

## CLINICAL COURSE OF JUVENILE RHEUMATOID ARTHRITIS AND ITS TREATMENT OPTIMIZATION

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✓ **Resume**

*The article presents the clinical course of juvenile rheumatoid arthritis and the effectiveness of chronotherapy in treatment. Nonsteroidal anti-inflammatory drugs administered with chronotherapy have been found to be effective in juvenile rheumatoid arthritis and chronic arthritis. This disease is characterized by a more rapid onset of remission, an increase in its duration and a decrease in the side effects of drugs.*

*Key words: juvenile rheumatoid arthritis, nonsteroidal anti-inflammatory drugs, chronotherapy.*

## ЮВЕНИЛ РЕВМАТОИД АРТРИТНИ КЛИНИК КЕЧИШИ ВА УНИ ДАВОЛАШНИНГ ОПТИМАЛ УСУЛИ

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✓ **Резюме**

*Мақолада ювенил ревматоид артритнинг клиник кечиши ва даволашда хронотерапия усулини самараси келтирилган. Хронотерапия усули билан берилган ностероид яллигланишга қарши препаратлар ювенил ревматоиднинг бугим шаклида ва узок кечувчи артритларда самарали эканлиги аниқланди. Бу касалликнинг ремиссия даврини тезроқ бошланиши, унинг муддатини узайиши ва доривор препаратларнинг ножўя таъсирини камайиши билан ифодаланади.*

*Калит сўзлар: ювенил ревматоид артрит, ностероид яллигланишга қарши препаратлар, хронотерапия.*

## КЛИНИЧЕСКОЕ ТЕЧЕНИЕ ЮВЕНИЛЬНОГО РЕВМАТОИДНОГО АРТРИТА И ЕГО ОПТИМИЗАЦИЯ ЛЕЧЕНИЯ

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✓ **Резюме**

*В статье представлены клиническое течение ювенильного ревматоидного артрита и эффективность хронотерапии в лечении. Было обнаружено, что нестероидные противовоспалительные препараты, вводимые при хронотерапии, эффективны при ювенильном ревматоидном артрите и хроническом артрите. Это заболевание характеризуется более быстрым наступлением ремиссии, увеличением ее продолжительности и уменьшением побочных эффектов лекарств.*

*Ключевые слова: ювенильный ревматоидный артрит, нестероидные противовоспалительные препараты, хронотерапия.*

**Relevance**

Juvenile rheumatoid arthritis is one of the most common disabling rheumatic diseases in infants. Functional disability often occurs at an early stage of the disease. In this regard, the improvement of methods for treating JRA seems to be extremely important [1, 2]. There are many factors that activate the mechanism of disease formation. The most common are viral or mixed bacterial-viral infection, joint injury, excessive insolation or frostbite, preventive vaccinations carried out against the background or immediately after an acute respiratory infection (ARI) of a viral or bacterial nature.

The development and progression of JRA is determined by a difficult combination of genetically determined and acquired deficiencies in regulatory mechanisms that limit the pathological activation of the immune system in response to potentially bacterial and often physiological stimuli. The development of JRA is a dynamically developing process, conditionally subdivided into several stages:

The early stage is characterized by a pronounced activation process in peripheral blood lymphocytes and

synovial fluid, an increase in the level in the synovial tissue of activated CD4 + T-lymphocytes and macrophage cytokines, the pro-inflammatory and destructive activity of which plays a decisive function in joint damage, as well as intensive synthesis of antibodies in peripheral blood, leading to the formation of immune complexes caused by B-cell activation.

With all pathological processes in the body, the temporary organization of physiological functions is disturbed, the depth of which correlates with the severity of the disease. Medicines must be used taking into account the rhythm of the body's sensitivity to their effects. In recent years, the chronopharmacological approach to the treatment of diseases has been gaining wider acceptance, since it reflects the modern principle of individual, effective and safe drug therapy for a particular patient [3, 4].

In recent years, scientific research devoted to chronotherapy has intensified abroad. The results of scientific research confirm the high effectiveness of the above treatment approach.

