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# Associations between joint status and immunological parameters in children with juvenile idiopathic arthritis

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Laboratory diagnostics of juvenile idiopathic arthritis (JIA) allow us to clarify the diagnosis, determine the subtype of the disease, and assess the inflammatory and immunological activity.
**The aim** of our study was to assess the associations between joint status and immunological parameters.
**Materials and methods**. Our study included 80 JIA patients aged 2 to 18 years: 39 (48.8%) boys and 41 (51.2%) girls. The Control group consisted of 20 children: 5 (25.0%) boys and 15 (75.0%) girls. All children underwent physical examination, complete blood count (CBC), biochemical and immunological blood tests, and X-ray examination of the affected joints. Correlation relationships were determined using the ρ-Spearman criterion.
**Results**. Among all classes of immunoglobulins, the most interesting observations were those regarding IgA. Thus, we obtained a significant positive correlation between IgA and arthritis of several joints: hand joints, elbow joints, shoulder joints, knee joints. A positive correlation was established between an increase in concentration of IgG and lesions of the following joints: hand joints (arthritis), shoulder joints (stiffness, arthritis), temporomandibular joints (tenderness). Also, we obtained a significant positive correlation between IgM and tenderness of elbow joints. Involvement of the joints of the upper limb in the process is more common in polyarticular forms of JIA, with an aggressive course, so, high concentrations of IgA correlate with the severity of the process. IL-6 positively correlated with lesions of the knee joints (stiffness; arthritis) and ankle joints (arthritis)
**Conclusions**. Thus, the obtained significant positive correlations between immunological parameters and the condition of the joints allow us to assert that immunoglobulins A, M, G, and IL-6 correlate with the severity of the disease and the processes of joint damage.
The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of all participating institutions. The informed consent of the patient was obtained for conducting the studies.
No conflict of interests was declared by the authors.
**Keywords:** juvenile idiopathic arthritis, cytokines, immunoglobulins.

## Зв'язок між станом суглобів та імунологічними показниками в дітей із ювенільним ідіопатичним артритом

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Лабораторна діагностика ювенільного ідіопатичного артриту (ЮІА) дає змогу конкретизувати діагноз, визначити підтип захворювання та оцінити запальну та імунологічну активність.
Метою нашого дослідження є оцінка зв'язку між станом суглобів та імунологічними показниками.
**Матеріали та методи**. У дослідженні взяло участь 80 хворих на ЮІА віком від 2 до 18 років: 39 (48,8%) хлопчиків та 41 (51,2%) дівчинка. У контрольній групі було 20 дітей: 5 (25,0%) хлопчиків та 15 (75,0%) дівчаток. Усім дітям було проведено фізикальне обстеження, зроблено загальний аналіз крові (ЗАК), біохімічні та імунологічні аналізи крові, а також здійснено рентгенологічне дослідження уражених суглобів. Кореляційні зв'язки визначено за допомогою критерію Спірмена.
**Результати**. З-поміж усіх класів імуноглобулінів найцікавішими були спостереження щодо IgA. Таким чином, ми отримали значну позитивну кореляцію між IgA і артритом декількох суглобів: суглобів кистей, ліктьових суглобів, плечових суглобів. Позитивна кореляція встановлена між підвищенням концентрації IgG та ураженням наступних суглобів: суглоби кистей (артрит), плечові суглоби (тугорухливість, артрит), скронево-нижньощелепні суглоби (болючість). Також отримано значну позитивну кореляцію між IgM і болючістю ліктьових суглобів. Залучення до процесу суглобів верхньої кінцівки найчастіше зустрічається при поліартикулярних формах ЮІА, з агресивним перебігом, тому високі концентрації IgA корелюють із тяжкістю процесу. IL-6 позитивно корелював з ураженнями колінних суглобів (тугорухливість; артрит) та гомілковостопних суглобів (артрит).
**Висновки**. Таким чином, отримані значні позитивні кореляції між імунологічними показниками та станом суглобів дають змогу стверджувати, що імуноглобуліни A, M, G та IL-6 корелюють із тяжкістю перебігу захворювання та процесами ураження суглобів.
Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом усіх установ, які беруть участь. На проведення досліджень отримано інформовану згоду пацієнта.
Автори заявляють про відсутність конфлікту інтересів.
**Ключові слова**: ювенільний ідіопатичний артрит, цитокіни, імуноглобуліни.

## Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic condition in childhood. JIA is an umbrella term for arthritis of unknown origin, lasting for >6 weeks with onset before 16 years of age. JIA is very rare in infancy, with the highest frequency in preschool age [1].

According to the International League of Associations for Rheumatology (ILAR) classification, seven mutually exclusive categories of JIA exist based on disease manifestations during the first 6 months of disease [5].

JIA is one of the most common causes of part-time or long-term disability. New research on the disease pathogenesis is the basis for the development of new and better treatments for JIA [6]. The goal of such treatments is not just to relieve pain, but also to control inflammation and stop irreversible joint damage and long-term disability [7].

The incidence of JIA in the world is from 2 to 16 people per 100 thousand children. The prevalence of JIA in different countries varies from 0.05 to 0.6%. The disease occurs in all age groups, is registered in all countries of the world and all climatic and geographical zones, affects all racial and ethnic groups. Arthritis affects girls more often. Mortality is within 0.5–1% [2].

Laboratory diagnostics of JIA includes the determination of a large number of indicators that allow both to clarify the diagnosis and determine the subtype of the disease and to assess the inflammatory and immunological activity, the severity of the course. This allows for timely prescription of adequate therapy and monitoring of treatment and, consequently, to avoid destructive changes in the joints, which develop in the first two years of the disease in 70% of patients [3].

The development of autoimmune inflammation in JIA is impossible without the participation of a wide range of cytokines [4]. One of the important mediators of inflammation in JIA is interleukin-6 (IL-6). In JIA, there is a significant increase in the level of IL-6 in synovial tissue, synovial fluid, and blood plasma. The pathological effect of IL-6 in JIA consists of stimulating the production of acute phase proteins, secretion of immunoglobulins, activation of osteoclasts, etc. [9]. Stimulation of production and differentiation of osteoclasts leads to an imbalance in bone tissue formation, one of the valuable markers of metabolism of which is ionized calcium (Ca++) [9]. Human immunoglobulins of classes A, M, G (IgA, IgM, IgG) in rheumatic diseases and, in particular, in JIA represent autoantibodies [8].

***The aim*** of our study was to assess the associations between joint status and immunological.

## Materials and methods of the study

This study included 80 JIA patients aged 2 to 18 years who met the classification criteria for JIA as proposed by the ILAR (2007). 20 age-matched practically healthy children formed the Control group. The study was conducted at the Educational-Therapeutic Clinic at the Department II of Children's Diseases of the Azerbaijan Medical University. The study was approved by the Local Ethics Committee of the Azerbaijan Medical University. The informed consent was obtained from all patients/their representatives.

*The inclusion criteria* for the study were as follows: age 2 to 18 years, active phase of JIA with DAS28>2.6 (Disease Activity Score28); absence of pathologies in various organ systems accompanied by severe impairment of their functions. *The exclusion criteria* from the study were: age under 2 years, the presence of other autoimmune rheumatic diseases accompanied by joint syndrome, as well as concomitant infectious diseases.

Of the 80 patients with JIA, 39 (48.8%) were boys and 41 (51.2%) were girls. The Control group consisted of 20 children: 5 (25.0%) boys and 15 (75.0%) girls.

Among 80 patients with JIA, 3 (3.8%) children were in early childhood (2–3 years), 17 (21.3%) were in the preschool age group (4–6 years), 32 (40.0%) were in the primary school age group (7–12 years), and 28 (35.0%) were in the secondary school (adolescent) group (13–18 years).

Of the 20 children in the Control group, 6 (30.0%) were in the preschool age group, 5 (25%) were in the primary school age group, and 9 (45.0%) were in the secondary school (adolescent) age group.

All children underwent a range of clinical, laboratory, and instrumental research methods in accordance with generally accepted standards: physical examination, complete blood count (CBC), biochemical and immunological blood tests, and X-ray examination of the affected joints.

