

Breastfeeding and Genetic Features of Juvenile Rheumatoid Arthritis

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Abstract

The article describes the clinical and genetic features of juvenile rheumatoid arthritis and the consequences of the disease after treatment with chronotherapy. The clinical features of the disease, the results of laboratory analysis are important when choosing an effective treatment method. An effective treatment method is characterized by a faster onset of remission, an extension of its duration and a decrease in the side effects of drug treatment. The benefits of breastfeeding for babies are well known, but there is growing evidence that breastfeeding has a positive impact on a mom's health as well. Research shows that breastfeeding lowers a risk for juvenile rheumatoid arthritis.

Keywords: Juvenile Rheumatoid Arthritis, Prognosis, Chronotherapy, Breastfeeding.

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INTRODUCTION

Currently, there is an increase in the number of rheumatic diseases among various segments of the world's population, and the widespread spread of juvenile rheumatoid arthritis among children is of great importance as an urgent problem that occupies a special place. In Europe, juvenile rheumatoid arthritis occurs in 16 out of 100,000 children, the disease is observed in pubertal and in puberty children, is accompanied for a long time by signs of inflammation in the joints, has limited mobility in several joints and causes early disability in children with juvenile rheumatoid arthritis. In this regard, despite extensive experience in the diagnosis and treatment of juvenile rheumatoid arthritis, it is necessary to improve the effectiveness of methods of early diagnosis, treatment and prevention of the disease.

There are many factors that trigger the development of the disease. The most frequent cases are viral or mixed bacterial-viral infection, joint injury, excessive sun exposure or hypothermia, and preventive vaccinations carried out against or immediately after an acute respiratory infection (ARI) of a viral or bacterial nature [3, 11]. In rheumatoid arthritis, proinflammatory cytokines are long acting,

resulting in prolonged inflammation with damage to the structure and function of the joints. One of the important factors in the pathogenesis of RA is the activation of T-lymphocytes with a predominance of the synthesis of pro-inflammatory cytokines, the effects of which are associated with the appearance of inflammatory changes in joints, the progression of bone and cartilage destruction, and the development of a systemic inflammatory response. TNF- α and IL-1 are the most well-studied, as 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 joints and in the blood serum of patients with RA. IL-1, as a genetic marker of RA. The IL-1 and IL-1RA genes are located on chromosome 2 and are candidate genes for the development of RA.

The dynamics of clinical and laboratory manifestations of juvenile rheumatoid arthritis (JRA) is one of the widely discussed problems of rheumatology, the relevance of which is determined by two main aspects—the features of the course of the disease in children with different types of onset and the effectiveness of various approaches to basic therapy. The results of retrospective studies of JRA reflect the authors' controversial opinions about the age-related

evolution of the disease – the number of patients with continuous progression of the disease varies from 33% to 75 %, some researchers believe that only 10-20% of patients have serious disability, and the majority of children have a favorable course of the disease [1-4]. At the same time, the literature also presents negative dynamics of the course of JRA – the development of severe functional deficit in 30% of cases and disability in 51.5% of patients with various debut variants.

The development and progression of JRA is determined by a complex combination of genetically determined and acquired defects in regulatory mechanisms that limit the pathological activation of the immune system in response to potentially pathogenic and often physiological stimuli. Juvenile progression is a dynamically developing process that is conventionally divided into several stages:

- The early stage is characterized by distinct activation process in lymphocytes of peripheral blood and synovial fluid, increase of the level in the synovial tissue of activated CD4+ T-lymphocytes and cytokines macrophage origin, proinflammatory and destructive activity which plays a crucial role in the defeat of the joints, as well as an intense synthesis of antibodies in peripheral blood, leading to the formation of immune complexes caused by b-cell activation; [10,12]
- The advanced stage is manifested by impaired angiogenesis, endothelial activation, cell migration, infiltration by activated CD4+ T-lymphocytes of synovial tissue, formation of rheumatoid factors and immune complexes, synthesis of "pro-inflammatory" cytokines, prostaglandins, collagenase, metalloproteinases.
- The late stage is characterized by defects in synovial cell apoptosis [7,8].

This suggests that it is in the first few years after the onset of the disease that the course of JRA is particularly aggressive, and therefore most researchers consider it necessary to draw attention to the diagnosis and treatment of the early stage of JRA.

