Introduction

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

JIA is a form of systemic destructive-inflammatory disease of connective tissues with an unknown etiology, a complex immunoaggressive pathogenesis, predominantly affecting the musculoskeletal system. The disease is characterized by symmetrical chronic arthritis, systemic damage to internal organs, leading to disability in sick children [1]. The pathology is caused by a dysfunction of the immune system, manifested by severe autoaggression, which leads to the development of abnormal immune reactions.

As is known, in the pathogenesis of JIA, a key role is played by the processes of autoimmunity and autoinflammation associated with genetically determined and induced environmental factors, defects in the activation of the acquired and innate immune response [12, 18, 19, 21]. The basis of the pathogenesis is defects in T and B cell immune reactions, leading to overproduction of pro-inflammatory cytokines and a wide range of organ-specific autoantibodies that induce inflammation and destruction of joints and other body tissues [19].

Active inflammation in children with different variants of JIA is characterized by the involvement of almost all parts of the immune system, activation of the cellular and humoral immunity [3, 4, 13].

The pathogenesis of the disease is as follows: normally the joint is lined with a synovial membrane, which consists of two layers of cells covering the connective tissue and blood vessels — type A cells of bone marrow origin, belonging to the macrophage lineage, and type B cells — tissue cells of mesenchymal origin.

The pathological process in JIA, as a rule, begins in the joint, more precisely in the synovium [3, 4, 8, 12, 15]. In this case, massive infiltration of blood cells of bone marrow origin develops — monocytes and lymphocytes, which mainly infiltrate the synovial membrane itself, and polynuclear leukocytes migrating into the synovial fluid. These immune cells produce cytokines that bind to receptors on the surface of immune and other cell types and regulate the cascade of reactions that result in chronic inflammation [1, 17, 21].

The inflamed synovial membrane is called pannus and is richly vascularized. Pannus initiates local destructive processes leading to damage to cartilage tissue. Cytokines can potentiate or, conversely, suppress inflammation. In affected joints in JIA, pro-inflammatory cytokines predominate over anti-inflammatory ones [13, 16].

Cytokines, being low molecular protein molecules, provide the process of intercellular communications during inflammation, immune response, and intersystem interactions, and participate in the regulation of normal biological processes in the body.

Conventionally, cytokines are divided into several groups, among which pro-inflammatory (interleukins IL-1, IL-6, IL-8, IL-17, tumor necrosis factor α (TNF-α)), inter-
Overproduction of pro-inflammatory cytokines underlies damage to the synovial membrane of the joint, cartilage, as well as the development of systemic manifestations of the disease. Among the large number of pro-inflammatory cytokines, TNF-α, IL-6, IL-1β occupy a central place in the development of rheumatoid synovitis [7, 19]. Despite a lot of work and research, the causes and distinctive features of the immune response in JIA of various subtypes remain unsolved and this process remains to be fully elucidated.

In the pathogenesis of the disease, the leading place belongs to the activation of CD4+ T lymphocytes of the Th1 type with the subsequent synthesis of pro-inflammatory cytokines — IL-1, IFN-γ, TNF-α and others (Vorontsov I.M., 2013). A key pro-inflammatory cytokine leading to the development of both chronic inflammation and cartilage destruction and bone loss is tumor necrosis factor. TNF-α, one of the three forms of TNF, is produced primarily by macrophages and T lymphocytes. This is an “early” cytokine that appears at the onset of the inflammatory reaction [18, 21]. It can both directly induce an inflammatory response and induce (regulate) the expression of other pro-inflammatory cytokines, including IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor [3, 13, 16]. In addition, TNF-α can induce the expression of adhesion molecules — intercellular adhesion molecules and E-selectin, which lead to further infiltration of the synovial membrane by immune cells. It can enhance the production of metalloproteinases (especially stromelysin and collagenases), which exacerbate the destruction of cartilage and other tissues. The action of TNF-α and other cytokines likely underlies many manifestations of rheumatoid synovitis: issue inflammation, cartilage and bone damage, and systemic manifestations of JIA [3, 16]. From a morphological point of view, a marker of JIA, as well as rheumatoid arthritis in adults, is cartilage erosion [4]. The quantity and quality of erosion correspond to the severity of the process. Impaired blood supply, the growth of pannus, and the erosive process of cartilage lead to a narrowing of the joint space, bringing together damaged articular surfaces, and ultimately to ankylosis [3, 21]. At the same time, deformities and subluxations in the joints develop, the range of movements decreases, and the gait of sick children is impaired [4, 21].

