Aleksandra Kowalska

Laboratory tests in the diagnosis and treatment monitoring of juvenile idiopathic arthritis

Summary

Background:

Juvenile idiopathic arthritis (JIA) is the most common chronic arthropathy in the population of children and adolescents. It is a disease of autoinflammatory or autoimmune nature and of undefined etiology. The clinical picture of the disease in the first six months allows to classify it into one of seven subtypes. A common characteristic of all the subtypes is inflammation within the joints, accompanied by swelling, pain, and stiffness. Destructive lesions may affect periarticular tissue, tendon sheaths and attachments, as well as muscles and bones.

Early diagnosis of JIA and implementation of an effective treatment plan allows to block or minimize the inflammatory and autoimmune activity of the disease, and to prevent or reduce the progress of osteoarticular lesions and organ complications.

Aim:

Due to the heterogeneity of clinical symptoms, the diagnosis of JIA involves a complex process. There are no fully specific biomarkers whose qualitative or quantitative assessment would allow for a quick and accurate diagnosis of the disease and adequate treatment implementation.

The aim of the paper was to assess the value of selected laboratory parameters in diagnosing and monitoring the treatment of juvenile idiopathic arthritis. The following were analyzed: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, vitamin D3, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, antinuclear antibody (ANA), synovial fluid. Analysis was also performed with respect to the prevalence of immune and genetic markers (anti-CCP antibodies, RF, ANA, HLA-B27 antigen) in the serum of JIA patients, as well as the correlation of their presence and levels with the subtype of the disease and the activity of the inflammatory process.

Patients and methods:

The study was based on a retrospective analysis of medical records of patients receiving treatment at the J. Brudziński Provincial Children's Hospital in Bydgoszcz between 1 January 2012 and 31 March 2022. The analysis involved 403 patients (246. females and 157 males) divided into groups based on individual JIA subtypes as per diagnostic criteria.

The study involved an assessment of the patients' medical history, physical examination, and laboratory test results: CRP, blood count (white blood cell count (WBC), hemoglobin levels (HGB), platelet count (PLT)), biochemical tests (creatinine, AST, ALT, vitamin D3), ESR, immunology tests (RF, ANA, anti-CCP antibodies, HLA-B27 antigen).

Analysis of laboratory test results was divided into two parts. The first part, pertaining to the diagnosis stage, aimed at assessing the diagnostic value of the analyzed laboratory parameters in identifying and differentiating between JIA subtypes, and assessing their prevalence and mutual correlations.

The second stage involved analyzing selected laboratory parameters (blood count, CRP, ESR, creatinine, liver enzymes: AST, ALT) throughout a period of two years in order to assess the safety and efficiency of the implemented treatment and to monitor the activity of the disease process.

Results:

The study population included patients with all subtypes of JIA. The largest group consisted of patients with oligoarticular JIA (61.8%), while only 3 patients (0.7%) were diagnosed with the undifferentiated subtype.

Analysis of inflammatory response markers (CRP, ESR, WBC, HGB, PLT) at the time of diagnosis showed significantly higher levels of those parameters in patients with systemic-onset JIA. Elevated levels of CRP, ESR, WBC and PLT were also found in a considerable number of patients with seropositive polyarticular JIA. Patients with the oligoarticular subtype demonstrated normal or slightly elevated levels of inflammatory markers. Connective tissue diseases are accompanied by hematological symptoms. Mild anemia, severe leukocytosis and thrombocytosis were diagnosed mainly in patients with systemic and seropositive polyarticular JIA.

The prevalence of the rheumatoid factor (RF) in the study population was low (2.6%). Its presence was determined in all patients with seropositive polyarticular JIA and in 2.1% of patients with the oligoarticular type. Autoantibodies against citrullinated peptides and

proteins proved to be a promising serological marker for JIA. In the study population, they were detected in all subtypes of the disease, though with varying prevalence. Anti-CCP positivity was determined in all individuals with RF-positive polyarticular JIA, 21.4% of patients with psoriatic arthritis (PsA), 13.9% of patients with RF-negative polyarticular JIA, 11.1% of patients with enthesitis-related arthritis (ERA), 10.9% of individuals with oligoarticular JIA, and – the fewest – 8.3% of patients with systemic-onset JIA.

