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Clinical, Laboratory, And Immunological Changes In The Urinary System In Children With Juvenile Idiopathic Arthritis

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Abstract: Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of the joints in children, characterized by autoimmune damage to connective tissue and systemic manifestations. Among extra-articular lesions, particular importance is attached to the involvement of the urinary system, which significantly affects the course, prognosis, and treatment strategy of the disease.

Objective: To study the clinical and immunological changes in the urinary system in children with juvenile idiopathic arthritis.

Materials and Methods: A total of 80 patients aged 4–17 years were examined. All patients underwent clinical, laboratory, and immunological studies.

Results: Urinary system involvement was detected in 66 (82.5%) children, manifested by leukocyturia (79%), proteinuria (52%), hematuria (35%), and the presence of salts in the urine (32%). Serum IL-6 levels were elevated 5.8-fold, particularly in polyarticular and systemic forms of the disease.

Keywords: Juvenile idiopathic arthritis, urinary system, kidneys, immunological changes.

Introduction: Relevance of the Problem

Diseases of the joints in children remain an urgent issue in pediatrics and rheumatology. Juvenile idiopathic arthritis (JIA) is a common chronic inflammatory joint disease in children, the development of which is influenced by various factors. The disease can occur at any age and is characterized by a prolonged, progressive course that may lead to contractures and loss of joint function. JIA is a systemic chronic disease of connective tissue with a predominantly autoimmune pathogenesis, lasting for more than six weeks, developing in children under 16 years of age, and clinically manifested by arthritis after exclusion of other joint pathologies. The pathological process leads to the destruction of affected joints and, in some patients, is accompanied by pronounced extra-articular manifestations. One of the most significant extra-articular manifestations in JIA is the involvement of the urinary system [10,12,13,14,20,21,28,30]. The frequency of urinary system pathology (USP) in JIA ranges from 13% to 73%. In terms of frequency of renal involvement, JIA ranks third among rheumatic diseases, following systemic lupus erythematosus (SLE) and systemic vasculitis [28,30].

Urinary system involvement in rheumatoid arthritis (RA) occupies a special place among other systemic manifestations of the disease and has a significant impact on its prognosis, therapeutic approaches, and

outcomes. According to various authors [5,6,8,11,16,19,20,21,27], renal pathology occurs in 20–75% of patients with RA.

Renal changes are characterized by the early appearance of transient leukocyturia, mild proteinuria, and hematuria, which are most often observed at the onset of the disease or during exacerbation. These findings are associated with disease activity and severity, as well as the patient's age [7,8,9,17,21].

JIA is one of the major diseases leading to secondary amyloidosis [18]. The incidence of amyloidosis in adult RA patients ranges from 2% to 50% [3,12,24], while in children it is less common—3–15%—and develops predominantly in those with systemic forms of the disease at any age [1,22,29].

Autoimmune and autoinflammatory processes play a key role in the development of rheumatic diseases, associated with genetically determined and environmentally induced defects in the activation of both the innate and adaptive immune responses [4,9,25,27,30]. During active inflammation in children with different variants of JIA, almost all components of the immune system are involved, leading to activation of both the cellular and humoral immune responses [2,21,23,26].

Systemic manifestations of interleukin-6 (IL-6) activity, such as fever and morning stiffness, are related to the circadian rhythm of cytokine secretion. IL-6 stimulates osteoclast differentiation and activation, enhances bone resorption, and consequently contributes to the development of generalized osteoporosis and erosive joint changes [1,17,30].

The state of the cytokine network in various forms of JIA has not been fully elucidated. Some authors report maximal IL-6 elevation in systemic JIA compared with other forms. A correlation has been observed between the levels of proinflammatory cytokines (IL-1β, IL-6), chemokines (IP-10), and clinical-laboratory indicators of disease activity (ESR, CRP, and number of affected joints) [1,17,24].

Thus, the development of chronic inflammation in rheumatic diseases is mediated by multiple immune system abnormalities, and the degree of inflammation correlates with the altered synthesis of a wide range of immune mediators.

Objective of the Study

To investigate the clinical and immunological changes in the urinary system in children with juvenile idiopathic arthritis (JIA).

METHODS

A total of 80 children with JIA were examined, including 54 (67.5%) with the articular form, 13 (16.2%) with the polyarticular form, and 11 (13.7%) with the systemic form of the disease. Among them, 48 (60%) were boys and 32 (40%) girls, aged from 4 to 17 years.

All patients underwent standardized clinical, laboratory, bacteriological, and immunological examinations. Clinical evaluation included medical history (anamnesis of life and disease), assessment and monitoring of current somatic status, and analysis of disease dynamics. Laboratory studies consisted of a complete blood count, urinalysis, biochemical blood tests (including creatinine and urea levels), and the Nechiporenko urine test. Urine cultures were performed for bacteriological evaluation.

Immunological methods included the measurement of proinflammatory cytokines, particularly interleukin-6 (IL-6), in the peripheral blood serum.

