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THE IMMUNE SYSTEM INDICATOR FEATURES OF PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS

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ABSTRACT

Background: It has been established that JRA is a multifactorial disease, the pathogenesis of which is very complex and is largely insufficiently studied. Based on the modern concepts, one of the key links in the development of the pathological process in rheumatoid arthritis is the dysfunction of the immune system. **Objective:** 53 children with juvenile rheumatoid arthritis were taken a clinical and immunological examination. **Methods:** We studied a concentration of circulating immune complexes (CIC), phagocytic activity, and the level of pro-inflammatory cytokines (IL-1β, TNF-α, and IL-6) among the children with various forms of the disease depending on the duration of the course of JRA. **Result:** It was revealed that the children with the juvenile disease are characterized by changes in indicators of innate immunity and cytokine status. Probably, these changes are associated in the active phase of the disease with a bright protective reaction of the body, and with prolonged antigenic stimulation, with a depletion of the functional activity of the immune system. **Conclusion:** Summarizing the foregoing, we can conclude that among the children with juvenile deformity there is a desynchronization of the immune system what is manifested in the increased secretion of pro-inflammatory cytokines. The most pronounced disorders are observed among the patients with a systemic form of the disease accompanied by a visual activity of the pathological process and depending on the duration of the disease.

KEYWORDS: Children, rheumatoid arthritis, immune status.

INTRODUCTION

Juvenile rheumatoid arthritis (JRA) is an immuno-aggressive inflammatory joint disease of unknown etiology that occurs among children under 16 with symptoms of progressive erosive-destructive polyarthritis and frequent involvement of vital organs and systems in the process.[1,2,3] JRA is one of the most common rheumatic diseases of childhood which significantly affects the quality of the life of children and often leads to early disability.[2.5]

It has been established that JRA is a multifactorial disease, the pathogenesis of which is very complex and is largely insufficiently studied. Based on the modern concepts, one of the key links in the development of the pathological process in rheumatoid arthritis is the dysfunction of the immune system.[4,5,6] All parts of the immune system function are in close interaction, therefore, a dysfunction of a single link inevitably leads to a chain reaction of immunological changes. And immunity, as you know, has a leading role in regulating a body's homeostasis, both in the norm and as the main links of adaptation in various pathological conditions.[3, 6]

The aim of this study is to study indicators of innate immunity and pro-inflammatory cytokines among the patients with JRA.

MATERIALS AND RESEARCH METHODS: A total of 53 children (29 boys and 24 girls) with JRA aged from 4 to 16 years old who were admitted for treatment at the RSNPMTs of Pediatrics were examined. All the children underwent general clinical and laboratory studies. Immunological studies included determining the level of phagocytic activity and the concentration of circulating immune complexes (CEC). Phagocytic activity was determined by use of latex particles (Research Institute of Biological Instrumentation, Moscow). Serum CEC levels were determined by use of PEG-6000 (Nichol, Tashkent) in accordance with the instructions for use. The concentration of cytokines (IL-1β, IL-6 and TNFα) was determined by ELISA by way of using the Cytokine test systems (St. Petersburg, Russia) in blood serum. Statistical processing of the obtained data was carried out on a personal computer using a software package.

RESULTS AND ITS DISCUSSION: Analysis of the clinical data of the sick children showed that the articular-visceral form of the disease was observed

among the 10 children, mainly articular was observed among the 43 sick children (Fig. 1).

