ISSN NO: 2770-2936
Date of Publication:06-05-2023

Interleukin-17 In Juvenile Idiopathic Arthritis

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Abstract. Joint diseases of childhood are an actual problem of pediatrics. Juvenile idiopathic arthritis (JIA) is a common chronic systemic inflammatory joint disease in children, the etiological factors of which remain not fully known. The disease can affect children of any age, it is characterized by a long progressive course, leading to the development of contractures and functional insufficiency, and thus the disability of children.

Key words: juvenile idiopathic arthritis, symmetrical chronic arthritis, contracture, interleukin-17, glomerulonephritis,

Introduction. Rheumatic diseases in children are an important and most socially significant part of the general rheumatological problem (Baranov A.A., 2010). One of the most frequent and disabling rheumatic diseases is juvenile idiopathic arthritis (JIA) (Alekseeva E.I., 2010).

Juvenile idiopathic arthritis is a destructive and inflammatory disease of the joints with unknown etiology, complex immunoaggressive pathogenesis, which is characterized by symmetrical chronic arthritis, systemic damage to internal organs, leading to disability in sick children [1].

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

In the pathogenesis of the disease, the leading place is given to the activation of CD4 + T-lymphocytes by the Th-1 type, followed by the synthesis of pro-inflammatory cytokines - interleukin-1 (IL-1), interferon-gamma (IFN-γ), tumor necrosis factor-α (TNF-α) and others (Vorontsov I.M., 2003).

In 2003, a new type of T-helpers, Th-17, was discovered, producing interleukin-17 (IL-17). Differentiation of Th-17 occurs in a way independent of Th-1, Th-2. Interleukin-17 exhibits a pronounced pro-inflammatory activity in vitro and in vivo, is able to induce the synthesis of various inflammatory mediators, including TNF-α, IL-1, IL-6, thereby contributing to the development of autoimmune pathological reactions (Bettelli E., Carrier Y., 2003), including the induction of inflammation in rheumatoid arthritis (Fossiez F. et al., 2006).

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

There are kidney lesions that are directly related to the disease itself, and iatrogenic lesions that are associated with the effects of drug therapy. Pharmacotherapy of JIA remains one of the most difficult problems of modern clinical medicine (Kuzmina N.N., 2003). For treatment, a wide range of antirheumatic drugs is used (glucocorticoids, gold preparations, sulfasalazine, leflunomide, methotrexate, cyclosporine), the effectiveness of combination therapy has been shown (Lyskin A.G., 2004). And often, treatment for juvenile idiopathic arthritis hastens or precipitates kidney damage. Glucocorticoids and cytostatics reduce renal function, 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 through the body's immune response mechanisms [7]. To assess the severity of renal damage in autoimmune diseases, it is recommended to use the index of chronicity as an additional indicator. If the indicator is high, 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 with an outcome in chronic renal failure and renal amyloidosis [11]. All this dictates the need to optimize early diagnosis, prognosis, correction and prevention of complications from the urinary system in juvenile idiopathic arthritis.

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Kidney damage in JIA occupies a special place among other systemic manifestations of this disease and has a huge impact on the prognosis of the disease, approaches to its therapy, and outcome [2].

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 such diseases as SLE and SV. [6, 10].

A promising direction is the use of genetically engineered drugs that have a selective effect on the components of a pathological autoimmune reaction (Nasonov E.L., 2005, Alekseeva E.I., 2008). However, the dynamics of changes in immunological parameters, including cytokine status, during JIA therapy has not been sufficiently studied, which will allow a more accurate assessment of the effectiveness of the treatment.

Thus, given the interest of the components of the immune system, it is relevant to study the role of interleukin-17 in JIA in order to clarify the role of this cytokine in the pathogenesis of the disease in order to determine additional diagnostic criteria and evaluate the effectiveness of treatment.

Aim. To determine the role of interleukin-17 for the early diagnosis of juvenile idiopathic arthritis.

Materials and methods of investigation: An in-depth clinical-immunological and laboratory-instrumental examination of 38 children with juvenile idiopathic arthritis was carried out.

Immunological studies of the content of interleukin -17 were performed on the basis of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan. Of the 38 patients, there were 20 (52.7%) girls and 18 (47.3%) boys aged 3 to 17 years (mean age 10 years). The duration of the disease ranged from 3 months to 8 years. Girls predominated among the examined patients depending on gender.

