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RESEARCH ARTICLE



Diagnostic and prognostic markers of seronegative rheumatoid arthritis

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ABSTRACT

Introduction. Rheumatoid arthritis (RA) is the most common inflammatory disease of the joints, the prevalence of which is increasing in the population, leading to the emergence of new cases of the disease in young and middle-aged people, which has enormous medical and social significance. The study objective was to optimize the diagnosis and prediction of seronegative early rheumatoid arthritis outcomes by identifying the most significant clinical, laboratory and instrumental predictors of joint destruction.

Material and methods. The study includes 82 patients (22 men and 60 women), aged 17 to 70 years (average of 45.02±12.4 years), with the presence of articular syndrome (arthritis). All subjects were classified in the following groups: group I – 41 patients - 11 men and 30 women, whose average age was 44.46±13.36 years (average duration of the disease 6.0±2.9 months) with early seronegative rheumatoid arthritis (eRA), and group II consisted of 41 patients aged 45.55±11.12 years - 11 men and 30 women, with a diagnosis of seropositive rheumatoid arthritis (RA) (average duration of the disease of 6.8±3.7 months).

Results. In the seronegative eRA group, the average Value of “prognostic index” (PrI) calculated from the data at the time of the initial survey was 5.67±1.72 points. PrI values in patients with transformation in RA within 1 year were significantly higher – 6.68±1.61, than without transformation in RA 4.52±0.96 points, $p < 0.0001$. At the same time, the values of PrI < 6 points were observed in 17 (20.7%) patients, PrI > 8 – in 25 (30.48%) patients, intermediate values (between 6 and 8 points) – in 40 (48.78%) patients, $p < 0.001$. Thus, in most patients with transformation in RA, the PrI values were more than 6 points.

Conclusions. In 53% of patients with seronegative RA, there is a transformation into seropositive rheumatoid arthritis during the first 18 months of the development of the disease. Features of early rheumatoid arthritis, in comparison with stabile RA are a polyarthritis presentation of the onset with damage to the joints of the hands, prolonged morning stiffness (more than 1 hour), moderate or high level of activity, the presence of productive synovitis and erosion during ultrasonography.

Keywords: seronegative, rheumatoid arthritis, prognostic index.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

A comprehensive assessment of the features regarding the course of seronegative rheumatoid arthritis is given and the predictive significance of the „prognostic index”.

The research hypothesis

Additional clinical, serological, immunological and instrumental features of the debut, variants of the course and outcomes of early rheumatoid arthritis were revealed. It is demonstrated that the ul-

trasonography is a more sensitive method of studying peripheral joints than radiography in the initial stages of development of rheumatoid arthritis.

The novelty added by the manuscript to the already published scientific literature

The principles of determining diagnostic and prognostic risk factors for the development of erosive-destructive changes in the joints in patients with early seronegative rheumatoid arthritis are substantiated.

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory disease of the joints, the prevalence of which is increasing in the general population [1-3], leading to the emergence of new cases in young and middle-aged people, which has enormous medical and social impact [4].

It has been established that it is the first years of the disease that are decisive in the development and progression of the pathological process. In the earliest period of RA, when the disease is in the primary, exudative phase, its reversibility is significantly higher, due to the not yet developed autoimmune mechanisms and the lack of a morphological basis for articular destruction – synovial pannus [2, 3, 5, 6].

However, to date, the specific signs of the early stage of the disease have not been fully determined [1, 7]. In recent years, an opinion has been expressed about the inconsistency of the criteria of the American College of Rheumatology (ACR, 1987) for early seronegative RA (eRA), while allowing with a sensitivity of 91-94% and a specificity of 89-90% to diagnose the disease with a detailed clinical picture [2-4].