Thus, an important role in the pathogenesis of JIA is played by the interaction of T cell receptors with HLA peptides and the imbalance between pro-inflammatory and anti-inflammatory cytokines [3, 8, 13, 16, 21]. The key cytokine in the immunopathogenesis of sJA is IL-6 [7]. Its overproduction is associated with extra-articular manifestations of the disease such as fever, hypochromic anemia, and thrombocytosis. IL-6 stimulates the production of acute-phase proteins (C-reactive protein, fibrinogen, amyloid A) by hepatocytes and the secretion of hepcidin, which reduces iron absorption and inhibits its release from macrophages, leading to iron deficiency and the development of anemia [21]. Manifestations of systemic action of IL-6 such as fever and morning stiffness are associated with the daily rhythm of secretion of this cytokine. IL-6 stimulates the differentiation of osteoclasts, activates them, and enhances bone resorption and, as a result, contributes to the development of generalized osteoporosis and erosive changes in the joints [5, 7].

The state of the cytokine network in various types of JIA has not been fully studied. Some authors indicate a maximum increase in IL-6 and IL-1 in sJA compared to other types of JIA. A significant increase in serum TNF-α was found in patients with polyarticular JIA [21]. TNF-α plays a significant role in the chronicity of the process [5]. The TNF-α content is significantly higher in patients with high RF values [19]. A high level of TNF-α was also detected in sJA. TNF-α occupies an important place in the pathogenesis of joint damage in all forms of JIA, but is not directly related to the systemic manifestations of the disease. Some authors [21] indicate that the concentration of TNF-α in the blood depends more on the activity than on the form of the disease.

There is also a point of view according to which a significant increase in TNF-α levels is associated with such a severe complication of sJA as macrophage activation syndrome, which is confirmed by the successful use of monoclonal antibodies to TNF-α in the treatment of this condition. However, the development of macrophage activation syndrome has been described as a complication of anti-TNF therapy [17].

Antigen-specific T cells likely play a central role in the pathogenesis of JIA. T cell infiltrates consist predominantly of CD4+ T lymphocytes and memory T cells. CD4+ lymphocytes stimulate B cells, monocytes, macrophages and fibroblasts to produce immunoglobulins and pro-inflammatory cytokines (IL-1, TNF-α, IL-6, IL-15, IL-16, IL-17, IL-18, IL-21, IFN-γ) [6]. In 2003, a new type of T helper cell was discovered, Th17, which produces interleukin-17A. Differentiation of Th17A occurs independently of Th1, Th2. Interleukin-17A exhibits pronounced pro-inflammatory activity in vitro and in vivo and is capable of inducing the synthesis of various inflammatory mediators, including TNF-α, IL-1, IL-6, thereby promoting the development of autoimmune pathological reactions (Bettelli E., Carrier Y., 2017), including inflammation in rheumatoid arthritis (Fossiez F. et al., 2016).

IL-17 is a pro-inflammatory cytokine that plays a key role in the immune response and inflammation. There is an association between IL-17 and juvenile arthritis, especially JIA syndrome, which includes various subtypes of the disease.

Here are some points that explain the connection between IL-17 and juvenile arthritis:

— role of IL-17 in the inflammation. IL-17 is produced by activated T lymphocytes, especially Th17 cells. This cytokine stimulates inflammatory processes in tissues and plays an important role in the pathogenesis of inflammatory and autoimmune diseases such as arthritis;

— presence of Th17 in joints. Studies show that Th17 cells and high levels of IL-17 are found in the joint tissues of patients with juvenile arthritis. This confirms the active participation of Th17 and IL-17 in the inflammatory process that affects the joints;

— association with JIA subtypes. Different subtypes of juvenile idiopathic arthritis may have different levels of
IL-17 activation. For example, enthesitis-related arthritis is often associated with elevated levels of IL-17;
— IL-17-targeted therapies. Due to the important role of IL-17 in the pathogenesis of arthritis, drugs have been developed aimed at inhibiting this cytokine. Drugs such as IL-17 inhibitors are used to treat some forms of arthritis, including juvenile arthritis.

