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Early arthritis – current state of knowledge**

Wczesne zapalenie stawów – aktualny stan wiedzy

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Summary

Early arthritis is often undifferentiated with various onset (mono, oligo or polyarticular) and the duration of the symptoms less than 3 months. Most of the patients have negative rheumatoid factor (RF-IgM) and also there is no present other clinical symptoms satisfied for fulfilling classification criteria. Majority of patients with undifferentiated arthritis, in the various period of time, progress to rheumatoid arthritis (RA). In this review focuses on the importance of occurrence anti-citrullinated peptides (ACPA), they level and nature in making the diagnosis and prognosis of early arthritis, the role of *Porphyromonas gingivalis* infection as potential etiological factor of inflammation in RA, difficulty in clinical assessment of synovitis and inability of conventional radiography to detect early destructive changes in the joints. The differences in the sensitivity and specificity of the old (ACR 1987) and new (ACR/EULAR 2010) classification criteria for RA was discussed.

Key words: rheumatoid arthritis, diagnostics

Streszczenie

Wczesne zapalenie stawów jest często nieodróżnionym zapaleniem o różnym początku (jedno-, kilku- i wielostawowym) w którym czas trwania choroby nie przekracza 3 miesięcy. U wielu chorych czynnik reumatoidalny (RF-IgM) jest ujemny oraz brak jest innych objawów umożliwiających spełnienie kryteriów klasyfikacyjnych. Większość chorych z wczesnym nieodróżnionym zapaleniem stawów rozwija w różnie długim okresie czasu reumatoidalne zapalenie stawów (RZS). W doniesieniu przedstawiono znaczenie występowania, miana i typu przeciwciał anty-cytrulinowych w diagnostyce i prognozowaniu we wczesnym zapaleniu stawów, rolę zakażenia *Porphyromonas gingivalis* jako potencjalnego czynnika etiopatogenetycznego w RZS, trudności w ocenie klinicznej wczesnego zapalenia błony maziowej i niską przydatność konwencjonalnej radiografii we wczesnym wykrywaniu zmian destrukcyjnych w stawach. Przedstawiono różnice w odniesieniu do czułości i specyficzności starych (ACR 1987) i nowych (ACR/EULAR 2010) kryteriów klasyfikacyjnych RZS.

Słowa kluczowe: reumatoidalne zapalenie stawów, diagnostyka

WHAT IS EARLY ARTHRITIS?

Early arthritis is a group of rheumatic and nonrheumatic disorders characterized by unclassified arthritis beginning with mono-, oligo-, or polyarthritis, lasting up to 3 months. Rheumatoid factor (RF-IgM) is negative in many patients, and the patients have so other symptoms corresponding to the classification criteria for other diseases. The course of the disease is impossible to predict, as well as the time needed to diagnose the disease in individual patients. There are no laboratory tests that clearly differentiate early rheumatoid arthritis from other types of early arthritis, such as arthritis in infectious (viral or bacterial), reactive arthritis, arthritis accompanying cancer and systemic connective tissue diseases (1, 2).

Early arthritis represents an essential diagnostic, prognostic and therapeutic issue, all the more that the majority of patients with early unclassified arthritis develop RA at different time points (3).

There are many reasons why it is difficult to diagnose RA at an early stage of its development. Early unclassified arthritis needs to be differentiated from a number of inflammatory joint diseases, such as: systemic lupus erythematosus and other systemic connective tissue diseases, reactive arthritis, psoriatic arthritis, osteoarthritis (mainly hand osteoarthritis), as well as arthritis associated with infections and cancer.

Other factors that make early RA diagnosis difficult can be as follows: low discriminative power of the conventional ACR 1987 classification criteria for early forms of the disease, inability to detect moderate synovitis in a physical examination, absence of diagnostically reliable laboratory tests, late detecting joint erosions in conventional radiography, and difficulty in obtaining early rheumatological consultation (tab. 1).

