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THE ROLE OF GENE POLYMORPHISM IN THE DEVELOPMENT OF JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN

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Abstract
The article describes the clinical and laboratory features of juvenile idiopathic arthritis and the consequences of the disease after treatment with chronotherapy. 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, chronotherapy.

Introduction

IN Currently, there is an increase in the number of rheumatic diseases among various segments of the population in the world, the widespread prevalence of juvenile idiopathic arthritis among children is of great importance as an urgent problem, occupying a special place [1,2,4,12,16]. In Europe, juvenile idiopathic arthritis occurs in 16 out of 100,000 children, the disease is observed in children of pubertal age, is accompanied by signs of inflammation in the joints for a long time, has limited mobility in several joints and causes early disability in children with juvenile idiopathic arthritis. In this regard, despite the extensive experience in the diagnosis and treatment of juvenile idiopathic arthritis, it is necessary to improve the effectiveness of early diagnosis, treatment and prevention of the disease [10,11,13,14,15,17,18] .

In idiopathic arthritis, proinflammatory cytokines act for a long time, which ultimately leads to prolonged inflammation with damage to the structure and function of the joints. One of the important factors in the pathogenesis of IA is the activation of T-lymphocytes with a predominance of the synthesis of proinflammatory cytokines, the effects of which are associated with the appearance of inflammatory changes in the joints, the progression of bone and cartilage destruction, and the development of a systemic inflammatory response. TNF-α and IL-1 have been studied most thoroughly, since they play an important role in the pathogenesis of joint destruction. Both of these cytokines are found in high concentrations in the synovial fluid of the joints and in the blood serum of patients with IA. IL-1 as a genetic marker of RA. The genes for IL-1 and IL-1RA are located on chromosome 2 and are candidate genes in the development of RA [3, 5,6,7,8,9] .

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The aim of the study is to study the clinical and genetic characteristics of juvenile idiopathic arthritis and determine prognostic criteria for the outcome of the disease.

Material and Methods

The study involved 364 children aged 3 to 16 years (mean age 11) with juvenile idiopathic arthritis, including 312 (85.71%) with the articular form and 52 (14.28%) with the systemic variant of the disease. Of the examined patients, 170 (46.7%) were boys and 194 (53.2%) were girls. The patients were divided into 2 groups depending on the therapy: 54 patients formed the main group, who received chronotherapy nimesulide and 30 patients on traditional NSAID therapy formed the comparison group. The control group consisted of 20 practically healthy children.

When diagnosing JIA, we were guided by the diagnostic criteria of JIA adopted in Russia. The frequency of occurrence of diagnostic clinical criteria of JIA among the patients examined by us is presented in Table 1.

Table 1. Frequency of occurrence of clinical criteria for JIA

No.	Clinical signs	abs .	%
1	Arthritis lasting 3 months or more	364	100
2	Arthritis of the second joint, which developed after 3 months and later	287	86.9
3	Symmetrical lesions of small joints	126	71.4
4	Joint contractures	110	47.6
5	Tenosynovitis or brucitis	64	51.2
6	Muscle atrophy (usually regional)	1 9	17.8
7	Morning stiffness	254	81.0
8	Rheumatoid eye disease	16	8.3
9	Rheumatoid nodules	19	22.6
10	Joint effusion	129	65.4

As can be seen from the table, the absolute majority of patients examined by us were characterized by such criteria as arthritis lasting 3 months or more, morning stiffness, arthritis of the second joint occurring 3 months or later, symmetrical damage to small joints, effusion into the joint cavity. Pain, swelling, deformation and limitation of movement, and increased skin temperature were observed in the affected joint. Large and medium joints were most often affected - knee, ankle, wrist, elbow, hip. In 110 (11.9%) patients, damage to the cervical spine was noted.

Clinical manifestations of JIA in the patients we examined were characterized by significant polymorphism of symptoms. Analysis of the anamnesis showed that the first clinical signs of the disease appeared 6 months to 2 years before the diagnosis of the disease.

At the onset of the disease, the absolute majority (86.9%) of patients examined by us had a deterioration in their general condition: weakness, morning stiffness, arthralgia, weight loss, subfebrile fever. All these symptoms, as a rule, preceded clinically expressed

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joint damage. In addition, 58.3% of patients with active joint syndrome had extra-articular manifestations: development of muscle atrophy located proximal to the joint involved in the pathological process, general dystrophy, growth retardation.