Corticosteroids attract the most attention among the drugs used taking into account the daily rhythm. It is for the treatment of these hormones that the simulation method was developed, since it was found that minimal changes in the function of the adrenal cortex are observed when corticosteroids are prescribed only in accordance with the natural daily rhythm of their secretion. When treating with corticosteroids, the opposite direction of action in the body of cortisol and aldosterone is taken into account. In this regard, the activity of mineralocorticoids (pro-inflammatory hormones) can be suppressed by the introduction of an adequate dose of glucocorticoids (anti-inflammatory hormones) in the afternoon. Based on the data on the daily rhythm of pro-inflammatory and anti-inflammatory hormones in the body, it can be assumed that NSAIDs have

a more pronounced effect in the afternoon and evening. The literature analysis shows aggressiveness and a high probability of disability in children with JRA. Traditional therapy of the disease is not always effective, which dictates the need to search for new effective methods of treating this disease. The chronotherapy method makes it possible to increase the effectiveness of treatment while simultaneously reducing the doses of the drugs used, as a result of which their side effects are reduced and the cost of treatment is reduced.

PURPOSE OF THE STUDY

To study the clinical and genetic features of juvenile rheumatoid arthritis and determine prognostic criteria for the outcome of the disease.

MATERIAL AND METHODS

The study included 84 children aged 3 to 16 years (mean age 11) with juvenile rheumatoid arthritis, including 74 (%) patients with the articular form, 10 (%) with the systemic variant of the disease. Of the examined patients, 47(56%) were boys and 37(44%) were girls. Patients were divided into 2 groups depending on the therapy performed: 54 patients were the main group who received chronotherapy with nimesulide and 30 patients on traditional NSAID therapy were the comparison group. The control group consisted of 20 practically healthy children.

When making the diagnosis of JRA, we were guided by the diagnostic criteria of JRA accepted in Russia. The frequency of occurrence of diagnostic clinical criteria for JRA among the patients examined by us is presented in Table 1.

Table 1: Frequency of occurrence of JRA clinical criteria

№	Clinical signs of	abs.	%
1	Arthritis lasting 3 months or more	84	84,100
2	Arthritis of the second joint that occurred after 3 months and later	73	86.9
3	Symmetrical lesion of small joints	60	71.4
4	Joint contractures	40	47.6
5	Tendosynovitis or brucitis	43	51.2
6	Muscle atrophy (more often regional)	15	17,8
7	Morning stiffness	68	81.0
8	Rheumatoid eye	7	8,3
9	Rheumatoid nodules	19	22.6
10	Effusion into the joint cavity	55	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 that occurred after 3 months or later, symmetrical damage to small joints, effusion into the joint cavity. The affected joint showed pain, swelling, deformity and restricted movement, and increased skin temperature. Large and medium joints – knee, ankle, wrist,

elbow, hip-were more often affected. 10 (11.9 %) patients had a lesion of the cervical spine.

The clinical manifestations of JRA in the examined patients were characterized by a significant polymorphism of symptoms. Anamnesis analysis showed that the first clinical signs of the disease appeared 6 months-2 years before the diagnosis of the disease.

At the onset of the disease, the absolute majority (86.9%) of the examined patients showed a deterioration in their general condition: weakness, morning stiffness, arthralgia, weight loss, and low-grade fever. All these symptoms, as a rule, preceded clinically expressed joint damage. In addition, 58.3% of patients with active joint syndrome had extra articular manifestations: the development of muscle atrophy located proximal to the joint involved in the pathological process, general dystrophy, and growth retardation.

data on the frequency of occurrence of genes and genotypes obtained during a study in 60 children without JRA at the Research Institute of Hematology and Blood Transfusion of the Ministry of Health of the Republic of Uzbekistan in the laboratory of "Molecular Medicine and Cellular Technologies". Children of the main group were divided into two subgroups: Ia subgroup-42 children with articular form and Ib subgroup-17 children with articular-visceral form. We determined the frequency of occurrence and structure of the IL -1b (T-31C) gene polymorphism from JRA development factors.

The distribution of the frequency of alleles and genotypes of the IL -1b (T-31C) 31C) polymorphism in the control group and children with articular and articular-visceral JRA is presented in Table 2.

RESULT AND DISCUSSION

Frequency of distribution and evaluation of the relationship of polymorphic variants of the IL - 1 B (T-31C) gene on the development and course of Jurassic period

For the purpose of genetic research, peripheral blood of 59 children with JRA was used. As a control group, we used

Table 2: Frequency distribution of IL - 1b polymorphism alleles and genotypes (T-31C31C) in the observation groups

Group	Frequency of alleles				Frequency of genotype distribution					
	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 (RCB) of the rs 1143627

polymorphism.