Many researchers state that the main reason for the difficulty of diagnosing seronegative eRA is the lack of clear criterion signs [3, 7]. In this regard, with a lack of classification parameters of any rheumatic disease, but in the presence of persistent arthritis of one or more joints, a group of undifferentiated arthritis is currently distinguished, from which transformation into RA is possible [2-5]. However, the allocation of this medical category is still a controversial issue, and the main concern is about finding criteria to predict how undifferentiated arthritis progresses into rheumatoid arthritis [1-3].

Along with the above, the problem of early diagnosis of RA in the absence of rheumatoid factor (RF) in the blood remains poorly understood. Such questions as features of the immunological picture of seronegative RA in the debut, the rate of progression and functional disorders are not specified. At the same time, the diagnostic and prognostic values of the RF is questionable. An important addition to the verification of rheumatoid inflammation can currently be antibodies to cyclic citrullinated peptides (anti-CCP) [5, 8]. According to preliminary data, anti-CCP has 85-97% specificity and 60-85% sensitivity for RA [2, 6, 9], while detecting 34-69.3% seronegative in the RF. However, some authors note lower rates of occurrence of this marker in eRA - in 40% in the general group and only in 14% of patients negative RF [3, 5, 10], and therefore, new studies are needed to

assess the value of anti-CCP as a diagnostic and prognostic marker of eRA, especially seronegative form.

Analysis of the data of recent years has proved that conventional radiography of the hands and feet for verification of seronegative eRA is quite poor [1-3, 8]. In recent years, ultrasound (USG) and magnetic resonance imaging have been introduced into the diagnosis of seronegative eRA, but the diagnostic effectiveness of these innovative methods requires further study [7-9].

Thus, these prerequisites dictate the need to improve diagnostic approaches and develop new effective prognosis criteria, especially at an early stage of seronegative RA, which determined the goals and objectives of this study.

The purpose of the study was to optimize the diagnosis and prediction of early seronegative rheumatoid arthritis outcomes by identifying the most significant clinical, laboratory and instrumental predictors of joint destruction.

The objectives of the study were:

- (1) Conduct a comparative analysis of clinical, laboratory and instrumental parameters in patients with undifferentiated and early seronegative rheumatoid arthritis.
- (2) Identify predictors of transformation and assess the possibility of using the „Prognostic Index” to determine the risk of progression of undifferentiated arthritis to rheumatoid arthritis.
- (3) Characterize the variants of the course of the disease in patients with early seronegative rheumatoid arthritis in the dynamics of observation.
- (4) Assess the diagnostic and prognostic significance of clinical, serological, immunological, and instrumental indicators for the development of destructive arthritis.

Materials and methods

The study was carried out between 2019 and 2022. Subjects were selected from the arthrology and rheumatology departments of the Timofei Moşneaga Republican Clinical Hospital. In total 82 patients were selected (22 men and 60 women), aged between 17 to 70 years (average 45.02±12.4 years), with the presence of articular syndrome (arthritis). During observation, all subjects were identified in two groups.

In group I were included patients with early seronegative rheumatoid arthritis. A patient was included if at the time of the examination, he showed signs of inflammatory joint damage, but there were a sufficient number of criteria for the diagnosis of RA according to ACR, 1987, and there were no certain criteria for other nosology. This group consisted of 41 patients - 11 men and 30 women, whose aver-

age was 44.46 ± 13.36 years. The duration of the disease on average was 6.0 ± 2.9 months.

Group II consisted of 41 patients aged 45.55 ± 11.12 years - 11 men and 30 women, with a diagnosis of seropositive RA and an average duration of the disease of 6.8 ± 3.7 months. The diagnosis of RA was made based on the criteria of the American College of Rheumatology/The European Alliance of Associations for Rheumatology (ACR/EULAR, 2010) for the early diagnosis of RA and ACR, 1987.

For the entire period of observation - from 12 to 18 months (on average 13.7 ± 4.3 months) from the undifferentiated arthritis group, 7 (17%) patients had converted to seropositive RA, 6 (14.6%) - spontaneous remission, 5 (12.2%) - other rheumatic disease, the rest had an indefinite joint syndrome.