According to the European League Against Rheumatism recommendations for the diagnosis of early

**The paper is dedicated to Profesor Eugene J. Kucharz on his sixtieth birthday.

Table 1. Difficulties in establishing an early diagnosis of rheumatoid arthritis.

- Differential diagnosis with other types of polyarthritis.
- Moderate synovitis is not detected in a physical examination.
- There are no reliable diagnostic laboratory tests.
- Conventional radiography does not detect early erosive lesions.
- Difficulties in obtaining early rheumatological consultation.
- The 1987 ACR classification criteria offer poor discriminative ability for early RA.

arthritis, patients presenting with arthritis of more than one joint should be referred to and seen by a rheumatologist, ideally within six weeks after the onset of symptoms. Another step in the diagnostic procedure should be also to try to determine the patients at risk of developing persistent erosive arthritis in order to introduce an optimum therapeutic strategy as early as possible (4).

ANTIBODIES AS AN EARLY RHEUMATOID ARTHRITIS BIOMARKER

RA is associated with two antibody systems: rheumatoid factor (RF) and ACPA-antibody to citrullinated peptide (5). Rheumatoid factor is an antibody to the Fc portion of immunoglobulin G (IgG) and has been the core factor used in the diagnostics and prognosis of RA. High rheumatoid factor levels are associated with severe erosive disease, rheumatoid nodules, vasculitis and extra-articular symptoms. The role of rheumatoid factor in pathogenesis and maintenance of RA is yet to be clearly understood. Rheumatoid factor was found not only in patients with RA, but also in patients with other diseases and in some healthy individuals, especially in the elderly, which reduces the factor's specificity and diagnostic reliability.

Anti-citrullinated protein antibodies (ACPA), i.e.: vimentin, filaggrin, collagen type II, fibrinogen and α -enolase, represent another powerful biomarker in RA diagnostics and prognosis.

The presence of citrulline generated posttranslationally by peptidylarginine diminaze (PAD2) is essential in citrullinated peptides (6). Anti-citrulline antibodies are detected in patients with RA and have been for many years used in RA diagnostics. Anti-citrulline antibodies include in particular: anti-keratin antibodies (AKA), anti-filaggrin antibodies (AFA) and antiperinuclear factor (APF). AKA, AFA and APF have a number of variables but they react with native filaggrin, and are therefore referred to as anti-filaggrin antibodies (AFA) (9, 10). They represent relatively high specificity for RA (> 90%), but have low sensitivity (> 30%) and do not meet the diagnostic test criteria. Anti-RA33 and anti-Sa antibodies were also thought to be useful in early RA diagnostics (11, 12). Anti-RA33 antibodies are antibodies against a specific heterogeneous nuclear ribonucleoprotein complex (A2-RNP). Anti-Sa antibodies were confirmed to be directed to vimentin found in human spleen and placenta extract. Anti-filaggrin antibodies like, anti-RA33 and anti-Sa antibodies show high specificity, but low sensitivity in RA diagnostics.

The ELISA method with the use of synthetic filaggrin-derived citrullinated peptides marked a significant progress in RA diagnostics. Anti-CCP1 (1st generation) test was based on incorporating cyclic peptide into a filaggrin molecule, representing 69% sensitivity and 81% specificity in RA diagnostics. In order to achieve higher sensitivity, citrullinated peptides were used instead of filaggrin to develop an anti-CCP2 (2nd generation) test representing 82% sensitivity and 95% specificity (13, 14).

Two new tests that detect citrullinated peptides autoantibodies have been introduced recently: anti-CCP3 (3rd generation) test and anti-MCV test for modified citrullinated vimentin. Anti-CCP3 test is based on a modified cyclic peptide used in anti-CCP1 and anti-CCP2 tests. Mutated citrullinated vimentin is used in the anti-MCV test (15-17). Anti-CCP3 test has comparable sensitivity and specificity to the anti-CCP2 test, which is similar to the anti-MCV test, which offers a clinically significant benefit – identification of anti-CCP2 negative patients.