During the physical examination, we assessed the condition of the joints according to the following parameters: tenderness, swelling, and stiffness. Tenderness was measured using the Ritchie index. The index is based on the summation of several quantitative evaluations of the pain experienced by the patient when the joints are subjected to firm pressure when exerted over the articular margin or in some instances on movement of the joint: 0 – no pain, 1 – patient says palpation is painful, 2 – patient winces, 3 – patient pulls away the limb from the examiner.

During the immunological study, the levels of IL-6, IgA, IgG, and IgM were determined in the blood serum. For this purpose, the serum obtained from the patient's blood on an empty stomach was used. The study was conducted using the ELISA method on the Medispec 6000 (RT-6000, Microplate Reader) device.

A radiographic assessment of JIA was conducted using the Plexa Vision device from Hiladzu (Japan). The X-ray stage of arthritis was determined according to the Steinbrocker classification:

*Table*

**Parameters of examined children with JIA in comparison with the Control group**

| Indicators | Control | | | | JIA | | | | pU |
|---|---|---|---|---|---|---|---|---|---|
| | M | Me | Q1 | Q3 | M | Me | Q1 | Q3 | |
| IL-6, pg/ml | 2.8 | 1.0 | 0.6 | 2.1 | 6.2 | 2.1 | 0.8 | 7.0 | 0.025* |
| IgA, g/l | 1.31 | 1.10 | 0.85 | 1.75 | 1.70 | 1.70 | 1.30 | 2.05 | 0.021* |
| IgM, g/l | 1.4 | 0.90 | 0.79 | 1.75 | 3.77 | 3.75 | 3.10 | 4.50 | <0.001* |
| IgG, g/l | 9.5 | 9.5 | 7.8 | 10.5 | 10.3 | 10.2 | 8.6 | 12.6 | 0.175 |

*Notes:* M – arithmetic mean, Me – median, Q1, Q3 are the 1st and 3rd quartiles of the variation series; PU – statistical significance of the difference according to the Mann–Whitney U criterion.

Stage I – epiphyseal osteoporosis;

Stage II – epiphyseal osteoporosis with narrowing of the joint space, isolated marginal defects (erosions);

Stage III – destruction of cartilage and bone, multiple erosions, joint subluxations;

Stage IV – destruction of cartilage and bone with fibrous or bony ankylosis.

The analysis of the obtained quantitative and qualitative parameters was carried out in the statistical package SPSS-26 using the variation (Mann-Whitney) and correlation (ρ-Spearman) methods. Arithmetic mean (M), median (Me), the 1st (Q1) and 3rd (Q3) quartiles of the variation series, Mann-Whitney U criterion. A 95% confidential interval (95%CI) was determined. Correlation relationships were determined using the ρ-Spearman criterion. The statistical significance of the correlation coefficient was determined by a 2-sided criterion. Hypothesis «0» is rejected at $p<0.050$.

## Results of the study and discussion

The average age of patients with JIA was 9.6±0.5 years (95% CI 8.7–10.6), while in children in the control group, it was 9.1±0.8 years (95% CI 7.4–10.7).

The results of the variation analysis revealed statistically significant differences in the indicators. The calculation results are presented in Table.

All patients with JIA underwent an X-ray examination of the affected joints to detect arthritis and determine its stages.

Thus, during the X-ray examination of the hand joints, arthritis was absent in 65 (81.3%) of patients. Stage I was diagnosed in 10 (12.5%) of patients, stage II – in 3 (3.8%), and stage III – in 2 (2.5%) of patients. With regard to the wrist joints, the following results were obtained: arthritis was absent in 67 (83.8%), stage I was diagnosed in 11 (13.8%) of patients, and stage II – in 2 (2.5%). Arthritis of the elbow joints was absent in 72 (90.0%) of patients, stage I was noted in 7 (8.8%), stage II – in 1 (1.3%) of patients. During the X-ray examination of the shoulder joints, stage I was detected in only 5 (6.3%) of patients. The remaining 75 (93.8%) had no arthritis. Arthritis was most often diagnosed in the knee joints. Stage I was observed in 26 (32.5%), stage II – in 6 (7.5%) of patients, and was absent in 48 (60.0%). In the ankle joints, a higher frequency of arthritis diagnosis was also noted compared to other joints. Stage I was observed in 15 (18.8%), stage II – in 5 (6.3%) of patients, and arthritis was absent in 60 (75.0%). Arthritis was least common in the temporomandibular joints. Only 1 (1.3%) had stage I arthritis. The remaining 79 (98.8%) had no arthritis. Arthritis of the hip joints was absent in 70 (87.5%) of patients. Stage I was observed in 8 (10%), and stage III arthritis was observed in 2 (2.5%).