In order to confirm the autoimmune basis of the disease, the patients were tested for antinuclear antibodies. The presence of ANA, usually at low titers, was determined in 63.7% of the study population, and constituted a significant risk factor for eye inflammation, mostly in female patients.

Presence of the HLA-B27 antigen was associated with the ERA and PsA subtypes (77.8% and 38.5%, respectively), and with the male sex. Mean levels of vitamin D with respect to all JIA types were between 20 ng/ml and 30 ng/ml, which is indicative of hypervitaminosis. Synovial fluid analysis was performed in 70 patients. The fluid was found to have inflammatory properties.

For the purposes of this study, the activity of the disease process was monitored and the safety of the implemented treatment was evaluated during a period of 24 months since diagnosis. Patients were treated with conventional synthetic DMARDs in monotherapy or in combination with glucocorticosteroids.

Patients with moderate disease activity constituted the largest group (83.10%), followed by individuals with high disease activity (14.25%). JIA was of low activity only in 2.64% of the study population.

Laboratory markers used to assess inflammatory activity in the analyzed population of JIA patients included CRP, ESR, and blood count parameters (WBC, HGB, PLT), which were determined during subsequent visits at the rheumatology outpatient clinic. The highest levels of inflammatory markers (CRP, ESR) at the time of diagnosis were found in patients with systemic-onset JIA (109.87 ng/l and 63.32), whereas the lowest – in patients with oligoarticular JIA (7.20 ng/l and 17.17). The highest dynamics of changes in both CRP and ESR concentration were seen in the first 3 months of observation. Normalization of the mean values of these parameters was noted most rapidly in the oligoarticular subtype – 3 months from the start of treatment for CRP, and 1 month in the case of ESR. In patients with the systemic-onset subtype, the process was longer and lasted 15 months for CRP and 9 months for ESR. In the

24th month of observation, mean values of both inflammatory markers were within the normal range for patients with all types of JIA.

A decrease in disease activity was also confirmed by reduced levels of leukocytes and blood platelets, as well as increased concentration of hemoglobin in the blood of all JIA patients undergoing pharmacotherapy. In a few patients from the study population, a temporary increase in liver enzymes (AST, ALT) was observed during treatment with MTX. All patients had normal creatinine levels throughout the entire observation period.

Conclusions:

The presented analysis demonstrated the usefulness of anti-CCP antibodies and the rheumatoid factor in confirming the diagnosis of RF-positive polyarticular JIA.

Due to the autoinflammatory nature of systemic-onset JIA, serological markers (RF, anti-CCP antibodies) are of low diagnostic value for this subtype of the disease.

The HLA-B27 antigen is a useful genetic biomarker, supporting the diagnosis of enthesitis-related arthritis and psoriatic arthritis.

Antinuclear antibodies occur significantly more frequently in oligoarticular JIA and constitute an important prognostic factor for JIA complications taking the form of uveitis.

Inflammatory markers (CRP, ESR, blood count parameters) constitute an effective marker of disease activity for systemic and RF-positive polyarticular JIA.

Assessment of disease activity using inflammatory response markers (CRP, ESR) in the third month of treatment correlates with clinical improvement and is in line with the "treat-to-target" strategy, which proposes that the first assessment of therapy effectiveness should be performed in the third month since the start of treatment. Normalization of the levels of inflammatory markers (CRP, ESR) occurs faster than the clinical criteria for disease remission are met.

Compared to ESR, C-reactive protein is a better and more stable marker demonstrating the activity of the inflammatory process in JIA.

Aleksandra Kowalska