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CYTOKINE-MEDIATED IMMUNOLOGICAL MECHANISMS AND CLINICAL MANIFESTATIONS OF JUVENILE RHEUMATOID ARTHRITIS

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Resume: *Juvenile rheumatoid arthritis (JRA) represents a chronic autoimmune pathology characterized by persistent synovial inflammation, progressive joint destruction, and systemic immune dysregulation. The disease arises from a multifactorial interplay of genetic predisposition, environmental triggers, and aberrant cytokine signaling that together drive chronic inflammation. In this study, the serum levels of key inflammatory mediators — IL-8, IL-17A, and IFN-γ — were examined in 106 children with JRA aged 3 to 18 years, alongside a control group of 40 healthy individuals. The analysis demonstrated a marked elevation of IL-8 and IL-17A concentrations, particularly among patients with the seropositive form of JRA, most prominently expressed in adolescents aged 15–18 years. Conversely, a significant suppression of IFN-γ production was recorded in both disease variants, with the most profound deficit observed in seropositive patients, indicating impaired Th1-type immune regulation. These immunological alterations emphasize the dominance of proinflammatory cytokine activity and the attenuation of protective immune responses in JRA. Collectively, the findings underscore the diagnostic and therapeutic potential of cytokine profiling as a biomarker-guided approach for assessing disease activity and tailoring personalized treatment strategies.*

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

ЦИТОКИН-ОПОСРЕДОВАННЫЕ ИММУНОЛОГИЧЕСКИЕ МЕХАНИЗМЫ И КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ ЮВЕНИЛЬНОГО РЕВМАТОИДНОГО АРТРИТА

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Резюме: *Ювенильный ревматоидный артрит (ЮРА) – это хроническое аутоиммунное заболевание, характеризующееся персистирующим воспалением синовиальной оболочки, прогрессирующей деструкцией суставов и системной дисрегуляцией иммунной системы. Заболевание развивается в результате многофакторного взаимодействия генетической предрасположенности, факторов окружающей среды и аномальной цитокиновой сигнализации, которые в совокупности способствуют развитию хронического воспаления. В данном исследовании сывороточные уровни ключевых медиаторов воспаления — ИЛ-8, ИЛ-17А и ИФН-γ — были исследованы у 106 детей с ЮРА в возрасте от 3 до 18 лет, а также у 40 здоровых лиц контрольной группы. Анализ выявил выраженное повышение концентраций ИЛ-8 и ИЛ-17А, особенно у пациентов с серопозитивной формой ЮРА, наиболее выраженное у подростков в возрасте 15–18 лет. Напротив, при обоих вариантах заболевания было зарегистрировано значительное подавление продукции ИФН-γ, при этом наиболее выраженный дефицит наблюдался у серопозитивных пациентов, что указывает на нарушение иммунной регуляции по Th1-типу. Эти иммунологические изменения подчеркивают доминирование активности провоспалительных цитокинов и ослабление*

защитных иммунных реакций при ЮРА. В совокупности полученные результаты подчеркивают диагностический и терапевтический потенциал профилирования цитокинов как биомаркер-ориентированного подхода для оценки активности заболевания и разработки персонализированных стратегий лечения.

