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ROLE OF CYTOKINE STATUS IN THE PROBLEM OF BRUCELLOSIS IN MODERN WORLD

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Summary. The increase in incidence, chronic relapsing course, and insufficient effectiveness of existing methods of treatment and prevention place brucellosis among the most pressing problems of human infectious pathology. It is noted that in terms of its distribution and socio-economic significance, this disease occupies one of the first places among zoonoses [1,5,9].

Features of the life cycle of Brucella and the infectious-allergic nature of brucellosis allow us to state the leading role of immune disorders in the pathogenesis of this disease. At the same time, many aspects of the immunology of brucellosis, in particular the features of intercellular relationships in the process of formation of anti-infective immunity in this pathology, have not been sufficiently studied, which does not allow the full use of the assessment of the immune status of patients with brucellosis to predict the chronicity of this infection [12,13,19].

The discovery of biologically active substances - cytokines, regulating the proliferation and level of functional activity of cells, both normally and in pathology, allows us to evaluate from a new perspective the mechanism of formation of inflammatory reactions, allergic and immune conditions and to develop new methods for predicting the nature of an infectious disease. Meanwhile, in the available literature, the role of cytokine metabolism disorders in brucellosis has not received sufficient coverage, which determines the relevance of research conducted in this direction.

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Key words: brucellosis, cytokine status, biologically active substances, interleukins.

Introduction: Brucellosis is a particularly dangerous and socially significant infection, causing significant economic damage and causing a high level of disability in patients. Brucellosis is a systemic zoonotic infection transmitted from animals to humans through consumption of contaminated foods, direct contact with infected animals, or inhalation of aerosols. Distributed everywhere, especially in the Mediterranean countries, the Persian Gulf, the Indian subcontinent, Mexico, Central and South America, East Asia, and Africa. Nutritional transmission of infection is possible through consumption of raw milk and dairy products of infected goats and cows.

Epidemiological features of morbidity largely depend on the species of the pathogen, the activity and massiveness of the epizootic focus. In foci of goat-sheep brucellosis, group diseases are not uncommon. People who, by virtue of their profession, are involved in caring for animals or who eat infected animal products become infected with brucellosis. Adults predominate among those affected, but in unfavorable areas children also often become ill [4,6,7,11,19,20,28,34].

According to the WHO Joint Expert Committee on Brucellosis, this disease among animals is registered in 155 countries around the world. Brucellosis is most widespread in the countries of the Mediterranean, Asia Minor, South and Southeast Asia, Africa, Central and South America [31,32]. According to the World Health Organization, half a million new cases of brucellosis are registered annually worldwide [30,31].

According to the Regional Meeting on the Control of Brucellosis in Central Asia and Eastern Europe (09-11 April 2013, Izmir), despite the high incidence rates of this infection, its actual level is much higher.

Increased population migration over the past two decades and insufficient veterinary and sanitary control over the import of animals from countries affected by brucellosis, including neighboring CIS countries, can currently complicate the already tense epizootic and epidemic situation regarding this infection. The weakening of sanitary and veterinary supervision over animals of individual farms in the CIS has created an alarming epizootic and epidemic situation. The latter dictates the need to improve surveillance , long-term forecasting of the dynamics and intensity of the epizootic process and its epidemic manifestations in order to timely implement adequate preventive measures [12,35].

Due to the asymptomatic onset of the disease, the incubation period may erroneously be set aside for several months before the period when the disease becomes symptomatic. Asymptomatic forms of the disease, despite the complete absence of clinical signs of the disease, can be diagnosed using serological tests. According to the duration of the disease, acute, subacute and chronic forms are distinguished. In the acute form of the disease, any organ can be involved in the process, but most often (in almost half of the cases) damage to the joints is noted. In modern Western literature, the involvement of individual organs in the pathological process in the acute form of brucellosis is considered as a complication, while in the chronic form this may be the only manifestation of the disease [2,19,23,33].

Many researchers who observed patients in endemic countries note that the clinical manifestations of the acute form of brucellosis can undergo significant changes due to the patients' independent and uncontrolled use of antibacterial and non-steroidal anti-inflammatory drugs [11,26].

The nonspecificity of the clinical picture of acute brucellosis, expressed in objective and subjective manifestations of intoxication syndrome, is a consequence of the leading link in pathogenesis - the development of bacteremia. However, the intoxication syndrome in brucellosis, in terms of the mechanism of its development and the duration of clinical manifestations, differs from the intoxication syndrome in diseases caused by bacterial pathogens that are not capable of long-term intracellular parasitism [5,12,23].