Result and Discussion

Distribution frequency and assessment of the relationship of polymorphic variants of the IL -1 gene β (T – 31C) on the development and course of JIA

For the purpose of genetic research, peripheral blood of 59 children with JIA was used. As a control group, data on the frequency of occurrence of genes and genotypes obtained during the study of 60 children without JIA at the Research Institute of Hematology and Blood Transfusion of the Ministry of Health were used . Ruz in the laboratory of "Molecular Medicine and Cellular Technologies". Children of the main group were divided into two subgroups: Ia subgroup – 42 with articular form and , Ib subgroup – 17 children with articular-visceral form. We determined the frequency of occurrence and structure of the polymorphism of the IL – 1 b (T – 31C) genes from the factors of JIA development.

Distribution of allele and genotype frequencies of IL – 1 b (T – 31C) polymorphism in the control group and children with articular and articular-visceral forms of JIA are presented in Table 2

Table 2 Distribution of the frequency of alleles and genotypes of the IL - 31C1 b (T-) polymorphism in the observation groups

Group	Allele frequency				Frequency distribution genotypes					
	T		C		T /T		T/C		C/C	
	n	%	n	%	n	%	n	%	n	%
Group I , main (n = 59)	98	83.05	20	16.95	41	69.49	16	27.12	2	3.39
Subgroup Ia , articular form (n = 42)	70	83.33	14	16.67	28	66,67	12	28.57	2	4.76
Subgroup Ib , articular-visceral form (n = 17)	30	88.24	4	11.76	13	76.47	4	23.53	0	0
Control group (n = 60)	107	89.17	13	10.83	48	80	11	18.33	1	1.67

We analyzed statistical differences between the expected and observed genotype frequencies according to the Hardy– Weinberg equilibrium (HWE) of the rs 1143627 polymorphism .

Thus, the analyzed nature of the distribution of genotypes of the rs 1143627 gene polymorphism revealed the independent nature of its association with the risk of serious disorders in children with JIA and proves the participation of the allelic variant rs 1143627 in the pathogenetic mechanism of the development and course of JIA.

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The polyarticular variant of JIA was observed in 35 examined patients, of whom 6 were seropositive for rheumatoid factor. In the seropositive subtype was characterized by a subacute onset with symmetrical polyarthritis. As a rule, the joints of the hand and feet were affected. Structural changes in the joints developed in the first 6 months of the disease. By the end of the first year of the disease, ankylosis had formed in the wrist joints of 2 patients. Destructive arthritis developed in 1 patient. According to the literature, this form of JIA is an early debut of rheumatoid arthritis in adults.

Seronegative The subtype had a subacute onset and was also associated with symmetrical polyarthritis. The course of arthritis was relatively benign.

Some features of the articular syndrome were established depending on the form of the disease, the nature of the course of JIA, sex and age of 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). Later, the wrist and elbow joints were most often added. In this case, the process progressed moderately and productive changes prevailed. Radiologically, mainly grade II according to Steinbrocker was determined. With an acute onset of this variant of the disease , the wrist, metacarpophalangeal and interphalangeal joints of the hand were most often involved in the process.

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.

In 4 patients the disease was accompanied by kidney damage, in 3 patients by heart damage, in 1 by lung damage, in 2 patients there were combined damages of internal organs. In 1 preschool-aged girl the disease was of the Still's syndrome type, and in 1 boy by the Wissler - Fanconi syndrome type . In systemic forms the joint syndrome also had its own distinctive features. Thus, 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. The duration of the arthralgia period without distinct signs of arthritis in this patient was 1.5 months. Then exudative and productive changes in the joints with rapid development of erosions and erosions joined in . The joint syndrome was most fully represented in Still's disease. In one girl patient with this form of the disease, generalized joint syndrome with involvement of the joints of the hand, foot, cervical spine, maxillotemporal, and larger joints developed at the earliest stages. The initial exudative phase was quickly replaced , over 2-3 months, by productive processes, erosions, and destruction of cartilage, leading to early ankylosis in the wrist joints.

Therapy of various forms of JIA, especially severe, progressive ones, is a difficult task, requiring joint efforts of the doctor, the sick child, his parents and the family as a whole.

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Effective therapy leads to remission of the disease and improvement of the patient's quality of life. The emergence in recent years of new biological agents (infliximab , etanercept, rituximab , adalimumab , etc.), significantly affecting the course of the disease, and the first experience of using some of them gives hope for improving the outcome of the disease.

Conclusions

1. Based on a set of clinical, genetic 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.
2. The use of a prognostic approach to determine the threat of an unfavorable outcome of JIA is a modern and effective way to prevent disease progression and select the most optimal therapeutic option.

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