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

YOSHLAR REVMATOID ARTRITINING SITOKINLAR BILAN BOG'LIQ IMMUNOLOGIK MEXANIZMLARI VA KLINIK KO'RINISHLARI

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Annotatsiya: *Yoshlar revmatoid artriti (YRA) - bu sinovial yallig'lanishning doimiyligi, bo'g'imlarning progressiv destruksiyasi va tizimli immunitetning buzilishi bilan tavsiflangan surunkali autoimmun kasallik. Kasallik genetik moyillik, atrof-muhit omillari va g'ayritabiiy sitokin signalizatsiyasi o'rtasidagi ko'p faktorli o'zaro ta'sir natijasida rivojlanadi, ular birgalikda surunkali yallig'lanishning rivojlanishiga hissa qo'shadi. Ushbu tadqiqotda asosiy yallig'lanish mediatorlari - IL-8, IL-17A va IFN-γ ning sarum darajasi 3 yoshdan 18 yoshgacha bo'lgan YRA bilan kasallangan 106 bolada, shuningdek, 40 ta sog'lom nazorat guruhida o'lchandi. Tahlil shuni ko'rsatdiki, IL-8 va IL-17A konsentratsiyasining sezilarli darajada oshishi, ayniqsa seropozitiv YRA bilan kasallangan bemorlarda, 15 yoshdan 18 yoshgacha bo'lgan o'smirlarda eng ko'p uchraydi. Aksincha, JRA ning ikkala varianti ham IFN-γ ishlab chiqarishda sezilarli darajada bostirilgan, eng aniq yetishmovchilik seropozitiv bemorlarda kuzatilgan, bu Th1 ga asoslangan immunitet disregulyatsiyasini ko'rsatadi. Ushbu immunologik o'zgarishlar proyallig'lanish sitokin faolligining ustunligini va JRA dagi himoya immun javoblarining buzilishini ta'kidlaydi. Birgalikda, bu topilmalar kasallik faolligini baholash va shaxsiylashtirilgan davolash strategiyalarini ishlab chiqish uchun biomarkerga asoslangan yondashuv sifatida sitokin profilini aniqlashning diagnostik va terapevtik salohiyatini ta'kidlaydi.*

Kalit so'zlar: *JRA, IL-8, IL-17A, INFy, seronegativ, seropozitiv.*

Relevance. Juvenile rheumatoid arthritis (JRA) remains a chronic autoimmune disease of childhood, characterized by persistent joint inflammation and progressive structural damage. In recent years, the incidence of JRA among school-aged children has shown an upward trend, associated with both genetic predisposition and adverse immune or environmental influences. Despite the achievements in pharmacotherapy, the immunopathogenic mechanisms underlying JRA are still not fully elucidated. Particular attention is currently directed toward the role of cytokine networks in sustaining inflammation and autoimmune dysregulation [1, 5, 7].

Immune imbalance in JRA, especially the disturbance in the ratio of pro-inflammatory and anti-inflammatory cytokines, contributes to persistent pathological inflammation. Elevated serum levels of IL-8 and IL-17A are linked with disease activity and joint destruction, whereas decreased INFγ reflects suppression of anti-inflammatory immune pathways. A detailed investigation of cytokine profiles not only enhances understanding of disease mechanisms but also identifies potential targets for immunomodulatory therapy. The study of these cytokines is thus crucial for establishing prognostic biomarkers of disease activity and treatment response. [4, 8, 12]

Currently, cytokine profiling is considered an important tool for assessing immune reactivity and monitoring therapeutic outcomes in children with JRA. A comprehensive

evaluation of IL-8, IL-17A, and INFγ provides insight into the specific immunological alterations associated with seropositive and seronegative disease forms. This approach opens new perspectives for personalized therapy aimed at restoring immune balance and preventing chronic inflammation. Therefore, studying the clinical and immunological characteristics of JRA holds significant scientific and practical importance [2, 6, 9].

Purpose of the study: To investigate the clinical course and cytokine profile characteristics (IL-8, IL-17A, INFγ) in school-aged children with juvenile rheumatoid arthritis, depending on the serological form of the disease.

Materials and methods of research: The study included 34 school-aged children (15–18 years old) diagnosed with JRA, who received inpatient treatment at a rheumatology department. The control group consisted of 20 age- and sex-matched healthy children. The diagnosis of JRA was established according to the American College of Rheumatology (ACR, 2019) criteria.

Immunological assessment involved measuring serum concentrations of IL-8, IL-17A, and INFγ using the enzyme-linked immunosorbent assay (ELISA) method with certified commercial kits.

Statistical analysis was performed using SPSS version 26.0, applying the Student's t-test and the Mann–Whitney U-test, with significance set at $P \leq 0.05$. Clinical evaluation of disease activity was carried out using the JADAS-27 and DAS-28 indices.

