesis *[2,7]* and could potentially serve as biomarkers of liver fibrosis. Prolonged cytokine synthesis can initiate the progression of the pathological process in the liver *[5]*.

Determination of cytokine status in chronic liver disease is important for determining prognosis, as the level of cytokines reflects the intensity of regenerative processes in the liver and the progression of the disease *[6]*.

When HCV and HBV infections interact with the immune system, both adaptive humoral reactions with the formation of virus-specific antibodies and T-cell reactions involving cytokines are activated. At the same time, the leading factor in the development of chronic viral hepatitis HBV, HCV is insufficient production of cytokines or a decrease in the sensitivity of viruses and body cells to them, which may be due to the influence of allelic variants of the polymorphism of cytokine genes

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[9].

Recent studies have shown that disruption of the balance of cytokine production Th1/Th2 cells has an important role in the immunopathogenesis of HCV infection: the predominant part of cytokines produced by Th2- cells is associated with viral persistence and chronization of the process in HCV infection, and Th1 is associated with spontaneous recovery in acute hepatitis C and elimination of the pathogen. IL-10, a Th2 cytokine, is mainly involved in the regulation of inflammatory responses. It was originally described as a murine Th2 cell factor inhibiting Th1 cell cytokine synthesis responsible for the humoral immune response *[7]*. The mechanisms of Th2/Th17 type action and the role of their synthesis products in viral liver diseases are still poorly understood. So IL-10 like iIL-17A is crucial in inflammation, but the relationship with liver fibrosis and cirrhosis remains unclear. In view of the above, the aim of the present study was to determine the serum concentration of IL-17A and IL-10 in a comparative aspect in patients with HBV and HCV-induced LC.

MATERIAL AND METHODS

The current study included 72 patients with an established diagnosis of liver cirrhosis (LC) caused by viral hepatitis (HBV = 40 and HCV = 32). The control group consisted of 28 apparently healthy individuals of the same age.

Immunological studies in examined women and men were carried out in the immunoregulation laboratory of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

The concentration of interleukin-17A (IL-17) and interleukin-10 (IL-10) in peripheral blood serum was determined by enzyme immunoassay using test systems of CYTOKIN ZAO (Russia, Sankt-Petersburg). Quantitative evaluation of the results was carried out by the method of plotting a calibration curve reflecting the dependence of absorbance on the concentration for the standard antigen and allowing comparison of the test samples with it.

Statistical processing of the obtained data was carried out using the computer program Statistica 6.0. The reliability of the differences in the mean (p) of the compared indicators was assessed by the Student's criterion (t).

RESULTS.

Immunological studies conducted to determine the serum content of IL-17A and IL-10 in patients with LC showed significantly increased values, which are given below in Table 1. and in Table 2.

Table 1.

Serum IL-17A content in examined patients with LC

Measure	M±m, pg/ml	Me [Q1; Q3]	Min, pg/ml	Max, pg/ml
Control group, n=28				
IL-17A	17,59±1,35	17,45 [12,12; 23,60]	5,9	31,4
with LC at HBV, n=40				

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IL-17A	114,56±6,10***	106,50 [80,92; 152,85]	56,9	183,2
with LC at HCV,n=32				
IL-17A	96,61±3,53***	96,75 [82,52; 110,35]	59,8	137,3

*Note: * - significantly compared to the control group (* - P<0,05, ** - P<0,01,*** - P<0,001). Me – median, Q1(percentile) –25%, Q3 (percentile) – 75%.*

Th17 cells are a subtype of pro-inflammatory cells. Formation, development and function of Th17 cells are different from Th1 and Th2 cells *[8].*

Interleukin 17 (IL-17) is a novel family of cytokines consisting of six family members (called IL-17A to IL-17F) that are encoded by individual genes. IL-17A has been characterized as a major effector cytokine that is secreted by Th17 cells *[10].* IL-17A plays a dual role in immune responses to infection. The first role benefits the host in the fight against infection *[11];* However, it is also associated with negative effects such as autoimmune and other immune-related disorders *[12].* As can be seen in Table 1, the serum concentration of IL-17A in this sample of patients was significantly increased. Analysis of the data revealed that the level of the studied pro-inflammatory mediator of the immune response in the group with HBV was increased by 6.5 times with a mean value of 114.56 ± 6.10 pg/ml, with an individual range from 56.9 to 183.2 pg/ml, compared with the control group 17.59 ± 1.35 pg/ml (P<0,001).