Th17 are important participants in fibrogenesis, which is typical for the development of pulmonary, myocardial, and liver fibrosis. Thus, IL-17 indirectly induces fibrosis by enhancing the inflammatory response and activating fibroblasts. The inflammatory cytokines IL-1β and IL-23 play an important role in the initiation of the profibrogenic Th17 response [21].

Thus, the connection between IL-17 and juvenile arthritis is that elevated levels of IL-17 promote inflammation in the joints, which can ultimately lead to symptoms and joint damage in children and adolescents suffering from this disease. Treatments aimed at blocking IL-17 represent an approach to manage inflammation and reduce symptoms of juvenile arthritis.

In most patients with JIA, TNF-α and IL-1 are detected in the synovial fluid or tissue. These pro-inflammatory cytokines are produced by activated monocytes, macrophages, and synovial fibroblasts. It is believed that TNF-α and IL-1 are of great importance in the destruction of cartilage.

IL-17 is produced by Th17 cells and induces a massive tissue response due to the wide distribution of receptors for this cytokine. IL-17 is present in significant quantities in the inflamed synovium and in small quantities in the peripheral blood of patients with JIA.

K. Nistala et al. (2008) found high levels of Th17 and IL-17A in the joints of children with JIA [7]. IL-17 is believed to play a key role in autoimmune inflammation [8]. IL-17 stimulates synoviocytes and macrophages that produce pro-inflammatory molecules such as TNF-α and IL-1, and synergizes with these cytokines to increase IL-6 and IL-8. In addition, IL-17 directly contributes to co-destruction by regulating matrix metalloproteinases and stimulates osteoclastogenesis through activation of the receptor inducing nuclear factor-κB (RANKL).

In children with RD, a significant role is played by the absolute amount of production of certain cytokines, but by the imbalance of pro- and anti-inflammatory cytokines, which can arise under the influence of a damaging factor such as a viral infection. In most children, after eliminating the effect of the damaging factor, the normal ratio of cytokines is restored, but in children with a genetic predisposition, the imbalance remains, which leads to the development of RD [16]. The level of pro-inflammatory cytokines correlates with the activity of inflammation and reflects the severity of the disease, and also determines further prognosis [5].

Thus, the development of chronic inflammation in RD is mediated by various disorders in the immune system; the activity of inflammation correlates with changes in the synthesis of a wide range of immune mediators. According to modern concepts, the pathogenesis of immunoinflammatory RDs is based on a combination of genetically determined (HLA system, polymorphism of cytokine genes) and acquired defects (imbalance) immunoregulatory mechanisms that limit the pathological activation of the immune system in response to potentially pathogenic environmental factors such as infections, microbiota disturbances, hypothermia, isolation [18].

The leading risk factors for decreased life expectancy in JIA are diseases of the cardiovascular system, damage to the urinary, gastrointestinal tract, infections and lymphoma [3]. Kidney pathology occurs in JIA with a high frequency — from 57 to 73 % according to various authors [8, 9]. In many patients with JIA, kidney damage determines the prognosis and outcome of the disease, including death [4, 6].

A distinction is made between kidney damage, which is directly related to the disease itself, and iatrogenic damage, which is associated with the effects of drug therapy. Pharmacotherapy of JIA remains one of the most difficult problems of modern clinical medicine (Kuzmina N.I., 2020). A wide range of antirheumatic drugs are used for treatment (glucocorticoids, gold preparations, sulfasalazine, leflunomide, methotrexate, cyclosporine), and the effectiveness of combination therapy has been shown (Lyskin A.G., 2014). And often, treatment for juvenile idiopathic arthritis accelerates or provokes kidney damage. Glucocorticoids and cytostatics reduce the function of kidneys, which leads to their diseases [5].

Most drugs used to treat JIA can cause kidney damage. This is due to their direct nephrotoxic effect or the body’s immune response mechanisms [7]. To assess the severity of renal damage in autoimmune diseases, it is recommended to use the chronicity index as an additional indicator. If the indicator is high, the kidney changes are irreversible, immunosuppressive therapy is ineffective, and this, in turn, is considered a poor prognostic sign. Changes in the kidneys are usually diffuse in nature, resulting in chronic renal failure and renal amyloidosis [2]. All this dictates the need to optimize early diagnosis, prognosis, correction, and prevention of urinary complications in juvenile idiopathic arthritis.

According to various authors, renal pathology occurs in 20—75 % of patients with this disease. In terms of the frequency of kidney damage, JIA ranks third among rheumatic diseases, second only to SLE and WS [6].