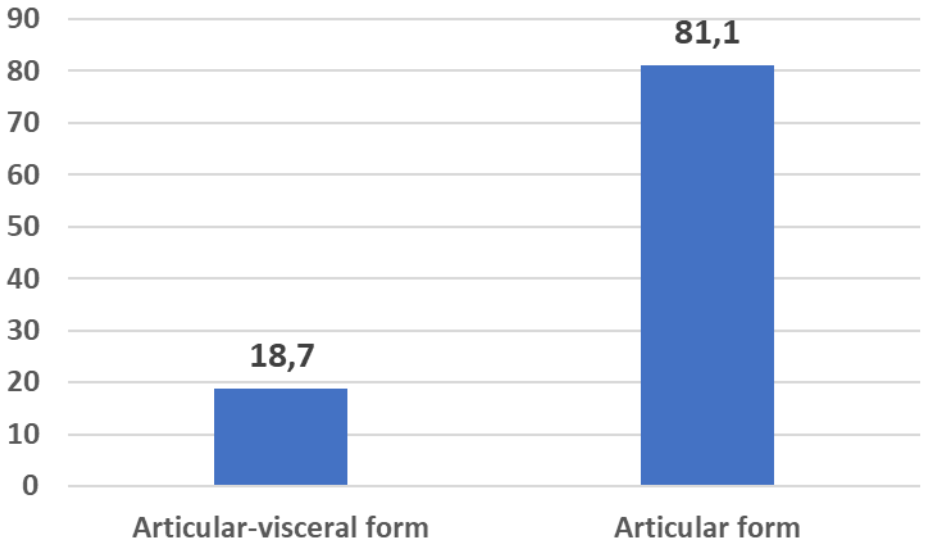

Fig. 1: Forms of Rheumatoid Arthritis among the examined children, %.

During the examination period, exacerbation was observed among the 24 (45.3%) patients, a moderate degree of process activity was observed among the 12 (22.6%) children, and 9 children (16.98%) had a low process activity.

The duration of the JRA course was as follows: among the 22 children the length of illness was from 1 to 3 years, among the 12 - from 3 to 6 years, and among the 19 children - more than 6 years (Fig. 2).

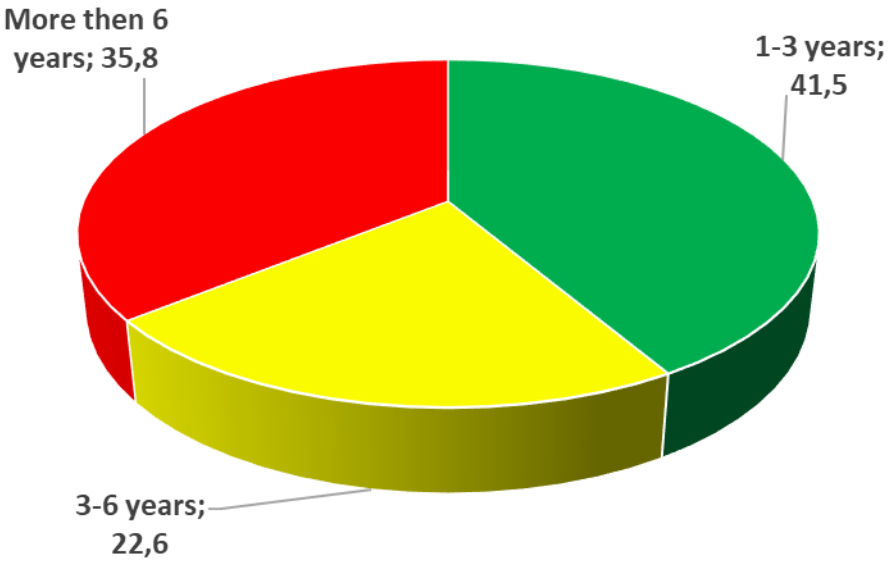

Fig. 2: Duration of the disease among the examined children (%).

Under conditions of rheumatoid inflammation, the acute protective inflammatory reaction transforms into a chronic uncontrolled pathological process affecting all human organs and systems.[6] An analysis of the results of studies on the study of nonspecific defense factors among the patients with JRA showed a reduced level of phagocytic activity against the background of an increase in the concentration of circulating immune complexes compared with the data of the control group (Table 1). Moreover, the changes depended on the form of activity and the duration of bolevaniya. So, it was found that in the systemic version, the level of phagocytic activity decreases ($P < 0.05$) and the level of CRICs is increased 1.4 times ($P < 0.01$) compared with the articular version of JRA.

Table 1: The level of phagocytic activity and circulating immune complexes among the patients with JRA depending on the form, activity and duration of the disease.

