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# Comparative Assessment of Indicators Cytokine Status in Children with Juvenile Rheumatoid Arthritis

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**Summary:** This scientific article examines the immunological mechanisms of the pathogenesis of juvenile rheumatoid arthritis, the importance of cytokines such as IL-8, IL-17A and INFy in intercellular immune connections and in the development of the inflammatory process. An imbalance of cytokines leading to a cascade of disturbances in immunological reactivity subsequently contributes to the development of autoimmunization and chronicization of the pathological process in JRA. We studied changes in the production of cytokine levels depending on age, dividing JRA into seronegative and seropositive forms. As a result, it was revealed that the level of IL-8, IL-17A was increased in children aged 15-18 years and the highest rates were in the seropositive form (38.3±4.06 pg/ml and 41.25±5 .14 pg/ml, respectively). And the level of INFy was sharply reduced in both groups of examined children with JRA. Next, we conducted a correlation analysis, which showed significant connections between IL-17A and INFy. Based on the results obtained, a disease prognosis index was compiled.

**Keywords:** JRA, IL-8, IL-17A, INFy, seronegative, seropositive.

**Relevance:** According to modern medical data, juvenile rheumatoid arthritis (JRA) is a chronic autoimmune disease characterized by destructive and inflammatory joint damage and occurring in children under the age of 16 years. Serious complications such as carditis, interstitial lung disease and serositis occur. Half of the patients experience chronic polyarthritis with or without systemic manifestations, progressive osteochondral joint destruction and functional failure [1, 5, 16, and 22].

Modern research suggests considering JRA not only as a classic autoimmune disease, but also as an autoinflammatory one. However, the full mechanisms of development of this disease remain poorly understood [2, 4, 7, 18, 20].

The development and progression of inflammation in rheumatic diseases is caused by autoimmune mechanisms, which are based on impaired tolerance to self-antigens, leading to the development of an immune response against normal tissues. This process is mediated by a complex interaction of genetic, immunological factors, various infectious agents and other environmental influences, defects in hormonal and neuroendocrine regulation [3, 6, 11, 19].

The basis of inflammation is a cascade of biochemical and immunological processes, the regulation of which is carried out by a large number of humoral mediators. Among them, a special place is occupied by cytokines - low molecular weight proteins that ensure the process of intercellular interactions [4, 8, 12, 21]. Currently, changes in the cytokine profile are considered as possible trigger mechanisms for the development of juvenile rheumatoid arthritis (JRA).

**Purpose of the study:** to study the role of IL-8, IL-17A and INFy in the development of juvenile rheumatoid arthritis in children and determine their prognostic significance.

**Materials and research methods:** The collection of material was carried out during 2021-2023. on the basis of the department of cardiorheumatological diseases of the clinic of the Tashkent Pediatric Medical Institute. A total of 106 patients aged from 3 to 18 years were examined. All patients underwent a comprehensive clinical examination, including laboratory and instrumental studies. As a control group, 40 healthy children were examined for comparison.

To determine the concentration of IL-8, IL-17A, IFNγ in the blood serum of the study groups, we used the three-stage "sandwich" method - this is a type of three-phase ELISA "Vector-Best" (Novosibirsk, Russian Federation).

The obtained data were subjected to statistical processing using the Fisher-Student variation statistics method and the Pearson $\chi^2$ test was used.

**Research results:**IL-8 is an important mediator of the inflammatory process in the musculoskeletal system and is considered, according to a number of authors, to be a diagnostic marker of the attacking period of rheumatoid arthritis, the level of which is associated with the duration of the disease. It is produced under the influence of tumor necrosis factor, interleukin-1 [9, 13, 15, 18].