Table 3: Frequency distribution of alleles and genotypes polymorphism of the rs 1143627 polymorphism of the IL -1b (T-31C31C) gene in the main group

SNPrs	Localization		Genotype	Frequency of the genotype		Significance of differences in PCV	
	chromosomal	gene		observed (H _{obs})	expected (H _{exp})	χ ²	P
1143627	1p36. 22	11796321	C / C	0.03	0.03	0.05	0.1
			C / T	0.27	0.28		
			T/T	0.69	0.69		
			total	1.00	1.00		

As can be seen from the data in Table. 2, 3 polymorphism rs 1143627 was characterized by the presence of all possible genotypes in children in the observation groups. At the same time, both in the main group and in the control group, the

genotype frequencies actually obtained are consistent with the expected frequencies of their distribution, i.e., the distribution of genotypic frequencies does not deviate from the RCV (χ²<3.8; p>0.05).

This means that approximately 35% of children with JRA carry the functionally unfavorable T allele in the heterozygous state (Table 1). At the same time, the control group, on the contrary, showed an insignificant deficit of the heterozygous C/T genotype (0.29/0.35, respectively; $p=0.1$).

The level of observed heterozygosity of the rs1143627 polymorphism in the control group was lower than expected ($D=-0.04$). For children of the main group, the indicator H had a rather high positive value, i.e. it was less than >0 ($H=->0.17$) (Table 1), which makes it possible to predict the effect of the heterozygous C/T genotype of the IL - 1 β (T-31C) polymorphism on the formation of the disease.

Thus, the analyzed 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 JRA and proves the involvement of the rs 1143627 allele variant in the pathogenetic mechanism of JRA development and course.

Polyarticular JRA was observed in 35 examined patients, 6 of whom were seropositive for rheumatoid factor. The seropositive subtype had 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, 2 patients developed ankylosis in the wrist joints. 1 patient developed destructive arthritis. According to the literature, this form of JRA is an early onset of adult rheumatoid arthritis.

The seronegative subtype had a subacute onset, and symmetrical polyarthritis was also noted. 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 JRA, gender 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 were most often affected. At the same time, the process progressed moderately and productive changes prevailed. X-raylogically determined mainly II grade II according to Steinbrocker. In the acute onset of this variant of the disease, the wrist, metacarpophalangeal, and interphalangeal joints of the hand were 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, which is intermittent and does not decrease during antibiotic treatment. Against the background of fever, patients had a polymorphic rash of bright pink color. An increase in all groups of peripheral lymph nodes was characteristic. Several joints were involved in the process – knee, ankle, elbow, and neck. All the joints were painful and swollen. There was an increase

in the size of the liver and spleen.

In 4 patients, the disease occurred with kidney damage, in 3 patients with heart damage, in 1 with lung damage, in 2 combined lesions of internal organs were noted. In 1 preschool-aged girl, the disease was Still syndrome - like, and in 1 boy, it was Wissler-Fanconi syndrome-like. 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 the large (knee, hip) and medium (ankle, wrist, and elbow) joints without visible changes in them. The duration of the arthralgia period without clear signs of arthritis was 1.5 months in this patient. Then there were exudative and productive changes in the joints with the rapid development of users and erosions. The articular syndrome in Still's disease was most fully presented. One sick girl with this form of the disease developed generalized joint syndrome at the earliest stages, involving the joints of the hand, foot, neck, maxillofacial spine, as well as larger joints. The initial exudative phase was quickly replaced by productive processes, erosion and destruction of cartilage, which led to early ankylosis in the wrist joints.

From the instrumental methods of research, we conducted an X-ray study, which allows us to judge the degree of joint damage and determine the stage of anatomical changes in accordance with the Steinbrocker criteria. In the first months of the disease, the main radiological indicator is epiphyseal osteoporosis, small-cystic reconstruction of the bone structure of the epiphysis. Then erosion occurs. The frequency of occurrence of JRA radiological criteria according to the Steinbrocker criteria is presented in Table 4.

