

Cytokine Estimation in Chronic Viral Hepatitis with Autoimmune Impairments

Umida Nabieva, Adolat Ismailova

Immunocytokine DPT, Institute of Immunology, Academy of Science, Uzbekistan

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ABSTRACT

The pattern of autoimmune impairments was studied in patients with chronic viral hepatitis in association with the level of inflammatory cytokines and interferon status. Study was conducted in groups of patients with various levels of the detected autoantibodies to ssDNA. Autoantibodies to ssDNA were found in 37.7% of patients with HCV. In the group of HCV patients with autoimmune disorders, the levels of the cytokines and interferon levels were considerably higher than those in the group of patients without associated autoimmune diseases.

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Corresponding Author:

Adolat Ismailova,

Immunocytokine DPT,

Institute of Immunology,

74 Yahyo Gulyamov, Tashkent 100060, Uzbekistan.

Email: ismadolat@rambler.ru

1. INTRODUCTION

Despite significant increase in knowledge of etiology and immunopathogenesis of the chronic diseases of liver for the last decade [2];[6], many questions related to mechanisms for the development and progression of the pathological process remain unclear. Until very recently, the mechanisms of the immune response were studied on some populations of cells of the immune system; in the same time deeper mechanisms as cytokine were not studied at all. It is well known that cytokines play an important role in the immune response; they take an active part in the developing of inflammatory process and destroying of liver, particularly in viral hepatitis B and C [2];[4];[8];[18]. There are contradictory data regarding role of the regulatory cytokines interleukin 10 (IL-10), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α) in the course and outcome of hepatitis C and their connection with the development autoimmune disorders. In the same it is known that regulatory cytokines (IL-10, IL-6, TNF- α) make significant contribution to the developing of chronic hepatitis [5];[7];[18]. The interferon's system that participates in antiviral and anti-neoplastic protection has an essential value in the development of the chronic hepatitis C and possesses anti-proliferation, immunomodulating and radio protective qualities [3];[9];[10].

Full value of response of an organism to a viral infection depends on sufficient production of interferons. They protect an organism from invading viruses, limit distribution of a virus from the infected cages, reduce the period of viremia, reduce the severity of a current infectious process, protect from bacteria, the elementary, activate lymphocytes, suppress growth of malignancies, basically, they are an important mediators of immune system. The current state and the disease outcome depend on them. Delayed or lowered production of endogen interferon can lead to chronization of process up to a lethal outcome [11]-[13].

It is known, that at long persistency of hepatitis C viruses there is a possibility of development of autoimmune reactions directed against the own tissues of an organism. [1], and it aggravates current state of chronic hepatitis [16];[17].

Active process of disease course leads to development of auto-aggression, expressed in the releasing of high titers of antibodies. It can promote occurrence of inflammatory reactions and harm body tissues. Detecting of G class autoimmune antibodies of to one-chained DNA (ssDNA) is typical to assess an auto-immunization in patients with chronic viral hepatitis. Autoantibodies to denatured (single stranded) DNA (ssDNA) are not specific to certain diseases and they are main parts of the majority of nuclear antibodies [14]. Produced autoantibodies lead to pro-and anti-inflammatory cytokins disbalance, playing very important role in the developing of the immune response of an organism. Therefore the detection of one-chained DNA and detection and assessment of the spectrum of pro-and anti-inflammatory cytokins play an important role in diagnostics, and also in treatment tactics of patients with chronic viral hepatitis.

