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Clinical and immunological features of heart and vascular damage in children with juvenile arthritis with systemic onset

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ABSTRACT

Objectives. To study the clinical and immunological features of cardiac and vascular damage in children with juvenile arthritis with systemic onset.

Materials and methods. The study included 30 children with juvenile arthritis with systemic onset who were hospitalized in the cardio-rheumatology department of the Republican Specialized Scientific and Practical Medical Center of Pediatrics. All patients underwent clinical and anamnestic, functional, instrumental and laboratory research methods.

Conclusion. Clinical and immunological features of lesions of the heart and blood vessels in children with JAWSO depend on the timing of the disease manifestation, the activity of the systemic inflammatory process and are characterized by impaired functional activity of the heart, overexpression of vascular endothelial growth factor - VEGF, which determines the degree of risk of cardiovascular complications in this pathology.

Keywords: juvenile arthritis with systemic onset, damage to the heart, children, vascular endothelial growth factor

INTRODUCTION

Juvenile arthritis is the most common chronic inflammatory disease in children and adolescents. Half of all children with this form of arthritis experience severe, often lifelong, disability within the first 10 years of the disease. A third of children develop rheumatic diseases between the ages of 9 months and 1.5 years [1-3].

Juvenile arthritis with systemic onset (JAWSO) in children is a unique variant of JA, distinguished by its various forms of course and outcomes. This disease leads to a pronounced deterioration in the quality of life of patients and a high level of disability [1-6].

The severity of the process in JAWSO is due to the involvement in the pathological process not only of joints, but also of many internal organs and systems, including organs of the cardiovascular system [7-11].

In patients with JAWSO, due to the asymptomatic or minimally symptomatic course of cardiovascular lesions, their diagnosis is difficult and they are mainly detected during instrumental examinations (ECG, EchoCG, chest x-ray) [12,13].

The most important role in the pathogenesis of juvenile arthritis with systemic onset (JAWSO) is also given to inflammatory mediators - immunological markers (cytokines). They cause a spectrum of various multi-organ extra-articular clinical manifestations associated with immunoinflammatory damage to internal organs. One of them is vascular endothelial growth factor (VEGF; Vascular endothelial growth factor), which is a heterodimeric glycoprotein growth factor induced by various growth factors and cytokines, including tumor necrosis factor and IL-1β. VEGF serves as part of the system responsible for restoring oxygen supply to tissues in situations where blood circulation is insufficient [14,15].

Not only cytokines, but also drugs used to treat the disease have a damaging effect on the heart. Under the influence of corticosteroid drugs, there is an

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increase in blood pressure, changes in blood sugar levels, an increase in the patient's weight, as well as the cardiotoxic effect of non-steroidal anti-inflammatory drugs [16-20].

Based on the above, the study of clinical and immunological features of cardiovascular complications in children with JAWSO is relevant.

Objectives. To study the clinical and immunological features of cardiac and vascular damage in children with JAWSO

MATERIALS AND METHODS

The study included 30 children with juvenile arthritis with systemic onset who were hospitalized in the cardiorheumatology department of the Republican Specialized Scientific and Practical Medical Center of Pediatrics. The age of the children ranged from 2 to 18 years, and on average was 8.5±7.1 years. All patients underwent clinical and anamnestic, functional, instrumental and laboratory research methods. The determination of the immunological marker - vascular endothelial growth factor (VEGF) was carried out in the laboratory of the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

The diagnosis was made on the basis of complaints, anamnesis (obstetric history of the mother, history of life and illness of the child, previous diseases, nature of the course and duration of the disease), clinical and functional (ECG, EchoCG), laboratory (general hematological analysis, biochemical blood test with determination of general protein, albumin, glucose, total bilirubin and its fractions, urea, creatinine, ALT, AST, LDH, C-reactive protein, rheumatoid factor, antistreptolysin O, calcium, sodium, potassium) and instrumental (radiography of joints and internal organs, ultrasound examination of internal organs, multislice computed tomography) examination methods according to ILAR Edmonton criteria (2001). Statistical processing of the results was carried out using the software package for IBM PC "Statistica 7.0".

RESULTS

A study of the timing of the onset of the disease showed that the earliest age of onset of the disease was observed at 1 year of life, and the latest age at 13 years. On average, the onset of the disease was observed at 5.4±3.2 years. In 29.9% of patients, JAWSO manifested itself in children under the age of 5 years (Figure 1).

The main clinical signs of the disease began with an increase in body temperature, followed by pain in the joints, morning stiffness due to joint pain, enlarged lymph nodes, enlarged liver and spleen, which were detected in the early stages of the disease.

