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Early Diagnosis and Evaluation of Cytokine Profiles in Children with Juvenile Idiopathic Arthritis

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Abstract

The article describes the clinical and immunological features of juvenile idiopathic arthritis and the consequences of the disease after treatment. Clinical features of the disease, laboratory analysis results are important when choosing an effective treatment method. An effective treatment method is characterized by a faster onset of remission, prolongation of its duration and reduction of side effects of drug treatment.

Keywords: Juvenile idiopathic arthritis, prognosis.

1. Introduction

Juvenile idiopathic arthritis (JIA) is a destructive inflammatory disease of the joints with unknown etiology, complex immunoaggressive pathogenesis, characterized by symmetrical chronic arthritis, systemic damage to internal organs, leading to disability of sick children. Long-term observation of patients has established that the most important factor determining the severity of the condition, the severity of bone destruction and the progression of joint syndrome is the activity of the disease. [1,2,4,6,8,9]. Immunological mechanisms are dominant in the pathogenesis of JIA; their pathological development largely characterizes the diversity of clinical manifestations in JIA. Of significant importance for assessing the state of immunity, including the cytokine profile in children with JIA, is the study of the level of production of pro- and anti-inflammatory cytokines, due to which intercellular regulation of body functions occurs.

2. Methodology

During the work, immunological examination was conducted in 122 children with JIA. All children were divided into 3 groups: 1 - the main group consisted of 58 children with the polyarthritic variant of JIA, 2 - the comparison group consisted of 45 children with the oligoarthritic variant of JIA and 3 - the control group consisted of 20 practically healthy children.

An important physiological role in the processes of immunoregulation is played by the proinflammatory cytokine - IL-1 β , which initiates inflammation and is sometimes the main link in the pathogenesis of many diseases, including immune-mediated ones . Violation of the cytokine balance towards hyperproduction of IL-1 β can be the central link in the pathogenesis of many known chronic diseases.

3. Results

We conducted a study to determine the level of IL-1 β production. as an important mediator, which is one of the most universal regulators of immunity and inflammatory reactions with a wide range of biological effects, including proliferation of T- and B-lymphocytes, antibody formation, induction of synthesis of other cytokines. It was found that in healthy children, individual indicators of IL-1 β production ranged from 140 to 260 pg / ml, while the average value of this cytokine was 200.5 ±6.28 pg / ml. In children with JIA, polyarthritic variant, the level of proinflammatory cytokine IL-1 β before treatment in the peripheral blood was 514.8 ±6.05 pg / ml , remaining reliably high ($P < 0.001$) in relation to control values, and was 1.2 times higher than in children with JIA, oligoarthritic variant. The high level of IL-1 β production in children with JIA suggests the presence of a certain dependence of its concentration on the nature of the pathological process , as evidenced by its increase in children with JIA, the oligoarthritic variant.

Table 1. Cytokine concentration levels in children with JIA

Indicators pg /ml	Control (n= 44)	Main group (n= 58)	Comparison group (n= 45)	R
IL-1β	200.5 ± 6.28	514.8±6.05	417.4±4.08	P< 0.001
IL-6	14.2±1.64	21.8±1.02	19.3±0.98	P< 0.005
IL-17a	60.8±1.5 6	26.7±1.19	27, 4 ±1,07	P< 0.001
TNF- a	25.7 ± 1.56	17.0±0.65	16.3±0.62	P< 0.001

Proinflammatory cytokine IL-6 is a potent proinflammatory cytokine with a broad range of biological activities; it is produced by both lymphoid and non-lymphoid cells.

It has been established that IL-6 has a major effect on the regulation of the immune response: it stimulates the proliferation and differentiation of B cells, enhances antibody formation, participates in the production of multipotent colony-forming factors and megakaryocytes, and can suppress neutrophil apoptosis [42] . The production of IL-6 in children of the main group was 21.8±1.02 pg /ml, compared to the control 14.2±1.64 pg /ml and was 1.5 times higher (P< 0.001), and 1.1 times higher compared to the comparison group. In children with JIA, polyarthritic In this variant, the concentration of IL-6 was 19.3±0.98 pg /ml, which is 1.3 times higher than the control values (Table 4.1).

Currently, some of the main causes of the development of immunodeficiency states are becoming clear. One of the

reasons for this is the disruption of the body's immunoregulatory processes under the influence of various factors, including asphyxia , carried out by Th 1 and Th 2 helpers. As is known, the former synthesize cytokines that stimulate cellular immunity (IL-1, 2, 6, 8, 12, IFN, etc.), the latter synthesize cytokines that stimulate humoral immunity (IL-4, 5, 10, TGF- b , etc.). In a normally functioning organism, there is a certain balance of interaction between Th 1 and Th 2 helpers. But a strong change in their activity under the influence of any impact can lead to serious adverse consequences in the functioning of the immune system as a whole. It has been established that hypoxia can cause activation of Th 2 helpers and the synthesis of cytokines that have a suppressive effect on cellular immunity [12,16,18,22,24,34,3644,46,].