Radiographic stages of arthritis of the affected joints in patients with JIA according to the Steinbroker classification are shown in Fig. 1.

Among all classes of immunoglobulins, the most interesting observations were those regarding IgA.

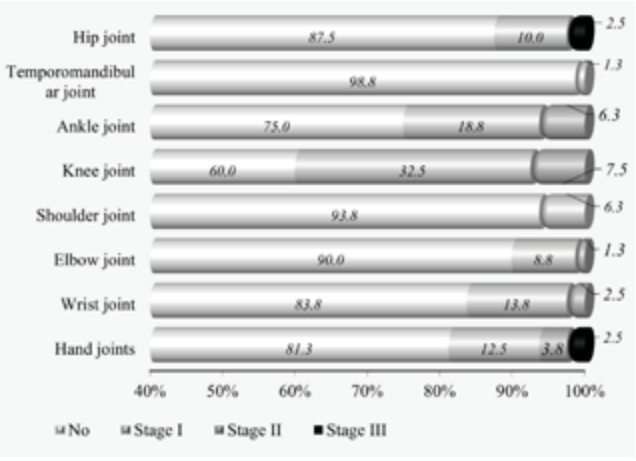


***Fig. 1.*** Radiographic stages of arthritis of the affected joints

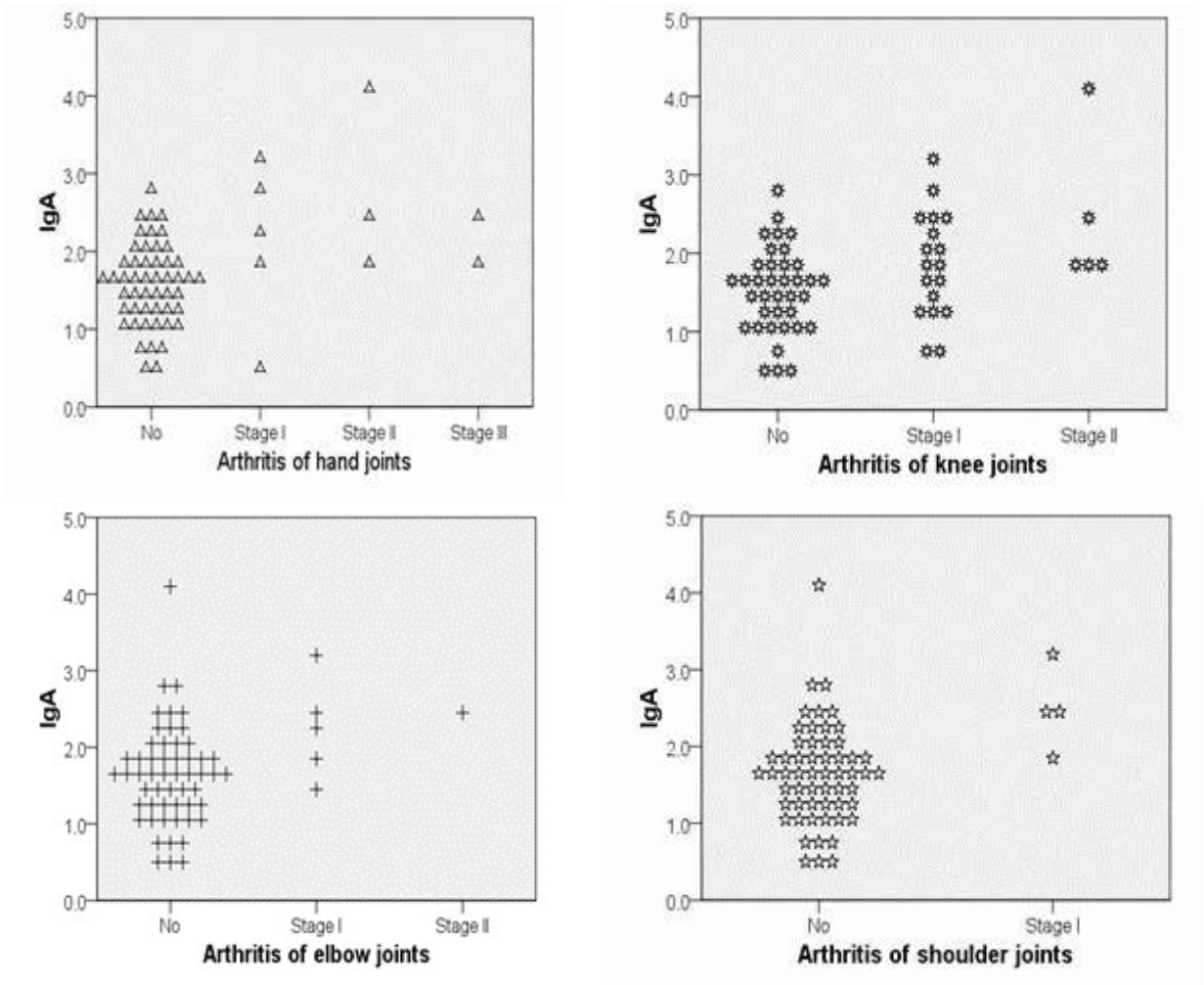


***Fig. 2.*** Graphic representation of the correlation relationships between IgA and arthritis

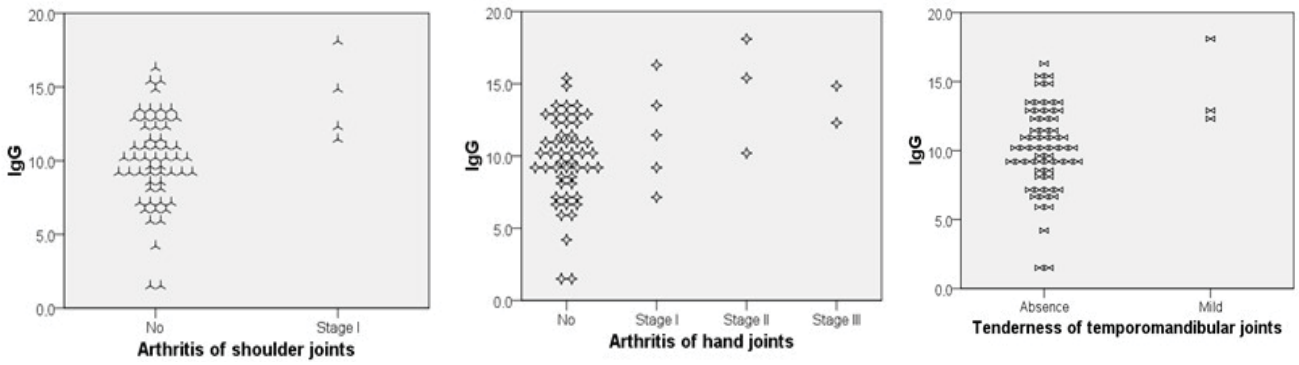


**Fig. 3.** Graphical representation of the correlation between IgG and joint lesions

Thus, we obtained a significant positive correlation between IgA and arthritis of several joints: hand joints (ρ=+0.397, p=0.002), elbow joints (ρ=+0.299, p=0.020), shoulder joints (ρ=+0.331, p=0.010), knee joints (ρ=+0.366, p=0.004) (Fig. 2).

With IgG, we saw a nearly identical picture. A positive correlation was established between an increase in the concentration of IgG and lesions of the following joints: hand joints (arthritis ρ=+0.317, p=0.014), shoulder joints (stiffness ρ=+0.294, p=0.023, arthritis ρ=+0.291, p=0.024), temporomandibular joints (tenderness ρ=+0.276, p=0.033) (Fig. 3).

