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PROINFLAMMATORY CYTOKINES IN JUVENILE ARTHRITIS WITH KIDNEY INVOLVEMENT

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Abstract.

Research Objective: To determine the role of pro-inflammatory cytokines in the early diagnosis of juvenile idiopathic arthritis (JIA) and kidney involvement. **Materials and Methods**: The study included data on patients treated at the cardio rheumatological department of a multidisciplinary clinic of TMA from 2021 to 2023. Among them, there were 105 children with the articular form of juvenile idiopathic arthritis, who comprised the main study group. The control group consisted of 30 practically healthy children of similar age undergoing dispensary observation at Family Polyclinic No. 35 in the Chilanzar district. All subjects underwent comprehensive clinical-immunological and laboratory-instrumental examinations. **Results**: The findings indicate that the duration of JIA in children ranges from 3 months to 8 years, with more frequent involvement of large and medium-sized joints—knee, ankle, wrist, elbow, and hip joints. Persistent disease was observed in 28.9% of the patients, while 71% exhibited progressive disease. Gender-specific analysis of the joint syndrome showed boys had a less pronounced exudative component (39%), with productive-dystrophic changes predominating (61%) in the lower limb joints. In girls, exudation was predominant in the upper limb joints (85%). The average age of patients was 7 years. Radiologically, the severity was mostly assessed as grade II according to Steinbrocker's classification. In children with JIA, an increase in the levels of pro-inflammatory cytokines was noted to be 5-10 times higher, depending on whether the disease had an articular or systemic variant. **Conclusions**: The analysis of clinical variants and the course of juvenile idiopathic arthritis indicates the aggressive and progressive nature of the disease, reflecting the contemporary age evolution of the condition, as well as kidney involvement among internal organs. This underscores the necessity to seek effective methods for optimizing treatment and preventing the toxic effects of medications on the kidneys. The increase in pro-inflammatory cytokines (IL-17A) in serum is more than twofold, and it can be utilized to diagnose JIA early.

Key words: Juvenile idiopathic arthritis, symmetrical chronic arthritis, contracture, TNF-α, nephropathy.

Introduction. Rheumatic diseases in children constitute an important and socially significant part of the overall rheumatological problem. One of the most common and disabling rheumatic diseases is juvenile idiopathic arthritis (JIA) (Alekseeva E.I., 2017).

Juvenile idiopathic arthritis (JIA) is a form of systemic destructive-inflammatory connective tissue disease of unknown etiology, characterized by a complex immune-aggressive pathogenesis that predominantly affects the musculoskeletal system. The disease is marked by symmetrical chronic arthritis and systemic involvement of internal organs, leading to disability in affected children [1]. The pathology is due to impaired immune system function, manifesting as pronounced autoaggression, which triggers abnormal immune responses.

It is well established that autoimmune and autoinflammatory processes play a key role in the pathogenesis of JIA, driven by genetically determined and environmentally induced factors, as well as defects in the activation of acquired and innate immune responses [2,3]. In active inflammation, nearly all components of the immune system are involved in children with various JIA variants, with activation of both cellular and humoral immunity [3,4].

Therefore, optimizing the correction of JIA remains an extremely urgent issue from both scientific

and practical pediatric perspectives. The pathogenesis of JIA is primarily associated with the activation of CD4+ T-lymphocytes via the Th-1 pathway, leading to the synthesis of pro-inflammatory cytokines such as interleukin-1 (IL-1), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), among others (Vorontsov I.M., 2013).

The primary risk factors for reduced life expectancy in JIA include cardiovascular diseases, urinary tract involvement, gastrointestinal disorders, infections, and lymphomas [3,5]. Renal pathology is highly prevalent in JIA, occurring in 57-73% of cases according to different authors [8,9]. In most patients with JIA, kidney damage significantly impacts prognosis and disease outcome, sometimes leading to mortality [4,6,8].

According to various studies, renal pathology is observed in 20-75% of JIA patients. In terms of kidney involvement, JIA ranks third among rheumatic diseases, following systemic lupus erythematosus (SLE) and systemic vasculitis (SV) [6,7,9]. Renal changes are characterized by the early appearance of transient leukocyturia, mild proteinuria, and hematuria, which are most commonly seen at disease onset or during exacerbations. These changes are associated with JIA activity, severity, and patient age [5,6]. Moreover, even minimal urinary changes can correspond to significant structural and functional renal impairments, reducing patient survival and necessitating treatment adjustments for JIA [7,8,10]. This highlights the importance of early nephropathy diagnosis in JIA.

However, the dynamics of immunological markers, including cytokine status, in JIA treatment remain insufficiently studied, which would allow for a more accurate assessment of therapeutic effectiveness.