Research results: When analyzing the distribution of children with juvenile rheumatoid arthritis (JRA) by age, it was found that the largest proportion of cases occurred in school-aged children. Specifically, children aged 3 to 7 years accounted for 11.1% (n=5), those aged 7 to 14 years constituted 57.8% (n=26), while 33.3% (n=15) were aged 14 years and older. A slight predominance of males (53.0%) compared to females (47.3%) was observed. Joint pain in the lower and upper extremities was reported in 88.6% (n=40) and 64.4% (n=29) of patients, respectively. Local manifestations of JRA, such as swelling and restriction of movement, were documented in 77.6% of the examined children.

Clinical symptoms of systemic intoxication — including fever, fatigue, decreased appetite, tachycardia, and shortness of breath — were recorded in an average of 39.1% of patients. Neurological disturbances, such as convulsive syndrome and irritability, were noted in 37.7% of cases. Analysis of concomitant somatic pathologies revealed that ENT diseases were the most frequent, affecting 91.1% of children. Cardiovascular disorders were observed in 64.4%, while anemia was present in 53.3% of patients. Diseases of the nervous system were registered in 31.1%, indicating systemic involvement typical of chronic autoimmune inflammation.

Comorbid pathologies were also represented by disorders of the urinary system (20.1%), rickets (13.2%), and intestinal dysbiosis (15.6%). Less frequent conditions included dysmetabolic nephropathy, ophthalmologic impairments, and allergic reactions, which were collectively found in 7.74% of children. The presence of TORCH infections was confirmed in 6.67% of cases, suggesting possible viral or congenital factors contributing to disease onset. The high frequency of multisystemic comorbidities underscores the complexity of JRA and the importance of comprehensive immunological and metabolic evaluation. Such findings support the necessity for multidisciplinary management and targeted immunomodulatory interventions.

Interleukin-8 (IL-8) plays a crucial role as a dual-function chemokine in the inflammatory cascade of JRA. It can both suppress macrophage production of pro-inflammatory mediators and stimulate acute-phase protein synthesis, thereby promoting corticosteroid release and activation of T- and B-lymphocytes. In the examined cohort, the highest IL-8 levels were detected in children with the seropositive form of JRA, averaging 38.3 ± 4.06 pg/ml, which was nearly threefold higher than the control group and 1.3 times greater than

in the seronegative form (29.5 ± 3.23 pg/ml) (P ≤ 0.05). These findings demonstrate the pronounced proinflammatory potential of IL-8 in maintaining immune activation in JRA. Elevated IL-8 concentrations may serve as an indicator of disease activity and joint destruction, emphasizing its diagnostic and prognostic value in pediatric rheumatology (Fig. 1)

