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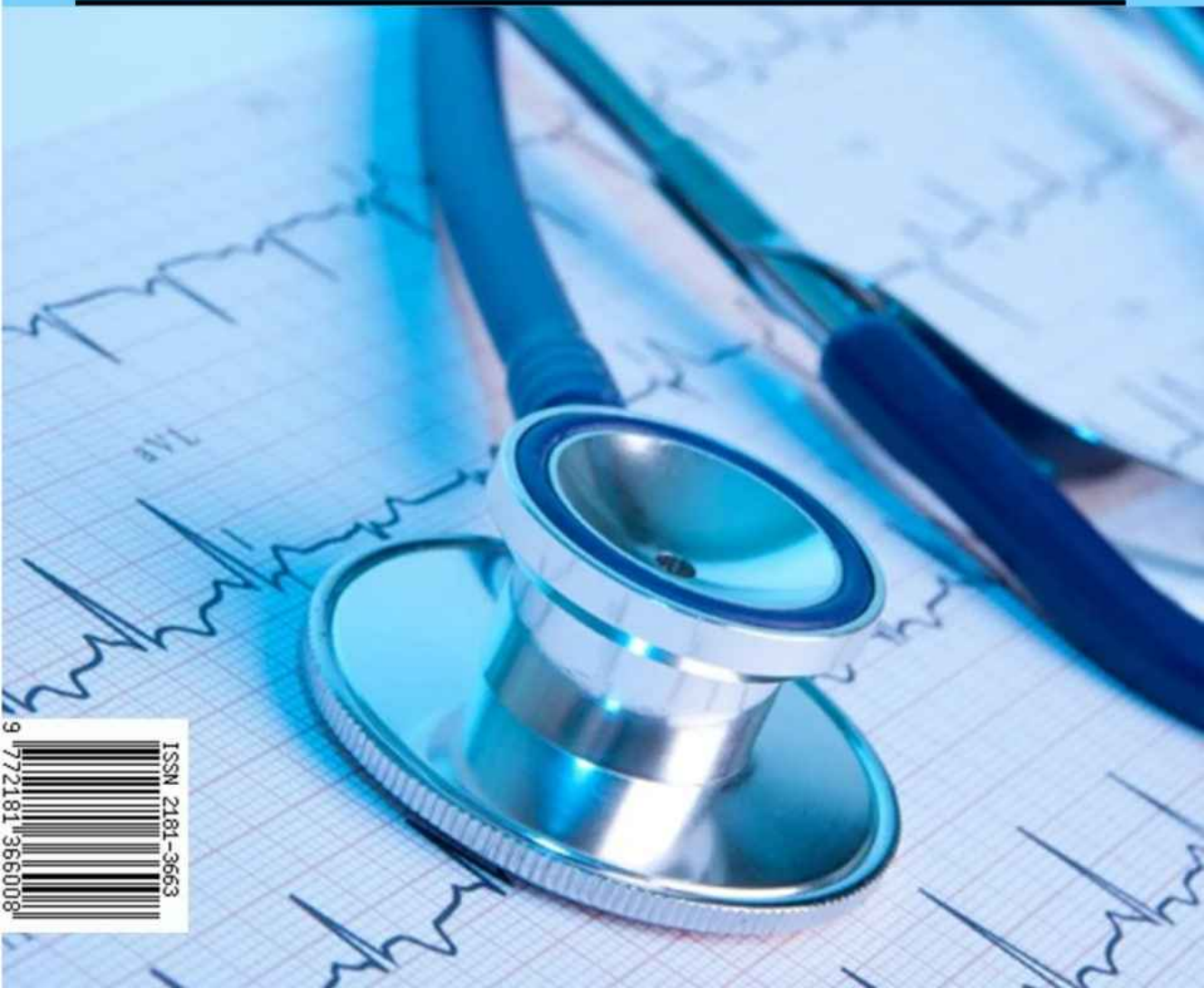

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Immunoinflammatory aspects of cytokine imbalance in juvenile rheumatoid arthritis in children

Arofat SADIKOVA[1], Malika RUZIBAKIEVA[2], Shakhista YULDASHEVA[3]

Tashkent State Medical University. Kimyo International University in Tashkent.