Comparison of IL-8 levels in children with various forms of juvenile rheumatoid arthritis (JRA) showed that in the age group from 15 to 18 years (38.3±4.06 pg/ml), the concentration of IL-8 in children with a seropositive form exceeded the levels recorded in children of the same age category from 7 to 14 years (20.9±3.12 pg/ml), by 1.85 times. Similar trends were noted in the group with seronegative JRA, where IL-8 levels in children aged 15 to 18 years (29.5±3.23 pg/ml) were higher than in their peers aged 7 to 14 years (17.2±2.07 pg/ml), exceeding them by 1.52 times (P≤0.05). In general, there is an increase in the level of IL-8 in both seropositive and seronegative forms of JRA with age, which may indicate the progression of the inflammatory process (Fig. 1).

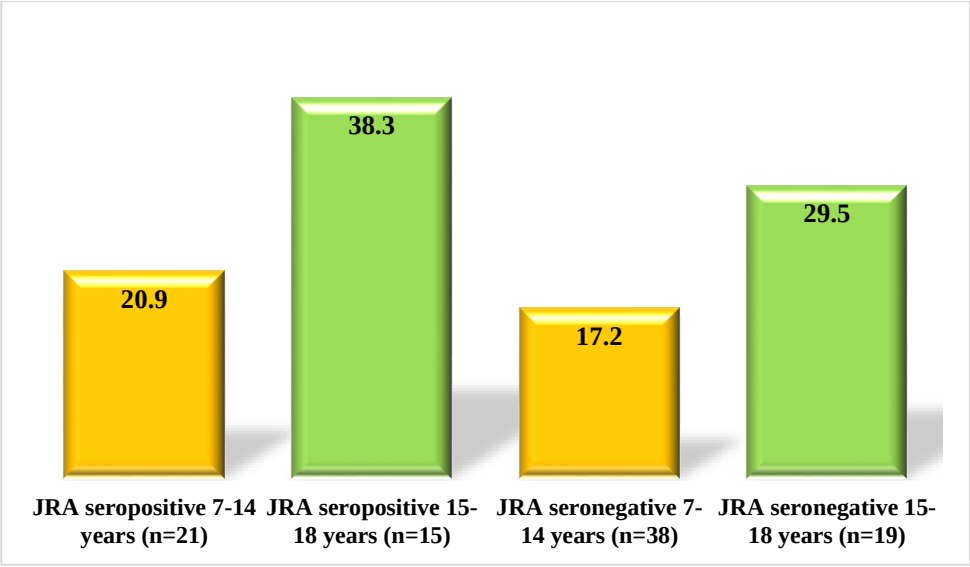


**Fig.1. Comparison of IL-8 levels in children with JRA different age groups, pg/ml P≤0.05**

Particular interest is currently being shown in the study of interleukin-17A (IL-17A), which is a pro-inflammatory cytokine that can induce the synthesis of various inflammatory mediators (TNF-α, IL-1, 6), leading to the development of autoimmune reactions. In JRA, a connection between the development of articular syndrome and hyperproduction of IL-17A has been proven [10, 14]

In a study of the level of IL-17A in children with juvenile rheumatoid arthritis (JRA), it was found that in the group of children from 15 to 18 years old with a seropositive form of JRA (41.25±5.14 pg/ml), the levels of IL-17A were higher, than in children of the same age category with a seropositive form of JRA from 7 to 14 years (30.25±4.61 pg/ml), exceeding them by 1.37 times. The second group of children from 15 to 18 years old with a seronegative form of JRA (38.3±4.83

pg/ml) had IL-17A levels that were significantly different from the levels in children with a seronegative form of JRA from 7 to 14 years old (23.25± 2.57 pg/ml), exceeding them by 1.65 times(P≤0.05). (Fig. 2).