Thus, given the involvement of immune system components, studying the role of pro-inflammatory cytokines in JIA is relevant to elucidating their role in disease pathogenesis and establishing additional diagnostic criteria for assessing treatment effectiveness.

Objective: To determine the role of pro-inflammatory cytokines in the early diagnosis of juvenile idiopathic arthritis and kidney involvement.

Materials and Methods: A total of 105 children with the articular form of juvenile idiopathic arthritis were examined as the main study group. The control group included 30 practically healthy children of the same age who were under dispensary observation at Family Polyclinic № 35 of the Chilanzar District. All study participants underwent comprehensive clinical, immunological, laboratory, and instrumental examinations. The research was conducted at the Cardiorheumatology Department of the Multidisciplinary Clinic of Tashkent Medical Academy (TMA).

Immunological studies of interleukin content were performed at the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Results and Discussion: The gender distribution of the main group showed that the disease was equally common among boys and girls in early school-aged children (7-10 years) at 15.2%. Among older school-aged children (11-14 years), the disease was more common in girls (22.8%), whereas in adolescents (15-17 years), it was more frequent in boys (20%).

The majority of patients (over 50%) had a disease duration of up to one year, with only two patients having had the disease for more than five years. The diagnosis period ranged from four months to three years. Diagnosis was made by the second version of the ILAR (International League of Associations for Rheumatology) classification and ICD-10.

Our study identified certain characteristics of joint syndrome depending on disease form, JIA progression, gender, and patient age. The articular form of JIA with a subacute onset was associated with arthritis primarily affecting the knee and ankle joints (68% and 28%, respectively). Later, the wrist and elbow joints were also frequently involved. The disease progressed moderately, with a predominance of productive changes. Radiographically, stage II by Steinbrocker classification was the most common. In cases with an acute onset, the wrist, metacarpophalangeal, and interphalangeal joints were most often affected.

Gender-based analysis of joint syndrome showed that boys had a less pronounced exudative component (7-39%), with predominant productive-dystrophic changes (11-61%) in the lower limb joints (hip, knee, ankle, and foot joints). In contrast, girls had predominant exudative changes in the upper limb joints (wrist, elbow, and small hand joints) during early disease stages (17-85%).

In this study, we examined clinical-laboratory features of nephropathy in children with JIA. Nephropathy was detected in 51 (48.5%) of 105 children in the main study group (Table 1). Among JIA subtypes, nephropathy was most prevalent in the polyarticular JIA group, affecting 76.5% (35 out of 47) of patients, while it was found in only 27.5% (16 out of 58) of patients with oligoarticular JIA.

Table-1

Frequency of nephropathy in children with JIA

JIA Form	Main Group (n = 105)	%	Patients with Nephropathy (n = 51)
Oligoarticular	58	55.2	16 (27.5%)
Polyarticular	47	44.8	35 (76.5%)

In all groups, nephropathy was more common in boys, consistent with literature data. The average age of JIA patients with nephropathy was 11.08±0.3 years. At the start of observation, children with kidney involvement were significantly older than those without nephropathy ($p<0.05$). The disease duration was also significantly longer in children with nephropathy compared to those without ($p<0.05$).

Laboratory tests (Figure 2) showed that anemia (grades 2 and 3) was significantly more common in JIA patients with nephropathy compared to those without it. Elevated erythrocyte sedimentation rate (ESR ≥40 mm/h) was found in 70.4% of nephropathy cases compared to 31.9% of cases without nephropathy.

Further analysis of pro-inflammatory cytokines, particularly TNF-α levels, revealed significantly elevated levels in JIA patients, correlating with disease activity and kidney involvement.

The activity of nephropathy in children manifested through changes in urine analysis. Urinary changes in children with the polyarticular form of juvenile idiopathic arthritis (JIA) with nephropathy were characterized by proteinuria in 62 (59.0%) patients, microhematuria in 44 (41.9%) patients, and leukocyturia in 79 (72.5%) patients. In children with the oligoarticular form with nephropathy, urine abnormalities included the presence of salts and leukocyturia. According to several authors, pro-inflammatory cytokines are currently considered a key mediator in the formation of the pathophysiological stage of autoimmune reactions in JIA.

This study examined the synthesis features of pro-inflammatory cytokines and tumor necrosis factor-alpha (TNF-α) in 105 children with JIA, who were divided into two groups based on subtypes: 58 children with oligoarticular JIA (oJIA) and 47 children with polyarticular JIA (pJIA) (Table 1). Additionally, 40 practically healthy children without pathologies were included as a control group. The study included children aged 7 to 17 years, who, according to J.B. Solomon's concept, were further divided into two subgroups (children aged 7 to 11 years and children aged 12 to 17 years).

Tumor necrosis factor-alpha (TNF-α) is a multifunctional cytokine that plays a crucial role in various cellular events. TNF-α is primarily produced by monocytes/macrophages, endothelial cells, mast cells, myeloid cells, LAK cells, neuroglial cells, and, in specific cases, activated T-lymphocytes.