2. RESEARCH METHOD

We examined blood serum of 220 patients for HBsAg and anti HCV IgG. Duration of illness in examined patients was from 2 to 10 years. The diagnosis of the chronic hepatitis B and C was made based on the combination of collected clinical, epidemiological, laboratory and instrumental data according to the Regulatory Order of the Ministry of Health of Uzbekistan. Patients were divided into two groups and according to the appearance of the auto-antibodies to ssDNA (the first group with positive autoantibodies to ssDNA, the second group – negative). Additionally, for confirmation of morphological lesions and chronic process the ultrasound of liver was conducted that revealed diffuse parenchyma changes and hepatosplenomegaly. Levels of ssDNA, IL-10, IL-6, TNF- α , IFN- α , IFN- γ in peripheral blood were detected by sandwich ELISA (solid-phase enzyme immunoassay (EIA) with using peroxidase as a indicator enzyme (reagents sets “Vector Best” Novosibirsk, the Russian Federation).

3. RESULTS AND ANALYSIS

The analysis of the collected data of the detected autoimmune disorders markers has shown: that in average 37.8% of the examined patients with chronic hepatitis C have autoantibodies to ssDNA.

It is known, that the interferon system is an integrated part of the immune system which provides coordination of proliferation, differentiation and activation of effector immune cells. An evaluation of a functional condition of system of interferons is the interferon status that includes a detection of IFN - α . IFN - γ which are powerful stimulators and inductors of the non-specific immune response.

IFN - α has a direct anti-viral and mediated immunomodulating activity, that play one of the basic roles in elimination of hepatitis C. IFN - α is produced by practically all cells of an organism, but in the greatest measure by macrophages and lymphocytes. IFN - α is a powerful antiviral protein, it and has served as a reason for detecting of IFN - α at patients with chronic viral hepatitis.

The analysis of the collected data has shown, that in groups of patients compared not depending to revealing of antibodies to ssDNA, the level IFN - α has been considerably suppressed. In group of patients with positive result for autoantibodies to ssDNA interferon, the-alpha level has been suppressed in 1, 9 times comparing to a control group ($p < 0,001$), and in group of patients with negative result of revealing autoantibodies to ssDNA – in 2, 6 times ($p < 0,001$) (fig. 1).

IFN - γ is one of cytokines produced by Th-1 – type and possesses antiviral and against tumor qualities; activates mediated monocytes and macropages, natural killers (cytotoxicity), proliferation and differentiation of T-lymphocytes: stimulates maturing of marrow cells – predecessors of monocytes; suppresses the growth of tumors, reproduction of viruses in cells, proliferation, production and secretion of cytokins by Th-2 lymphocytes (IL-4, IL-10, etc.), proliferation of B cells and synthesis of immunoglobulin E, proliferation of somatic cells, secretion of immunoglobulin G, strengthens a differentiation of tumor cells, antiviral, anti-microbial, anti-parasitic resistance and tumorocid activity of TNF - α , and as well противовирусную activity. In this connection detection of IFN - γ in blood is rather important.

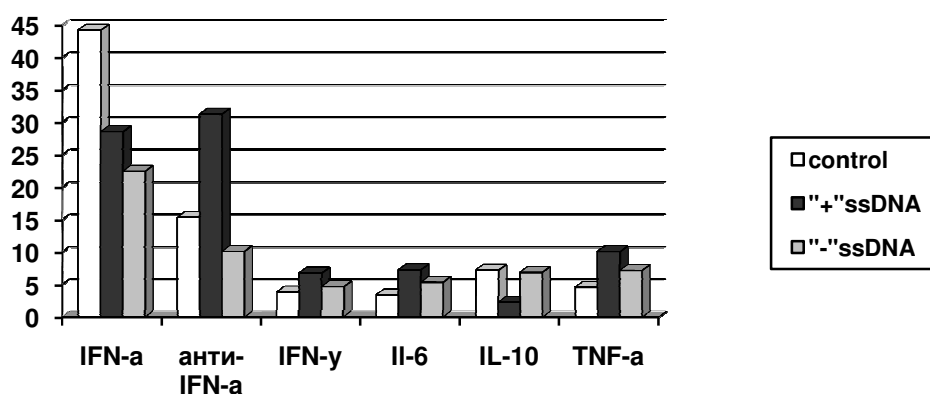


Figure 1. Interferons and core cytokines of immune system at patients with chronic viral hepatitis in connection with detection of antibodies to ssDNA

It was detected by the conducted research that the levels of IFN – γ in the blood serum of patients with positive oDNA was not significantly (in 1, 2 times) raised and authentically did not differ from indicators of control group ($> 0,05$), and in group of patients with negative o-dnk the increase in its concentration in blood was marked almost in 2 times in comparison with group of healthy people ($p < 0,001$).