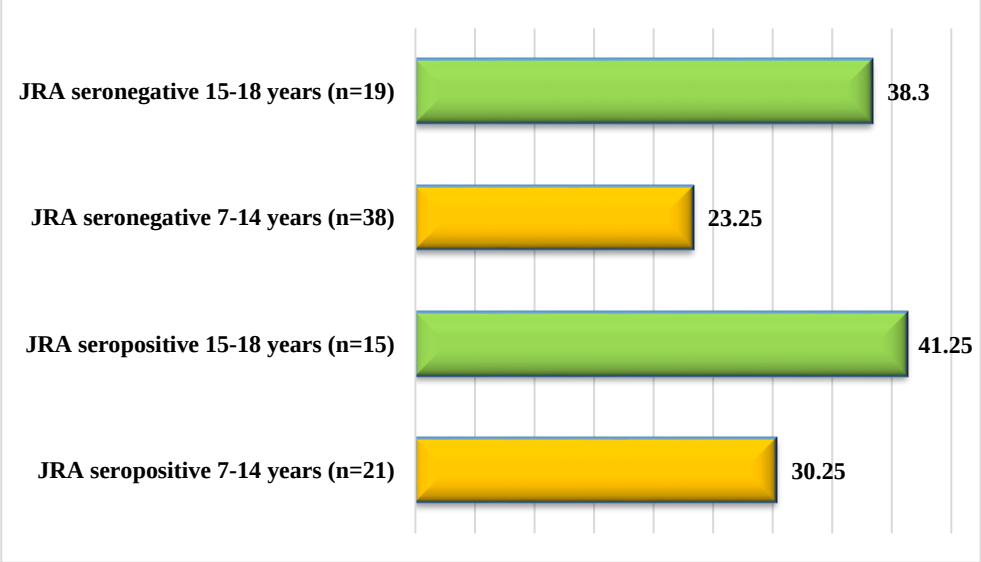


**Fig.2. Comparison of IL-17A levels in children with JRA different age groups, pg/ml P≤0.05**

A decrease in the body's resistance to microbial infection is associated with an immunosuppressive state, which is expressed in a decrease in the level of interferons, especially interferonγ[9, 19].

The body's own interferon system is one of the main means of defense against infections. Many pathogenic microorganisms have interferon-inducing activity [5, 17].

Analysis of the level of interferon-γ in children with juvenile rheumatoid arthritis revealed a deficiency of this cytokine in all groups, however, the most pronounced deficiency was observed in children of the second group aged 15 to 18 years with a seropositive form of JRA (9.3±1.13 pg/ml ). In the first group of children with JRA, regardless of the form, the production of interferon-γ averaged 12.4±1.95 pg/ml, which was statistically significantly lower than the values in the control group by 1.55 times (P<0. 05). These data indicate the importance of taking into account the level of interferon-γ when assessing the immune status of children with various forms of JRA and age-related characteristics. (Fig.3)

