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Primary Chronic Brucellosis in Children: Between Infection and Immunity

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Abstract: Clinical and immunological examinations of 19 patients showed that in children with the primary chronic form of brucellosis, the clinical picture of the disease was characterized by its diversity and was distinguished by a slightly milder course compared to the acute and subacute forms of brucellosis. Immunological studies in these patients revealed an imbalance in the cellular immunity, where an increase in leukocytes and lymphocytes was observed against a background of a sharp decrease in T-lymphocyte subpopulations (CD3+, CD4+, CD8+) compared to the control group. Imbalances were also observed in B-lymphocytes, the humoral immune system, and the cytokine group of the immune system.

Keywords: Brucellosis, primary chronic form, cellular and humoral immunity, cytokines.

1.Introduction:

A study of clinical and immunological parameters in 45 patients showed that the subacute form of brucellosis is characterized by an acute onset (78.8%) and a moderate course of the disease (73.8%), with bone and joint lesions as the predominant manifestation. Against the background of an imbalance in cellular immunity - with the prevailing suppression of major T-cell subsets and an increase in cytotoxic T-lymphocytes, the expression of CD16+ and CD23+, and elevated values of the CD25+ receptor - there is an indication of a functional inadequacy of the anti-infectious immune response in patients with subacute brucellosis during the activation of the inflammatory process.

Changes in cellular immunity directly affect the progression of cytokine immunity disorders, involving both pro-inflammatory and anti-inflammatory

interleukins.

Background. Brucellosis is a widespread zoonotic infection that causes significant economic and social damage in many countries with developed livestock industries[2,7,8].In the Republic of Uzbekistan, an area with a developed livestock sector, brucellosis is widespread not only among farm animals but also among people [1,4].The significance of this problem is further underscored by the fact that the disease presents in several clinical forms (acute, subacute, primary chronic, and secondary chronic), with the acute and especially the subacute forms often (in up to 50% of cases) progressing to chronic brucellosis [6,8].

Although various methods for treating brucellosis have been used for many years, none of them, even when immunomodulators are included in the treatment regimen, ensures the complete recovery of patients. Therefore, an in-depth study of the immune mechanisms of brucellosis development, using modern immunological advances and immunocorrection methods based on the specific disorders identified in the immune systems of patients, is an important and promising area of research [5].

Currently, cytokines, whose significance in pathological processes is beyond doubt, are known to play an important role in the pathogenesis of many diseases, including infectious ones. However, the nature of cytokine changes in combination with other immunological parameters, and their relationship to the clinical forms, severity, stage, and outcome of brucellosis, have not been fully studied [3,6,8].

Objective. To study the clinical and immunological status of patients with primary chronic brucellosis (PCB).

2. Methods

A total of 29 patients were examined, 19 of whom underwent comprehensive serological and immunological testing. The control group consisted of 20 healthy individuals. The age distribution of the pediatric patients was as follows: 15% (n=3) were 7-10 years old, 50% (n=10) were 11-14 years old, and 35% (n=7) were 15-17 years old. It was established that small ruminants were the primary source of infection (64.8%). The children were infected mainly through contact and contact-alimentary routes. The diagnosis was established based on clinical, epidemiological, and laboratory data (Huddleson, Wright, and IHA serological tests).

In addition to the standard laboratory methods confirming the diagnosis of brucellosis, 19 patients underwent an assessment of their immune system. The relative and absolute counts of CD3+, CD4+, CD8+, CD16+, CD20+, CD23+, CD25+, and CD95+ were determined using a panel of monoclonal antibodies;

3. Results

Upon admission to the hospital, patients complained of high body temperature (33.1%), chills (57.9%), sweating (63.1%), general weakness (57.9%), headache (47.4%), and aches and pain in the limb joints (42.1%).

Objective examination most frequently revealed anemia, muffled heart sounds, and electrocardiographic changes (diffuse myocardial changes, hypotension, predominance of subfebrile fever). Other common findings included digestive system disorders (anorexia, abdominal pain, coated tongue), enlargement of the liver and peripheral lymph nodes, and changes in the musculoskeletal (arthralgia of large joints in the upper and lower extremities) and nervous (poor sleep, headaches, manifestations of radiculitis, neuritis, and plexitis) systems. Lesions of the genital organs (orchitis, orchiepididymitis) were also observed.

