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# Significance of Juvenile Idiopathic Arthritis in Pediatric-Phthisiatric Practice (Review)

Juvenile idiopathic arthritis (JIA) is a heterogeneous group that includes all forms of childhood chronic arthritis (joint inflammation lasting more than 6 weeks) of unknown cause in children under 16 years of age. JIA is the most common rheumatic disease in childhood (with an annual incidence from 1.6 to 23.0 new cases per 100,000 adolescents) and is characterized by an often hidden onset and a chronic relapsing course after diagnosis. Tuberculosis plays a special role among opportunistic infectious diseases in JIA, because rheumatic diseases are associated with an increase in the overall risk of developing tuberculosis. Children's phthisiologists often deal with the differential diagnosis difficulty of tubercular lesions of the joints with JIA, and first of all, with oligoarthritis. Clinical symptoms in JIA can be very diverse, and some characteristics of arthritis, not necessarily significant in JIA diagnosis, may have multiple etiologies that need to be carefully differentiated. It was detected during review that JIA is of urgent importance in children's phthisiatric practice due to various reasons: oligoarthritis in JIA has similar clinical manifestations as in tuberculosis arthritis, which significantly complicates differential diagnosis and delays timely treatment of a correctly diagnosed disease; there is a high frequency of diagnosis of latent tuberculosis infection (LTBI) in JIA, which requires the appointment of preventive treatment to reduce the risk of LTBI progression to an active form of tuberculosis; patients with JIA receiving tumor necrosis factor blockers and/or methotrexate have a higher risk of tuberculosis activation, which is a serious problem in the treatment plan, and require constant monitoring for the possible development of tuberculosis. Therefore, in all pediatric patients with JIA, mandatory diagnostic screening (combination of tuberculin skin test methods with QuantiFERON®-TB Gold In-Tube, taking into account the high frequency of false-negative result of the tuberculin skin test due to immunosuppression caused by JIA) for timely detection of LTBI, and with a positive result of preventive antimycobacterial treatment, which will prevent the development of an active form of tuberculosis.

Therefore, all pediatric patients with JIA should undergo mandatory diagnostic screening (combination of tuberculin skin test methods with QuantiFERON®-TB Gold In-Tube, considering the high frequency of false-negative result of tuberculin skin test due to immunosuppression caused by JIA) for timely detection of LTBI. When there is a positive result of the screening tests, it is necessary to carry out prophylactic antimycobacterial treatment, which will prevent the development of an active form of tuberculosis.

**Keywords**

Juvenile idiopathic arthritis, latent tuberculosis infection, tuberculosis, review.

Juvenile idiopathic arthritis (JIA; earlier, the term was used — juvenile rheumatoid arthritis (JRA), Still's disease, etc.) is a heterogeneous group that includes all forms of childhood chronic arthritis (joint inflammation lasting more than 6 weeks) of unknown cause in children under 16 years of age [1, 3, 22]. JIA is the most common rheumatic disease in childhood (with an annual incidence from 1.6 to 23.0 new cases per 100,000 adolescents) and is characterized by an often hidden onset and a chronic relapsing course after diagnosis [5, 8, 10, 18, 29]. Also, JIA can develop over several days to weeks, which makes it difficult to make a diagnosis at the time of detection, and the first thing to make a clinical diagnosis of JIA is to rule out arthritis of known etiology. Excessive delay in the early diag-

nosis of JIA, and as a result, untimely treatment, can lead to further damage to joints and other organs [22]. The progressive nature of JIA and the possibility of a chronic course with the development of disability indicate an urgent need for rapid and accurate diagnosis [18]. Tuberculosis plays a special role among opportunistic infectious diseases in JIA, because rheumatic diseases are associated with an increase in the overall risk of developing tuberculosis [16, 25, 26].

**Objective** — to review the literature about the significance of juvenile idiopathic arthritis in pediatric phthisiatric practice.

## Materials and methods

The literature search was done using databases: Web of Science, Scopus, PubMed, MedLine, The Cochrane Library, Google Scholar. Search depth was 15 years (from 2008 to 2023).