Anti-CCP2 and anti-MCV positive test combination shows 69% sensitivity and 89% specificity in the diagnostics of early rheumatoid arthritis; anti-MCV and RF-IgM positive test combination shows 71% sensitivity and 88% specificity. The highest sensitivity and specificity was shown for anti-CCP2 + RF-IgM test combination (74% and 96%, respectively), which was used in the development of the new classification criteria for RA (tab. 2) (15).

Table 2. Sensitivity and specificity of anti-CCP, anti-MCV and RF-IgM tests in patients with early rheumatoid arthritis.*

Test	Sensitivity (%)	Specificity (%)
Anti-CCP1	69	71
Anti-CCP2	82	95
Anti-CCP3	82	92
Anti-MCV	84	92
RF-IgM	68	84
Anti-CCP2 + anti-MCV	68	89
Anti-MCV + RF-IgM	71	88
Anti-CCP2 + RF-IgM	74	96

*Van der Linden MPM et al. Arthritis Rheum 2009; 60: 2232-41 (the summary of results modified by the author).

ANTI-CITRULLINE AUTOANTIBODIES IN THE DIAGNOSTICS AND PROGNOSTICS OF EARLY RHEUMATOID ARTHRITIS

The diagnostic parameters of anti-CCP2 test for early RA were confirmed in a number of studies. Anti-CCP2 test was found to offer 82% sensitivity and 95% specificity in the diagnostics of early RA lasting up to 3 years (19). In steady long-term RA, the test sensitivity equalled 77%. Goldbach-Mansky R et al. (20) have demonstrated 41% sensitivity and 91% specificity of the anti-CCP2 test in a group of 238 patients with very early arthritis lasting up to 3 months, while

the rheumatoid factor (RF-IgM) was demonstrated to offer 66% sensitivity and 87% specificity. The differences in the assessment of anti-CCP2 test sensitivity may depend on the selection of study subjects (very early RA vs. early RA vs. advanced RA, etc.). It is commonly claimed that the anti-CCP2 test has the highest specificity for RA (97%). Rheumatoid factor (RF-IgM) shows a slightly higher sensitivity than the anti-CCP2 test (68.4%), but has a lower specificity (84%). Anti-CCP2 test is positive in 40% RA patients who remain negative for the rheumatoid-factor, which reflects the test's additional diagnostic value. The high predictive value of anti-CCP2 and rheumatoid factor for RA development and progress was demonstrated in a number of studies (22). The presence of anti-CCP2 antibodies and the rheumatoid factor may be the predictive factor of RA, as shown on a group of blood donors and patients with unclassified arthritis (23).

Anti-CCP2 antibodies and the rheumatoid factor (RF-IgM) are the best predictors of persistent RA in patients with very early synovitis.

Based on two years of observation of a group of patients with early synovitis, Visser H et al. used a logistic regression model to develop prediction criteria for the course of early arthritis to differentiate patients with self-limiting, non-erosive, progressive and progressive erosive type of the disease. Anti-CCP2 antibodies, the rheumatoid factor and early joint erosions were once again proved to be powerful predictors of erosive RA.

Kastbom A et al. demonstrated that anti-CCP2 positive patients typically exhibit high inflammatory activity and are more likely to develop joint erosions at an early stage of the disease as compared to anti-CCP2 negative patients.

In another study, Syversen S et al. demonstrated that RA patients with high levels of anti-CCP2 antibodies are 10 times more likely to develop joint erosions in comparison to anti-CCP2 negative patients and approximately 5 times more likely as compared to patients with low anti-CCP2 antibody levels. The study outcomes contributed to the development of a new classification criteria for early RA, and confirmed the importance of early introduction of biological therapy.

Anti-MCV antibodies detect an antigen that occurs naturally in the body, while anti-CCP3 antibodies detect synthetic citrullinated peptide. Anti-MCV antibodies are less frequently detected in early polyarthritis as compared to anti-CCP2 antibodies, despite being more powerful predicting factors of severe erosive course of the disease. Patients with anti-MCV and anti-CCP2 antibodies represent a similar subtype of RA. The level of antibodies in synovial fluid is substantially higher than in serum, which indicates that they are generated and produced locally, depending on genetic predisposition (27).