In addition, analysis of the data revealed significantly increased values of almost 5.5 percent in the group of patients with HCV. Thus, the serum IL-17A level in the group of patients with CP with HCV averaged 96.61 ± 3.53 pg/ml, with an individual span ranging from 59.8 to 137.8 pg/ml, while in the control group this indicator was 17.59 ± 1.35 pg/ml (P<0,001).

As you know, viruses are able to modulate the immune response of the host, which leads to the development of secondary immunodeficiency, manifested by an imbalance of immunological functions. In persistent viral infections, the immune response is strong enough to develop autoimmune complications and insufficient to eliminate the virus. Our findings suggest that IL-17A overexpression is likely strongly associated with the progression of chronic HBV and HCV infection and thus severe presentation of liver cirrhosis. According to the literature data with which our results are consistent, high serum IL-17A indicates severity of liver injury and fibrosis, which is an unfavorable predictor.

According to literature, IL-10, an important anti-inflammatory cytokine, plays an immunosuppressive role in fibrogenesis. The results we obtained are shown in Table 2. suggest an inadequate immune response indicative of chronization and fibrogenesis.

Table 2.

Serum IL-10 in examined patients with LC

Measure	**M±m, pg/ml**	**Me [Q1; Q3]**	**Min, pg/ml**	**Max, pg/ml**
Control group, n=28				

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IL-10	11,28±0,46	10,70 [9,47; 13,12]	7,7	17,1
with LC at HBV, n=40				
IL-10	43,74±1,54***	41,9 [35,85; 51,55]	28,7	59,9
with LC at HCV,n=32				
IL-10	37,05±1,34***	37,25 [31,15; 42,0]	21,9	49,1

*Note: * - significantly compared to the control group (* - P<0,05, ** - P<0,01,*** - P<0,001). Me – median, Q1(percentile) –25%, Q3 (percentile) – 75%.*

IL-10 inhibits various immune functions such as antigen presentation, cytokine production, macrophage activation, and antigen-specific T cell proliferation *[2]*. Major producers of some types of regulatory T cells, cytotoxic T lymphocytes, B1 lymphocytes, monocytes/macrophages, dendritic and mast cells. According to functional activity, IL-10 inhibits Th1 activation and functional activity of cytotoxic cells, as well as stimulates collagen production by hepatic stellate cells, which is one of the key events in the development of hepatic parenchyma fibrosis *[6]*.

Analysis of the concentration of the studied anti-inflammatory IL-10 in the group of patients with LC with HBV determined a significantly increased value of 3.8 times, with an average of 43.74 ± 1.54 pg/ml, with an individual range from 28.70 to 59.90 pg/ml, while in the control group this indicator was 11.28 ± 0.46 pg/ml (P<0,001).

Also, the assessment of serum IL-10 levels found that in the group of patients with HCV, the synthesis of the studied anti-inflammatory cytokine was almost 3.3 times higher than the control values. Thus, serum IL-10 concentration in the group of patients averaged 37.05 ± 1.34 pg/mL, with an individual range from 21.9 to 49.1 pg/mL, against control values of 11.28 ± 0.46 pg/ml (P<0,001).

Our results suggest that its increased content of IL-10 in patients with liver cirrhosis is probably associated with the action of immunosuppressive mechanisms, because the outcome of infection is determined by the balance of the Th mode of functioning of the immune system in order to eliminate virally infected cells by triggering apoptosis. Insufficient activity of the immune system, as well as the predominance of anti-apoptotic factors, immune deviation towards Th2 lymphocytes contribute to the incomplete destruction of infected cells with persistence of the pathogen, a decrease in the histological activity of hepatitis, chronization of the process, an increase in the risk of cirrhosis of the liver, hepatocellular carcinoma.

DISCUSSIONS. Thus, in groups of patients with liver cirrhosis caused by HBV and HCV, an imbalance of the immune system is observed, in which a simultaneous increase in cytokine production in the Th17/Th2 system is recorded. Cytokines play an important role in the pathogenesis of LC, determining the severity of the disease, the development of hepatic and extrahepatic complications. Analysis of the results of cytokine status in our study once again indicates that viruses are able to modulate the host immune response, leading to the development of secondary immunodeficiency, manifested by an imbalance of immunological functions with a pronounced hypersecretion of IL-17A and IL-10.

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CONCLUSIONS

1. In patients with LC, a simultaneous increase in cytokine production in the Th17/Th2 system is recorded.
2. A significant increase in serum IL-17A concentration was found in the group of patients with LC with HBV by 6.5 times and 5.5 times in the group of patients with LC with HCV.
3. A significantly increased IL-10 value was detected in a group of patients with LC with HBVв 3.8 and in a group of patients with LC with serum HCV 3,3 times.

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