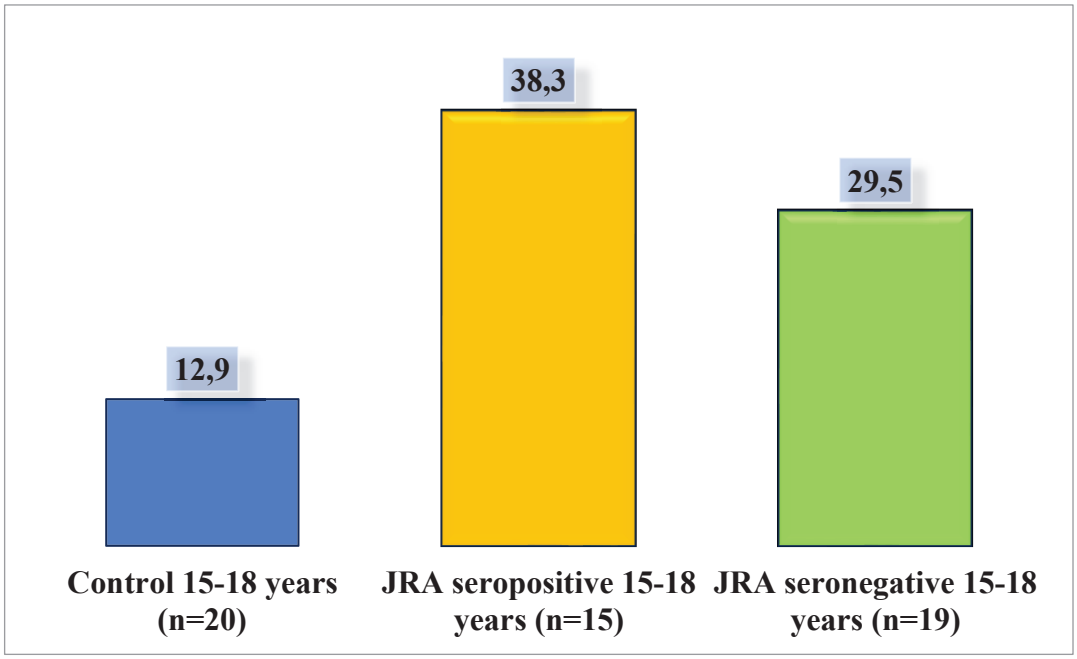


Fig. 1. **IL-8 levels in children with JRA aged 15-18 years, pg/ml P≤0.05**

It is well established that three major subpopulations of T-helper (Th) lymphocytes — Th1, Th2, and Th0 — play critical roles in immune-mediated inflammation. Each subset is characterized by distinct cytokine production profiles that determine the direction of immune responses. In juvenile idiopathic arthritis (JIA), the Th1 subpopulation of $CD4^+$ T-lymphocytes is typically predominant, secreting cytokines such as IFN-γ, TNF-α, IL-2, and IL-12, which drive cellular immune reactions. However, more recent studies have identified another specialized subset of T-helpers, known as Th17 cells, that exert powerful proinflammatory effects. These cells produce interleukin-17A (IL-17A), a cytokine with broad immunomodulatory properties involved in chronic inflammation and tissue damage. The differentiation of Th17 cells occurs independently of the Th1 and Th2 pathways, indicating their unique role in autoimmune pathogenesis.

IL-17A is recognized as a potent proinflammatory cytokine capable of inducing the expression of numerous secondary inflammatory mediators, including IL-6, IL-8, and matrix metalloproteinases, in target tissues. Its biological activity contributes to the amplification of synovial inflammation, recruitment of neutrophils, and progressive destruction of articular cartilage and bone. Several experimental and clinical studies have demonstrated a strong correlation between serum IL-17A levels and disease activity in patients with JIA. The cytokine enhances autoantigen presentation and supports the survival of autoreactive T cells, thereby perpetuating immune dysregulation. Elevated IL-17A concentrations are also associated with increased radiographic evidence of joint erosion and poor therapeutic response. Consequently, IL-17A is now considered a promising biomarker and therapeutic target for modulating the inflammatory cascade in JIA.

When analyzing the serum IL-17A levels in children with JRA, significantly elevated values were observed in the group with the seropositive form of the disease. The mean IL-17A concentration reached 41.25 ± 5.14 pg/ml, exceeding the control group's values by 3.55-fold, which reflects an intensified inflammatory activity. In comparison, the seronegative group demonstrated slightly lower IL-17A levels (38.3 ± 4.83 pg/ml), though the difference was not statistically significant (P ≤ 0.05). Such data indicate that the activation of the Th17-IL-17 axis is a common immunopathogenic feature of both seropositive and seronegative forms of JRA. Persistent overproduction of IL-17A may sustain chronic inflammation and facilitate autoimmune joint destruction even in the absence of serological markers. These findings highlight the pathophysiological importance of IL-17A and justify further exploration of anti-IL-17 therapeutic strategies in pediatric rheumatology (Fig.2)