The main clinical manifestations of the disease in the examined children were fever of 39-40º C, the peak of which occurred in the daytime, transient maculopapular rash and arthritis. Among other symptoms, all patients had arthralgia and generalized lymphadenopathy, hepatosplenomegaly and serositis (Figure 2).

The study of laboratory parameters indicated that in children JAWSO occurred with an extremely high degree of laboratory activity in the form of leukocytosis, thrombocytosis, increased levels of

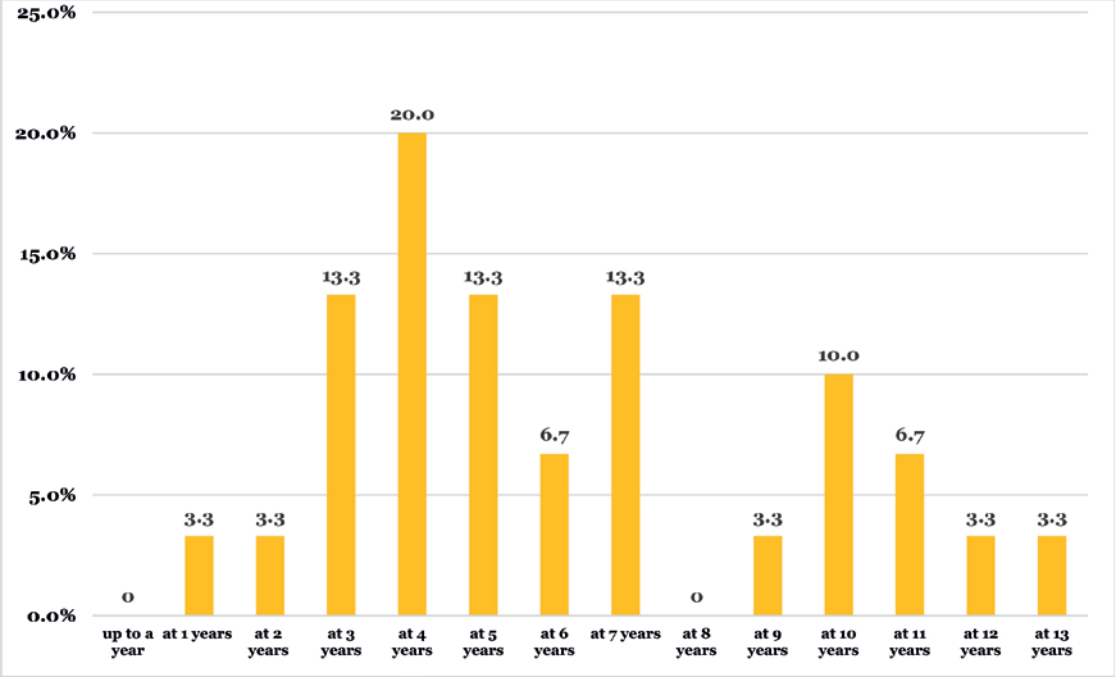


FIGURE 1. Timing of manifestation JAWSO in children

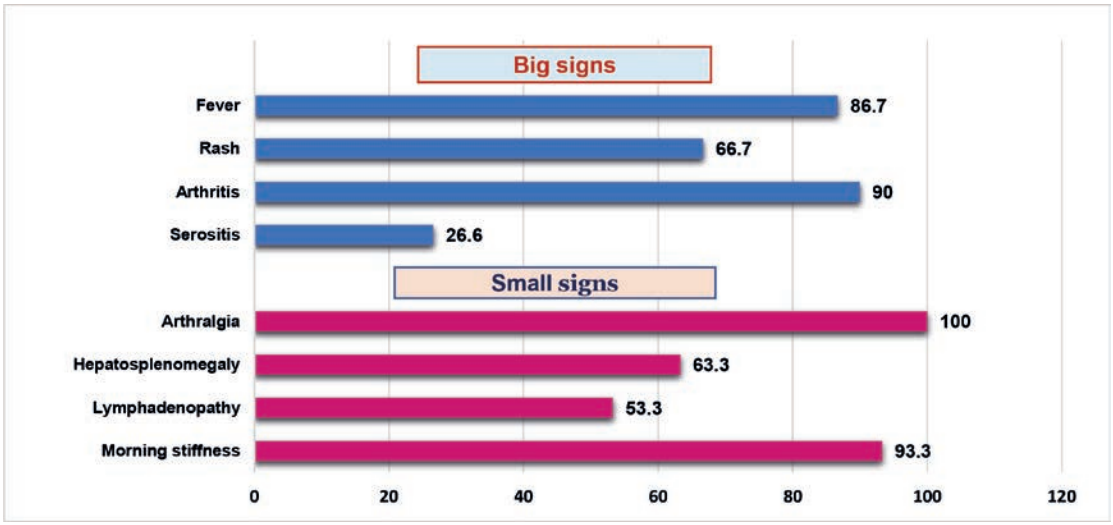


FIGURE 2. Frequency of clinical symptoms of patients with JAWSO

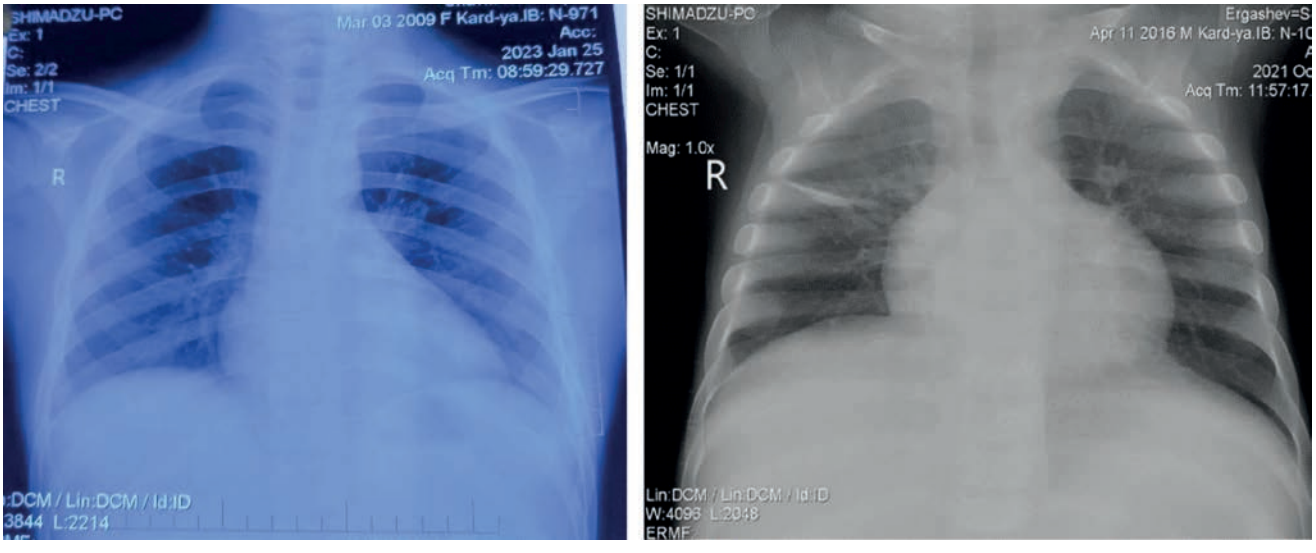
transaminases, progressive anemia, significantly accelerated ESR, high levels of CRP, and dysproteinemia.

Analysis of laboratory data during the acute phase of the disease showed the presence of varying degrees of severity of anemia in 83.3% of patients, an increase in the number of leukocytes - in 76.7% of patients. The most pronounced increase in ESR was in 86.7% of patients, which coincided with the studies of H. Maradit Kremers et al., which convincingly demonstrated that a severe systemic inflammatory process (persistent increase in ESR above 60 mm/h, rheumatoid vasculitis, rheumatoid lung disease or pneumonitis) is associated with a significant increase in the risk of death from cardiovascular diseases [21]. In 46.7% of patients, platelet counts were higher than normal. In children with JAWSO, the following clinical signs of heart failure were observed: chest pain, weakness, pale skin, shortness of breath, cardiac arrhythmias in the form of tachycardia and arrhythmia, as well as liver enlargement (Table 1).