Brucella are facultative intracellular pathogens, highly adapted not only to survival, but also to reproduction in cells, mainly of the reticuloendothelial system (RES). It is this fact that explains the damage in brucellosis mainly to organs and systems rich in RES cells. Brucella is capable of infecting both phagocytic and non-phagocytic cells. Unlike other pathogenic bacteria, classical pathogenicity factors have not been described for Brucella , although studies show that they have a surprisingly wide arsenal of defensive resources that provide them with long-term

persistence in the host body. Such mechanisms, implemented in the early stages of the disease, include a reduced ability of Brucella to activate the complement system, resistance to cationic proteins, and evasion of the body's recognition systems. Most of the Brucella entering phagocytes are destroyed after fusion and phagolysis . However, in some cells this process is inhibited, and so-called replicative cells are formed. phagosomes , or brucellosomes , in which the pathogen multiplies, maintaining the state of bacteremia [5,12,23].

Thus, the strategy of intracellular survival and reproduction of Brucella with the formation of long-term bacteremia ensures the infection of more and more new cells, which is manifested by the clinical progression of the disease with a high risk of the formation of a chronic form.

In addition, Brucella is able to suppress apoptosis of infected macrophages, which seems paradoxical, since the cells that should destroy bacteria become the site of their preservation and replication [37]. Long-term persistence of Brucella is accompanied by a pronounced immunological restructuring of the body with the development of immunopathological reactions such as delayed-type hypersensitivity and increased levels of immune complexes, which may underlie clinical manifestations such as glomerulonephritis , hepatitis, arthritis, skin vasculitis [2,11,12,19,22,26,39]. This aspect of pathogenesis is very important for understanding the mechanisms of development of possible unusual manifestations of brucellosis infection at different stages of the process.

Chronic forms of brucellosis today constitute a special group of human pathologies. Paradoxical as it may seem, there are no uniform, generally accepted and understandable criteria for their diagnosis [22,30,33]. According to the formal criteria, the chronic form of brucellosis is established in the case of a disease duration of more than 12 months. At the same time, many authors note the heterogeneity of this group of patients, which requires special studies.

The incidence of brucellosis in the Republic of Uzbekistan has increased in recent years. At the same time, the source of infection during the epidemiological investigation of the outbreak of brucellosis was determined up to 60%, and according to the veterinary service - only 0.001%. The clinical symptoms of brucellosis, due to the facultative nature of manifestations with a number of infectious and non-infectious diseases, do not allow timely diagnosis. Even in regions where they are well acquainted with this disease, it is possible to diagnose no more than 10% of patients, and 90% of patients with brucellosis are treated under other diagnoses - influenza, acute respiratory infections, radiculitis, vitamin deficiencies, arthritis, prostatitis, etc. The polymorphism of the brucellosis clinic, the presence of different forms of the pathogen (S, R, L), providing a huge number of undetected sources of infection, intracellular persistence of Brucella , determine the complexity of various aspects of this infection [12,22,30,33,37,38].

Untimely identification of sources of infection and optional clinical manifestations are the reason for the delay in treatment and preventive measures.

Long-term intramacrophagic persistence of Brucella , selectivity of damage by the pathogen to connective tissue and reproductive organs, combined with the lack of effective methods of elimination therapy, are the pathogenetic basis for the high probability of chronicity of the disease. The significant amount of disability in the working population due to this infection leads to social problems and economic damage [6,7,11,13,17].

Spontaneous recovery from brucellosis is very rare. The chronic recurrent course of brucellosis over time inevitably leads to disability in people, often at a young and working age. A timely diagnosis of acute brucellosis ensures successful treatment only with adequate etiotropic therapy and immunocorrection [11,13,22,23].

Currently, the most important are the genetic characteristics of patients. This is due to the fact that about 50%, and according to some estimates, up to 90% of all “unfavorable” responses to drugs are due to the patient’s genetic factors. Therefore, individual genetic differences between people are a serious factor that causes many adverse drug reactions (ADRs), including those leading to death or disability of patients (bleeding, damage to the liver, kidneys, bone marrow, etc.) [13-17 ,31].

One of the studied genetic factors of important clinical significance is polymorphism of the multidrug resistance gene (MDR/MDR1/ Multidrug resistance 1), encoding the drug transporter glycoprotein – P (Pgp) [13,16].

