

The Position of the Cytokine Profile and Cytolysis Enzymes in Patients with Viral Hepatitis before Tooth Extraction

O.U.Rakhmatullaeva¹, Kh.E.Shomurodov², A.A.Hadjimetov³, X.Kh.Sadiqova⁴,
Z.Z.Nazarov.⁵

Tashkent State Dental Institute

Abstract. It is known that in chronic liver diseases, secondary immunodeficiency is formed, which is of great importance for the dental system and the entire body as a whole. Therefore, it becomes clear the importance of studying the state of the protective system of oral tissues in chronic viral liver pathology, which requires timely and constant correction. The aim of this study was to evaluate the activity of proinflammatory cytokines and cytolytic enzymes in patients with chronic viral hepatitis before tooth extraction. The level of cytokine IL-1 in patients with CVI before tooth extraction was on average 43.97 ± 3.56 pg / ml, whereas in healthy people the studied indicator was on average 5.41 ± 0.42 pg / ml. The patients showed an increase in the level of IFN in the blood serum by an average of 6.2 times, the level of interleukin-18, belonging to the IL-1 family, was statistically significantly increased by 2.4 times in patients with CVI, compared with the control group. The features of CVH are dissociations between the levels of proinflammatory cytokines IL-1, IL-6, IL-18 and interferon. This indicates the disintegration of the inflammatory process occurring in the periodontal tissues and with the transition to a chronic course of the disease. Changes in the level of IL-1, IL-6, IL-18 and interferon in the blood serum of patients with CVI from normal parameters before tooth extraction is an indicator of the severity of the inflammatory process in the liver, as evidenced by changes in the dynamics of cytolytic enzymes.

Keywords: viral hepatitis, tooth extraction, cytokines, enzymes.

INTRODUCTION

With any surgical intervention in the oral cavity, an unsatisfactory level of oral hygiene and inflammatory periodontal diseases significantly increase the risk of general infectious complications caused by pathogenic periodontal microflora. An important role in the development of complications during surgical manipulations in the oral cavity is played not only by microbial toxins, but also by viral intoxication. Viral hepatitis both in our country and abroad occupies a significant place in the general human pathology, causing significant socio-economic damage to society. Among the important problems of modern practical dentistry are the issues of improving the diagnosis, prevention and treatment of complications after tooth extraction in patients with chronic viral hepatitis, which remain relevant to the present time and have great social significance. As is known, after tooth extraction, the filling of the wound space with granulation tissue begins approximately four days after the injury. At this time, macrophages, fibroblasts, and new capillaries appear in the wound. Blood vessels provide the delivery of oxygen and nutrients to the cells of the new stroma. Macrophages are the main source of growth factors that stimulate fibroblasts and angiogenesis. Cytokines produced at this stage of wound healing mainly affect fibroblast proliferation and / or collagen production, as well as extracellular matrix production.

Interleukin-1 (IL-1), being the most important mediator of the development of inflammation, has a wide range of biological activity and stimulates the functions of almost all cells involved in protective reactions, including cells of the central nervous, endocrine and hematopoietic systems. Cytokine synthesis begins in response to tissue damage or infection. The main cells that produce IL-1 in the body are monocytes and macrophages, as well as cells that share a common origin with macrophages. IL-1 is also produced by fibroblasts, lymphocytes, NK cells, keratinocytes, endothelial cells, and neutrophils. The IL-1 action can be implemented both at the system level and at the local level. Since almost all cells in the body have receptors for IL-1, this cytokine very quickly activates almost all types of cells involved in the formation of a local inflammatory response. At the systemic level, IL-1 causes activation of the neuro-endocrine system, affects immunopoiesis, immunostimulation, synthesis of acute-phase proteins in the liver, and stimulation of bone marrow hematopoiesis. At the local level, IL-1 can regulate the functions of virtually all cell types involved in local inflammation and repair. The role of IL-1 and other cytokines in the development of local inflammation and wound healing is currently of great interest to researchers. The increased production of IL-1 in the early stages of wound healing serves to trigger the cascade of synthesis of other cytokines and growth factors, as well as to regulate and coordinate the functions of cells involved in the wound process. IL-1 can stimulate the growth and metabolism of connective tissue, as well as the re-epithelization of wounds. The main causes of wound healing complications in these cases are ischemia, neuropathy, and infections. When the wound heals, a massive formation of new blood vessels occurs in the granulation tissue. The main causes of delayed wound healing in inflammatory processes, especially in the combination of its pathology of viral etiology, are prolonged inflammation on the one hand, and a decrease in reparative processes in wounds on the other. At the same time, there is a dysregulation of the production of chemotactic factors for white blood cells, which leads to a prolonged presence of neutrophils and macrophages in the wound and an elongation of the inflammatory phase of the wound process. Thus, IL-1 is one of the most important cytokines that regulate the local inflammatory process and wound healing.