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ABSTRACT

This research paper provides a detailed analysis of the immunological mechanisms underlying the pathogenesis of juvenile rheumatoid arthritis (JRA) and the role of key cytokines—IL-8, IL-17A, and IFN-γ—in shaping the inflammatory response and intercellular immune interactions. It has been established that cytokine imbalance initiates a cascade of immunological failures that contribute to the development of autoimmune reactions and chronic inflammation. The study included a comparative analysis of cytokine production in children with seronegative and seropositive JRA. The findings revealed a significant increase in IL-8 and IL-17A levels in the seropositive form of the disease, reflecting more pronounced inflammatory activity. Meanwhile, interferon-gamma (IFN-γ) levels were significantly reduced in both groups of patients. These results highlight the leading role of cytokine imbalance in the pathogenesis of JRA and the need for immunocorrective approaches in therapy.

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Bolalarda yuvenil revmatoid artritda sitokinlar muvozanatining buzilishiga oid immunoyallig‘lanish jihatlari

Kalit so‘zlar:
YURA,
IL-8,

ANNOTATSIYA

Ushbu ilmiy tadqiqot yuvenil revmatoid artrit (YURA) patogenezining asosidagi immunologik mexanizmlarni va IL-8, IL-17A hamda IFN-γ kabi asosiy sitokinlarning yallig‘lanish

[1] Tashkent State Medical University. Kimyo International University in Tashkent.
[2] Tashkent State Medical University. Kimyo International University in Tashkent.
[3] Tashkent State Medical University. Kimyo International University in Tashkent.

IL-17A,
INFy,
seronegativ,
seropozitiv.

jarayoni va hujayralararo immun o‘zaro ta’sirlarda tutgan o‘rnini batafsil tahlil qiladi. Sitokinlar muvozanatining buzilishi autoimmun reaksiyalar va surunkali yallig‘lanishga olib keladigan immunologik o‘zgarishlar zanjirini keltirib chiqarishi aniqlangan. Tadqiqot doirasida seronegativ va seropozitiv YURA bilan og‘rigan bolalarda sitokinlar ishlab chiqarilishining qiyosiy tahlili o‘tkazildi. Natijalar kasallikning seropozitiv shaklida IL-8 va IL-17A miqdori sezilarli darajada oshganligini ko‘rsatdi, bu esa yallig‘lanish jarayonining kuchliroq ekanligidan dalolat beradi. Shu bilan birga, bemorlarning har ikkala guruhida ham interferon-gamma (IFN-γ) miqdori sezilarli darajada pasaygan. Bu natijalar YURA patogenezida sitokinlar nomutanosibligining hal qiluvchi ahamiyatga ega ekanligini va davolashda immunokorreksion yondashuvlar zarurligini tasdiqlaydi.

Иммуновоспалительные аспекты дисбаланса цитокинов при ювенильном ревматоидном артрите у детей

Ключевые слова:
ЮРА,
IL-8,
IL-17A,
INFy,
серонегативный,
серопозитивный.

АННОТАЦИЯ

В данной научной работе представлен детальный анализ иммунологических механизмов, лежащих в основе патогенеза ювенильного ревматоидного артрита (ЮРА), и роли ключевых цитокинов - IL-8, IL-17A и IFN-γ - в формировании воспалительного ответа и межклеточных иммунных взаимодействий. Установлено, что цитокиновый дисбаланс инициирует каскад иммунологических нарушений, способствующих развитию аутоиммунных реакций и хронического воспаления. Исследование включало сравнительный анализ продукции цитокинов у детей с серонегативной и серопозитивной формами ЮРА. Результаты выявили значительное повышение уровней IL-8 и IL-17A при серопозитивной форме заболевания, что отражает более выраженную воспалительную активность. В то же время уровень интерферона-гамма (IFN-γ) был значительно снижен в обеих группах пациентов. Эти результаты подчеркивают ведущую роль цитокинового дисбаланса в патогенезе ЮРА и необходимость применения иммунокорригирующих подходов в терапии.

RELEVANCE

Juvenile rheumatoid arthritis (JRA) is one of the most common chronic autoimmune diseases of childhood, characterized by progressive joint damage and systemic inflammatory manifestations. According to international epidemiological studies, the incidence of JRA ranges from 0.05 to 0.6 per 1,000 children, highlighting its

significant impact on the quality of life and social adaptation of patients. In school-age children, the disease often becomes persistent, with the development of erosive changes and functional limitations. Timely identification of immunological predictors of inflammatory activity is crucial for individualizing therapy. [1, 5]

The immunopathogenesis of JRA is associated with an imbalance between proinflammatory and anti-inflammatory cytokines, which regulate the proliferation and activation of immune cells. This cytokine imbalance contributes to chronic inflammation, activation of autoimmune reactions, and damage to articular cartilage [2, 4, 7].