The disease onset was assessed by type—systemic, polyarticular, or oligoarticular. The overall condition of the patient and the dynamics of clinical manifestations were evaluated, along with data from the pharmacological history (background basic therapy, previous use of NSAIDs, and reported adverse drug reactions).

RESULTS AND DISCUSSION

The clinical manifestations of JIA in the examined patients were characterized by considerable polymorphism of symptoms. Analysis of medical histories showed that the first clinical signs of the disease appeared 6 months to 2 years before diagnosis. At the disease onset, the vast majority (87.3%) of children presented with general malaise: weakness, morning stiffness, arthralgia, weight loss, and subfebrile fever.

In 13 children, a persistent oligoarthritis variant was observed, characterized by involvement of up to four joints throughout the course of the disease. Progressive oligoarthritis was found in 28 patients, with an increase in the number of affected joints after six months of disease progression.

Certain features of joint involvement were established depending on the form, disease course, sex, and age of the patients. The articular form with a subacute onset was accompanied by arthritis predominantly affecting the knee and ankle joints. Subsequently, the wrist and elbow joints were most frequently involved.

The articular-visceral (systemic) form was observed in 11 patients and was clinically characterized by high intermittent fever, unresponsive to antibiotic therapy. During febrile periods, patients developed a polymorphic bright-pink rash.

Among the examined children with JIA, cases of urinary system involvement were identified in the form of

urinary tract infections and nephritis. Analysis of nephritis frequency revealed that urinary abnormalities were detected in 46 out of 80 prospectively observed children aged 4–17 years. At the time of observation, children with urinary system involvement were significantly older than those without such manifestations ($p \leq 0.05$).

Urinary system activity in children was manifested by proteinuria in 34 patients, hematuria in 23, and leukocyturia in 52. Salts in urine were found in 21 patients: oxalaturia in 16, triple-phosphate crystalluria in 3, and uraturia in 2 (Table 1).

Table 1.
Main Laboratory Indicators of Urinary System Involvement in Children

Indicators	Urinary System Involvement (N = 66)
Proteinuria	34
Microhematuria	23
Leukocyturia	52
Oxalaturia	16
Triple-phosphate crystalluria	3
Uraturia	2

Laboratory studies revealed that, compared to children without urinary system involvement, those with JIA and urinary manifestations more frequently demonstrated anemia (grade II–III in 18.1% vs. 3%), elevated ESR (40 mm/h in 39.3% vs. 17.6%), and increased white blood cell and neutrophil counts, although without statistically significant differences.

Microalbuminuria was detected in 14 patients (21.2%) with JIA and urinary system involvement. The urinary abnormalities in these children included proteinuria in 34 (52%), hematuria in 23 (35%), leukocyturia in 52 (79%), and urinary salts in 21 (32%) patients—oxalaturia in 16 (24%), triple-phosphate crystalluria in 3 (5%), and uraturia in 2 (3%) cases. Mixed urinary abnormalities were observed in 22 (33%) patients. Further, serum creatinine levels and glomerular filtration rate (GFR) were evaluated in this group of patients according to the Schwartz formula (Table 2).

Table 2.
Indicators of Renal Functional Status (Schwartz Formula)

Renal Status	Children with Urinary System Involvement (N = 66)
Preserved renal function (n=52)	GFR = 90–97 mL/min/1.73 m²
Decreased glomerular filtration (n=14)	GFR = 30–67 mL/min/1.73 m²

As shown in the table, impaired renal function was noted in most children with JIA and urinary system involvement at the time of examination.

Immunological studies were conducted to assess the level of the proinflammatory cytokine interleukin-6 (IL-6) in children with JIA, aiming to identify the relationship between cytokine production and disease activity and severity.

The serum IL-6 level was found to be 5.8 times higher than in the control group, averaging 47.28 ± 2.93 pg/mL ($P < 0.001$), with individual values ranging from 20.7 to 55.4 pg/mL. Elevated levels above the mean were found in 72.4% of cases.

In children with polyarticular and systemic forms of JIA, IL-6 levels were more than 10-fold higher than in controls, averaging 87.52 ± 7.41 pg/mL ($P < 0.001$). Analysis showed that IL-6 levels were near the lower limit in 20% of patients, while 30% had values above the average.

Thus, the analysis of clinical forms and disease course in juvenile idiopathic arthritis confirms its aggressive and progressive nature, reflecting the modern age-related evolution of the disease, as well as the frequent involvement of internal organs—particularly the urinary system. These findings highlight the need for effective treatment strategies and preventive measures to minimize the nephrotoxic side effects of

medications.

CONCLUSIONS

1. Laboratory studies demonstrated that children with JIA and urinary system involvement more frequently exhibited anemia, elevated ESR, microalbuminuria, and increased creatinine and urea levels compared to children without urinary manifestations.

2. The increase in the number of painful and swollen joints, intensified pain and exudation, proteinuria, and hematuria indicates a shared pathogenetic basis for joint and renal involvement in JIA.

3. Severe JIA is characterized by hyperactivation of the immune system and excessive IL-6 production, which underscores the need for developing effective therapeutic strategies and preventing the nephrotoxic effects of medications on the urinary system.

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