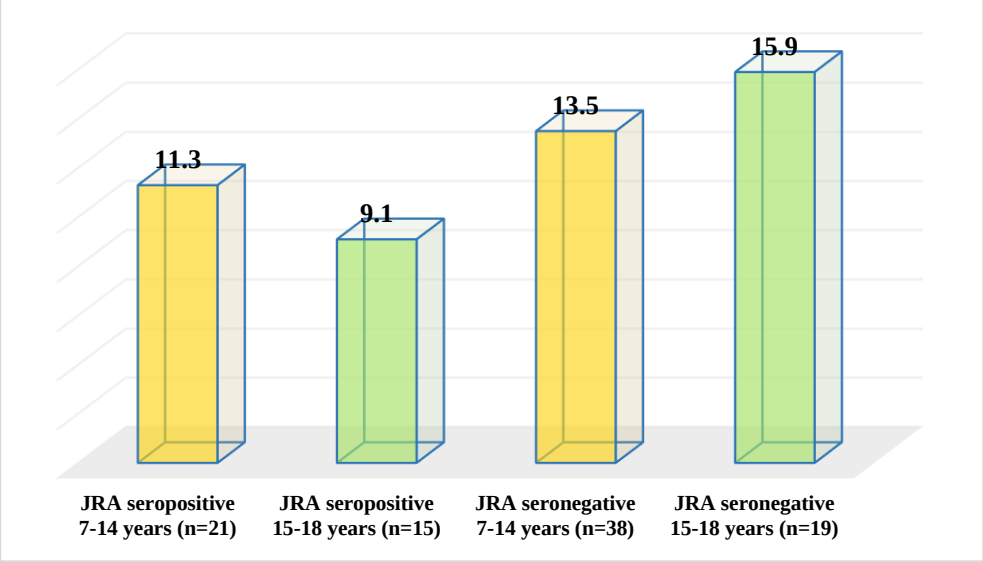


**Fig.3. Comparison of IFNy levels in children with JRA different age groups, pg/ml P≤0.05**

**Table 1. Cytokine concentrations in children with juvenile rheumatoid arthritis in different age groups**

| | Control 7-14 years (n=20) | JRA seropositive 7-14 years (n=21) | JRA seronegative 7-14 years (n=38) | Control 15-18 years (n=20) | JRA seropositive 15-18 years (n=15) | JRA seronegative 15-18 years (n=19) |
|---|---|---|---|---|---|---|
| **IL-8** | 11.3±1.02 | 20.9±3.12 * | 17.2±2.07 | 12.9±3.10 | 38.3±4.06* | 29.5±3.23 |
| **IL-17A** | 10.5±2.31 | 30.25±4.61* | 23.25±2.57 | 12.3±2.44 | 41.25±5.14 * | 38.3±4.83 |
| **IFNγ** | 19.3±0.83 | 11.3±1.93 * | 13.5±2.54 | 18.8±3.52 | 9.1±1.13 * | 15.9±2.87 |

** P≤0.05 significant compared to the control group*

Thus, a comparison of the levels of IL-8 and IL-17A in children with various forms of juvenile rheumatoid arthritis (JRA) shows an increase in the concentration of cytokines with age. The observed differences in the levels of IL-8 and IL-17A between children from 7 to 14 years old and from 15 to 18 years old indicate a progressive inflammatory process in the body of patients with JRA. (Table 1). Analysis of the level of interferon-γ emphasizes its deficiency in all children with JRA, especially pronounced in children of the older age group with a seropositive form of JRA, which emphasizes the importance of taking into account age-related characteristics when assessing the immune status of children with this pathology.

One of the main tasks of scientific research is to study the relationships between the indicators under consideration. Our study analyzed 8 main immunological parameters: 1) IL-8; 2) IL-17A; 3) INFy; 4) CRP; 5) ASLO; 6) RF; 7) Vitamin D; 8) Lactoferrin. The values were determined with medium (r=0.3-0.69) and high degree (r=0.7-1.0).

Correlation analysis of 8 immunological parameters of the main group in children with juvenile rheumatoid arthritis revealed 28 relationships, of which 4 were direct and 4 were feedback. No high degree values (r=0.7-1.0) were identified in this group.

Thus, among these correlation relationships, the direct connection between IL-8 and IL-17A (r = 0.51) was significant and reliable; there were inverse connections between IL-8 and INFy (r = -0.50), IL-17A and INFy (r=-0.62) (P≤0.05).

Also, one significant significant inverse relationship was identified, but with a weak indicator, between antistreptolysin O and vitamin D (r=-0.33) (P≤0.05). (Fig.4)