## Results and discussion

JIA is manifested by arthralgia, most often, which is primarily a manifestation of the general intoxication syndrome in infectious diseases, which causes objective difficulties in the differential diagnostic search [4]. Therefore, A.J. Garner et al. [18] recommend using the latest methods such as infrared thermal imaging, three-dimensional visualization, accelerometry and artificial neural networks for the timely diagnosis of JIA.

As is well known, the basis of JIA is the dysfunction of the immune system. Children with rheumatic diseases, including JIA, are at risk of infection with infectious diseases not only due to the use of immunomodulatory drugs, but also due to their immune dysfunction [5, 8, 13]. It was determined that infectious diseases (including tuberculosis) and their complications are the main cause of morbidity and mortality in patients with JIA [15]. Therefore, R.D. Castillo et al. [13] indicate that doctors should constantly be on the lookout for infectious diseases, as their timely diagnosis and treatment are important for further improvement of the treatment results of rheumatic diseases. A. Adrovic et al. [5] emphasize a multidisciplinary approach in the follow-up of patients with JIA, including a pediatric rheumatologist and an infectious disease specialist.

Tuberculosis is an infectious disease characterized by high morbidity and mortality among children and adolescents worldwide. Children's phthisiologists often deal with the differential diagnosis difficulty of tubercular lesions of the joints with JIA, and first of all, with oligoarthritis. Clinical symptoms in JIA can be very diverse, and some characteristic of arthritis, not necessarily significant in JIA diagnostic, may have multiple etiologies that need to be carefully differentiated [22].

If a child has arthritis of 1—4 joints during the first 6 months of the disease — oligoarticular JIA is diagnosed, it is characterized by some features of the articular syndrome, immunological changes and the further course of the disease, which transforms into various rheumatic diseases in adulthood [4]. O.A. Oshlyanska and O.M. Okhotnikova in their research found the following errors during the diagnosis of oligoarticular JIA: JIA diagnosis, when the duration of arthritis is more than 6 weeks without conducting an additional examination to exclude other causes of arthritis, including post-vaccination joint damage; recognition of arthralgias as active arthritis; recognition of arthralgias as active arthritis; not taking into account «referred pain»; lack of initial X-ray examination of the joints; hyperdiagnosis of synovitis according to ultrasound; partial serological examination; lack of repeated examinations when initially negative values of all indicators; making a diagnosis, based only on the number of affected joints at the time of examination without taking into account previously affected joints, features of anamnesis and localization; laboratory errors; insufficient use of magnetic resonance imaging (MRI) in monoarticular seronegative lesions to clarify the diagnosis; not taking into account the presence of concomitant acute or chronic pathology in a child with articular syndrome.

In juvenile idiopathic oligoarthritis the joints of the lower extremities (knee and ankle) are damaged and only one joint is damaged (monoarthritis) in 50—60 % of cases at the disease manifestation [1], which creates problems in differential diagnosis with other diseases, including tuberculous arthritis. So M.J. Al-Matar et al. [6] described 2 cases of tuberculous arthritis in young children with monoarthritis of the knee joint when the previous diagnosis in both cases was JIA with an oligoarthritic manifestation. The authors note that both cases had an atypical course of JIA with no response to intra-articular corticosteroids and the diagnosis of tuberculous arthritis was made only by synovial biopsy. Therefore, researchers emphasize the vigilance of physicians regarding isolated tuberculosis monoarthritis in the absence of changes in the lungs for timely differential diagnosis with JIA.

The clinical case described by C. Guillou-Debuisson et al. also testifies to the complexity of the differential diagnosis of tuberculosis of the joints with oligoarthritis (JIA) [19]. Initially, a 6-year-old child was hospitalized to the pediatric rheumatology department with signs of subacute arthritis of the right knee and JIA suspected. Then the articular symptoms were accompanied by a short-term increase in temperature and pain in the right thigh. The child was thoroughly examined during which

the following were found: cervical lymphadenitis, night sweats, primary pulmonary tuberculosis characteristics were diagnosed on the X-ray of the chest cavity. On the basis of a hyperergic tuberculin skin reaction (infiltrate of 20 mm) tuberculosis of the lungs, right hip and knee joints was diagnosed in the child. Antimycobacterial therapy had a positive effect. This clinical case demonstrates the relevance and importance of tuberculin skin test performing in the differential diagnosis between JIA and tuberculosis.