Interleukin-18 (IL-18) belongs to the interleukin-1 family, it is also, like interleukin-1, a mediator of inflammation. Interleukin-18 (IL-18) occupies a special position among immunoregulatory mediators, as it is one of the key cytokines involved in the formation of innate and acquired immune responses. Having the ability to stimulate the production of IFN- γ adhesion molecules and apoptosis factors. IL-18 is involved in the activation of cytotoxic T-lymphocytes, NK cells, macrophages, and dendritic cells and contributes to the formation of an effective anti-infective immune response. Nevertheless, the most pronounced activity of IL-18 is considered to be the ability to stimulate the differentiation of the Th1 type and their production of IFN- γ , which ultimately leads to the activation of the cellular link of the immune response, which is necessary in the case of infectious processes (viral and bacterial). Currently, the coordinating role of proinflammatory IL-18 as an additional stimulator of interferon production (primarily interferon- γ), which largely determines the antiviral defense of the body, has been established. IL-18 is involved in the antiviral defense of the body, in particular, in the formation of an immune response against hepatitis B virus antigens. The protective immune response during viral hepatitis B (HBV) is associated with the induction

of the cellular link of the immune system and is implemented through type 1 T helper cells. The presentation of the antigen and the determination of the type of immune response is carried out by antigen-presenting cells, in particular, dendritic cells (DC). The direction of immune responses is determined by the profile of cytokines produced by DC. Important in the pathogenesis of chronic viral hepatitis B are proinflammatory cytokines (INF- γ , IL-1, TNF) and, in particular, IL-18. IL-18 has been shown to inhibit viral hepatitis replication in the liver of transgenic mice. On the other hand, an increase in the level of endogenous IL-18 in chronic liver diseases is associated with the activation of mechanisms of immune damage to the liver mediated through the fas ligand.

In the acute phase of inflammation, the synthesis of more than 40 proteins increases, which, depending on the nature of the stimulus, have pro-inflammatory or anti-inflammatory properties. C-reactive protein, the main protein of the acute phase of inflammation, binds various pathogenic factors and decay products of damaged cells, promotes opsonization of these substances and activates the complement system. From this point of view, the increase in the synthesis of acute phase proteins under the influence of IL-6 can be considered a protective mechanism that limits tissue damage. Increased IL-6 production is often associated with tissue damage: infections, immune hypersensitivity reactions, and autoimmune diseases. IL-6 is one of the main mediators of such clinical and laboratory manifestations of tissue damage, leukocytosis, an increase in the blood level of proteins of the acute phase of inflammation and a decrease in the level of albumin. IL-6 stimulates the development of plasmocytosis and hypergammaglobulinemia, and also activates the hypothalamic-pituitary-adrenal system.

It is known that in chronic liver diseases, secondary immunodeficiency is formed, which is of great importance for the dental system and the entire body as a whole. Therefore, it becomes clear the importance of studying the state of the protective system of oral tissues in chronic viral liver pathology, which requires timely and constant correction. In the available literature, there are few publications on the state of periodontal tissues and oral mucosa in patients with viral hepatitis, but studies of the cytokine profile and the enzyme status of blood in surgical patients before tooth extraction were not studied at all, which was the reason for choosing this research topic. The aim of this study was to evaluate the activity of proinflammatory cytokines and cytolytic enzymes in patients with chronic viral hepatitis before tooth extraction.

RESEARCH MATERIALS AND METHODS

58 patients with chronic viral hepatitis were examined. The studies were conducted in strict accordance with the requirements of biomedical ethics in accordance with the Geneva Convention on Human Rights (1997) and the Helsinki Declaration of the World Medical Association (2000), based on the permission of the local ethics committee. In the group with chronic hepatitis, patients were divided by gender as follows: men-58%, women-42%, the average age of patients was 35.6 ± 10.7 years. All patients received written voluntary informed consent to participate in the study. Inclusion criteria: verified diagnosis of chronic viral hepatitis B and C detected by polymerase chain reaction (PCR) using a test system, patients