Special immunological studies included determination of rheumatoid factor (RF) in plasma by nephelometry; antibodies to anti-CCP by immunoelectrophoresis using the Set Anti-CCP ORG 220, OR-GENTEC (Germany) and other lab-tests according to the National Protocol for rheumatoid arthritis.

All patients underwent conventional radiography of the hands and distal parts of the feet from a direct (anteroposterior) projection using standard modes on the X-ray diagnostic complex "Bennett" (USA). The X-ray stage of RA was determined by the modified Steinbrocker method. All patients underwent USG of joints. USG diagnostics was carried out on the device "Toshiba 1200" linear sensor with a frequency of 7 to 17 MHz.

Statistical analysis of the results was carried out by using the standard packages of statistical programs SPSS for Windows (version 11.5) and STATISTICA (version 9.0). To create the database, the Microsoft Excel 7.0 spreadsheet editor was used. To describe the nature of the distribution of quantitative features, standard methods of variational statistics were used with the determination of the arithmetic mean value of the variable (M), the mean quadratic standard deviation (SD) and the standard error of the average value (t). The average values in the study were presented in the form $M \pm SD$. To assess the reliability of quantitative parameters, a paired Student's t-criterion was used, as well as the Mann-Whitney test. The Wilcoxon matched pairs test criterion was used to evaluate dynamic changes within groups. When assessing the differences in the distribution of rank variables, the X^2 criterion was used. The analysis of the relationship of variables was carried out using correlation analysis using Pearson and Spearman methods, regression analysis, and binary logistic regression model. Differences were considered significant at the bilateral level of significance of $p < 0.05$.

Evaluation of the effectiveness of forecasting various parameters, indices, and tests was carried out by calculating the operational characteristics - building a characteristic curve, estimating the area under the curve with the determination of the predictive value of a positive result and the predictive value of a negative result, diagnostic efficacy, and diagnostic accuracy of the test.

Results

Of the 81 patients of the observation group, 41 patients were identified in the seronegative eRA group - 11 men and 30 women, the average age - 44.46 ± 13.36 years. The duration of the disease on average was 6.7 ± 2.9 months, while with the duration of the joint syndrome - from 3 to 6 months 14 (34.1%) patients were observed, from 6 to 12 months - 16 (39%), from 12 to 18 months - 11 (26.8%) patients.

A patient was included in the seronegative eRA group if at least one of the modified criteria for the alleged diagnosis of RA was present during the initial examination: (1) the presence of arthritis of at least one joint; (2) a positive symptom of compression of the hands and / or feet; (3) the presence of morning stiffness lasting 30 minutes or more.

Treatment of patients with seronegative eRA was carried out in accordance with the recommendations of EULAR, 2010 with the following scheme: the appointment of non-steroidal anti-inflammatory drugs (NSAIDs), if necessary, glucocorticoids (mainly intra-articular). With the persistence of arthritis during the 3-month observation period, the question of prescribing therapy with disease-modifying antirheumatic drugs (DMARDs) was decided. In most cases, sulfasalazine was prescribed as the first drug at a dose of 2-3 g/day - 20 (48.8%) patients and methotrexate - 21 (51.2%) patients.

In the seronegative eRA group, with an increased duration of the disease, the number of patients with transformation into seropositive RA increased. By the end of observation, 24 patients (58.5%) began to correspond to the diagnosis of seropositive RA.

During the observation of patients with seronegative eRA, to predict the development of RA in this category of patients, at the time of the initial examination, the prognostic index (PrI) was calculated using the method proposed by Van der Helm-van Mil *et al.* We used the same methods as the authors of this index.