Throughout 30 months of observation study by Guziana MC et al. on group of 253 patients with early polyarthritis, changes in the autoantibody levels were confirmed to be induced by intensive therapy with disease-modifying antirheumatic drugs (DMARDs).

Treatment-related changes or reversions in RF-IgM levels can occur, especially if the antibody titre is low at the beginning of the disease, which is a favourable prognostic factor for radiographic progression. Anti-MCV antibodies may disappear or re-occur during the treatment. However, the presence of anti-MCV autoantibodies – irrespectively of any possible antibody level fluctuations or reversions – remains an independent predictor of a severe course of the disease and is associated with a low likelihood of remission. Unlike RF-IgM and anti-MCV, the level of anti-CCP2 antibodies is generally stable during the treatment.

Anti-CCP antibodies indicate aggressive course of the disease and correlate positively with the genetic factors predisposing to the development of RA, such as in particular: protein tyrosine phosphatase N22 gene (PTPN22) and shared epitope (SE), mainly HLA-DRB104 (29). Anti-CCP antibodies do not identify any specific antigen initiating or maintaining an inflammatory immune response in the joint, but are directed towards a variety of citrullinated proteins and have limited cross-reactivity.

PORPHYROMONAS GINGIVALIS – A POTENTIAL ETIOLOGICAL FACTOR OF RHEUMATOID ARTHRITIS

RA is characterized by specific autoimmunity to citrullinated proteins. Protein citrullination is part of physiological processes, such as the presence of citrullinated filaggrin in healthy skin. If anti-citrullinated protein antibodies are formed, which is the case in RA, the immune toleration may be broken to trigger inflammation. The factors that break the tolerance against citrullinated proteins are not precisely known. Citrullinated fibrin deposits were observed in various inflammatory joint diseases in which no autoantibodies were simultaneously produced, which suggests that their induction depends on some genetic, environmental or other factors. Exposure to nicotine and shared epitope were identified as risk factors for the occurrence of citrullinated protein autoantibodies, in particular, α -enolase and vimentin, but the list of risk factors is not all-inclusive.

Porphyromonas gingivalis (*P. gingivalis*), a periodontal pathogen, was investigated in recent studies on RA pathogenesis (30). Inflammation of the periodontal tissues (*periodontitis*) caused by *P. gingivalis* is a chronic, inflammatory disease of the gums, which occurs in 4.2% of U.S. population.

P. gingivalis is detected in 80-90% of patients with periodontitis and in 10-30% of healthy individuals (31). An epidemiological link between RA and periodontal inflammation was investigated because of specific PAD (peptidylarginine deiminases), also known as PPAD (*P. gingivalis* PAD), and the potential role of *P. gingivalis* in RA etiology, leading to the creation and generation of citrullinated antigens. Pathophysiological mechanism of periodontal inflammation is similar to RA. The disease is characterized by bone resorption in periodontitis and is mediated by several proinflammatory cytokines, such as TNF- α and IL-1B, prostaglandin E2 and

matrix metalloproteinases. It was shown that RA-specific autoantibody to citrullinated α -enolase cross-reacts with citrullinated *P. gingivalis* enolase through molecular mimicry between both peptide epitopes (32).

With the use of electrophoresis, immunoblotting method and spectrophotometry, Wegner N et al. (33) showed that *P. gingivalis* is the only bacteria within the mouth capable to induce protein citrullination. Citrullinated peptides were detected in the *P. gingivalis* cytoplasm, in and under the cell membrane.