who did not receive antiviral therapy. Exclusion criteria: patients under 18 years of age with concomitant viral hepatitis D or other diseases that cause liver damage, HIV infection, a history of pulmonary tuberculosis, autoimmune, oncological diseases, as well as pregnant women. In order to determine the control values of the studied parameters of the hemostasis system, 16 practically healthy individuals aged 25 to 45 years, who gave informed consent to the examination, did not differ from patients by sex and age, did not have a history, the results of biochemical and serological studies of viral hepatitis, as well as other liver diseases, were examined. The following instrumental studies were used: ultrasound examination of the abdominal organs, clinical and laboratory methods (determination of total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gammaglutamyltranspeptidase (GGTP), homocysteine, total protein and protein fractions, cholesterol, amylase, urea, creatinine. Indication of HCV-PHK, determination of the virus genotype, the level of viral load by polymerase chain reaction (PCR). The indicated cytokines IL-1,6,18 and γ -interferon in blood serum were determined by the method of enzyme immunoassay using reagent kits (manufacturer of CJSC Vector-Best, Russia). The optical density measurement and calculation of the results were carried out on a COBAS-411 photometer according to the attached instructions, the results were expressed in pg / ml. Cnfnbcnxbtcrbq f analysis was carried out using modern statistical analysis packages: statgraphicsPlusfor Windows version 4.0, Statisticafor Windows version 8.0. Statistical methods of descriptive statistics, correlation analysis, and establishing the reliability of the difference between the data in the main and control groups based on the calculation of the Student's criterion were used. The data in the text and tables are given as $M \pm m$ (mean value \pm standard error of the mean value). The results with a significance level of <0.05 (95% confidence interval) were taken as reliable.

RESEARCH RESULTS AND DISCUSSION

As is known, the pathogenesis of chronic viral hepatitis (CVI) is based on deep violations of the immune response with an imbalance in the quantitative and qualitative composition of immunocompetent cells, with a violation of their functional activity and cellular cooperation. The features of the immune response have a relationship with the ratio of cytokines produced by immunocompetent cells, so in the study of the pathogenesis of chronic viral hepatitis, a qualitative and quantitative assessment of the cytokine profile is of great importance. The results of numerous studies indicate that cytokines play an important role in the control of viral replication, damage processes, inflammatory infiltration, regeneration, and liver fibrosis.

To diagnose and predict the course of chronic hepatitis of viral etiology, we used the definition of AlAT, AsAT CRP. The presence of cytolytic syndrome was judged by the change in the AlAT level, which was on average 139.52 ± 9.78 IU/l in patients with CVI, while the AlAT values in the comparison group were 18.63 ± 1.74 IU/ l, and by the AsAT level, the concentration of which was 118.41 ± 9.78 IU/l in patients with CVI, compared to 15.42 ± 1.13 IU/l in the group of healthy individuals. A similar dynamics was observed with respect to the C-reactive protein, where its concentration exceeded the initial indicator by 25 times.

A sufficient range of cytokines was studied to characterize the immune response in patients with CVH. It included a group of proinflammatory cytokines produced in response to the direct action of the virus: IL-1, IL-6, IL-18, and a regulator of immune inflammation: Y-Interferon.

Since the intensity of viral replication is not always associated with the severity of the inflammatory response and clinical manifestations of viral hepatitis, we studied the cytokine profile in patients with CVI, which is presented in Table 1. Interleukin-1 (IL-1) is known to be one of the main cytokines responsible for the development of a local inflammatory response and an acute phase response at the level of the entire body. IL-1 is a multifunctional cytokine that plays a key role in the development and regulation of non-specific defense and is one of the first to be included in the body's defense response when exposed to pathogenic factors. IL-1, produced by phagocytes in the lesion site, triggers the synthesis of acute liver phase proteins (CRP) and participates in the neuro-endocrine stimulation of protein synthesis.

The analysis of the results of the studies presented in Table-1 showed that the level of cytokine IL-1 in patients with CVI before tooth extraction was on average 43.97 ± 3.56 pg / ml, while in healthy people the studied indicator was on average 5.41 ± 0.42 pg / ml. In our opinion, the highest production of IL-1 in the blood serum of the examined patients with CHB is associated with the activation of macrophages. The results obtained confirm the literature data on the increase of this cytokine in patients with CHB as a mediator reflecting the intensity of inflammation.