In patients with primary chronic brucellosis, blood analysis revealed a slight change in the leukocyte count, whereas no significant changes were observed in the differential leukocyte count, with the exception of moderate monocytosis (3-5%).

Analysis of the main lymphocyte populations and subpopulations revealed a significant suppression of the total T-lymphocyte count (Fig. 1).

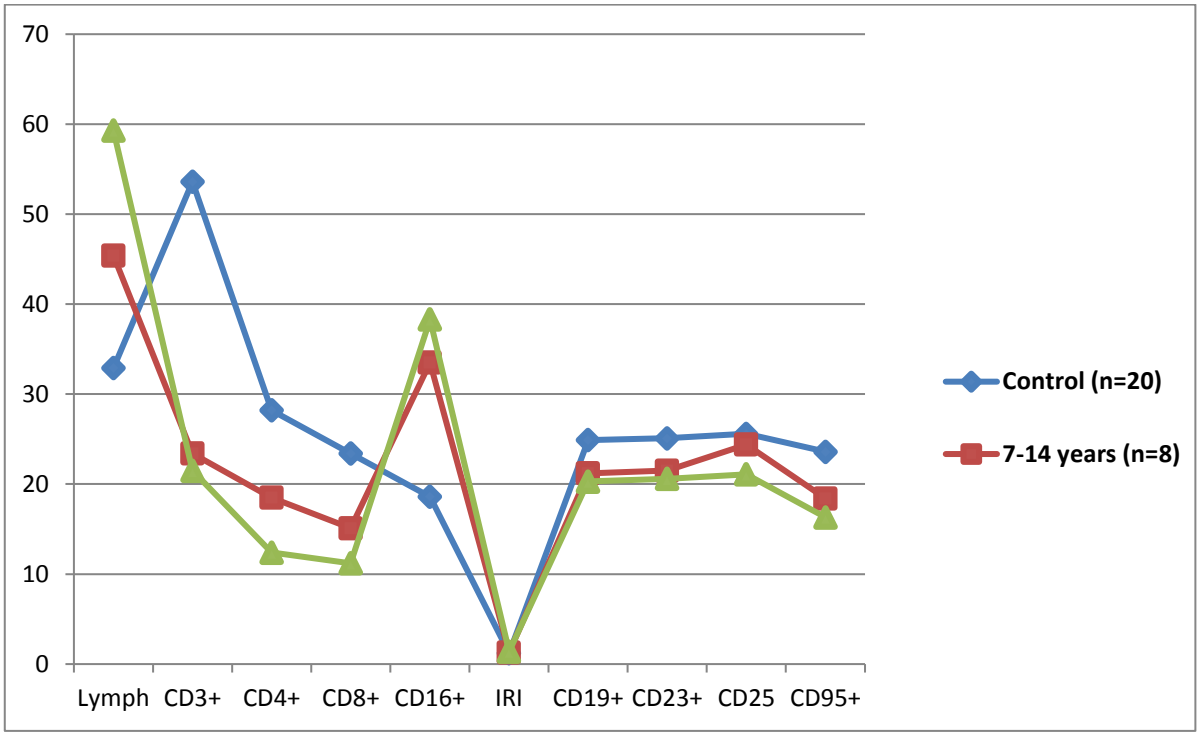

Fig. 1. Cellular immunity parameters in children with the primary chronic form of brucellosis.

As shown in Figure 1, patients with primary chronic brucellosis exhibit a significant decrease in the levels of CD4+ (T-helpers/inducers) and CD3+ (T-lymphocytes) by 1.3-fold and 1.1-fold, respectively. The CD4+ T-cell response is an important defense mechanism, as T-helpers/inducers stimulate antibody production by B-lymphocytes and activate cytotoxic T-lymphocytes. A significant decrease in the relative number of CD8+ cells was also found, which was 1.1-fold lower than the control values. Therefore, the immunoregulatory index (IRI) was significantly decreased in patients with PCB.

CD8+ cytotoxic lymphocytes are known to 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 a complex with MHC class I molecules [5,6].The immunoregulatory index has significant prognostic value in inflammatory processes; normally, it should be greater than 1, whereas in patients with PCB, it was only 1.0±0.1 ($p<0.05$).