Neudakhin E.V. (2018), based on long-term studies of circadian biorhythm in various diseases in infants: atopic

dermatitis, malnutrition (PEM), cystic fibrosis, established the high efficiency of the chronopharmacological approach to treatment.

Dhaon P., et al (2018) found that oral divided doses of methotrexate in patients with rheumatoid arthritis are better than an oral single dose and are similar to parenteral administration of methotrexate in terms of effectiveness [5].

The main problems of JRA treatment are the achievement of clinical remission and the preservation of a good quality of life for the longest possible period: relief of pain, stiffness and swelling of the joints, a decrease in the severity of common symptoms of the disease - malaise, and decrease in body weight - muscle mass. The JRA treatment plan provides for the use of 4 groups of drugs: 1) non-steroidal anti-inflammatory drugs (NSAIDs); 2) "basic" drugs; 3) glucocorticosteroids (GCS); 4) "biological" agents. One of the most important measures is the early prescription of disease-modifying antirheumatic drugs (PMPP) in RA, which are basic, which provide a slow, gradually developing therapeutic effect, suppressing the clinical, biochemical and immunological manifestations of the rheumatoid process.

Despite the availability of a large number of antirheumatic drugs for the treatment of JRA, an active search for new drugs with the highest efficiency and safety continues. In view of the fact that most BMPPs are canceled within the first 2 years after appointment due to side effects or lack of effectiveness (for example, only 29% of patients take sulfasalazine for more than 5 years) and when taking basic drugs, regular monitoring of the patient's condition is necessary, the search for new methods is urgent. treatment of JRA [7, 9]. It is known that the main pathogenetic factors of JRA leading to joint destruction are cartilage degradation, inflammation in the joint cavity, and proliferation of synovial tissue with the formation of pannus. According to modern data,

Chronotherapy contributes to the further development of the principle of an individual approach to the treatment of patients, which is especially important in pediatrics. Studies devoted to the development of a chronopharmacological approach in the treatment of rheumatoid arthritis with modern NSAIDs were not found in the analysis of the literature, which prompted this study.

Purpose of the study.

To study the dynamics of clinical manifestations of JRA and develop new approaches to the treatment of this disease.

## Materials and methods

Examined 36 patients with JRA (aged 5-16 years); of them 26 (72.2%) with an articular form 10 (27.8%) with an articular-visceral form of the disease. Of the 34 patients, 13 were boys and 21 girls aged 5 to 16 years. The duration of the disease ranged from 3 months to 8 years. None of the patients were taking anticancer drugs during the study. The dynamics of the clinical manifestations of juvenile rheumatoid arthritis was monitored and the chronopharmacological approach to the basic therapy of JRA was substantiated.

## Research results

We established an oligoarthritic variant in 19 (73.1%) patients with the articular form of the disease. 12 of them

had a persistent variant of oligoarthritis, which was characterized by the fact that up to 4 joints were affected during the entire period of the disease. Progressive oligoarthritis was diagnosed in 7 examined patients and it was characterized by an increase in the number of affected joints after 6 months of illness. The polyarticular variant of JRA was detected in 7 (26.9%) examined patients: 3 were seropositive for rheumatoid factor and 4 were seronegative. By the end of the first year of the disease, ankylosis developed in the wrist joints in 2 patients, and destructive arthritis developed in 1 patient.

19 (73.1%) patients received prednisolone and non-steroidal anti-inflammatory drugs (NSAIDs), 7 (26.9%) patients - only NSAIDs (ortofen, indomethacin and ibuprofen).

The articular-visceral form was clinically characterized by a high temperature reaction of an intermittent nature, which did not decrease with antibiotic treatment, as well as an increase in the size of the liver and spleen. The disease proceeded with damage to various organs: in 4 patients - the kidneys, in 3 - the heart, in 1 - the lungs, in 2 - there were combined lesions of the internal organs. All patients received prednisolone (a dose of 1 mg / kg / day, followed by a decrease under the control of clinical and laboratory parameters). 80% of patients received methotrexate (5mg / m<sup>2</sup> of body surface. 1 time per week for a year).