In the seronegative eRA group, the average value of PrI calculated from the data at the time of the initial survey was 5.67 ± 1.72 points. PrI values in patients with transformation in RA within 1 year were significantly higher 6.68 ± 1.61 , than without transformation in RA 4.52 ± 0.96 points, $p < 0.0001$. At the same time, the values of PrI < 6 points were observed in 17 (20.7%) patients, PrI > 8 - in 25 (30.48%) patients, intermediate values (between 6 and 8 points) - in 40 (48.78%) patients, $p < 0.001$. Thus, in most patients with transformation of RA, the PrI values were more than 6 points.

Application of prognosis criteria for patients with seronegative eRA, proposed by Van der Helm-van Mil *et al.* in 2007 it gave a satisfactory result in patients with high rates of diagnostic significance (Table 1). It is worth noting that in our study, RF and anti-CCP were used as immunological markers of rheumatoid inflammation.

In the group of patients with seronegative eRA, a positive result for the RF was recorded in 3 (7.3%), while in patients with transformation to seropositive RA, this immunological marker was detected in 5 (12.2%) examined. The result on

anti-CCP in this group was positive in 4 (9.75%) patients, and in patients with transformation to seropositive RA, positive anti-CCP were found in 7 (17.07 %) of patients, other remain seronegative.

Table 1. Diagnostic value of determining the „predictive index” of the transformation of seronegative eRA in seropositive RA.

Index, n = 82	PrI
Diagnostic sensitivity, %	82
Diagnostic specificity, %	94
Predictive value of a positive result, %	92
Predictive value of a negative result, %	74
Diagnostic effectiveness of the test, %	87
The plausibility relation of a positive result, %	5.1
The plausibility relation of a negative result, %	0.34

Note: PrI - predictive index, eRA – early seronegative rheumatoid arthritis, RA – rheumatoid arthritis.

The analysis showed a high diagnostic effectiveness of anti-CCP and not RF determination in patients with eRA (Table 2).

Table 2. Diagnostic value of anti-CCP and RF determination.

Index, n = 82	anti-CCP	RF
Diagnostic sensitivity, %	99*	65
Diagnostic specificity, %	87*	70
Predictive value of a positive result, %	91*	73
Predictive value of a negative result, %	99*	62
Diagnostic effectiveness of the test, %	94*	68
The plausibility relation of a positive result, %	7.8*	2.2
The plausibility relation of a negative result, %	0.01*	0.52
“Cut-off”, IU/ml	20	

Note: * - reliability of differences in the analyzed indicators $p < 0,05$, anti-CCP - antibodies to cyclic citrullinated peptides, RF – rheumatoid factor.

Thus, anti-CCP is a highly specific and sensitive method for diagnosing RA, which allowed us to use it as one of the estimated indicators of PrI.

The obtained results justify the expediency of allocating seronegative eRA as a separate nosological unit, since transformation into RA is possible from this group of patients, which requires more thorough diagnostic approaches. At the same time, the results of the study proved the high diagnostic effectiveness of the determination of anti-CCP for RA verification among patients with seronegative eRA.

The early RA group consisted of 41 patients, of which 28 (68.2%) were diagnosed within the first 4-8 months, 13 (31.7%) patients were identified in this group from the seronegative eRA. Persistent articular syndrome in 41 (100%) of the examined patients was preceded by the appearance of a typical RA picture of the prodromal period. Its most frequent manifestations were: arthralgia – in 37 (90.24%), increased fatigue – 33 (80.48%), a feeling of numbness of the hands/feet – 26 (63.41%), myalgia – 33 (80.48%), which appeared on average 10-12 weeks before the onset of arthritis.

The survey group was dominated by women (ratio M:F = 0.1:4.5). In the dynamics of observation, pre-erosion stages of RA were recorded in 17 (41.6%) patients; single erosions of articular surfaces were recorded in 23 (56.09%) cases. Patients with a moderate degree of RA activity prevailed – 23 (56.09%). Seropositive in anti-CCP arthritis was in 28 (68.29%) patients, in the RF – in 11 (26.82%) patients. The „classic” presentation of the RA debut (persistent symmetrical, gradually increasing polyarthritis with a predominant lesion of the joints of the hands) by the end of observation was recorded in 19 (46.34%) of the subjects. In 23 (56.09%) patients in the initial period of the disease, oligoarthritis was observed mainly in the knee, elbow and shoulder joints and in 11 (26.83 %) – monoarthritis. Prolonged (more than 1 hour) morning stiffness was recorded in 41 (100%) patients. The test of transverse compression of the hands/feet was positive in 41 (100%) patients with eRA. On average, extra-articular manifestations were observed after 6.7 ± 3.1 months from the onset of the disease.