Table 4: Frequency of occurrence of JRA radiological criteria

Stages	Signs of	abs.	%
1	Epiphyseal osteoporosis	53	63.1
2	Narrowing of the articular fissure, single erosions	27	32,1
3	Destruction of cartilage and bone	3	3,6
4	Fibrous and bone ankylosis	1	1,2

As can be seen from the table, half of the patients we examined had the first stage of anatomical changes according to Steinbrocker, i.e. epiphyseal osteoporosis, in 1/3 of the patients we found narrowing of the joint gap and the presence of single erosions. Destruction of cartilage and bone occurred in three patients with a disease duration of more than 3 years. Ankylosis was formed in one sick girl with Still's syndrome.

Therapy of various forms of JRA, especially severe and progressive ones, is not an easy task, requiring joint efforts of the doctor, the sick child, his parents and the family as a whole. Effective therapy leads to achieving remission of the disease and improving the patient's quality of life. The

appearance in recent years of new biological agents (infliximab, etanercept, rituximab, adalimumab, etc.) that significantly affect the course of the disease, and the first experience of using some of them gives hope for improving the outcome of the disease.

We have developed algorithms for predicting the health status of schoolchildren. In the table below, compiled on the basis of Wald's sequential analysis, each of the features has its own numerical value with the sign (+) or (-). The numerical threshold for making a certain conclusion (with 95% probability) is ± 13 . It is obtained by algebraically adding the predictive coefficients of each feature proposed in the table. When forecasting, it is assumed as the main condition that the student will be in certain standard conditions of existence, receive currently generally accepted drugs for the treatment of diseases, etc., It is excluded, or rather partially refers to the forecast error, deviations, both for the worse and for the better.

In the presented algorithms, approximately 5% forecast error is planned. The discrepancy between the forecast and reality is due to two reasons. Firstly, at the time of making the forecast, all influencing factors are not taken into account; secondly, the child's health status is affected by factors that have joined later, are not valid and therefore are not taken into account at the time of making the forecast. It is quite clear that if the doctor can take these factors into account from the first stage of the examination and anticipate their occurrence, the accuracy of the prognosis increases.

The presence of prognostically unfavorable signs: active disease (a large number of painful and swollen joints), the presence of erosions at an early stage, increased RF, increased ESR and/or CRP gives grounds to predict the progression of the disease and a high risk of disability of the patient. Poor prognosis in JRA also means radiological progression of joint destruction, the formation of an irreversible decrease in the function of the musculoskeletal system, an increase in the risk of needing joint surgery, and a decrease in the life expectancy of patients.

Juvenile idiopathic arthritis (JIA) is considered to be an autoimmune disease, but the etiology is unknown. We decided to study the influence of early nutrition on later development of JIA.

An increased risk for JIA was found in children who had breast fed for less than 6 months, as opposed to those who were continued on breast milk beyond 6 months of age (aOR 3.5, 95% CI 1.4-7.5; $p = 0.006$). A short duration of exclusive as well as total breastfeeding was associated with an increased risk of JIA (aOR 1.3, 95% CI 1.1-1.4; $p = 0.008$ and aOR 1.2, 95% CI 1.1-1.3; $p < 0.001$). All associations between breastfeeding and JIA persisted after adjustment. There was no relationship between early nutrition and non-chronic arthritis. Our results indicate that there are different disease mechanisms for different types of arthritis in childhood. Longer duration of breastfeeding

(both total and exclusive) may protect against development of JIA. Mothers should be encouraged to breast-feed their babies exclusively, if at all possible, for 6 months and continue partial breastfeeding for an extended time when foreign proteins are introduced.

Predicting an unfavorable outcome is not fatally inevitable, it should mobilize all the forces and means of modern medicine to prevent such an outcome.

CONCLUSION

1. Based on a complex of clinical, laboratory, instrumental and functional research methods, the clinical variant of the disease, its degree of activity, and course features were clarified. All this is the basis for the development of a complex of therapeutic measures.
2. Breastfeeding for at least two years decreased the risk of rheumatoid arthritis by 50%. This was total time spent breastfeeding all children. Breastfeeding for less than one year total did not decrease rheumatoid arthritis risk.
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 the progression of the disease and choose the most optimal therapeutic option.