Management of patients with JIA requires the use of targeted therapy, including the use of tumor necrosis factor (TNF) blockers — anti-TNF therapy. TNF is an important pro-inflammatory cytokine involved in the pathogenesis of a number of inflammatory and autoimmune diseases, including JIA and tuberculosis. Management of a patient with JIA treated with anti-TNF therapy is a complex and long-term complex process that involves the cooperation of rheumatologists with doctors of related specialties, such as infectious disease specialists, phthisiologists, immunologists and dermatologists. The purpose of such interaction is quality control of treatment side effects as patients need regular screening for pathological conditions (tuberculosis, hepatitis B, infectious complications) [2]. At the same time, the failure of the immune mechanism can lead to the emergence of tuberculosis and the triggering mechanism can be the use of drugs with antibodies against TNF.

Therefore, patients with JIA who receive targeted therapy have a higher risk of tuberculosis, which requires diagnosis and treatment of latent tuberculosis infection (LTBI) [7, 20, 28]. So J.B. Brunelli et al. [11] evaluated the effectiveness of LTBI screening and its primary prevention in 69 patients with JIA before the use of anti-TNF therapy (the average age of the patients was (17.4 ± 5.8) years with an average duration of JIA 5 years). Patients were screened for LTBI before initiation of anti-TNF therapy by tuberculin skin test, chest X-ray, and anamnesis of tuberculosis infection, they were followed up regularly every 2 months thereafter. The researchers found that only 3 patients (4.3 %) who underwent prophylactic treatment had a positive screening for LTBI and no one developed active tuberculosis during the study period. The authors concluded that screening for LTBI and primary prevention in patients with JIA before prescribing anti-TNF therapy is effective in a country with a high tuberculosis burden and the tuberculin skin test is the most sensitive parameter to identify these patients.

Contrary to previous authors, F. Gabriele et al. [17] indicate that QuantiFERON®-TB Gold In-Tube (QFT-GIT) rather than tuberculin skin test is a more effective and reliable diagnostic method for LTBI in children with rheumatic diseases before prescribing antirheumatic treatment. In addition, to achieve a successful diagnostic screening of LTBI in patients with JIA before prescribing anti-TNF therapy, it is recommended to use a combination of tuberculin skin test methods with QFT-GIT, since the latter method allows to prevent a false-negative result of tuberculin skin test due to immunosuppression caused by JIA [9 , 12, 23, 24].

It was found that the use of anti-TNF therapy despite screening for LTBI before antirheumatic therapy is associated with an increased risk of tuberculosis activation [23]. At the same time the frequency of tuberculosis that occurred in a patient with JIA after a year of anti-TNF therapy taking is higher than that of tuberculosis that occurred in the first year of this therapy using [27]. Also Y.C. Hsin et al. [21] found that children with JIA compared to children without JIA who were treated with methotrexate without anti-TNF therapy had a significantly higher rate of tuberculosis infection than children who received anti-TNF therapy. Children with JIA who either received anti-TNF therapy or never used methotrexate and anti-TNF therapy had rates of tuberculosis infection comparable to those in children without JIA.

Academician of the National Academy of Sciences of Ukraine, professor V.M. Kovalenko recommends that LBTI diagnostics as a priority should be offered in the following patients who will be prescribed immunosuppressive treatment [2]: persons who have recently been in contact with a tuberculosis patient; persons born in, living in, or frequently traveling to countries with a high prevalence of tuberculosis; employees of closed organizations (prisons, etc.); persons with LTBI who are being treated with immunosuppressive drugs; persons abusing alcohol or other toxic substances; patients with X-ray signs of tuberculosis; immunocompromised persons; patients with pathologies that increase the risk of tuberculosis developing.