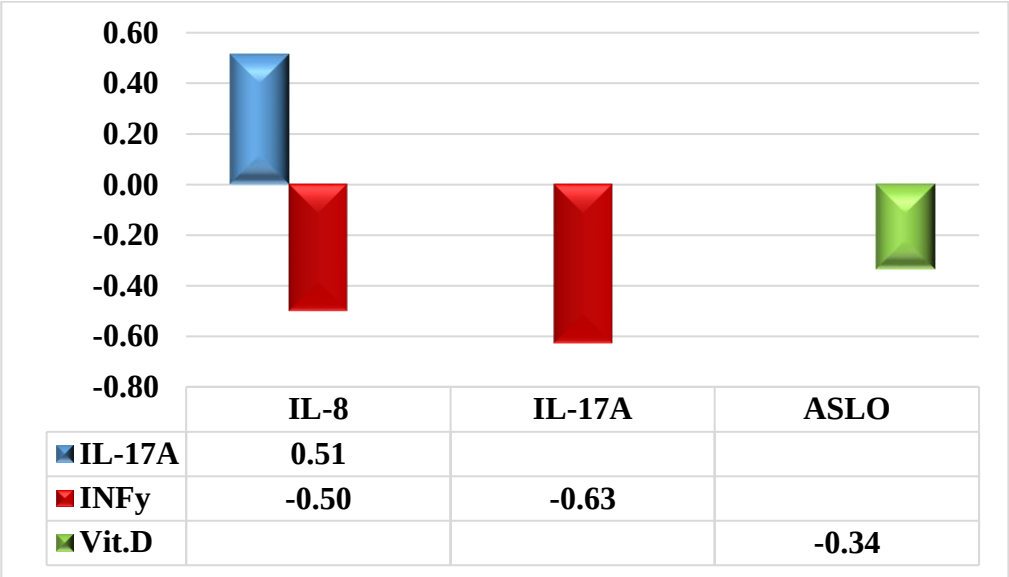


**Fig.4. Significant correlations of immunological parameters in children with JRA (P≤0.05)**

The remaining detected correlations of immunological parameters had a weak, unreliable connection from r=-0.27 to r=0.41. So IL-8 with CRP (r=0.16), ASLO (r=0.15), RF (r=-0.17), Vit.

D (r=0.34), lactoferrin (r=-0.14); IL-17A with CRP (r=0.15), ASLO (r=0.14), RF (r=0.09), Vit. D (r=0.34), lactoferrin (r=-0.02); INFy with CRP (r=-0.27), ASLO (r=-0.22), RF (r=-0.01), Vit. D (r=-0.27), lactoferrin (r=0.04); CRP with ASLO (r=-0.04), RF (r=-0.11), Vit. D (r=-0.10), lactoferrin (r=-0.02); ASLO with RF (r=0.04), lactoferrin (r=-0.23); RF with Vit. D (r=-0.12), lactoferrin (r=0.41); vitamin D (r=0.02) with lactoferrin.

Our previous studies revealed that in children with JRA the levels of cytokines - IL-17A and IFNγ - undergo more dramatic changes. In this regard, we calculated the index, the inverse ratio of these indicators, according to the following formula: DPI = IL-17A/IFNγ (DPI is the disease prognosis index). To achieve this goal, we divided the sample of children with JRA (n=93) aged 7 to 18 years into two groups with seropositive and seronegative forms.

According to the calculation data, it turned out that in practically healthy people (control group), the disease prognosis index was greater than 1 and amounted to 1.71±0.15 (Table 2).

This indicator increased in patients with the seropositive form of JRA and amounted to 3.50, and in the seronegative form = 2.09.

**Table 2 The content of IL-8 and IFNγ in the peripheral blood serum of the examined children**

| Indicators | Patients examined | | |
|---|---|---|---|
| | C.gr. | Seronegative JRA | Seropositive JRA |
| IL-17A | 11.4 | 30.8 | 35.75 |
| IFNγ | 19.5 | 14.7 | 10.2 |
| IPTZ | 1.71 | 2.09 | 3.50 |

Analysis of the results of calculating the disease prognosis index showed that among those examined, an increased index corresponded to a more severe clinical condition. For example, in patients with seropositive JRA with a disease prognosis index equal to 3.50 or higher, a higher percentage of complications, a severe protracted course in combination with symptoms of intoxication, was observed.

RatioIL-17A and IFNγ can serve as reliable prognostic and diagnostic criteria for the course of this disease.

**Conclusion:**The disease prognosis index, identified based on the ratios of IL-17A and IFNγ, makes it possible to predict the course of the disease. In determining the choice and duration of necessary therapy, the determination of the index will make a great contribution to practical healthcare.

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