The vast majority of patients (more than 50%) were children with a disease period of up to 1 year, more than 5 years of disease was in 2 observed children. The timing of diagnosis ranged from 4 months to 3 years. The diagnosis was established in accordance with the classification of juvenile idiopathic arthritis according to the second version of ILAR "International League of Associations for Rheumatology" 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 the patients we observed in more than a third of cases, and only 13 (34.2%) patients were diagnosed in a timely manner. Considering the aggressiveness of the course of JIA, the timing of the diagnosis is of great importance, because. timely treatment leads to a further favorable prognosis of the disease.

Results and discussion. We analyzed the frequency of occurrence of diagnostic clinical criteria for JIA among the examined groups of patients. The absolute majority of the examined patients (29-76.3%) were characterized by such criteria as arthritis lasting 3 months. and more, morning stiffness, arthritis of the second joint, which arose after 3 months. and later, symmetrical damage to small joints, effusion into the joint cavity. In the affected joint, pain, swelling, deformity and limitation of movement, an increase in local skin temperature were noted. Large and medium joints were more often affected - in 26 (68.4%) knee, ankle, wrist, elbow, hip joints. In 7 (18.4%) patients there was a lesion of the cervical spine, in 5 (13%) patients bilateral sacroiliitis, in 1 (2.6%) the disease was accompanied by Raynaud's syndrome and in 1 (2.6%) the patient was accompanied by a genetic disease mucopolysaccharidosis, Hunter type.

In 11 (28.9%) patients observed by us, a persistent variant of oligoarthritis was noted, characterized by the fact that up to 4 joints were affected during the entire period of the disease. Progressive oligoarthritis occurred in 27 (71%) of the examined patients 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 established depending on the form of the disease, the nature of the course of JIA, the sex and age of patients. Thus, the articular form of the disease with a subacute onset was accompanied by the development of arthritis with a predominant lesion of the knee and ankle joints (68% and 28%, respectively). In the future, the wrist and elbow joints joined more often than others. At the same time, the process progressed moderately and productive changes prevailed. X-ray was determined mainly II degree according to Steinbrokker. In the acute onset of this variant of the disease, the wrist, metacarpophalangeal and interphalangeal joints of the hand were more often involved in the process.

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The study of the characteristics of the articular syndrome depending on gender showed that the exudative component is less pronounced in boys (7-39%), productive-dystrophic changes (11-61%) in the joints of the lower extremities (hip, knee, ankle, foot joints) predominate, the idiopathic factor in blood serum is determined extremely rarely. In girls at the initial stages of the disease, exudation prevailed in the joints of the upper extremities - the wrist, elbow, small joints of the hand (17-85%).

The articular-visceral form was noted in 10 (26.3%) of the patients examined by us and was clinically characterized by a high temperature reaction, which was of an intermittent nature and did not decrease during antibiotic treatment.

In 28 (60.5%) patients, the disease proceeded with kidney damage, in 5.2% of patients with heart damage, in 2.6% - with lung damage, in 10.5% - there were combined lesions of internal organs. In systemic forms, the articular syndrome also had its own distinctive features. So, in one patient with an allergic-septic variant, the disease began with persistent arthralgia in large (knee, hip) and medium (ankle, wrist and elbow) joints without visible changes in them.

All patients were divided into 3 groups according to generally accepted signs of JIA activity. The first degree of disease activity was established in 11 (28.9%) patients with lesions of no more than 4 joints, with minimal ESR values up to 20 mm/hour, with a normal level of C-reactive protein (CRP); the second degree was documented in 19 (50.1%) patients with intermittent arthritis and ESR values of not more than 40 mm/hour, borderline elevated CRP; the third degree was registered in 8 (21%) children, in the presence of systemic manifestations of arthritis, a large number of swollen and painful joints, duration of morning stiffness for more than an hour and high humoral activity - high CRP and / or positive RF, ESR > 40 mm / h.

In half of the examined patients, the first stage of anatomical changes according to Steinbrokker was noted, i.e. - epiphyseal osteoporosis, in 1/3 of the patients we noted narrowing of the joint space and the presence of single erosions. Cartilage and bone destruction occurred in 3 (7.8%) patients with a disease period of more than 3 years.