Among the NK surface receptors, CD16 should be noted. In our research, this indicator was 1.2-fold higher than the control. Apparently, the increased level of natural killer cells is due to the immune system's fight against the infectious agent and possibly indicates a functional deficiency of the anti-infectious immune response in patients with PCB.

In some conditions, including primary chronic brucellosis, IL-4 activation leads to the expression of CD23+ (the low-affinity Fc receptor for IgE) on B-cells, along with a simultaneous increase in the expression of the CD25+ receptor (the IL-2 receptor). Additionally, 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 major histocompatibility complex (MHC) class II molecules.

A slight decrease in CD95+ levels is also observed, which likely indicates a functional deficiency in the anti-infective immune response.

Thus, we identified a cellular imbalance, which manifested as the suppression of the main cell subpopulations of the immune system against a background of increased T-cytotoxic lymphocytes.

The most important indicators of the humoral response are immunoglobulins G, M, and A. The study of the humoral arm of immunity revealed a significant difference in IgG levels between patients with subacute brucellosis and the control group (Fig. 2).

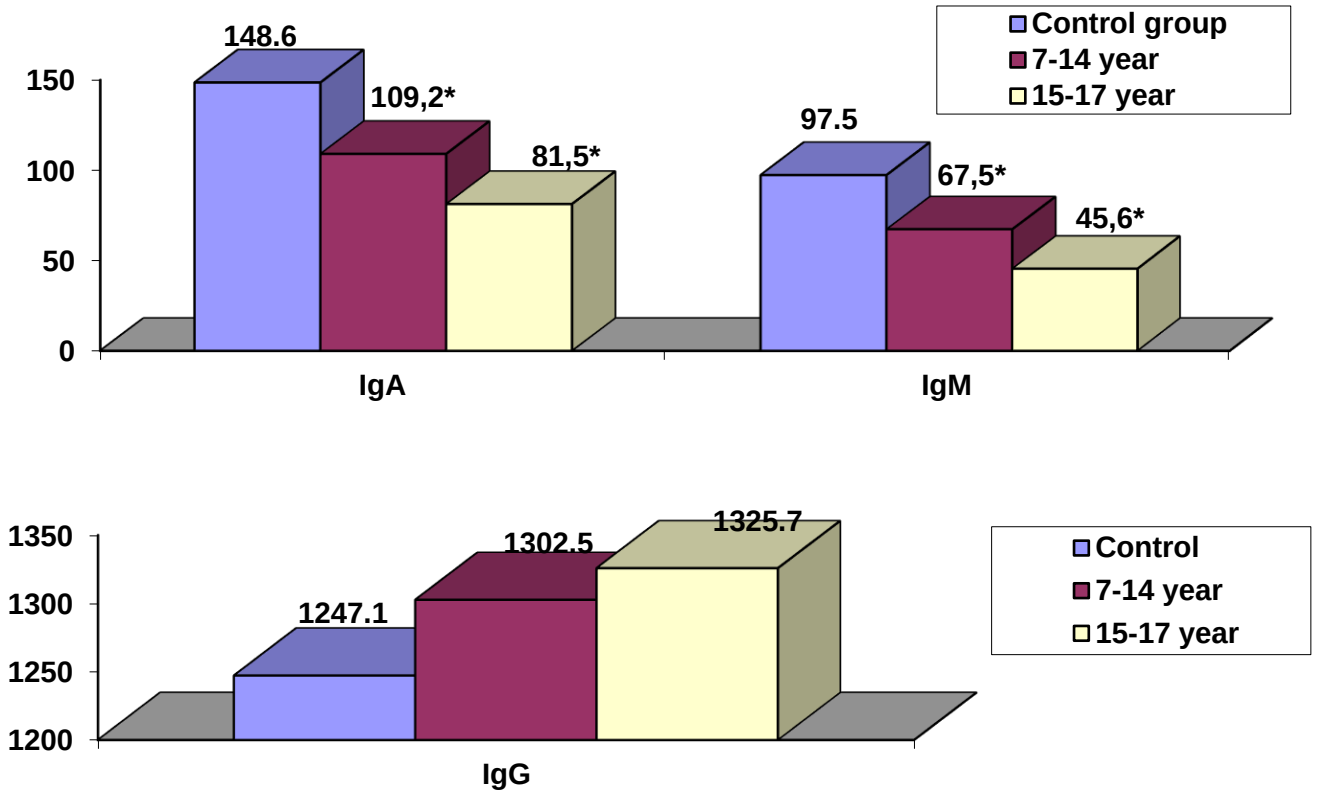

Fig. 2. Indicators of humoral immunity in children with the primary chronic form of brucellosis.