Characteristic	Indicators	
	Phagocytosis,%	CEC, (conventional units)
Control group	54,2 ± 1,4	22,6 ± 1,6
Joint form	49,1 ± 2,1*	58,5 ± 2,3*
Joint-visceral form	42,7 ± 2,0*	81,3± 2,8*

Note: * Values are significant in relation to the control group (P <0.05 - 0.001)

Exacerbation was accompanied by an increased level of CEC (97.6 ± 3.5 conventional units) and a decrease of a phagocytic activity (40.2 ± 2.7%) (P <0.001). With moderate activity, the studied parameters were significantly lower than during exacerbation: CEC - 74.2 ± 2.7 srvc.; phagocytosis - 45.8 ± 1.8% (P <0.05). With low disease activity, there was a tendency to a decrease in the level of phagocytosis relative to the data of the control group - 51.2 ± 2.1% versus 54.2 ± 1.4%. However, the level of the CEC was significantly higher than the control values - 56.9 ± 2.6 srvc. against 22.6 ± 1.6 conventional units (P <0.01).

As is known, a phagocytic reaction initiates an immune response; a decrease in the activity of phagocytic defense naturally provides a low level of the immune response, including a delay in the products of assimilation, imbalance and tolerance to autoantibodies.[10] The presence of a deficiency in the reserve of immunocompetent cells causes a risk of accumulation of abnormally high concentrations of CEC. CECs are formed by the interaction of specific antibodies formed in the body - immunoglobulins with antigens that induced an immune response and the production of these antibodies.[8]

To date, the key role of cytokines in the pathogenesis of JRA has been proven.[7] The primary antigenic stimulus activates antigen-presenting cells, which induces the synthesis and secretion of cytokines, which stimulate the production of local inflammatory mediators, activation of complement factors, coagulation systems, proteolytic enzymes. Normally, the overlapping, synergistic and inhibitory activity of cytokines in relation to each other ensures optimal development and interruption of immune inflammation. With JRA, under conditions of a disturbed immune response, there is an excessive activation of CD4 + T lymphocytes of the Th1 type and the development of the acute phase of inflammation. Further, the imbalance between the overproduction of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukins (IL) 1, 6, 8 and anti-inflammatory cytokines (IL-4, IL-10, soluble antagonist of IL-1, soluble receptors), with the predominance of the former over the second supports the inflammatory process.[5]

Our studies on the level of pro-inflammatory cytokines depending on the form of rheumatoid arthritis revealed the following changes: the concentration of IL-1β progressively increased, the maximum value of which was observed in children with articular-visceral form (P <0.001). The level of IL-6 in the systemic form was increased 3.3 times compared with the control group, and the level of TNFα was 4.6 times (P <0.001). With exacerbation of the disease, but with low activity of the rheumatoid process, the level of ACTH is significantly higher than with exacerbation (27.2 ± 0.9 pkg / ml versus 15.2 ± 0.7 pkg / ml with exacerbation, P <0.05). The lowest cortisol value was detected with low disease activity (57.4 ± 1.5 nmol / L versus 69.3 ± 1.8 nmol / L, P <0.05). When considering the condition of the pituitary-adrenal axis, depending on the prescription of JRA, the highest levels of hormones were obtained in the initial period of the disease with a subsequent decrease in their content with an increase in the duration of the disease (Fig. 3). The results obtained indicate that in juvenile hemoglobin activation occurs, but it is insufficient in conditions of enhanced antigenic stimulation of the body. With an increase in the activity of JRA, a decrease in the level of cortisol is observed, possibly due to its increased utilization. At the same time, a lower hormone content is less effective in countering pro-inflammatory stimuli.

The decrease in cortisol production depends on the severity and duration of the pathological process, which is probably associated with a decrease in the functional activity of the adrenal cortex. Suppression of ACTH secretion may be associated with a prolonged inhibitory effect of cortisol.

Changes in the levels of thyroid-stimulating hormone, triiodothyronine, and thyroxine in children suffering from rheumatoid arthritis are presented in Table No. 2. A study of the concentration of hormones in the pituitary-thyroid system in children with juvenile arteries showed that their TSH levels are significantly lower compared to the data of children in the control group, moreover, in children with articular-visceral form lower than in articular form (P <0.01).