Table 1
Clinical forms of JIA

№	Indicator	Number of patients	%
1	Arthritis lasting 3 months. and more	29	76,3
2	Damage to large and medium joints	26	68,4
3	Damage to the cervical spine	7	18,4
4	Bilateral sacroiliitis	5	13
5	Raynaud's syndrome	1	2,6
6	Mucopolysaccharidosis	1	2,6
7	Persistent variant of oligoarthritis	11	28,9
8	Progressive oligoarthritis	27	71
9	Exudative component	7	39
10	Productive-dystrophic changes	11	61
11	Articular-visceral form	10	26,3
12	Kidney damage	28	60,5
13	Heart failure Lung injury	2	5,2
14	Lung injury	1	2,6
15	Combined lesions of internal organs	4	10,5

Cytokines are currently considered as a mediator link in the formation of the pathophysiological stage of autoimmune reactions in JIA.

Table 2
The content of cytokines in the blood of children with JIA depending on the variant of the disease

ISSN NO: 2770-2936
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Indicator pg/ml	Oligoarthritis, persistent	Oligoarthritis progressive	Polyarthritis, seronegative
IL-17	4,8±2,1*	7,0±3,2	7,1±3,4*

Note: *- statistically significant differences with the control group at $p<0.05$

Analyzing the content of pro-inflammatory cytokines (table 2), revealed a statistically significant increase in performance in patients with JIA in all variants of the disease.

The highest levels of IL-17 were observed in the progressive variant of JIA with a large number of affected joints.

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

The concentration of IL-17 in the blood serum significantly decreased with an increase in the duration of the disease. In our opinion, the identified changes in IL-17 parameters are associated with the ongoing therapy, and a significant decrease is associated with the effectiveness of the selected drug.

Among the children examined by us, patients with JIA with kidney damage in the form of nephritis were identified. An analysis was made of the frequency of nephritis in patients with JIA, during which it was found that the urinary syndrome was detected in 28 children out of 38 prospectively observed children, that is, in 60.5%. When distributing by gender, girls predominated in all groups. The age of children with JIA with kidney damage during the observation period was on average the same and amounted to 7 years. Moreover, children with JIA at the beginning of the observation with kidney damage were significantly older than in the group without nephritis ($p < 0.05$). Therefore, the duration of JIA disease in the group of children with nephritis was significantly higher than in patients without kidney damage ($p<0.05$).

Laboratory studies have shown that significantly more often in children with secondary nephritis in JIA compared with children who did not have kidney damage, anemia was detected (grade 3 in 4 - 10.8% of children with kidney damage and 1 - 1.2% without lesions), accelerated ESR (40 mm / h in 15 - 40.5% of patients with kidney damage and in 6 - 7.1% without nephritis). There was also an increase in the level of leukocytes, stab and segmented neutrophils, but without significant differences.

An early sign of kidney damage in various diseases is microalbuminuria (MAU). Among patients with JIA, microalbuminuria was detected in 7 patients (13.2%). In 42.8% of patients, an increase in the concentration of albumin in the urine of more than 20 mg / l was observed in patients with a duration of juvenile idiopathic arthritis for more than 5 years, 28.6% - in children with a disease duration of 1-3 and 3-5 years.

The functional state of the kidneys in patients was assessed in accordance with the content of creatinine. Thus, among the examined sick children with JIA, the content of creatinine in the blood in children with kidney damage was significantly higher 19 (68%) out of 28 than in children without kidney damage 6 (15%).

Thus, it follows from the study that the duration of the course in JIA in children ranges from 3 months to 8 years, large and medium joints are more often affected - knee, ankle, wrist, elbow, hip. A persistent course was noted in 28.9%, and a progressive course - in 71%. In boys, the exudative component is less pronounced 39%, productive-dystrophic changes predominate 61% in the joints of the lower extremities, rheumatoid factor in the blood serum is extremely rare. In girls, exudation in the joints of the upper extremities prevailed - 85%. X-ray was determined mainly II degree according to Steinbrokker. An increase in the pro-inflammatory cytokine IL-17 in blood serum by more than 2 times can be used for early diagnosis of JIA.

Kidney damage in the form of nephritis was observed in 60.5% of patients, microalbuminuria was detected in 13.2%, in 68% of patients - an increase in the concentration of creatinine in the blood.

Conclusion: Thus, the analysis of the clinical variants and course of juvenile idiopathic arthritis indicates the aggressiveness and progressive nature of the course of the disease, which reflects the modern age evolution of the disease, as well as damage to internal organs, especially the kidneys, which dictates the need to find effective methods for optimizing treatment and preventing toxic effects of drugs on the kidneys.

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ISSN NO: 2770-2936
Date of Publication:06-05-2023

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