REFERENCES

- Akulova S.S., Semikina Ye. L., Filyanskaya Ye. G., Zakirov R. Sh., Mayanskiy N.A., Valieva S.I., Bzarova T.M. Sposobnost limfotsitov krovi k produktii tsitokinov u detey s yuvenilnim idiopatsicheskimi artritami na fone biologicheskoy terapii. // *Meditinskaya immunologiya*. 2015. T. 17. № S. S. 119.
- Bagatskaya N.V., Medzyanovskaya Ye.V. Tsitogeneticheskie osobennosti v limfotsitax perifericheskoy krovi in vitro bolnix s razlichnymi variantami techeniya yuvenilnogo revmatoidnogo artrita. // *Vestnik problem biologii i meditsin*. 2015. T. 2. № 4 (125). S. 248-252.
- Vinokurova F.V., Golderova A.S., Yefremova S.D., Tixonova O.G., Grigoreva L.V. TSitokinovy profil u detey s yuvenilnimi formami artritov. // *Yakutskiy meditsinskiy jurnal*. 2015. № 4 (52). S. 83-85.
- Davidova M.A. Razvitiye i prognoz destruktivnykh izmeneniy sustavov u detey s yuvenilnim idiopatsicheskimi artritami. // *Voprosy prakticheskoy pediatrii*. 2017. T. 12. № 3. S. 46-53.
- Jolobova Ye.S., Shaxbazyan I.Ye., Torosyan G.G. Diagnostika i lechenie sistemnoy form yuvenilnogo idiopatsicheskogo (revmatoidnogo) artrita // *Doktor.Ru*. 2012. № 6 (74). S. 30-33.
- Igisheva L.N., Pritchina S.S., Kulchitskaya N.G., Tsukanova A.V., Bkova Yu.A. Opit vedeniya patsienta s sistemnim variantom yuvenilnogo idiopatsicheskogo artrita. // *Mat i ditya v Kuzbasse*. 2015. № 2 (61). S. 105-108.
- Kaladze N.N., Sarchuk Ye.V. Osobennosti strukturno-funktsionalnogo sostoyaniya kostno-mishechnoy sistem u bolnix s yuvenilnim revmatoidnim artritami. // *Zdorove rebenka*. 2012. № 4 (39). S. 52-56.
- Kojevnikov A.N., Moskalenko M.V., Pozdeeva N.A., Novik G.A., Larionova V.I. Rol narusheniy apoptoza v formirovaniy yuvenilnogo idiopatsicheskogo artrita. // *Pediatricheskaya farmakologiya*. 2012. T. 9. № 3. S. 52-57.
- Kostik M.M., Chikova I.A., Isupova Ye.A., Dubko M.F., Masalova V.V., Lixacheva T.S., Snegiryova L.S., Gaydar Ye.V., Kalashnikova O.V.,

- Chasnk V.G. Primenenie tosilizumaba u 40 patsientov s poliarhtikulyarnym variantom yuvenilnogo idiopaticeskogo artrita: rezultat retrospektivnogo issledovaniya. //Vopros sovremennoy pediatrii. 2017. T. 16. № 2. S. 148-155.
- Krasnopolskaya A.V., Soldatova O.N., Samoshkina Ye.S., Il'yokina N.V., Balkova L.A. Opt primeneniya tosilizumaba pri sistemnom variante yuvenilnogo idiopaticeskogo artrita. //Vopros sovremennoy pediatrii. 2015. T. 14. № 5. S. 579-585.
- Kulakova G.V., Glushkova T.A. Otsenka effektivnosti protivorevmaticheskoy terapii u patsientov s yuvenil artriti.// Nauchne stremleniya. 2015. № 13. S. 5-8.
- Ledyayev M.Ya., Jukova Yu.A., Zolotareva N.M., Koroleva M.M., Gluxova G.I., Ananeva Ya.A. Opt primeneniya immunosuppressivnoy terapii u bolnix tyazelim yuvenilnim revmatoidnim artritom. //Lekarstvennyy vestnik., 2012. T. 6. № 7 (47). S. 22-25.
- M'Rabet L, Vos AP, Boehm G, Garssen J. Breast-feeding and its role in early development of the immune system in infants: consequences for health later in life. *J Nutr.*, 2008; 138(9): 1782S–1790S. [PubMed] [Google Scholar]
- Rosenberg AM. Evaluation of associations between breast feeding and subsequent development of juvenile rheumatoid arthritis. *J Rheumatol.*, 1996; 23(6): 1080–1082. [PubMed] [Google Scholar]
- Ellis JA, Ponsonby AL, Pezic A, Chavez RA, Allen RC, Akikusa JD, et al. CLARITY - Childhood arthritis risk factor identification study. *Pediatric rheumatology online journal.* 2012; 10(1): 37. [PMC free article] [PubMed].