Therefore, the possibility of tuberculosis infection in countries with a high epidemic risk for tuberculosis should always be considered in patients with JIA, receiving targeted therapy, even after LTBI prophylaxis with isoniazid [14].

## Conclusions

JIA is of urgent importance in children's phthisiatric practice due to various reasons:

- oligoarthritis in JIA has similar clinical manifestations as in tuberculosis arthritis, which significantly complicates differential diagnosis and delays timely treatment of a correctly diagnosed disease;

- there is a high frequency of diagnosis of LTBI in JIA, which requires the appointment of preventive treatment to reduce the risk of LTBI progression to an active form of tuberculosis;
- patients with JIA receiving tumor necrosis factor blockers and/or methotrexate have a higher risk of tuberculosis activation, which is a serious problem in the treatment plan, and require constant monitoring for the possible development of tuberculosis.

Therefore, in all pediatric patients with JIA, mandatory diagnostic screening (combination of tuberculin skin test methods with QFT-GIT, taking into account the high frequency of false-negative results of the tuberculin skin test due to immunosuppression caused by JIA) for timely detection of LTBI, and with a positive result of preventive antimycobacterial treatment, which will prevent the development of an active form of tuberculosis. At the same time, detection of LTBI or active tuberculosis in children with JIA requires multidisciplinary case management including a pediatric rheumatologist and a pediatric phthisiatrician.

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# Значущість ювенільного ідіопатичного артриту в дитячій фтизіатричній практиці (огляд літератури)

Ювенільний ідіопатичний артрит (ЮІА) – це гетерогенна група, що об'єднує всі форми хронічного артриту (запалення суглобів, що триває понад 6 тиж) невідомої етіології в дітей віком до 16 років. Ювенільний ідіопатичний артрит є найпоширенішим ревматичним захворюванням у дитячому віці (від 1,6 до 23,0 нових випадків на 100 тис. підлітків щорічно) та характеризується часто прихованим початком і хронічним рецидивним перебігом після встановлення діагнозу. З опортуністичних інфекційних захворювань при ЮІА на особливу увагу заслуговує туберкульоз, оскільки ревматичні захворювання пов'язані з підвищенням загального ризику розвитку туберкульозу. Дитячі фтизіатри нерідко мають справу зі складністю диференційної діагностики туберкульозного ураження суглобів та ЮІА, особливо олігоартриту. Клінічні симптоми при ЮІА можуть бути дуже різноманітними, а деякі, характерні для артриту, не обов'язково діагностичні для ЮІА, можуть мати множинну етіологію, яку необхідно ретельно диференціювати. Установлено, що ЮІА має актуальне значення в дитячій фтизіатричній практиці, оскільки клінічні вияви олігоартриту при ЮІА подібні до таких при туберкульозному артриті, що значно ускладнює диференційну діагностику та призводить до затримки з призначенням лікування, при ЮІА висока частота діагностики латентної туберкульозної інфекції (ЛТБІ), що потребує призначення профілактичного лікування для зниження ризику прогресування ЛБТІ та розвитку активної форми туберкульозу. Пацієнти з ЮІА, які отримують блокатори фактора некрозу пухлин та/або метотрексат, мають вищий ризик активації туберкульозу, що є проблемою при виборі лікування та потребує постійного нагляду щодо можливого розвитку туберкульозу.

Тому в усіх педіатричних пацієнтів з ЮІА слід проводити обов'язковий діагностичний скринінг (комбінація методів туберкулінової шкірної проби з QuantiFERON®-TB Gold In-Tube через високу частоту хибнонегативного результату на туберкулінову шкірну пробу внаслідок імуносупресії, спричиненої ЮІА) на своєчасне виявлення ЛТБІ, а в разі позитивного результату — профілактичне антимікобактеріальне лікування, що дасть змогу запобігти розвитку активної форми туберкульозу. Виявлення ЛТБІ чи активного туберкульозу в дітей з ЮІА потребує мультидисциплінарного ведення випадку із залученням ревматолога та дитячого фтизіатра.

***Ключові слова:*** ювенільний ідіопатичний артрит, латентна туберкульозна інфекція, туберкульоз, огляд.

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