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Immunological Characteristics of Brucellosis According to The Form of The Disease

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Abstract: In the analysis of clinical and immunological parameters of 179 patients aged 17 to 60 with various forms of brucellosis, an imbalance in cellular and humoral immunity was established, which was more pronounced in the chronic process. The persistence of the pathogen in the bodies of brucellosis patients is associated with the activation of cytokine-mediated immunity, involving both pro- and anti-inflammatory interleukins, against a background of decreased IFN-γ.

Keywords: Brucellosis, clinical aspects, immune status.

1.Introduction:

Brucellosis is a highly contagious, zoonotic, and widespread disease, most commonly found in areas with developed livestock farming, including the regions of Central Asia and Uzbekistan [1, 3, 7].

Consequently, brucellosis is a pressing issue for the public health authorities of several administrative districts, especially in endemic regions, which have long accounted for three-quarters of all registered cases in the republic. The intensive incidence rate of brucellosis (per 100,000 population) in these regions exceeds the national average by two to three times [3].

The urgency of this problem is further underscored by the fact that this pathology presents in several clinical forms (acute, subacute, primary chronic, and secondary chronic), with the acute and especially subacute forms often (up to 50% of cases) progressing to the chronic form of brucellosis [4, 8].

Therefore, a multifaceted and in-depth study of the immune mechanisms of brucellosis development, incorporating advances in modern immunology and

developing improved methods of immunocorrection that account for identified disorders in the immune systems of brucellosis patients, is a timely and promising direction in medicine [2, 5, 6].

Objective: To study the clinical and immunological parameters associated with various clinical forms of brucellosis.

The study was based on data from 179 patients aged 17 to 60 with various forms of brucellosis. Analysis of the sex distribution showed that males were 2.5 times more common than females (71.2% and 28.8% respectively; $p<0.05$). According to the classification by N.I. Rogoz (1955), the secondary chronic form of brucellosis was the most frequently encountered, accounting for 27.9% of cases (Fig. 1).

2. Methods

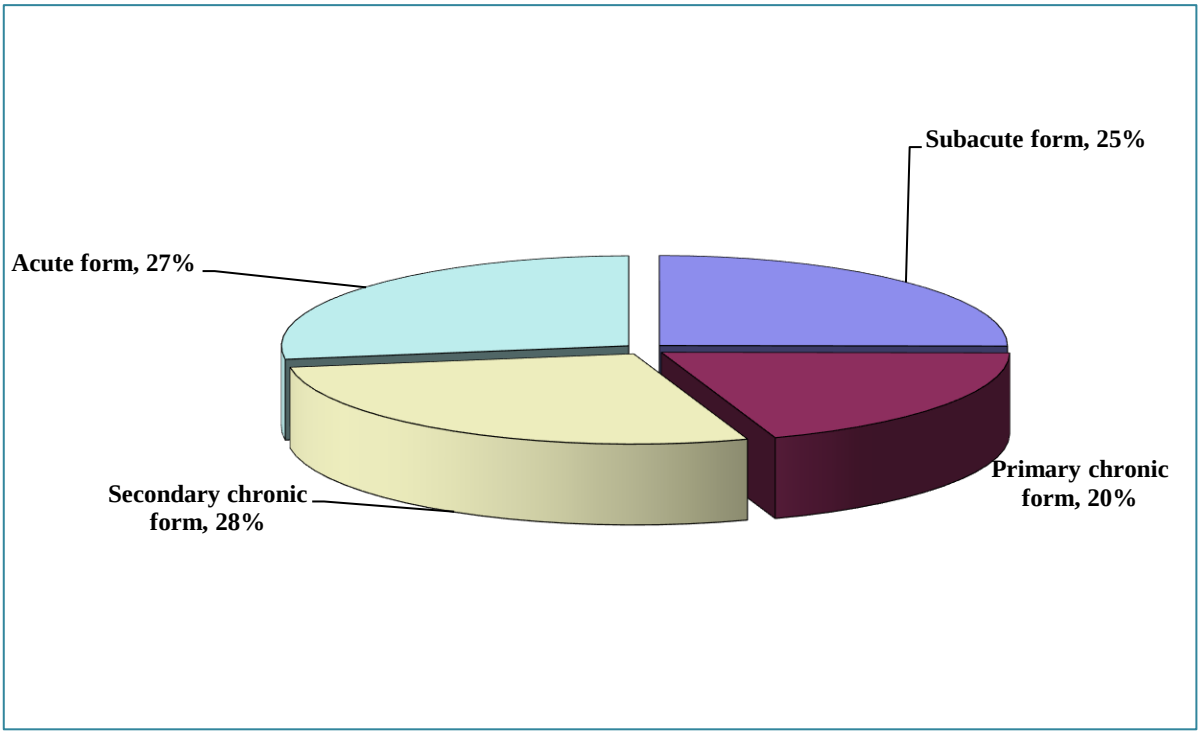

Fig. 1. Distribution of patients by form of brucellosis (n=179)