Analysis of the initial manifestations of the joint syndrome showed a certain dynamic of transformation of clinical and laboratory parameters. In the first 3-6 months from the debut of the disease, more than half of the patients recorded mono-, oligoarthritic nature of the lesion, which by the end of the year in 17 (40%) transformed into polyarthritis. Thus, after 18 months from the debut, the polyarthritis nature of RA was observed in 66% of the examined patients, which is significantly ($p < 0.05$) more than in the debut.

Taking into account the critical attitude of classification criteria ACR (1987) in patients with eRA, we conducted a comparative assessment of the diagnostic significance of these parameters and RA classification criteria ACR/EULAR (2010).

As a result of the study in patients with very early seronegative RA, the classification criteria ACR, 1987 corresponded to 30% and in patients with advanced RA – 70%; while the ACR/EULAR, 2010 – in 48% and 100%, respectively. Thus, the diagnostic efficacy of the ACR/EULAR criteria, 2010 was significantly higher than the ACR criteria, 1987 in patients with eRA.

As an immunological marker, along with the RF, we used the level of anti-CCP. It is noteworthy that in an earlier period, RA anti-CCP showed less sensitivity than in the advanced stage of the disease with a consistently high specificity. In patients with a duration of 3-6 months, 27 (65.85%) were positive for anti-CCP, for RF – 17 (41.46%), with a duration of 6-12 months and more than – 100% and 70.1%, respectively. Thus, in the group with eRA by the end of 12-18 months of observation, the diagnostic titer of anti-CCP was recorded in all (100%) patients. Thus, a high diagnostic value of the determination of anti-CCP in the verification of early RA was registered. At the same time, the data obtained indicate that there is no advantage in the diagnostic value of the combination of RF and anti-CCP, compared with the study of only the level of serum anti-CCP.

Currently, it is established that more than 50% of cases of erosive-destructive changes in the joints develop within the

first 3-6 months from the debut of RA, which determines an unfavorable prognosis for the course of the disease. At the same time, half of the most pronounced destructive changes in radiography are observed only after 2 to 6 years from the debut of the disease, which requires a revision of the importance of radiography of the joints in the early stages of the development of RA in favor of other methods of instrumental examination (Table 3).

Table 3. Diagnostic value of USG and radiography in patients with early seronegative RA.

Indicator; n = 82 (group I = 41; group II = 41)	USG	PrI
Diagnostic sensitivity, %	71*	29
Diagnostic specificity, %	63*	61
Predictive value of a positive result, %	92*	62
Predictive value of a negative result, %	88*	21
Diagnostic effectiveness of the test, %	97*	34
The plausibility relation of a positive result	5.7*	0.8
The plausibility relation of a negative result	0.04*	1.1

Note: * is the reliability of the differences between $p < 0.01$, RA – rheumatoid arthritis, USG – musculo-skeletal ultrasound, PrI - predictive index.

In our study, ultrasound signs of seronegative RA were: thickening of the synovial membrane, its hypervascularization in large (knee) joints; tenosynovitis, inflammation of the ligaments and fragmentation of articular surfaces in small joints. In most patients, signs of productive synovitis and destructive arthritis (bone erosion) were detected in the dynamics of observation in the absence of radiographic data.

Table 4. Frequency of occurrence of clinical and instrumental signs of structural changes in patients with different duration of eRA.