The following stage of our research has been devoted to studying of spectrum pro-and anti-inflammatory cytokines IL-6, IL-10 and TNF- α . IL-6 and TNF- α are primary anti inflammatory cytokines are extremely pleiotropic and activate tissues around them. They trigger wide range of biological activity by lymphoid and non lymphoid cells. It is detected that IL-6 and TNF- α induce before immune response inflammation, regulate immune and acute phase response, inflammation, oncogenesis and hemogenesis. TNF- α also plays a role in the destroying of liver, exacerbate development of fibrosis and portal inflammation in hepatitis C patients. One of the major functions of IL-6 is to regulate the maturation process of the antibody producing cells from B cells, as well as a production of immunoglobulins. IL-6 participate in activation of T lymphocytes, induces synthesis of many acute phase proteins: fibrinogen, haptoglobin, C reactive protein.

Studying of the spontaneous production of IL-6 and TNF- α has shown significant difference between data in the both groups of patients with chronic hepatitis C and control group ($p < 0,05$). All patients with chronic hepatitis C have higher levels of these cytokines in comparison with control group, but if in the group of patients without autoantibodies they have been higher in 1.57 for TNF- α and in 1.47 times for IL-6, in groups of patients with autoantibodies they were higher in 2.31 and in 2.18 times respectively ($p < 0,05$).

Cytokine IL-10 that is produced by Th-2 cells, B-cells, monocytes, macrophages and mast cells is important in the pathogenesis of hepatic lesions. The main mechanisms of action of IL-10 are resolving, immunomodulatory, immunosuppressive. Moreover, IL -10 leads to transformation of B cells to plasma cells and stimulates the secretion of immunoglobulins. Additionally, the level of IL-10 is informative to assess the activity of regulatory T4 cells (T-reg), which are major producers of the immunosuppressive cytokine IL-10 [15].

Analysis of the collected data revealed that there is a tendency of the decrease of IL-10 in the chronic patients. It was shown, that patients with positive autoantobodies have levels of IL-10 suppressed by 3.2 fold ($p < 0.05$) and patients without antibodies have levels of IL-10 were slightly below normal ($p > 0.05$).



4. CONCLUSION

Patients with positive autoimmune markers have the disbalance of interferons that was shown by suppressed production of IFN - γ , and activated production of IFN - α . There was disbalance of produced cytokines by Th-1 and Th-2 cells, shown by suppression of production IL-10, and activation of production IL-6.

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BIBLIOGRAPHY OF AUTHORS

	<p>Dr. Umida Nabieva is a scientist of the laboratory of immuno-cytokines of the Institute of Immunology of Uzbekistan. She has research interests in the field of fundamental immunology, immunodeficiency syndromes, immunodiagnostics of different diseases, infectious diseases, chronic hepatitis, autoimmune disorders, and pediatric gastroenterology. Dr. Nabieva was responsible for implementation of two national research programs that have to create a better diagnostic and prognosis for hepatitis C patients.</p>
	<p>Dr. Adolat Ismailova is a Deputy Director of the Institute of Immunology of Uzbekistan and a head of the laboratory of immuno cytokines as well. Dr. Ismailova has works on fundamental immunology, immunodeficiency syndromes, immunodiagnostics of different diseases and immunotherapy. Her PhD research was on "Molecular mechanisms of the formation of neoplasm and current approaches to the early immunodiagnostic of the tumor". Dr. Ismailova is currently leading two national research programs.</p>