In addition to standard laboratory methods used to confirm the diagnosis of brucellosis, 104 patients underwent an assessment of their immune system. The following were determined: the relative and absolute counts of CD3+, CD4+, CD8+, CD16+, CD19+, CD23+, CD25+, and CD95+ lymphocytes using a panel of monoclonal antibodies; the levels of interleukin-1β (IL-1β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), and γ-interferon (IFN-γ); serum immunoglobulin (A, M, G) levels by the radial immunodiffusion method according to G. Mancini et al. (1965); and the nitroblue tetrazolium (NBT) reduction test as per the method of B.N. Park et al. (1968), modified by M.G. Shubich and V.G. Mednikova (1978).</2>

The control group consisted of 27 practically healthy individuals matched for age and sex.

Statistical analysis of the obtained data was performed using programs developed in the EXCEL suite with its library of statistical functions. Differences between mean values were considered significant at a significance level of $P<0.05$.

3. Results and Discussion

Of the 179 patients examined, 27.4% (49 patients) were diagnosed with acute brucellosis, which was characterized by an acute onset (96%) and presented with fever in 83.4% of cases. The course of acute brucellosis was accompanied by chills (75.5%), sweating (87.7%), weakness (70.8%), headaches (58.3%), irritability (36.4%), and insomnia (50.0%).

Upon examination, lymph node enlargement was detected in 67.3% of the patients. Hepatolienal syndrome manifested as an enlarged liver in 65.3% and an enlarged spleen in 24.5% of patients.

The subacute period of brucellosis is a direct continuation of the acute form of the disease. Delayed

diagnosis and untimely treatment lead to the development of the subacute form of brucellosis [8]. Among the patients we examined, an acute onset of the disease was noted in 78.8%, a gradual onset in 17.1%, and an imperceptible onset in 4.1%. A moderate course of the disease was predominant among patients (73.8%), with mild (16.5%) and severe (9.7%) courses being less common. The duration of the illness upon admission to the clinic was 1.5 to 3 months for 74.1% of patients, and 3 to 4 months for 25.9%. Upon admission to the hospital, patients complained of: high body temperature (64.1%), chills (45.6%), sweating (61%), general weakness (92.5%), headache (37.3%), and aching and pain in the limb joints (42.2%).

When analyzing the duration of the disease, we found that the infectious process in primary chronic brucellosis has a longer course, averaging 7.5±0.6 years, and is characterized by moderate to minimal activity. Patients with primary chronic brucellosis repeatedly sought medical attention at their local polyclinics and outpatient clinics. For a long time, physicians were unable to provide a correct diagnosis, and symptomatic treatment did not lead to an improvement in the patients' general condition.

1,5 см2 смUpon admission to the hospital, patients with secondary chronic brucellosis presented with various complaints, including general weakness, headaches, dizziness, periodic fever, and profuse sweating, as well as pain in the upper and lower extremities (36% and 40% of cases, respectively). Examination revealed enlarged lymph nodes (axillary, inguinal, submandibular), ranging in size from a pea to a large bean, in 62% of cases. In 56% of patients, the liver was enlarged, of medium density, and minimally tender. A slight enlargement of the spleen was observed in 44% of those examined. These findings indicate more pronounced cardinal symptoms in secondary chronic brucellosis.

The study of immunological parameters established that the acute form of brucellosis was associated with a significant decrease in the levels of CD3+ and CD4+ cells and in the CD4+/CD8+ ratio, against the background of a statistically significant increase in CD8+ and CD16+ levels, compared to those of healthy individuals (Fig. 2).