A significant increase in cachexin was observed in children with oJIA compared to the control group. The TNF-α level in the group of children aged 7 to 11 years with oJIA was elevated by 5.5 times, averaging 56.9±1.47 pg/mL ($P<0.001$), whereas in practically healthy children of the same age, this indicator was 10.4±0.36 pg/mL. Furthermore, it was found that the level of the studied immune response mediator in children aged 12 to 17 years with oJIA without kidney involvement exceeded the normative values by 7.3 times, averaging 76.4±1.08 pg/mL ($P<0.001$), while in children of the same age with oJIA and nephropathy, it exceeded the normative values by 8.7 times, averaging 80.17±1.19 pg/mL ($P<0.001$), compared to control group values of 12.7±0.80 pg/mL.

The elevated TNF-α levels in children with oJIA are associated with the characteristic pathology of this JIA subtype. Likely, increased cachexin synthesis is directly related to immune imbalance and dysregulation, where functional disturbances in the immune system include cell activation imbalances and cytokine release, potentially leading to increased TNF-α production. Additionally, in the selected cohort of children with oJIA, an autoimmune reaction occurs, wherein the immune system attacks its

joints, further stimulating the release of TNF-α and other inflammatory mediators. TNF-α is primarily produced by activated macrophages.

The inflammation characteristic of oJIA can lead to macrophage activation, stimulating TNF-α release.

The results of elevated TNF-α expression suggest that TNF-α secretion contributes to the inflammatory response associated with active disease in all children with oJIA. However, the highest values in the group of children aged 12 to 17 years with oJIA and nephropathy indicate that increased synthesis is not only associated with joint inflammation leading to osteodestructive processes but also changes in the synovial membrane, where immune cell infiltration may enhance TNF-α release. It is essential to consider that most children in this group were girls. TNF-α, secreted by the endometrium in response to estrogen and progesterone, modulates follicular development in girls at high concentrations, which may manifest at a systemic level rather than just a local one.

TNF-α is a pro-inflammatory cytokine whose synthesis is stimulated by angiotensin II. TNF-α is involved in myofibroblast differentiation and activation of the transcription factor NF-κB, which plays a key role in regulating genes involved in inflammatory and immune responses. Persistent TNF-α elevation is known to be associated with multi-organ failure and mortality, causing hypotension, tachypnea, diarrhea, hematuria, thrombopoiesis, metabolic acidosis, and multiple tissue injuries commonly observed in acute inflammation.

Analysis of the results presented in Figure 2 confirmed a significant increase in TNF-α in children with pJIA compared to the control group. The cachexin level in children aged 7 to 11 years with pJIA was elevated by 6.3 times, averaging 79.68±1.33 pg/mL ($P<0.001$), whereas in practically healthy children of the same age, this indicator was 10.4±0.36 pg/mL. Additionally, it was found that the immune response mediator level in children aged 12 to 17 years with pJIA exceeded normative values by 9.4 times, averaging 119.82±3.42 pg/mL ($P<0.001$), compared to the control group value of 12.7±0.80 pg/mL.

The obtained results suggest that elevated serum TNF-α levels in children with renal insufficiency may be due to various factors. In the context of renal issues, TNF-α may play a role in inflammatory and regulatory mechanisms related to kidney function. Possible reasons for increased TNF-α levels in children with renal insufficiency include kidney inflammation and stress, autoimmune processes, renal function dysregulation, drug therapy, and medical procedures.

All the aforementioned factors are exacerbated in pJIA. As TNF-α is a key cytokine in inflammatory and immune processes, systemic inflammation in pJIA may lead to increased TNF-α production. Autoimmune mechanisms in pJIA can exacerbate inflammation and, consequently, increase TNF-α levels, reflecting inflammatory processes affecting both joints and kidneys.

Conclusions: An increased synthesis of pro-inflammatory cytokines TNF-α with an imbalance in their regulation was observed in different age groups of children with oligoarticular and polyarticular JIA. High levels of these immune response mediators were identified in children with the polyarticular form of JIA and kidney involvement, significantly elevated during the fifth critical period of immune system development (corresponding to ages 12-17). These cytokine levels may serve as biomarkers of JIA activity and severity, both with and without nephropathy, which is crucial for early diagnosis of severe disease progression and kidney involvement ($p < 0.05$).

Thus, the analysis of clinical variants and JIA progression highlights the aggressive and progressive nature of the disease, reflecting its modern age-related evolution and internal organ involvement, particularly affecting the kidneys. This underscores the need for effective treatment optimization methods and prevention of medication-induced nephrotoxicity. An increase in TNF-α levels in blood serum by more than twofold may serve as an early diagnostic marker for JIA and its severe progression.

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