An important role in coordinating the functional conjugacy of the multicomponent immune system is played by interferons, which are a group of biologically active proteins or glycoproteins synthesized by the cell during the protective reaction to foreign antigens. It is known that one of the important mediators for characterizing the state of the immune system of patients is TNF-a, which regulates the intensity of the immune response, increasing the bactericidal activity of phagocytic cells, and has antiviral and immunomodulatory activity[48,54,56,58,62,64]

The interferon system is aimed at recognizing and eliminating foreign genetic information. The most important function of TNF-a is its participation in the implementation of relationships between lymphocytes and macrophages, as well as in the regulation of cellular and humoral immune responses. In our studies, the level of TNF-a production in healthy newborns averaged 25.7 ±1.56 pg / ml..

The children of the main and comparison groups were characterized by the presence of decreased production of TNF-a before treatment by 1.5 times in relation to the control group, which amounted to 17.0 ±0.65 pg / ml and 16.3 ±0.62 pg / ml, respectively ($P < 0.001$), which once again reflects the degree of dysfunction of the immune system in JIA. The concentration of TNF-a among children of the main and comparison groups did not have reliable differences. The low ability of newborns to synthesize TNF-a causes a violation of the immunoregulatory index indicators towards the predominance of the suppressor activity of T-lymphocytes and a decrease in the killer activity of cells.

We also analyzed the state of the cytokine profile in children with JIA in the study groups depending on the clinical variant (Table 4.2.).

As can be seen from the presented data, in children of the main group with the articular variant of JIA, the concentration of the proinflammatory cytokine IL-1 β (525.5±8.8 pg /ml) was significantly higher ($P<0.001$) than in children with the oligoarthritic variant of JIA (501.5±6.9 pg /ml).

Table 2. The state of the cytokine profile in children with JIA depending on the clinical variant

Indicators	Main group		Comparison group	
	Polyarthritic variant option n-32	Oligoarthritic option n -26	Polyarthritic variant option n-20	Oligoarthritic option n-25
IL-1β	525.5±8.8*	501.5±6.9	425.1±7.7	411.3±7.0
IL-6	22.7±1.3	20.8±1.4	19.8±1.9	18.9±1.7
IL-17a	6.0±0.4	5.4±0.5	6.3±0.6	7.2±0.5
TNF-a	17.0±0.9	17.0±0.8	16.1±1.0	16.44±1.1

Note: *- difference between JIA variants within groups $P< 0.001$. ^- difference between JIA variants between groups $P< 0.001$.

In the comparison group, no significant differences were observed between the variants. A significant difference was also found between the IL-1 β cytokine values in children with the polyarthritic variant of JIA in the main group (525.5±8.8 pg /ml) and the polyarthritic variant in the comparison group (425.1±7.7 pg /ml), as well as with the oligoarthritic variant in the main group (501.5±6.9 pg /ml) and the oligoarthritic variant in the comparison group (411.3±7.0 pg /ml).

Thus, our studies have shown that in children with JIA, especially in the polyarthritic variant, there is a significant imbalance in the production of proinflammatory (IL-1β, IL-6, IL-17a increase by 2.6; 1.5; 3.6 times, TNF-a decreases by 1.5 times). Moreover, the most pronounced changes were found in children with the oligoarthritic variant of JIA.

4. Discussion

The articular-visceral form was observed in 10 patients examined by us and was clinically characterized by a high temperature reaction of an intermittent nature, not decreasing with antibiotic treatment. Against the background of fever, patients developed a polymorphic rash of a bright pink color. An increase in all groups of peripheral lymph nodes was characteristic. Several joints were involved in the process - knee, ankle, elbow, neck. All joints were painful and swollen. An increase in the size of the liver and spleen was noted.

Functional studies allow us to evaluate the functional activity of joints and determine the patient's functional class in accordance with the Steinbrocker criteria. The distribution of the patients we examined by Steinbrocker functional classes is presented in Table 5.

Table 4

Steinbrocker 's functional class of the patient

No.	Classes	abs .	M ± m, %
1	I class functional capacity of joints is preserved	-	-
2	II - class limitation of functional ability of joints, without limitation of ability to self-care	35	41,6 ±0,58
3	III - limitation of the functional capacity of the joints, accompanied by a limitation of the ability to self-care	44	52,4 ±0,59
4	IV class - the child does not take care of himself, needs outside help, crutches, etc.	5	6.0±0.28

As can be seen from the table, the majority of patients examined by us had functional class III according to Steinbrocker , i.e. there was a limitation of the functional ability of the joints, accompanied by a limitation of the ability to self-care. This was characteristic mainly of the acute period of the disease. In the remission phase, the majority of patients had functional class II according to Steinbrocker .

5. Conclusion

1. Our studies have shown that in children with JIA, especially in the polyarthritic variant, there is a significant imbalance in the production of proinflammatory IL-1β, IL-6, IL-17a increases by 2.6; 1.5; 3.6 times, TNF-a decreases by 1.5 times.

2. Based on a set of clinical, laboratory, instrumental and functional research methods, the clinical variant of the disease, its degree of activity, and the characteristics of its course have been clarified. All this is the basis for developing a set of therapeutic measures.

3. The use of a prognostic approach to determine the threat of an unfavorable outcome of JRA is a modern and effective way to prevent disease progression and select the most optimal therapeutic option.

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