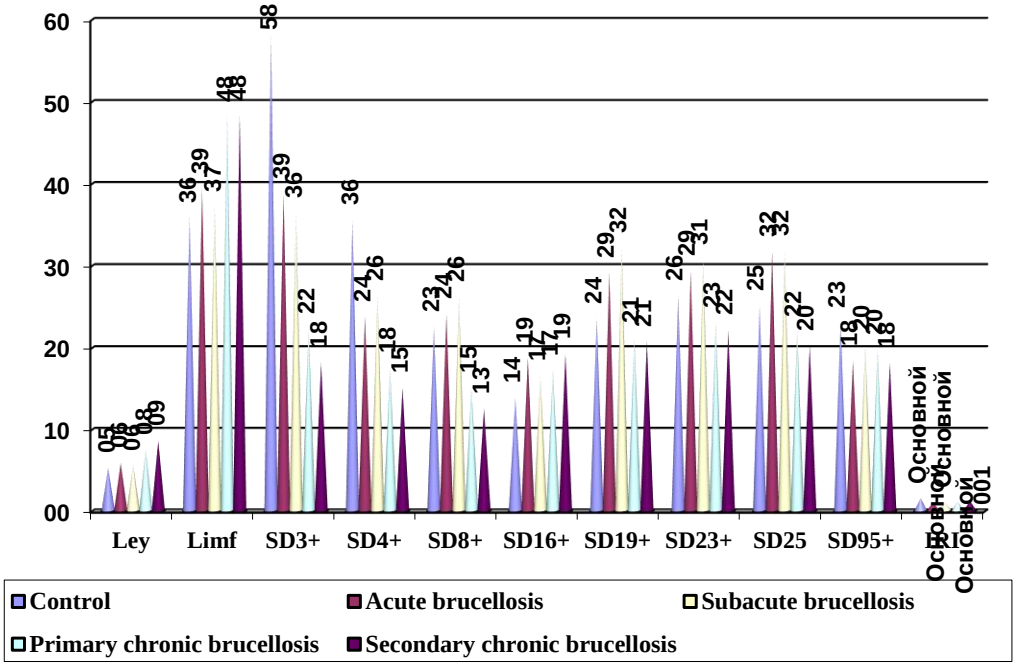

Fig. 2. A comparative analysis of immunological parameters in patients with primary and secondary chronic brucellosis

The immunoregulatory index, which is normally above 1, has significant prognostic value in inflammatory processes; however, in patients with the acute form of brucellosis, it was in most cases below the normal value (1.1±0.05 vs. 1.6±0.03).

Analysis of immunological data from the subacute form of brucellosis reveals a pronounced cellular immunodeficiency, characterized by an imbalance in the cellular immunity of the main subpopulations of the immune system: CD3+, CD4+, and CD8+. It is known that CD8+ cytotoxic lymphocytes play an important role in the pathogenesis of inflammatory infectious diseases. The function of these cells is to recognize antigens on the cell surface in complex with MHC class I molecules [3, 7]. The inflammatory process was accompanied by

increased expression of CD16+ on lymphocytes, which indicated a functional deficiency of the anti-infectious immune response in patients with subacute brucellosis during the activation of the inflammatory process.

In the primary chronic form, an imbalance of cellular immunity is recorded, characterized by a significant 1.3-fold increase in leukocytes and lymphocytes against a background of a sharp decrease in T-lymphocyte subpopulations (CD3+ by 2.5-fold; CD4+ by 2-fold; CD8+ by 1.5-fold) compared to control values. We also noted the activation of natural killer cells, with a 1.2-fold increase in this indicator compared to the control, which is apparently due to an increase in immature forms of natural killer cells in the peripheral blood.

The secondary chronic form of brucellosis is characterized by a change in the number of T-lymphocytes (CD3+) and T-helpers (CD4+), with a tendency to decrease, against a background of a significant increase in leukocytes and lymphocytes. The immunoregulatory index in patients with secondary chronic brucellosis was significantly lower compared to the control group (1.3±0.1 vs. 1.6±0.1; P<0.05).

An analysis of B-lymphocyte counts revealed a significant increase in both the relative and absolute numbers of B-lymphocytes in the group with acute brucellosis (p<0.05). These data differed significantly from those of the control group. Patients with this clinical form also showed a significant increase in the relative number of CD23+ (29.4±1.36 vs. 26.4±1.1; P<0.05) and CD25+ (P<0.01) lymphocytes, alongside a decrease in the absolute and relative levels of CD95+.

In certain conditions, including the subacute form of brucellosis, CD23+ (a low-affinity IgE Fc receptor) is expressed on B-cells following IL-4 activation, with a simultaneous increase in the expression of the CD25+ receptor (IL-2 receptor). Furthermore, IL-4 mediates an increase in IgE production, which is caused by the intercellular interaction of T- and B-lymphocytes via the T-cell receptor and MHC class II molecules. A slight decrease in CD95+ levels is observed relative to the control group values.

Changes in B-lymphocyte levels in the primary chronic form of brucellosis were evidenced by the levels of its CD23+ and CD25+ populations, which were reduced in comparison to control values. A decrease in CD95+ was also noted relative to the control group values. In secondary chronic brucellosis, the same pattern was observed in the B-cell component, characterized by a statistically significant decrease in the relative count of CD25+, CD23+, and CD95+.

The functional activity of B-lymphocytes can be assessed by the content of the main classes of immunoglobulins in peripheral blood serum. The most important indicators of the humoral response are IgG, IgM, and IgA (Table 1).

The humoral component indicators in patients with the acute form of brucellosis differed from and exceeded the control values. Specifically, IgA and IgG were elevated one-fold, but this was not statistically significant, whereas a statistically significant 1.2-fold increase in IgM was noted (p<0.05).