PPAD was detected using the PCR method in all *P. gingivalis* strains, but was not present in the remaining 11 types of bacteria within the mouth. PPAD has similar amino acid sequences to human PAD and has a special affinity for carboxyl arginine residues. Citrullination of bacterial and host proteins by PPAD can lead to the creation of new epitopes, which may represent a dangerous exogenous or endogenous signal to trigger the formation of both, bacterial and host anti-citrullinated protein antibodies in genetically predisposed individuals. A two-stage inflammation induction model in RA is proposed (33). At the first stage, the immune tolerance is broken to specific citrullinated proteins generated by *P. gingivalis* in area of gingivitis. At the second stage, the peptide epitopes penetrate to other, specific citrullinated proteins in the articular cavity through molecular mimicry of T and B cell activation and inflammation induction.

OTHER TESTS FOR EARLY RHEUMATOID ARTHRITIS DIAGNOSIS

Genetic factors that predispose to the development of RA can be determined in early disease diagnostics. This applies to the following antigens: HLA-DRB10401, DRB10404, DRB10405, and less frequently to DRB10408. These alleles have a shared epitope in common (SE). The shared epitope (SE) occurs in 50-60% of patients with RA and is correlated with morbidity and disease activity. A strong correlation was recently demonstrated between the presence of SF and anti-CCP2 antibodies, whereas the correlation with rheumatoid factor (RF-IgM) was found to be poor (34), despite the fact that anti-CCP2 antibodies are also found in patients with no SE.

Early synovitis diagnostics is another important issue, particularly in small or moderate inflammations, which may be undetectable in physical examination at the early development stage, especially in overweight patients. There is no data available on the sensitivity and repeatability of physical examinations in detecting moderate synovitis. Ultrasonography and magnetic resonance imaging (MRI) are much more reliable diagnostic tools as compared to physical examination. Changes in the cortical bone and erosions can be detected much earlier in USG and MRI than with conventional radiography. The detectability of synovitis increases significantly if power Doppler ultrasonography is used instead of the conventional gray scale sonography, and if gadolinium-based MRI is applied.

Ultrasonography requires considerable experience in assessing the disease-associated changes. This method is cheap and well tolerated without exposing the patient to the ionizing radiation. With the introduction of dynamic assessment, this method has become even more valuable (35), however, it needs to be validated for early RA diagnostics. MRI is an expensive, time consuming and poorly tolerated in some patients. However, it offers specific advantages, such as standardized protocol and absence of ionizing radiation (36).

According to EULAR recommendations, an early diagnosis of arthritis is the primary objective. Arthritis is characterized by joint swelling accompanied by pain and stiffness. Please note that the swelling may be caused by trauma. Patients presenting with arthritis of more than one joint should be referred to and seen by a rheumatologist, ideally within six weeks after the onset of symptoms.

Clinical examination remains the gold standard in detecting synovitis. However, in doubtful cases, ultrasonography, power Doppler or MRI should be performed. Imaging techniques were shown to have greater sensitivity in detection of synovitis and joint erosions in early RA as compared to physical and radiological examinations. There is evidence that bone oedema detected in MRI may be a sign of early arthritis (37). In case of arthritis, it is necessary to exclude other diseases than RA. This requires careful history taking, clinical examination and laboratory tests, such as complete blood cell count with differential white blood cell count, urinalysis, transaminases and antinuclear antibodies. In case of doubt, we should also examine uric acid levels, tests for the Lyme disease, parvovirus B19, urethral or cervical swab cultures, anti-bacterial serology, tests for hepatitis B and C, and chest x ray. Studies such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP), rheumatoid factor (RF-IgM), anti-CCP2 have recently been incorporated into the classification criteria for RA. These tests are related to the extent of the inflammation and the prognostic severity of the arthritis.

ACR 1987 AND ACR/EULAR 2010 CLASSIFICATION CRITERIA

The ACR 1987 classification criteria for RA have been developed by the American College of Rheumatology based on medical data of patients diagnosed with RA lasting for 8 years on average. These criteria offer 91% sensitivity (38) and 89% specificity for the advanced form of RA.

Radiological criterion is rarely met in early stages of the disease. During the first 3 months of the disease, erosions occur in 13% of patients, and are present in 50-70% of patients in the first 2 years from the disease onset.