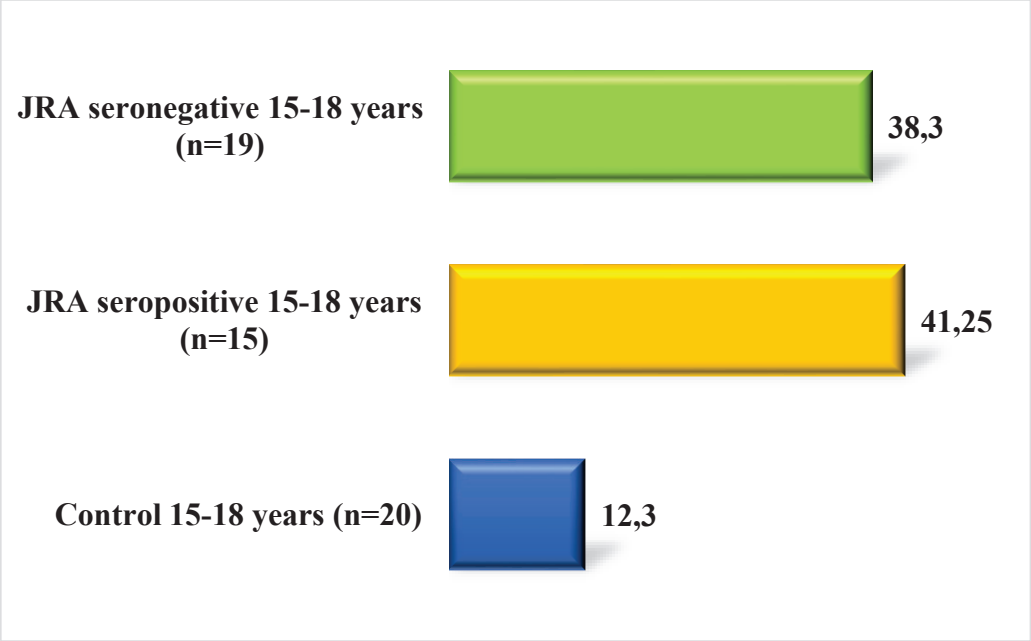


Fig. 2. **IL-17A level in children with JRA aged 15-18 years, pg/ml P≤0.05**

The interferon system represents one of the body's most fundamental mechanisms for antiviral and antimicrobial defense. Interferon-γ (IFN-γ), produced primarily by activated T-lymphocytes and natural killer (NK) cells, plays a pivotal role in modulating immune responses and enhancing macrophage activity. It exerts pronounced immunoregulatory effects by stimulating antigen presentation, upregulating major histocompatibility complex (MHC) expression, and promoting Th1-cell differentiation. Many pathogenic microorganisms possess interferon-inducing activity, which activates innate defense pathways to restrict infection dissemination [5, 8, 11]. In the context of autoimmune diseases, however, impaired IFN-γ production contributes to immune dysregulation and decreased pathogen resistance. Such deficiency is particularly relevant in juvenile rheumatoid arthritis (JRA), where chronic inflammation coexists with a weakened antiviral immune response.

The analysis of serum IFN-γ levels in children diagnosed with JRA revealed a clear pattern of immunosuppression in both studied subgroups. The most profound deficiency of IFN-γ was observed in patients with the seropositive form, where the mean value reached 9.1 ± 1.13 pg/ml. This concentration was nearly twofold lower than in the control group and 1.7 times lower than in the seroneg-

ative JRA subgroup, indicating substantial impairment of cytokine synthesis. The observed reduction suggests a marked suppression of Th1-cell activity and a possible shift toward Th2-dominant immune responses. Such imbalance favors chronic inflammation and persistent autoantibody production, characteristic of the seropositive variant of JRA. These findings emphasize that the severity of IFN-γ depletion correlates with immunopathological progression and systemic manifestations of the disease.