Table 1

Humoral immunity indicators in patients with brucellosis, depending on the clinical form

	Control group	Acute brucellosis	Subacute brucellosis	Primary chronic brucellosis	Secondary chronic brucellosis
IgA	130.27±3.8	135.28±3.9	134.0±4.8	127.12±2.6	128.4±2.6*
IgM	134.86±6.9	160.19±7.5*	146.6±9.3	127.56±4.0	127.2±4.0
IgG	1178.7±28.7	1236.08±32.8	1403.0±82.9*	1281.50±48.6	1290.1±63.6*

Note: * - statistical significance of data compared to the control group (* - p<0.05; ** - p<0.01; *** - p<0.001)

A study of the humoral immunity link revealed a significant difference in IgG levels between patients

with subacute brucellosis and the control group (P<0.05).

In primary chronic brucellosis, a slight decrease in IgA and IgM is recorded alongside an insignificant increase in IgG. In secondary chronic brucellosis, a significant increase in IgG levels was observed against a background of decreased IgA (P<0.05) and IgM in peripheral blood serum, which indicates the chronic nature of the process.

Thus, the data obtained indicate that patients with brucellosis, regardless of its clinical form, exhibit an imbalance in both the cellular and humoral links of immunity.

It is known that IL-1β and IL-6 are pro-inflammatory cytokines produced by Th2 cells. IFN-γ, IL-4, and IL-10 are anti-inflammatory cytokines of adaptive immunity produced by Th1 cells. Therefore, this provides an excellent opportunity to assess the functioning of the immune system and evaluate the observed imbalance in the spontaneous production of cytokines in patients with brucellosis (Table 2). As can be seen from the presented data, there is an increase in both pro-inflammatory and anti-inflammatory cytokines, alongside a significant decrease in IFN-γ in patients with the subacute form of brucellosis.

In patients with primary chronic brucellosis, particularly high levels of pro-inflammatory cytokines were noted: IL-1β was elevated 2.4-fold and IL-6 was elevated 3.7-fold. Activation of the anti-inflammatory cytokines IL-4 (1.9-fold) and IL-10 (2.5-fold) was also observed. Concurrently with these findings, a decrease in IFN-γ concentration (1.7-fold) was detected, which undoubtedly affects the phagocytosis system by reducing its functional activity and preventing the complete elimination of the pathogen from the body.

Table 2

A comparative analysis of cytokine status indicators in patients with brucellosis

Indicators	Control group	Acute brucellosis	Subacute brucellosis	Primary chronic brucellosis	Secondary chronic brucellosis
IL-1β	19.50±0.75	380.70±6.7***	286.03±17.7***	470.47±30.6***	540.2±37.0***
IL-4	20.11±0.96	22.05±3.2*	38.64±1.4***	38.32±1.5***	46.4±1.3***
IL-6	26.41±0.56	138.80±5.2***	61.90±2.5***	98.93±4.6***	110.2±4.9***
IL-10	14.21±0.25	20.91±0.38***	28.30±0.61***	35.30±0.7*	42.8±1.4**
IFN-γ	23.20±1.8	13.12±0.69***	19.24±1.7*	14.01±0.44**	18.5±1.4*

Note: * - significance of the data compared to the control group (* - p<0.05; ** - p<0.01; *** - p<0.001)

When studying cytokine levels in patients with secondary chronic brucellosis, the same pattern was observed as in other clinical forms; that is, a significant increase in the concentrations of IL-1β, IL-6, and IL-10 was recorded against a background of decreased IFN-γ.

Thus, a study of the clinical and immunological parameters in brucellosis, regardless of its clinical form, has shown that immunological disorders play a significant role in the pathogenesis of the disease. This process can be described as follows: after entering the body, brucellae multiply, and old cells die. When these cells break down, an endotoxin is released, in response to which macrophages and lymphocytes release pro-inflammatory cytokines. This is evidenced by elevated levels of IL-1β and IL-6. In turn, the production of anti-inflammatory cytokines, IL-4 and IL-10, increases. Concurrently, the data revealed a decreased concentration of IFN-γ, which undoubtedly affects the phagocytosis system by reducing its functional activity and preventing the complete elimination of the pathogen from the body.

4. Conclusions

1. The identified cellular immunodeficiency in patients with brucellosis manifested as an imbalance of the main cellular subpopulations of the immune system, indicating the functional inadequacy of the anti-infectious immune response, regardless of the clinical form of brucellosis.

2. The humoral immunity of patients with

brucellosis is characterized by a decrease in IgA and IgM in chronic forms and their activation in acute and subacute forms of the disease. The activation of IgG is observed in all forms of brucellosis.

3. In brucellosis accompanied by combined immunodeficiency, significant cytokine dysregulation is observed, characterized by a statistically significant increase in pro-inflammatory (IL-1β, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines, as well as a significant decrease in γ-interferons, regardless of the form of the disease.

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