Bacteria, viruses and other infectious agents have different ways of surviving and reproducing in the host . The immune response to the introduction of Brucella reflects the unique characteristics of the pathogen. The smooth lipopolysaccharide shell of Brucella (S-form) is not able to activate the alternative pathway of the complement system. Brucella resistant to the action of polymorphonuclear leukocytes due to suppression myeloperosidase and Cu / Zn superoxide dismutase . Inhibitors of AMP- and GMP-mediated intracellular reactions also play a role . In brucellosis, disturbances in the activity of natural killer cells and a decrease in the formation of free radicals by macrophages, a narrowing of the spectrum of interferon-gamma functions , suppression of phagocyte apoptosis and the expression of cytokines that provide an adequate immune response have been identified [3,25,27,35,36].

Immune changes in brucellosis are accompanied by disturbances in the interaction of innate immune factors, cellular and humoral immunity, and autoimmune processes [10, 11]. The ratio of pro- and anti-inflammatory cytokines and developing changes in the immune status of patients are of certain importance in the various stages of brucellosis infection [11–13]. Fluctuations in some parameters of the cytokine profile in patients with different forms of brucellosis are, according to researchers, multidirectional and very dynamic. In the early period of acute brucellosis, a decrease in the level of interferon gamma (IFN-γ) was detected, which is restored after antibacterial therapy [14]. In chronic brucellosis, a specific antigen (brucellin) has been shown to stimulate significant synthesis of IFN-α and IFN-γ. In patients with chronic brucellosis, a significant increase in the level of pro-inflammatory cytokines in the blood serum and a less pronounced increase in the content of interleukin-4 (IL-4) were detected [15].

According to research results, both in acute and in chronic and residual brucellosis, there is a decrease in the level of spontaneous IFN-γ in the blood serum. At the same time, zero values were recorded in 45.8 and 40% of cases with chronic and residual brucellosis, respectively.

A decrease in the production of Th1 cytokines (IFN-γ, IL-2) is associated with the immunity of T cells to Brucella antigens , which leads to the development of chronic brucellosis [18–20]. Multidirectional, complex, dynamically changing parameters of immune homeostasis in a patient with brucellosis cause difficulties in assessing the ongoing changes in the immune system, respectively, and ambiguous assessments of the identified disorders [10]. The level of cytokine expression depends to a certain extent on gene polymorphism. Genetically determined dysregulation of cytokines leads to the initiation of not only chronic inflammatory processes, but also generalized disorders [21]. Therefore, the search for genetic markers that control key links in the pathogenesis of brucellosis is one of the urgent and promising tasks of medical genetics. IFN-γ is one of the powerful cytokines, which plays a decisive role in protecting the body from Brucella [22–25]. The functions of IFN-γ are well known: it is a pro-inflammatory cytokine, which is secreted by Th1 cells, modulates the activation and transcription of a number of genes, the products of which are involved in the antigen presentation and degradation of the infectious agent,

proliferation and differentiation of lymphocytes. In humans, the gene encoding IFN-γ is located on chromosome 12 and contains 4 exons . The study of IFN-γ gene polymorphism in brucellosis has attracted the attention of a number of researchers. Results of studies that revealed a positive association between certain polymorphisms of the IFN-γ gene and brucellosis.

Vγ9Vδ T lymphocytes play an important role at the early stage of infection. In the blood, the content of these cells increases significantly. It has been shown that Vγ9Vδ T lymphocytes can be specifically activated by low molecular weight non-protein compounds obtained from B. suis lysate , or by factors produced by infected macrophages. Stimulated Vγ9Vδ-T lymphocytes secrete interferon gamma (γ-IF) and TNF-α and reduce the proliferation of Brucella in phagosomes , including due to cytotoxic activity [35].

The function of CD4 lymphocytes is of limiting importance and consists of a direct effect on infected macrophages, as well as stimulation of clonal proliferation of cytolytic CD8 cells. In these processes, Vγ9Vδ-T-cell receptors play a role. An increase in the number of γ/δ-CD4 and CD8 lymphocytes is characteristic of brucellosis [1,3,14,15,25].