	Clinical signs of synovitis	X-ray-signs of structural changes	USG signs of synovitis / structural changes
RA > 3 < 6 months, n = 56 (from 82)	31 (59%)	1 (2%)	54 (96%) *
RA > 6th < 12 months, n = 67 (from 82)	45 (71%)	15 (24%)	65 (97%) *
RA > 12 < 18 months, n = 75 (from 82)	69 (92%)	20 (28%)	75 (100%) *

Note: * - reliability of differences between radiological and USG signs of structural changes in joints $p < 0.001$, RA – rheumatoid arthritis, USG – musculo-skeletal ultrasound.

In patients with very early stage of seronegative RA, clinical signs of synovitis of the joints were detected in 59%, radiological – in 2%, and ultrasound – in 96% of patients. With an increase in the length of the disease, significant differences between radiographic and ultrasound indicators of structural changes in the joints persisted (Table 4). In addition, in 39% of the examined patients with RA only with ultrasound diagnostics, signs of concomitant osteoarthritis were determined.

Thus, in patients in the early stage of rheumatoid inflammation, USG is a diagnostically more valuable method

of studying the joints than radiography. As a result of the study, it was found that with the polyarthritis variant of RA, destructive changes are significantly more often detected by ultrasound of the joints at earlier stages – 64%, against 8% - with oligo-monoarthritis ($p < 0.001$); with radiography of the joints – 75% against 4%, respectively ($p < 0.001$).

Analysis of the distinctive features of seropositive and seronegative variants of RA showed the following: the seronegative variant of RA at an early stage was characterized by the absence of early symptoms in almost 70% of patients, while in the group of seropositive patients such signs are detected in more than 77% ($p < 0.05$); onset with mono-oligoarthritis (80% vs 57% with seropositive variant, $p < 0.05$), with primary lesions of the knee (80%), ankle (12%, $p < 0.01$), elbow (6%), joints of the feet (11%, $p < 0.05$), while for seropositive patients the debut of RA with damage to the small joints of the hands (54%, $p < 0.01$), knee (40% $p < 0.05$) of the shoulder joints (6%, $p < 0.05$). It is also characterized by a smaller number of swollen joints ($p < 0.05$) throughout the entire period of prospective observation; below the value of the DAS28 index ($p < 0.05$).

Conclusions

Seronegative RA is characterized mainly by an oligo-, monoarthritis presentation of the joint syndrome; low degree of activity of the inflammatory process; negative rheumatoid factor and anti-CCP antibodies; the absence of active synovitis in USG of joints and destructive changes on radiography. In 53% of patients with seronegative RA, there is a transformation into seropositive rheumatoid arthritis during the first 18 months of the development of the disease. Features of early rheumatoid arthritis, in comparison with stable RA are a polyarthritis version of the debut with damage to the joints of the hands; prolonged morning stiffness (more than 1 hour); moderate or high level of activity; the presence of productive synovitis and erosion during USG.

„Prognostic index” with a significant degree of reliability (diagnostic effectiveness of the test – 87%) allows predicting the development of rheumatoid arthritis in patients with seronegative arthritis. Early ultrasound signs of rheumatoid arthritis show an increase in the thickness of the synovial membrane and its hypervascularization in large joints; tenosynovitis, fragmentation and erosion of the articular surfaces of small joints. USG has a greater diagnostic efficacy – 91% than radiography – 32% ($p < 0.01$) for assessment of structural changes in peripheral joints in patients with early seronegative rheumatoid arthritis.

Predictors of the development of a destructive process in the joints in patients with early seronegative rheumatoid arthritis are a polyarthritis presentation of the debut with a high degree of activity; tenosynovitis and hypervascularization of the synovial membrane during USG.

Abbreviations

Anti-CCP - antibodies to cyclic citrullinated peptides; eRA – early seronegative rheumatoid arthritis; PrI - predictive index; RA - rheumatoid arthritis; RF – rheumatoid factor; USG – ultrasound.

Declaration of conflict of interest

Nothing to declare.

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