A promising direction is the use of drugs obtained by genetic engineering and having a selective effect on the components of the pathological autoimmune reaction (Nasonov E.L., 2015; Alekseeva E.I., 2018). However, the dynamics of changes in the immunological parameters, including cytokine status, during JIA therapy have not been sufficiently studied, which will allow a more accurate assessment of treatment effectiveness.

In this regard, the problem of increasing the efficiency of correction for JIA remains extremely relevant from the point of view of both scientific and practical pediatrics.

Thus, given the interest of the components of the immune system, it is relevant to study the role of interleukin-17A in JIA to clarify its role in the pathogenesis of the disease for determining additional diagnostic criteria and evaluating the effectiveness of treatment.

The purpose of the study is to determine the role of interleukin-17A in the early diagnosis of juvenile idiopathic arthritis.
Materials and methods

Thirty-eight children with juvenile idiopathic arthritis, who made up the main group, were examined. The control group consisted of 30 practically healthy children of the same age who underwent clinical observation at the Family clinic 35 of the Chilanzar district (Tashkent).

All subjects underwent in-depth clinical-immunological and laboratory-instrumental examination. The studies were conducted at the cardiorheumatology department of the Tashkent Medical Academy multidisciplinary clinic. Immunological studies of interleukin-17A content were carried out at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Of the 38 patients, there were 20 (52.6 %) girls and 18 (47.4 %) boys aged 3 to 17 years (average of 10 years). The duration of the disease ranged from 3 months to 8 years. More than 50 % were children with a disease duration of up to 1 year; the disease lasted for more than 5 years in 2 cases. The time frame for diagnosis ranged from 4 months to 3 years. The diagnosis was established using the classification of juvenile idiopathic arthritis according to the second version of ILAR and ICD-10.

Despite the sufficient clarity of the criteria for early diagnosis of JIA, it took more than a year to diagnose the disease in more than a third of cases, and only in 13 (34.2 %) patients the diagnosis was made in a timely manner. Considering the aggressiveness of JIA course, the timing of diagnosis is of great importance, because timely initiation of treatment leads to a further favorable prognosis of the disease.

Results and discussion

We analyzed the occurrence of diagnostic clinical criteria for JIA (Table 1). Most of the examined patients (29 (76.3 %)) were characterized by arthritis lasting 3 months or more, morning stiffness, arthritis of the second joint that appeared after 3 months and later, symmetrical damage to small joints, effusion into the joint cavity. Pain, swelling, deformation and limitation of movement, increased local skin temperature were noted in the affected joint. Large and medium-sized joints (knee, ankle, wrist, elbow, and hip) were most often affected — in 26 (68.4 %) cases. In 7 (18.4 %) patients, there was damage to the cervical spine, 5 (13.2 %) had bilateral sacroiliitis, in 1 (2.6 %) case, the disease was accompanied by Raynaud’s syndrome and 1 (2.6 %) patient had an accompanying genetic disease, mucopolysaccharidosis (Hunter syndrome).

In 11 (28.9 %) patients, there was a persistent oligoarthritis, characterized by the fact that up to 4 joints were affected during the entire period of the disease. Progressive oligoarthritis occurred in 27 (71 %) cases and was characterized by an increase in the number of affected joints after 6 months of illness.

Some features of the articular syndrome have been found depending on the form of the disease, the nature of JIA course, the gender and age of the patients. Thus, the articular form of the disease with a subacute onset was accompanied by the development of arthritis with predominant damage to the knee and ankle joints (68 and 28 %, respectively). Subsequently, the wrist and elbow joints were most often added. At the same time, the process progressed moderately, and productive changes prevailed. X-ray examination revealed predominantly Steinbrocker grade II. With the acute onset of this variant of the disease, the wrist, metacarpophalangeal and interphalangeal joints of the hand were most often involved in the process.