Also, we obtained a significant positive correlation between IgM and tenderness of elbow joints (ρ=+0.301, p=0.020).

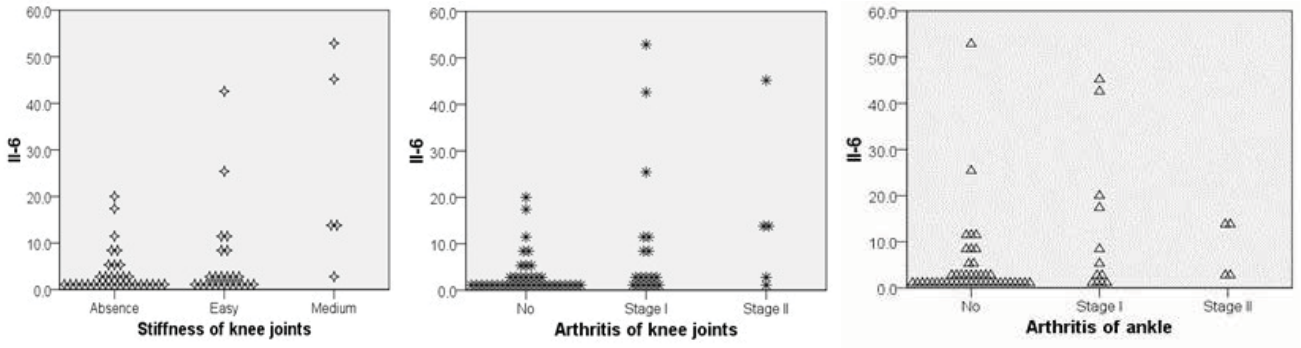


***Fig. 4.*** Graphical representation of the correlations between IL-6 and joint lesions

Moreover, with JIA, involvement of the joints of the upper limb in the process is more common in polyarticular forms of the disease, characterized by an aggressive course. This gives us reason to believe that high concentrations of IgA correlate with the severity of the process.

Our attention was also drawn to IL-6, which positively correlated with lesions of the knee joints (stiffness ρ=+0.284, p=0.028; arthritis ρ=+0.314, p=0.015) and ankle joints (arthritis ρ=+0.334, p=0.009) (Fig. 4).

Thus, as a result of the analysis, we obtained significant positive and negative correlations between various indicators.

Involvement of only these joints in the process is more common in children with the oligoarthritic form of the disease, which is characterized by damage to 1–4 large and medium joints. However, according to the literature, high concentrations of IL-6 are characteristic of systemic and polyarticular forms of JIA, when smaller joints are also involved in the process.

Biologic disease-modifying antirheumatic drugs (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy for patients with JIA. Many studies in previous years have indicated that one of the important mediators of inflammation in JIA is interleukin-6 (IL-6) [4, 7]. Our study also found changes in this parameter, which correlated with other immunological indicators and with individual coinciding manifestations.

In the 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis, in addition to IL-6, the role of IL-1 is also emphasized [7], but in our work, we did not assess this interleukin. Compared to our study the authors, who created Guideline, both 2019 and 2021, did not evaluate the role of immunoglobulins of various classes [1]. However, we revealed that these parameters significantly correlated with clinical features in children with JIA.

In several publications, recommendations were based on clinical phenotypes of JIA rather than a specific classification scheme. In particular, recommendations were made for JIA with oligoarthritis, temporomandibular joint arthritis, and systemic JIA. The researchers discussed various aspects of disease management, including factors influencing treatment choice and drug dose reduction [1,6]. Given that we found strong correlations with immunoglobulin classes G, M, and A, we suggest that these results may be useful for solving treatment issues.

## Conclusion

Thus, the obtained significant positive correlations between immunological parameters and the condition of the joints allow us to assert that immunoglobulins A, M, G, and IL-6 correlate with the severity of the disease and the processes of joint damage. Taking into account the above, we can conclude that the study of the parameters of radiography of the affected joints and immunological parameters can play an important role in determining the severity of the disease and in the application of new therapeutic methods.

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