We tested the chronopharmacological approach to the prescription of NSAIDs in patients with JRA. Acrophase of body temperature was used as a simple and very accessible criterion for choosing the time of prescribing drugs to a particular patient. For this purpose, 24-hour thermometry was performed in 20 patients. She showed 2 peaks of an increase in body temperature: in the morning from 5 to 7 o'clock, and in the afternoon from 16 to 20. Considering that the majority of our patients received prednisolone in the morning, we, according to the principles of chronotherapy in the second acrophase of body temperature, recommended that patients take NSAIDs - highly effective nimesulide. The drug was prescribed one hour before the onset of acrophase of body temperature once in a dose of 5-100 mg. Against the background of nimesulide therapy, the patient's condition is clearly improved: the number of involved joints decreases, arthralgia stops or decreases, the duration of morning stiffness decreases, the range of motion in the joints increases. Already after the first 2 weeks of the use of nimesulide, the effectiveness of treatment according to the ACR criteria in 57.6% of patients was 20, in 23% -50, in 3.8% -70. In the rest of the patients, a positive effect was observed by the end of the first month of treatment.

Follow-up observations of patients showed a more stable and prolonged remission - on average 8-12 months. Moreover, the complaints of patients about the side effects of NSAIDs significantly decreased. This gives grounds to consider chronotherapy with COX-2 inhibitors in JRA patients as the most optimal and safe method of treatment.

## Conclusions

1. The progressive nature of juvenile rheumatoid arthritis with damage to many organs has been established, which indicates that the disease is refractory to traditional therapy.

2. The development of a chronopharmakological approach to the treatment of JRA increased the effectiveness of therapy, which is expressed in accelerating the onset of remission, lengthening its duration and reducing the side effects of drugs.

#### REFERENCE LIST:

1. Alten R, Holt R, Grahn A, et al. Morning stiffness response with delayed release of prednisone after an ineffective course of immediate release of prednisone. *Rheumatoid Arthritis scandal*. 2015; 44 (5): 354-358.
2. Vinokurova F.V., Golderova A.S., Efremova S.D., Tikhonova O.G., Grigorieva L.V. Cytokine profile in children with juvenile arthritis. // *Yakutsk Medical Journal*. 2015. No. 4 (52). S. 83-85.
3. Davydova M.A. Development and prognosis of destructive changes in joints in children with juvenile idiopathic arthritis. *Practical issues of pediatrics*. 2017; 12 (3): 46-53.
4. Dhaon P, Das SK, Srivastava R, Agarwal G, Asthana A. Oral methotrexate in split dose weekly versus oral or parenteral methotrexate once weekly in rheumatoid arthritis: a short-term study... *Int J Rheum Dis*. 2018; 21 (5): 1010-1017.
5. Nasonova V.A., Karateev A.E., The use of nimesulide in rheumatology *Journal "Difficult Patient" Archive* 2010; 6-7: 55-60.
6. E.V. Neudakhin Chronotherapy in pediatrics is the basis for increasing the effectiveness of treatment of diseases in children. *Russian Bulletin of Perinatology and Pediatrics* 2018; 63 (6): 7-14.
7. Zholobova E.S., Shakhbazyan I.E., Torosyan G.G. Diagnostics and treatment of the systemic form of juvenile idiopathic (rheumatoid) arthritis // *Doctor of Ru*. 2012. No. 6 (74) .P. 30-33.
8. Kozhevnikov A.N., Pozdeeva N.A., Konev M.A., Melchenko E.V., Kenis V.M., Novik G.A. Juvenile arthritis, differential diagnosis: CACP syndrome. // In the book: the days of rheumatology in St. Petersburg - 2016 // Collection of abstracts of the congress with international participation. 2016.S. 109-111.
9. G. V. Kulakova, T. A. Glushkova Evaluation of the effectiveness of antirheumatic therapy in patients with juvenile arthritis. // *Scientific aspirations*. 2015. No. 13. P. 5-8.
10. Lagoda N.V. Comparative analysis of the effectiveness of basic drugs in the treatment of juvenile idiopathic arthritis in children. // In the book: Student science and medicine of the XXI century: traditions, innovations and priorities collection of materials of the IV All-Russian (78th Final) student scientific conference. Samara State Medical University. 2010.S. 196-197.

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