The most significant inflammatory mediators in JRA are interleukins IL-1β, IL-6, TNF-α, and IFN-γ, which play a central role in the development of synovial proliferation and tissue destruction. Cytokine status assessment allows for an objective assessment of the activity of the pathological process and the effectiveness of therapy. Establishing characteristic immunological patterns can form the basis for the development of pathogenetically targeted treatments [3, 6, 11].

In recent years, the potential for using cytokine profiling to predict the course and outcome of JRA has attracted the attention of researchers. Determining serum cytokine levels in children not only helps clarify the degree of disease activity but also identifies subclinical forms of inflammation. This paves the way for early initiation of therapy and the prevention of irreversible morphological changes in joints. Thus, studying the cytokine status of school-aged children with JRA is a relevant area of modern rheumatology and immunology, with practical implications for optimizing diagnosis and treatment [4, 8].

The purpose of the research is to determine the characteristics of the cytokine profile in school-aged children with juvenile rheumatoid arthritis depending on the clinical activity of the disease and to evaluate their diagnostic and prognostic significance.

MATERIALS AND METHODS OF RESEARCH

The study included 59 school-age children (aged 7 to 14 years) with juvenile rheumatoid arthritis, who were being treated at the specialized rheumatology department of Tashkent State Medical University. The control group consisted of 40 apparently healthy children of the same age. The diagnosis of JRA was established according to the ILAR criteria (International League of Associations for Rheumatology, 2019). Clinical indicators (number of inflamed joints, duration of morning stiffness, DAS28 activity index) and laboratory parameters (ESR, C-reactive protein) were used to assess disease activity.

Determination of cytokine concentrations IL-8, IL-17A, IFNγThe analysis was performed in blood serum using a solid-phase "sandwich" enzyme-linked immunosorbent assay (ELISA) kit from Vector-Best (Novosibirsk, Russia). Statistical data processing was performed using the Statistica 13.0 software package. Student's t-test and Mann–Whitney U-test were used to assess the significance of differences, with a significance level of $p < 0.05$.

RESEARCH RESULTS

In analyzing the age composition of the examined children with juvenile rheumatoid arthritis (JRA), it was found that younger patients (3–7 years) accounted for 11.1% (n=5), while the majority of the observed children belonged to the school group (7–14 years) — 57.8% (n=26), and adolescents over 14 years old — 33.3% (n=15).

The gender distribution showed a moderate predominance of boys - 53.0% compared to girls - 47.3%.

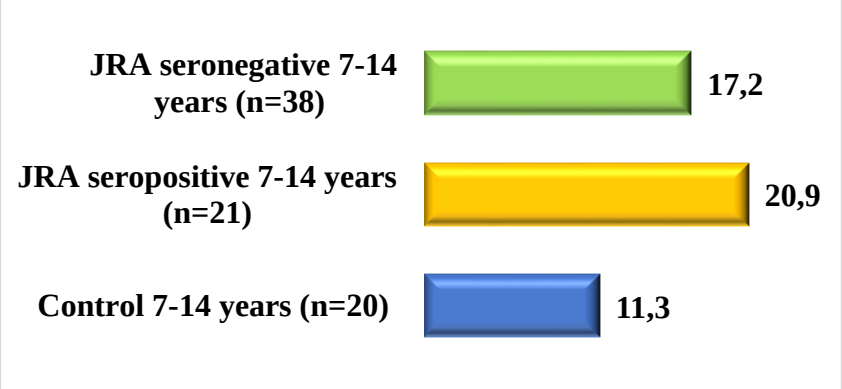
The leading clinical manifestation of the disease was joint pain, which was detected in the lower extremities in 88.6% of cases and in the upper extremities in 64.4%. Local inflammatory signs (swelling, limited joint mobility) were recorded in 77.6% of patients. Symptoms of general intoxication—fever, weakness, loss of appetite, tachycardia, and shortness of breath—were observed in an average of 39.1% of children. Neurological manifestations (seizures, irritability, emotional instability) were observed in 37.7% of patients.