Table 1
Values of biochemical parameters and proinflammatory cytokines in patients with viral hepatitis before tooth extraction

	Indicators	Healthy person n=16	Patients with viral hepatitis n=58
1	ASAT (U/l)	15,42±1,13	118,41±9,78*
2	Alat (U/l)	18,63±1,74	139,52±10,24*
3	CRP (mg/l)	0,75±0,06	18,63±1,33*
	IFN-γ (PG/ml)	3,86±0,28	23,84±1,21*
	IL-18 (PG/ml)	173,58±10,21	421,62±11,75*
	IL-1β (PG/ml)	5,41 ± 0,42	43,97±3,56*
	IL-6 (PG/ml)	5,13± 0,39	48,71±3,48*

Note: * - the significance of differences $P < 0.05$ relative to the indicators comparison groups

As is known, IL-1 and IL-6 are involved in the implementation of many local and systemic manifestations of the inflammatory response. IL-6 is an acute phase protein and at the same time causes the synthesis of acute phase proteins in the liver. IL-6 contributes to both

exacerbation of chronic and chronic acute inflammatory processes. It increases in the blood during any inflammatory processes. When determining the concentration of anti-inflammatory cytokines IL-6 in patients with CVI, there was a significant increase in their level compared to the control group. If we take into account that IL-6 is synthesized by activated macrophages in response to inflammation and tissue necrosis, then its high values in this cohort of patients also confirm the exacerbation of chronic viral pathology during tooth extraction. It can be assumed that the increased level of proinflammatory cytokines IL-1,6 in the blood serum of the examined individuals is due to the stimulation of mononuclear phagocytes and an increased cytotoxic reaction, which results in the elimination of the viral hepatitis antigen by hepatocytes in patients with CVI. In our opinion, the studied indicators of the cytokine system can be used as important diagnostic criteria before tooth extraction in patients with CVI.

The content of proinflammatory cytokine, namely, interferon-alpha (INF- α), which plays a key role in the antiviral defense of the body, was increased in patients with CVI. IFN-Y is an endogenous modulator, a type II inducer. According to the literature, IFN-U plays a central role in the development of chronic inflammation. It enhances the action of TNF-A by a number of cells. IFN-promotes the production of IL-8, activates the synthesis of acute phase proteins by liver cells. In chronic viral hepatitis, the observed patients showed an increase in the level of IFN in the blood serum by an average of 6.2 times, relative to the indicators of healthy individuals.

The level of interleukin-18, belonging to the IL-1 family, was statistically significantly increased by 2.4 times in patients with CVI, compared with the control group. An increase in the proinflammatory cytokine IL-18 characterizes the presence of immune inflammation at the systemic level due to the stimulation of hepatocytes. At the same time, there was also a significant increase in C-reactive protein (CRP). Consequently, the predominance of proinflammatory cytokines in individuals with CVH occurs within the framework of the acute phase reaction, as evidenced by a 25-fold increase in the concentration of C-reactive protein. An increase in IL-18 and CRP, as well as liver cytolytic enzymes (AlAT and AsAT), may indicate immune-mediated damage associated with a high rate of virus mutation, IL-18 gene polymorphism, leading to massive synthesis of pro-inflammatory cytokines by immune-competent cells and activating cytotoxic effector mechanisms that lead to liver damage (cytolysis syndrome).

Thus, the increased content of cytokines IL-1, IL-6, IL-18, IFN-Y, and their excessive activity can become a factor in the progression of the pathological process, which is observed in most patients with CVI. Excessive concentration of cytokines has a direct damaging effect on parenchymal cells, i.e. it is associated with cytotoxic and destructive effects observed in patients with CVI. Studies have shown that as the immune-inflammatory process develops, cytokines exhibit pro-inflammatory properties; they activate the proliferation of T-lymphocytes, increase the level of activation of the mononuclear phagocytosis system, and increase the adhesion of neutrophils to the endothelium. It can be assumed that the increased level of proinflammatory cytokines is due to the stimulation of mononuclear phagocytes and

an increased cytotoxic reaction, which results in the elimination of the virus antigen of infected hepatocytes in patients with CVI.

CONCLUSION

1. An increase in IL-1 in patients with CVI before tooth extraction is an important prognostic criterion, since it is involved not only in inflammatory processes, but also in destructive processes.
2. The features of CVH are dissociations between the levels of proinflammatory cytokines IL-1, IL-6, IL-18 and interferon. This indicates the disintegration of the inflammatory process occurring in the periodontal tissues and with the transition to a chronic course of the disease, which indicates the implementation of appropriate preventive measures.
3. It should be noted that changes in the level of IL-1, IL-6, IL-18 cytokines and interferon in the blood serum of patients with CVI from normal parameters before tooth extraction is an indicator of the severity of the inflammatory process in the liver, as evidenced by changes in the dynamics of cytolytic enzymes.
4. The obtained research results make it possible to use these indicators as important diagnostic criteria for the progressive course of chronic pathology not only of the liver but also of periodontal tissues.

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