Studies by a number of authors have shown that the main role in brucellosis is given to the effects of γ-IF, which stimulates the production of reactive oxygen species and NO by macrophages, induction of apoptosis , enhances the differentiation of lymphoid cells and the synthesis of cytokines, ensures the prevalence of IgG subclass 2a, increases the expression of major molecules histocompatibility complex (MHC – major histocompatibility complex). It was found that the severity of the effects of γ-IF depends on the polymorphism of its gene. It turned out that people homozygous for the +874A allele are more prone to brucellosis and tuberculosis. Typically, with brucellosis, the level of γ-IF in the blood is increased [14,15,18].

The studies carried out revealed in patients with brucellosis disturbances in various parts of the immune system, namely: T- and B-cell parts, mononuclear -phagocytic part, as well as cytokine status. The study of T- and B-cell immunity in patients with brucellosis revealed a significant decrease in the absolute number of CD3, CD4 and CD8 lymphocytes in the peripheral blood compared to the control group. A more significant decrease in these cells was detected in patients with acute brucellosis. The number of CD20 lymphocytes decreased in the group of patients with chronic and increased in patients with acute brucellosis [1].

When studying the state of cellular immunity, the content of circulating immune complexes, serum immunoglobulins and specific antibodies, the activity of phagocytosis in patients with brucellosis, K.B. Kurmanova revealed the presence of an imbalance in the interaction of T and B lymphocytes and their regulatory subpopulations , and a decrease in phagocytosis [15].

Pavlova O.M. [24] carried out a comprehensive, comparative assessment of the subpopulation composition of immunocompetent cells in the peripheral blood of patients with acute and chronic brucellosis. Comparative study in vitro of spontaneous and stimulated production of cytokines in a culture of mononuclear cells isolated from the peripheral blood of patients with acute and chronic brucellosis showed characteristic dynamics of changes in immunological parameters during the chronicization of brucellosis infection. The work of a number of authors has shown that in patients with acute brucellosis there is an increase in the number of DM 16 lymphocytes in the blood, an increase in the activity of neutrophils according to the NBT test and the activity of macrophages due to an increase in their production of IL1β and TNFα. During the process of chronic brucellosis, a decrease in the absolute number of neutrophils in the peripheral blood and a decrease in the activity of macrophages is observed due to the low level of production of IL1β and TNFα. In acute brucellosis, an increase in the activity of plasma cells is observed, as indicated by an increase in the level of immunoglobulins of all classes in the

blood serum. However, the final processes of differentiation of B lymphocytes into plasma cells in these patients are disrupted, as indicated by the low level of IL6 production and an increase in the content of CD21 lymphocytes in the blood. In patients with chronic brucellosis, the activity of plasma cells decreases, as indicated by a low level of IgM production . The differentiation of B lymphocytes into plasma cells is impaired at all stages, as evidenced by the low level of production of IL6 and IL4.

The activity of the cellular component of immunity in acute brucellosis is reduced, as evidenced by a decrease in the number of CD3 and CD4 lymphocytes and low production of IL2. In patients with chronic brucellosis, the impairment of cellular immunity progresses, which is confirmed by a decrease in the number of not only CD3 and CD4, but also CD8 lymphocytes, as well as a low level of production of IL2 and IL4. A decrease in the absolute number of neutrophils, monocytes, CD4, CD8, CD21 lymphocytes and Ig M in peripheral blood, as well as a decrease in spontaneous and stimulated production of IL1R, IL4, IL6 and TNFa in a mixed culture of mononuclear cells in vitro can be regarded as an unfavorable prognosis for the chronicity of brucellosis [24].

A study on volunteers vaccinated with Rev 1 against B. melitensis described the dynamics of the humoral immune response. Ig M and Ig G appear in the first and second weeks of the infectious process, respectively. Their levels peak at 4 weeks. Serum immunoglobulin M titers remain higher than Ig G levels during the first 6 months. In general, immunoglobulins M and G are present in the blood of vaccinated individuals for almost a year. The secretion of Ig A coincides with the appearance of Ig G and continues for 6 months, which indicates a chronic process. The humoral response in brucellosis, although not difficult to diagnose, has limited significance in the body's immune response [31]. There are also works that assessed the possibility of using data on immunological changes in predicting the course of brucellosis [1,8,9,32].

Thus, the discovery of biologically active substances - cytokines, regulating the proliferation and level of functional activity of cells both in normal conditions and in pathology, allows us to evaluate from a new perspective the mechanism of formation of inflammatory reactions, allergic and immune conditions and to develop new methods for predicting the nature of an infectious disease. Meanwhile, in the available literature, the role of cytokine metabolism disorders in brucellosis has not received sufficient coverage, which determines the relevance of research conducted in this direction.

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