TABLE 1. Frequency of clinical signs of heart failure

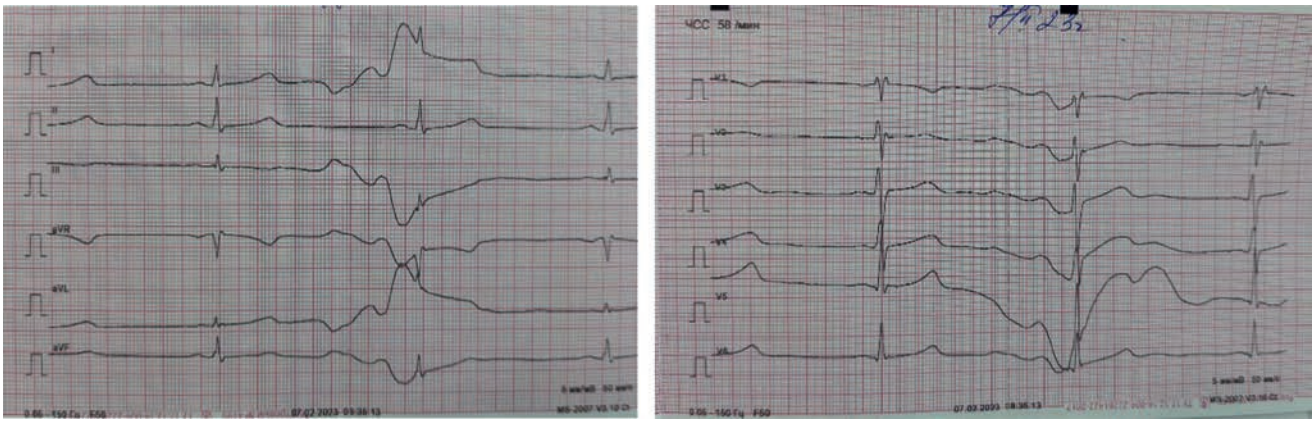
Sign	Detection rate, n (%)
Chest pain	7 (23.3)
Weakness	28 (93.3)
Pallor of the skin	8 (26.7)
Dyspnea	2 (6.7)
Heart rhythm disturbances in the form of tachycardia and arrhythmia	20 (66.7)
Liver enlargement	10 (33.3)

When examining the chest organs of children, an increase in the size of the heart was detected mainly due to the left sections in 20.0% of children ($p \leq 0.01$) (Figure 3).



A B

FIGURE 3. (A) X-ray of the chest organs of patient with JAWSO in a direct projection. CTI=0.55, signs of cardiomegaly; (B) X-ray of the chest organs of patient with JAWSO in a direct projection. CTI = 0.57, signs of cardiomegaly congestion in the lungs



A B

FIGURE 4. Electrocardiogram of patient B., 14 years old with JAWSO; (A) sinus bradycardia; (B) sinus bradycardia, signs of left ventricular overload

According to the results of ECG studies in children, the following changes were identified: signs of overload and hypertrophy of the RV (10%), LV hypertrophy (6.6%), overload of both ventricles (6.6%) and disturbance of the repolarization phase (6.6%). When analyzing the frequency of rhythm and conduction disturbances according to ECG data, the frequency of sinus arrhythmia was 6.7%, sinus tachycardia - 16.6%, bradycardia - 13.3% and right bundle branch block - 13.3% of cases (Figure 4).

According to the results of ECHO-CG studies in children, the following changes were identified: mitral valve insufficiency of the 1st degree, tricuspid valve insufficiency of the 1st degree, an additional chord in the cavity of the left ventricle and stenosis of the pulmonary artery (Table 2).

VEGF level in children with JAWSO showed that its average value was 236.13±20.7 pg/ml, which exceeds the permissible normal values (the norm is up to 211.65 pg/ml) by 1.1 times (Table 3).

TABLE 2. ECHO-CG data of patients with JAWSO

Sign	Detection rate, n (%)
Mitral valve insufficiency 1st degree	3(10)
Tricuspid valve insufficiency 1st degree	4(13.3)
Additional chord in the cavity of the left ventricle	9(30)
Pulmonary stenosis	1(3,3)

TABLE 3. Vascular endothelial growth factor indicator in children with juvenile arthritis with systemic onset

Index	JAwSO	Valid values	p
VEGF, pg /ml	236.13±20.7	up to 211.65	<0.001
IL-18, pg /ml	239.5±12.4	103-146	<0.001

High levels of VEGF were detected in 33.3% of children with JAWSO. In 13.3% of patients, VEGF values exceeded its reference value by 3.7-6 times (p ≤0.001). In 20% of patients, VEGF levels were 1.1-1.3 times higher than normal values (p ≤0.05) (Figure 5).