Reduced IFN-γ production weakens the protective capacity of the immune system, increasing susceptibility to opportunistic infections and viral reactivation. Moreover, insufficient interferon signaling may disturb the delicate equilibrium between pro- and anti-inflammatory cytokines, intensifying synovial inflammation and joint destruction. In combination with elevated levels of IL-6, TNF-α, and IL-17A, this deficiency forms a cytokine imbalance typical of JRA. The absence of adequate IFN-γ-mediated regulation limits the suppression of autoreactive lymphocytes and disrupts apoptosis of activated immune cells. Consequently, the persistence of inflammatory foci leads to chronic synovitis and further tissue degradation. Therefore, restoration of interferon activity represents a potential therapeutic approach aimed at normalizing immune homeostasis in children with JRA (Fig. 3)

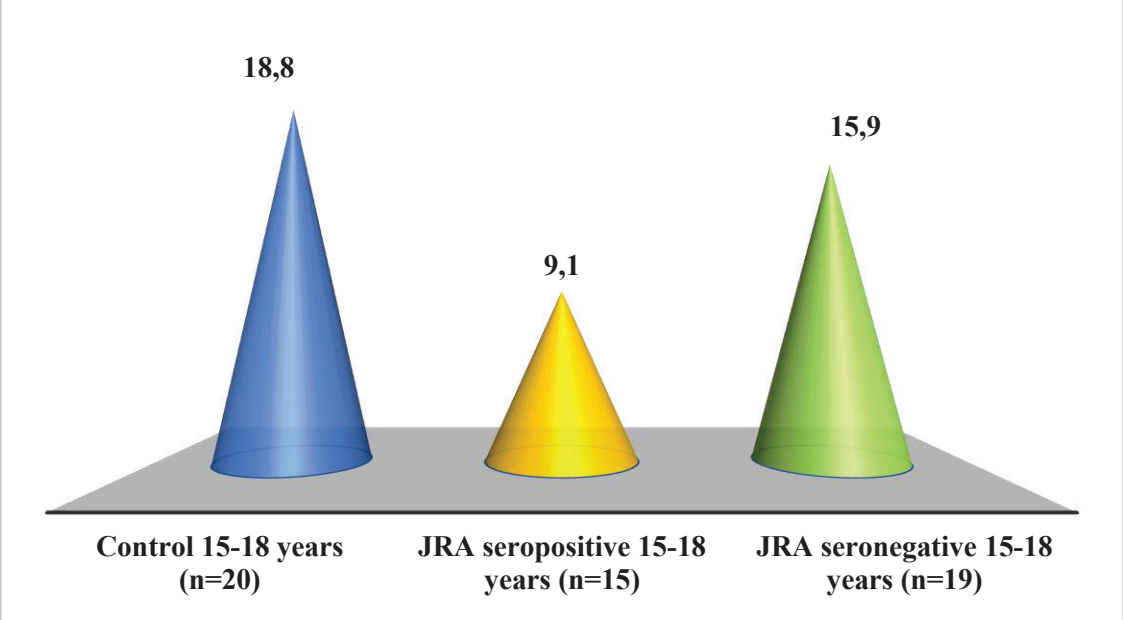


Fig. 3. **INFγ level in children with JRA aged 15-18 years, pg/ml P≤0.05**

Conclusion: The conducted study involving a cohort of children aged 15–18 years diagnosed with juvenile rheumatoid arthritis (JRA) revealed a distinct cytokine imbalance reflecting active autoimmune inflammation. A marked elevation in IL-8 and IL-17A levels was identified, particularly in patients with the seropositive form of the disease, indicating enhanced proinflammatory signaling. These cytokines are likely to contribute to the persistence of synovial inflammation and the progression of joint destruction. In contrast, a significant reduction in interferon-γ (IFN-γ) concentration was observed in both clinical variants of JRA, with the most profound suppression registered among seropositive patients. The decreased IFN-γ activity suggests impaired Th1-mediated immune regulation and weakened antiviral defense mechanisms. Collectively, these findings highlight a cytokine disequilibrium that underlies the pathogenesis of JRA and defines the immunological severity of its seropositive form.

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