An analysis of concomitant somatic diseases revealed a high frequency of ENT pathologies, occurring in 91.1% of patients with JRA. Cardiovascular disorders were recorded in 64.4%, and anemic syndrome in 53.3% of the examined children. Nervous system diseases were observed in 31.1% of patients, and urinary tract disorders in 20.1%. Furthermore, 13.2% of patients were diagnosed with rickets, 15.6% with intestinal dysbiosis, and 7.74% with ophthalmological and allergic disorders. TORCH infection was detected in 6.67% of children, indicating multiple organ involvement and immune instability in this patient group. These data highlight the systemic nature of the disease and the need for a comprehensive approach to the management of such patients.

Particular attention should be paid to the role of proinflammatory cytokines, in particular interleukin-8 (IL-8), which, according to the literature, is an important mediator of inflammation in the joints and can be considered as a diagnostic marker of the active phase of JRA [9, 10]. IL-8 synthesis is stimulated under the influence of tumor necrosis factor (TNF-α) and interleukin-1 (IL-1), enhancing neutrophil migration and maintaining chronic inflammation. In a study of school-age children with a seropositive form of JRA, the IL-8 level was 20.9±3.12 pg/ml, which was 1.85 times higher than the control group. In patients with a seronegative form, a reliable increase was also observed (17.2±2.07 pg/ml), which was 1.52 times higher than the control, but 1.2 times lower than the values in seropositive patients ($p \leq 0.05$). The obtained results indicate a direct dependence of the IL-8 level on the activity of the inflammatory process and the duration of the disease, which confirms its pathogenetic and prognostic significance (Fig. 1)

Fig. 1.

IL-8 level in children with JRA aged 7-14 years, pg/ml P≤0.05



Interleukin-17A (IL-17A) is a key proinflammatory cytokine that plays a significant role in the pathogenesis of autoimmune diseases, including juvenile idiopathic arthritis

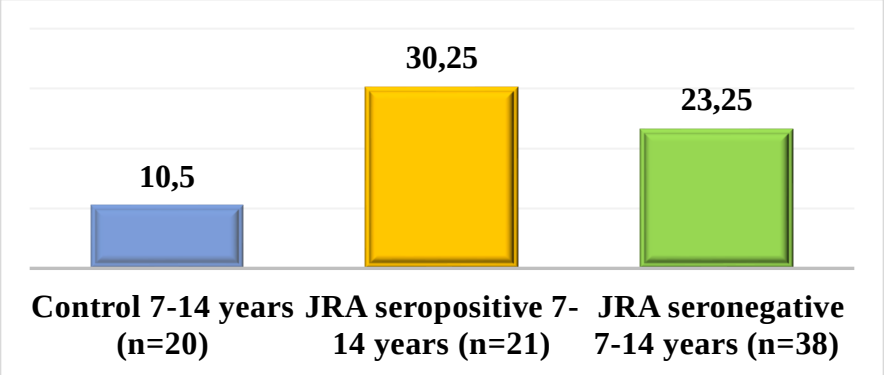
(JIA). It stimulates the synthesis of inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1, and interleukin-6, which contribute to the activation of inflammatory cascades and tissue destruction. Increased IL-17A expression leads to the development of chronic inflammation in the synovium and autoimmune reactions. Recent studies confirm that IL-17A hyperproduction is closely associated with joint disease activity in children with JIA. Therefore, this cytokine is considered a potential biomarker of disease activity and a target for immunotherapeutic intervention.

An analysis of IL-17A concentrations in children with various clinical and immunological forms of juvenile rheumatoid arthritis (JRA) revealed a significant increase in its level in both study groups compared to the control group. In patients with seropositive JRA, the IL-17A concentration was 30.25 ± 4.61 pg/ml, which is 2.88 times higher than the control group values. In the seronegative form of the disease, this indicator was slightly lower - 23.25 ± 2.57 pg/ml, which is 2.21 times higher than the control values. Nevertheless, the difference between the seropositive and seronegative forms was statistically significant ($p \leq 0.05$). The obtained data indicate pronounced activation of the Th17-cell component of immunity in all patients with JRA.

It should be noted that higher levels of IL-17A in children with a seropositive form of the disease indicate its involvement in maintaining chronic inflammation and progression of joint damage. This fact supports the hypothesis of the pathogenetic significance of this cytokine in the mechanisms of autoimmune inflammation in JRA. The combined increase in IL-17A with other inflammatory mediators, including TNF-α and IL-6, enhances the cytotoxic effect on synovial tissue and cartilage. Thus, IL-17A can be considered not only as a marker of inflammatory activity but also as a potential therapeutic target. Prospects for further research are related to assessing the effectiveness of drugs that block IL-17A in children with various forms of JRA (Fig. 2).