An exacerbation is characterized with a lower level of TSH (P <0.001). The level of triiodothyroninau in children with juvenile arteries was characterized by increased synthesis, as it was increased both in children with the articular form of rheumatoid arthritis and articular-visceral (P> 0.01), and in children with an initial period of the disease this indicator is higher than with a longer its course (P> 0.01). A study of the level of thyroxine showed its increase in patients with rheumatoid arthritis (P <0.01), which is almost 2 times higher than in healthy children. Under physiological

conditions, the synthesis of these hormones obeys a feedback mechanism: the hypothalamic thyroliberin stimulates the synthesis of TSH, which, in turn, leads to an increase in the production of T3 and T4.

Thus, the results obtained indicate the presence of disregulation of immune system parameters by the central and peripheral links of this system among the JRA patients.

Table 2: The level of cytokines among the children with JRA, (M ± m).

Characteristics	Indicators (pg / ml)		
	IL-1β	IL-6	TNFα
Control group	18,7 ± 1,8	17,3 ± 1,1	15,3 ± 1,4
Joint form	57,3 ± 2,9*	45,3 ± 2,2*	58,7 ± 2,9*
Joint-visceral form	64,5 ± 2,8*	56,8 ± 2,9*	71,2 ± 3,3*
Exacerbation	76,4 ± 3,7*	65,2 ± 3,8*	82,1 ± 0,5*
Moderate activity	62,1 ± 2,5*	58,3 ± 2,5*	60,8 ± 0,4*
Low activity	45,7 ± 2,9*	44,6 ± 2,1*	48,2 ± 2,3*
1-3 years	47,4 ± 1,7*	35,1 ± 1,5*	50,3 ± 2,7*
3-6 years	43,7 ± 1,3*	38,7 ± 2,1*	49,1 ± 2,4*
More than 6 years	59,3 ± 2, 9*	47,2 ± 2, 9*	52,7 ± 2,6*

Note: * Values are significant relative to the control group.
(P <0.05 - 0.001)

When analyzing hormone indices depending on the clinical form of the disease, the following were revealed: a decrease in TSH concentration with a more pronounced decrease in the systemic version of JRA, a significant increase in T4 content with the highest rates in the articular-visceral form. At the same time, the T3 level was slightly higher with the articular form.

These data indicate that more pronounced changes in hormone secretion were observed with a systemic, more severe variant of the disease.

In the state of the axis “pituitary - thyroid gland” in children with different disease activity, a clear influence of the degree of activity of the inflammatory process on the level of the studied hormones was revealed. The content of TSH progressively decreased, the lowest rates were observed in patients with a moderate degree of activity. At the same time, the concentration of T3 and T4 in blood serum increased.

Thus, with an increase in the activity of the pathological process, a decrease in the tropic function of the pituitary gland and an increase in the functional activity of the thyroid gland are observed. When studying the levels of the studied hormones, depending on the age of JRA, the following changes were revealed. The lowest level of TSH was found among the children with a disease duration of 3 to 6 years. The content of T3 and T4, although it was higher than that of the healthy children, but with an increase in the duration of the disease, there was a tendency to its decrease. Among the patients with a duration of JRA of more than 6 years, the levels of the studied hormones had the lowest rates.

To clarify the mutual influence of the studied hormones, a correlation analysis was carried out what revealed a lack of connection between the indicators of adrenocorticotropic hormone and cortisol. This fact indicates a violation of the regulation mechanism in the system "pituitary gland - adrenal cortex". Revealed: a statistically significant positive relationship between the activity of the inflammatory process and the thyroxine content ($r = 0.44$; $p < 0.001$), a negative correlation between the duration of the disease and the level of triiodothyronine ($r = –0.70$; $p < 0.001$) and cortisol ($r = –0.40$; $p < 0.001$).

CONCLUSION

Summarizing the foregoing, we can conclude that among the children with juvenile deformity there is a desynchronization of the immune system what is manifested in the increased secretion of pro-inflammatory cytokines.

The most pronounced disorders are observed among the patients with a systemic form of the disease accompanied by a visual activity of the pathological process and depending on the duration of the disease.

Perhaps these changes are associated in the active phase of the disease with a bright protective reaction of the body, and with prolonged antigenic stimulation - with the depletion of the functional activity of the immune system.

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