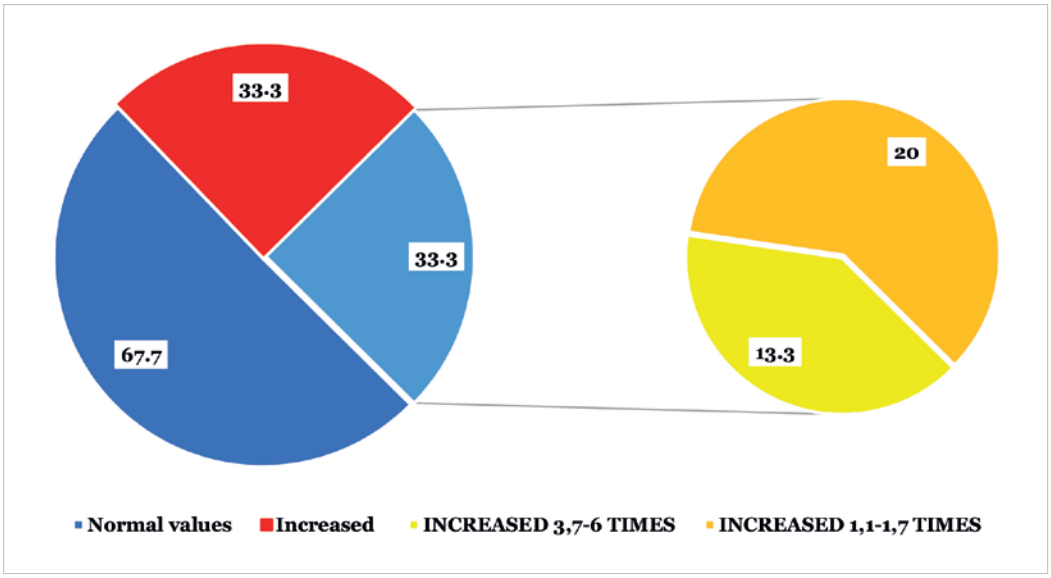


FIGURE 5. Number of patients with JAWSO with elevated rates (%).

The level of IL-18 was also significantly high in children with JAWSO, relative to reference values.

DISCUSSION

According to the literature, JAWSO can debut at any age, but more often occurs before puberty, which was confirmed by the results of our studies. Early onset of the disease indicates more systemic inflammatory processes and poorer outcome than in children with later onset of the disease [1,22].

Analysis of the clinical course of the disease among our examined patients indicates the presence of major and minor clinical symptoms, such as fever, rashes, lymphadenopathy, damage to joints, internal organs, hepato- and splenomegaly, which also coincides with literature data [23].

According to clinical and instrumental studies, among the patients we examined, the main clinical signs of cardiovascular lesions were the presence of varying degrees of severity of signs of cardiovascular failure, myocardial remodeling, as well as rhythm and conduction disturbances. According to the authors, myocardial damage is accompanied by systolic and diastolic dysfunction, decreased ejection fraction, dilation of the heart cavities and hypokinesia of the posterior wall of the left ventricle, which leads to relative insufficiency of the mitral and tricuspid valves. In most cases, inflammation of the pericardial and myocardial layers is observed together, in rare cases only isolated myocarditis is observed. In our study, there were no signs of pericardial damage in patients [24].

As is known, one of the most sensitive markers of acute inflammation is CRP, the synthesis of which occurs in hepatocytes and is regulated by proinflammatory cytokines, primarily IL-6, as well as IL-1 and TNF-α [24]. According to modern concepts, even a slight increase in CRP concentration is an independent prospective risk factor for cardiovascular complications [24,25]. Therefore, this indicator can serve to stratify patients with JA according to the degree of cardiovascular risk. In our study, high levels of CRP were detected in 73.3% of children [25].

Activation of the innate immune system and the production of proinflammatory cytokines by activated macrophages (IL-6, IL-1, IL-18, TNF-α) play a central role in pathogenesis [26]. Overproduction of proinflammatory cytokines is associated with the development of clinical manifestations of the disease (fever, polymorphic rash, serositis, enlargement of the liver, spleen and lymph nodes, destructive arthritis; hemophagocytic syndrome, osteopocrosis) and pathological changes in laboratory parameters (leukocytosis, thrombocytosis, haptoglobin, C-reactive protein, fibrinogen) [27].

Overexpression of VEGF can cause vascular diseases in certain parts of the body. Increased vascular formation (angiogenesis), resulting from the action of cytokines on tissue, also increases the destruction of cartilage [28]. The results of our studies indicate that in children with cardiovascular lesions there is an increase in VEGF. In addition, some drugs (genetically engineered biological drugs) created in recent years are capable of controlling or slowing down the course of such diseases by inhibiting VEGF [29-31].

CONCLUSION

Clinical and immunological features of lesions of the heart and blood vessels in children with JAWSO depend on the timing of the disease manifestation, the activity of the systemic inflammatory process and are characterized by impaired functional activity of the heart, overexpression of vascular endothelial growth factor - VEGF, which determines the degree of risk of cardiovascular complications in this pathology.

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