A study of the characteristics of joint syndrome depending on gender showed that in boys, the exudative component is less pronounced (7 (18.4 %)), dystrophic changes predominate (11 (28.9 %)) in the joints of the lower extremities (hip, knee, ankle, foot), idiopathic factor in blood se-

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis lasting 3 months and more</td>
<td>29</td>
<td>76.3</td>
</tr>
<tr>
<td>Damage to the large and medium-sized joints</td>
<td>26</td>
<td>68.4</td>
</tr>
<tr>
<td>Damage to the cervical spine</td>
<td>7</td>
<td>18.4</td>
</tr>
<tr>
<td>Bilateral sacroiliitis</td>
<td>5</td>
<td>13.2</td>
</tr>
<tr>
<td>Raynaud’s syndrome</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Mucopolysaccharidosis</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Persistent oligoarthritis</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Progressive oligoarthritis</td>
<td>27</td>
<td>71</td>
</tr>
<tr>
<td>Exudative component</td>
<td>7</td>
<td>18.4</td>
</tr>
<tr>
<td>Dystrophic changes</td>
<td>11</td>
<td>28.9</td>
</tr>
<tr>
<td>Articular-visceral form</td>
<td>10</td>
<td>26.3</td>
</tr>
<tr>
<td>Kidney damage</td>
<td>28</td>
<td>73.7</td>
</tr>
<tr>
<td>Heart damage</td>
<td>2</td>
<td>5.2</td>
</tr>
<tr>
<td>Lung damage</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Combined lesions of internal organs</td>
<td>4</td>
<td>10.5</td>
</tr>
</tbody>
</table>
rum is detected extremely rarely. In girls, at the initial stages of the disease, exudation predominated in the joints of the upper extremities — wrist, elbow, small joints of the hand (17 (44.7 %)).

The articular-visceral form was observed in 10 (26.3 %) patients we examined and was clinically characterized by a high temperature reaction, which was intermittent and did not decrease with antibiotic treatment.

In 28 (73.7 %) cases, the disease occurred with kidney damage, in 5.2 % with heart damage, in 2.6 % with lung damage, and in 10.5 % of cases, there were combined lesions of internal organs. In systemic forms, the articular syndrome also had distinctive features. Thus, in one patient with an allergic-septic variant, the disease began with persistent arthralgia in large (knee, hip) and medium-sized (ankle, wrist, and elbow) joints without visible changes in them.

According to several authors, pro-inflammatory cytokines are currently considered as a mediator in the formation of the pathophysiological stage of autoimmune reactions in JIA.

Analyzing the content of pro-inflammatory cytokine (Table 2), a statistically significant increase was revealed in patients with JIA in all variants of the disease. The highest levels of IL-17A were observed in the polyarthritic form of JIA with a large number of affected joints.

This is apparently due to the fact that in patients with the polyarticular variant of the disease, the maximum activity of the inflammatory process is observed.

**Conclusions**

1. Based on the study, the duration of JIA in children ranges from 3 months to 8 years; large and medium-sized joints are most often affected — knees, ankles, wrists, elbows, hips. A persistent course was observed in 28.9 % of cases, and a progressive course in 71 %.

2. Peculiarities of the joint syndrome depending on gender showed that in boys, the exudative component is less pronounced (18.4 %), dystrophic changes (28.9 %) in the joints of the lower extremities predominated. In girls, exudation in the joints of the upper extremities predominated — 44.7 %. X-ray examination revealed mostly Steinbrocker grade II.

3. In children with JIA, there is an increase in the level of pro-inflammatory cytokine IL-17A by 5–10 times, depending on the articular or systemic variants of the disease.

4. An increase in IL-17A in the blood serum by more than 2 times can be used for early diagnosis of different forms of JIA.

**References**


**Table 2. The content of IL-17A in the blood in children with JIA depending on its form**

<table>
<thead>
<tr>
<th>Cytokine, pg/ml</th>
<th>Oligoarthritic form</th>
<th>Polyarthritic form</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17A</td>
<td>87.60 ± 2.51*</td>
<td>114.5 ± 10.2*</td>
</tr>
</tbody>
</table>

* — values are reliable compared to healthy children (P < 0.05–0.001).


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Роль інтерлейкіну-17 при ювенільному ідіопатичному артриті

Резюме. Захворювання суглобів є актуальною проблемою педіатрії. Ювенільний ідіопатичний артрит є поширенім хронічним системним запальним захворюванням суглобів у дітей; його етіологічні фактори залишаються невідомими. Захворювання може вражати дітей будь-якого віку і характеризується тривалим прогресуючим перебігом, що призводить до розвитку контрактур і функціональної недостатності, а згодом і до інвалідності. На думку авторів статті, рівень інтерлейкіну-17 у сироватці крові дітей із ювенільним ідіопатичним артритом залежить від тривалості захворювання, а також його тяжкості. Ключові слова: діти; ювенільний ідіопатичний артрит; цитокіни

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