Fig.2.

IL-17A level in children with JRA aged 7-14 years, pg/ml P≤0.05



Decreased resistance to infectious agents in children with juvenile rheumatoid arthritis (JRA) is closely linked to the development of an immunosuppressive state. One of the key indicators of this condition is decreased production of interferons, particularly interferon γ (IFN-γ), which plays a key role in macrophage activation and the regulation of antimicrobial immunity. Insufficient IFN-γ production weakens antiviral and antibacterial defenses, contributing to the chronicity of the inflammatory process. In the setting of autoimmune inflammation, a decrease in this cytokine reflects the depletion of

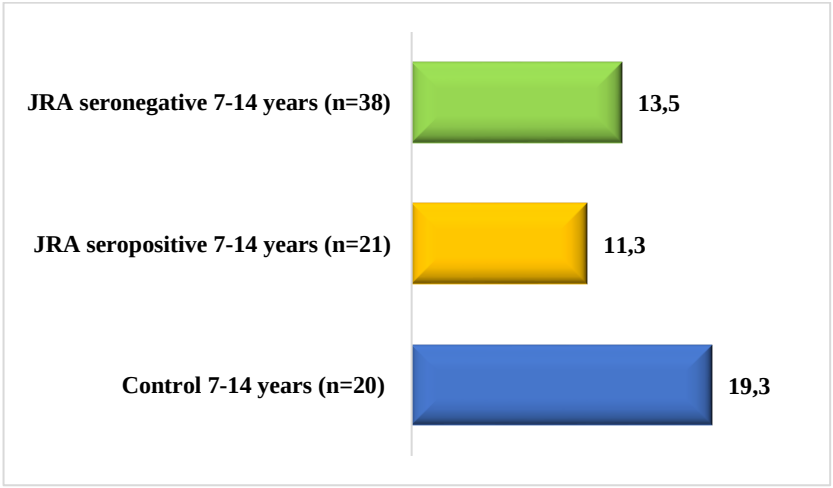
the functional activity of the T-cell component of the immune system. Thus, IFN-γ deficiency can be considered a pathogenetic factor in disease progression.

The analysis revealed a significant decrease in IFN-γ levels in children with various forms of JRA compared to the control group. Both study groups showed a significant trend toward suppressed production of this cytokine, indicating a disruption of anti-infective defense mechanisms. The most significant decrease in IFN-γ concentrations was observed in patients with a seropositive form of the disease, where the average level was 11.3 ± 1.93 pg/ml. This value was 1.7 times lower than the control group (19.3 ± 0.83 pg/ml) ($p \leq 0.05$). This pattern indicates a more severe course of the pathological process in the seropositive form of JRA.

The obtained results suggest that suppressed IFN-γ production in JRA is associated with impaired differentiation of type 1 T-helper cells (Th1) and reduced cytotoxic lymphocyte activity. A deficiency of this cytokine hinders the effective elimination of microbial agents and maintains chronic inflammation in the joint synovium. Furthermore, low IFN-γ levels contribute to a shift in the immune response toward the Th2 type, which enhances autoimmune reactions. Taken together, these changes reflect an imbalance between the proinflammatory and regulatory components of the immune system. Therefore, assessing IFN-γ levels can serve as an informative criterion for the severity and activity of the pathological process in JRA (Fig. 3).

Fig.3.

INFγ level in children with JRA aged 7-14 years, pg/ml P≤0.05



CONCLUSION

Thus, the study revealed significant changes in the cytokine profile in school-aged children (7–14 years) with juvenile rheumatoid arthritis (JRA). A significant increase in the levels of the proinflammatory cytokines IL-8 and IL-17A was observed in both seropositive and seronegative forms of the disease. These parameters reflect the activity of the inflammatory process and the degree of autoimmune aggression. At the same time, a decrease in the production of interferon-gamma (IFN-γ), which plays a key role in anti-infective defense and regulation of the immune response, was detected. The most pronounced decrease in IFN-γ levels was observed in patients with the seropositive form of JRA. The obtained results indicate a significant imbalance in the cytokine system,

which contributes to the progression of inflammation and the chronicity of the pathological process.

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