The serological criterion – rheumatoid factor (RF-IgM) – occurs in early disease stages in 15-20% of patients. If the standard RF-IgM level exceeds 50 IU/ml, this means that its specificity is also increased for early RA, however, its sensitivity is slightly lower.

As a rule, rheumatoid nodules do not occur within the first 3 months from the disease onset.

This means that only 4 out of 7 components of ACR 1987 for joints have the potential clinical significance in the diagnosis of early RA and may be met in the early stages of the disease. However, they have low specificity as they also occur in other diseases.

Another difficulty in meeting the four classification criteria is traced back to the criterion referring to at least three joint areas where the disease is manifested, whereas early RA may be manifested as mono- or polyarthritis, which also reduces the diagnostic value of the above mentioned criteria.

The 1987 ACR criteria fail to identify patients in whom RA will develop from within a group of patients with unclassified arthritis. Patients with poor prognosis in whom rapid aggressive drug therapy (including biological drugs) need to be applied cannot be differentiated from patients with good prognosis who need gentle therapy with synthetic DMARDs. Also, the 1987 ACR criteria do not correspond to the current recommendations for RA patients, i.e.: early diagnosis, remission, and sustained remission.

New ACR/EULAR 2010 criteria were developed by a group of experts in order to increase sensitivity and specificity that would allow to identify patients with early and chronic RA (39-42) (tab. 3). The criteria include four domains: the number and type of affected joints, serological tests (RF, ACPA), acute phase indicators (ESR, CRP) and duration of symptoms. The score range is 0-10. The total score of 6 or greater (≥ 6) means a “definite RA”. Score ≥ 6 means having definite RA at a specific time point. However, the future condition of the classified patients at some other time point remains unknown, both in terms of clinical symptoms and the disease activity. Patients who score less than 6 points (< 6) cannot be classified as “definite RA”, however, they can meet the criteria for “definite RA” at some point of time in the future. “Definite RA” can be also diagnosed in patients with erosions and long-term illness, regardless of disease activity, and in patients already treated with DMARDs whose condition has improved and who do not meet the ACR/AULAR 2010.

The introduction of new criteria for determining ACPA levels has a pathogenetic aspect. MTX is a valuable prognostic standard. Anti-ACPA antibodies are associated with genetic factors that may predispose to the development of RA. RA ACPA (+) and RA ACPA (-) are the major

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis.

– Target population of patients who have at least 1 joint with definite clinical synovitis (swelling) not better explained by another disease.	
– Classification criteria for RA: a score of $\geq 6/10$ is needed for the classification of a patient having definite RA.	
A. Joint involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints	2
(with or without involvement of large joints)	
4-10 small joints	3
(with or without involvement of large joints)	
>10 joints (at least 1 small joint)	5
B. Serology	
(at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

*Large joints refers to shoulders, elbows, hips, knees, and ankles.

**Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, thumb interphalangeal joints, and wrists. Does not refer to: distal interphalangeal joints, thumb metacarpophalangeal joints, hallux metatarsophalangeal.

disease subtypes indicating pathogenetic and prognostic aspect of the disease. This type of classification defines the principles of individual therapeutic procedure.

Recently, van der Linden et al. (43) investigated the differences in the classification of RA patients using the new ACR/EULAR 2010 and old ACR 1987 criteria on the cohort of 2258 patients with early arthritis. Both types of diagnostic criteria were evaluated at baseline and after one year of observation. After the period of one year, the diagnosis was changed in 18% of patients who met the criteria for ACR/EULAR 2010 at baseline. ACR/EULAR 2010 criteria represented 84% sensitivity and 60% specificity, while the 1987 ACR criteria showed 61% sensitivity and 74% specificity. **In ACR/EULAR 2010 classification, more patients are diagnosed with RA, also in the earlier stage of the disease, as compared to the 1987 ACR classification. The discriminative ability of the new criteria is satisfactory, however, they need to be validated and further analysed in comparative studies on large groups of patients.**

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