Thus, changes in the levels of peripheral blood lymphocyte subpopulations in patients during antibody production and increasing specific sensitization are associated with the redistribution of these cells from the peripheral blood into tissues and their participation in the clearance process, as well as in the development of focal inflammation.

We also studied several cytokines of the immune system. It is known that IL-1β and IL-6 are pro-inflammatory cytokines produced by Th2-type cells. IFN-γ, IL-4, and IL-10 are anti-inflammatory cytokines of adaptive immunity produced by Th1 cells. This provides an excellent opportunity to evaluate the functioning of the immune system and assess the observed imbalance in spontaneous cytokine production (Fig. 3).

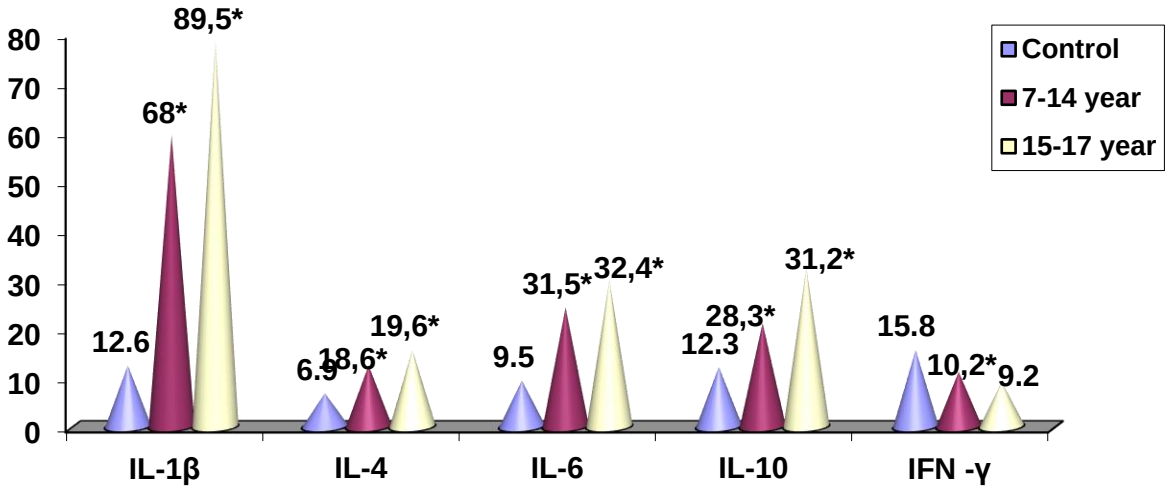

Fig. 3. Cytokine levels in children with primary chronic brucellosis

As can be seen from the presented data, patients with PCB exhibit an increase in the levels of both pro-inflammatory and anti-inflammatory cytokines, alongside a significant decrease in IFN-γ production.

Thus, the study of clinical and immunological parameters in the primary chronic form of brucellosis showed that immunological mechanisms play a significant role in the pathogenesis of the disease.

4. Conclusions

1. The predominant clinical feature of primary chronic brucellosis was damage to the musculoskeletal system. In patients with PCB, blood analysis revealed a slight change in the leukocyte count, while the differential leukocyte count showed no significant changes, with the exception of moderate monocytosis (3-5%).

2. The immune imbalance identified in patients with the primary chronic form of brucellosis was manifested by the suppression of the main cellular subpopulations of the immune system, alongside an increase in the level of T-cytotoxic lymphocytes and increased expression of CD16+ on lymphocytes, as well as increased expression of CD23+ and an increase in CD25+ receptor levels, which indicates the functional inadequacy of the anti-infectious immune response.

3. The persistence of the pathogen in the bodies of patients with the primary chronic form of brucellosis affects the imbalance of the cytokine component of immunity, concerning both pro-inflammatory and anti-inflammatory interleukins.

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