ISSN 2729-8043

INTERNATIONAL JOURNAL OF

ORIGINAL MEDICINE

Original Medicine. Volume 2 Issue 1 2023
ISSN 2729-8043
Impact Factor Search 5
https://www.original-medicine.eu/

Original Medicine is an open-access publication, providing authors with continuous publication of original research across a broad spectrum of medical, scientific disciplines and sub-specialties. The Original Medicine review process emphasizes submissions' scientific, technical and ethical validity. Novelty or potential for impact is not considered during the manuscript's evaluation or adjudication.

Editorial board

Manuscripts typed on our article template can be submitted through our website here. Alternatively, authors can send papers as an email attachment to info@original-medicine.eu

Original Medicine.
ISSN 2729-8043 https://www.original-medicine.eu
Michalská 2, Bratislava, Slovakia, 81121
E-mail: info@original-medicine.eu

Original Medicine. Volume 2 Issue 1 2023
ISSN 2729-8043
Impact Factor Search 5
https://www.original-medicine.eu/

CHARACTERISTICAL TRAITS OF THE CLINIC AND DIAGNOSIS OF RHEUMATOID ARTHRITIS IN EARLY STAGES

Abduazizova N.X., Berdiyeva D.U., Sharapov Z.A.

Tashkent Medical Academy Uzbekistan

Abstract The early stage of RA is strategically essential for treatment and at the same time, the most difficult for diagnosis. It is characterized by the prevalence of exudative changes in affected joints, frequent atypical flow and good response to treatment. If active treatment is administered at a very early stage, remission can be achieved in 6 months among 47% of patients and a year later, among 58.1% of patients. Prescription of combined baseline therapy in RA reduces the severity of clinical manifestations in "early" RA, improves functional activity and slows down the radiological progression of joint damage, improves the quality of life and reduces the risk of disability, reduces mortality in RA to a population level. The new markers are necessary for early diagnosis of rheumatoid arthritis, as seronegativity in both early and established RA remains the main limitation of both ACCP and RF. Protein 14-3-3 η may represent a new biomarker for the detection of RA.

Purpose of the research was studying of clinical features and diagnostic significance of 14-3-3η protein in the blood of patients at the early stages of disease.

Material and methods: The study included 68 patients with RA (meeting the EULAR / ACR criteria, 2010) aged 19 to 74 years (mean age 44.2 ± 3.2 years) with a disease duration of up to 1 year (from 6 to 52 weeks), who underwent inpatient treatment in the departments of cardio-rheumatology, rheumatology and were registered in the arthrology department of multidisciplinary clinic of TMA for the period 2019 - 2020. By sex, the patients were distributed as follows: 63 women (93%) and 5 men (7%) (F: M = 12: 1). The average duration of the disease was 8.6 ± 0.7 months. To determine RA activity, the following indicators were used: the severity of pain in joints, assessed by the patient on a visual analogue scale (VAS), the total activity of the disease was assessed according to the recommended EULAR

index DAS28 and ESR (mm / h) according to Westergren with the release of 3 main degrees and CRP in serum blood. To assess the functional capabilities of the patient, the definition of the functional class was used. The functional status of the patient was determined by the Stanford Health Assessment Questionnaire (HAQ, 1980) and Richie. Laboratory examination included general clinical and biochemical blood tests. Diagnostics of autoantibody panels included quantitative determination of RF by the Waaler-Rose method, as well as ACCP and 14-3-3η protein by enzyme-linked immunosorbent assay.

Results and Discussions: Patients with a course of RA less than 3 months accounted for 18.7% in Group I, 29.4% in Group II, 18.8% in Group III, and 21% in Group IV. Disease duration up to 6 months in group I was found in 56.3% of patients, in II - in 29.4% of patients, in III - 31.2% and in 10.7% of patients in group IV. The 12-month prescription of the disease was determined in group I in 12.5% of patients, in group II - in 23.6%, in group III - in 25%, and in group IV - in 36.8% of patients. The average value of morning stiffness in all examined patients was 79.1 ± 19.3 minutes. The duration of morning stiffness in patients of group I averaged 46.6 ± 15.8 minutes, in patients II - 75.6 ± 27.3 minutes, in patients in groups III and IV it averaged 65.6 ± 19.7 and 128, 4 ± 14.5 minutes, respectively, regardless of the duration of the disease. Analysis of the nature of the articular syndrome in patients with RA showed that polyarthritis, as a criterion for RA, was detected in 57.4% of patients, the mono-oligo-articular nature of joint damage was detected in 42.6% of those examined. The data presented indicate the highest percentage (72%) of hand joints lesions in RA patients, regardless of the duration of its course. In the onset of RA, the pathological process more often involved the joints of the hands (72%), less often - the knee (13.2%), foot joints (2.8%), shoulder (1.5%), elbow (2.9%) and ankle joints (7.6%). Only in 9 patients (13.2%), there was a simultaneous lesion of almost all joints. The analysis of the degree of activity according to DAS28 showed that in 23.5% of patients in group IV, the average value was 5.31 ± 0.49, which

corresponded to the III degree of activity, in 76.5% of patients, on average, 4.8 ± 0.1 (II degree of activity). There were no patients with a low degree of RA activity.

The average score of the HAQ index in the examined patients was 1.05 ± 0.03 and this was assessed as moderate functional disorders of the joints. The minimum functional impairment of the joints was observed in patients of group I (0.99 ± 0.03). In the remaining groups, there was an average degree of functional disorders of the joints according to the HAQ index (1.07 ± 0.03). The maximum indicator according to the Ritchie index, which includes the number of painful and swollen joints, was recorded in patients of group IV (26.6 ± 0.8), the minimum - in patients of group I (15.6 ± 0.3). The average score of the Richie index in the examined patients was 21.1 ± 0.4. The severity of joint pain according to the VAS showed the highest numbers (77.4 ± 2.1) (severe pain) in patients of group IV, when the lowest score was reached by patients in group I (49.4 ± 2.8) (moderate pain). The average VAS scores in patients of groups II and III were practically the same, which corresponded to 70 ± 2 and 70.6 ± 2.3 (severe pain). Among the examined patients, FC II was found in 40%, FC I - in 34%, FC III was established in 26% of patients. It should be noted that 74% of patients in group IV had a higher FC, namely FC III. In 81% of patients in group I, FC I was noted. Seroprevalence is of no small importance in the diagnosis of RA. According to the results of this study, seronegativeness was mostly observed in the early stage of RA. According to the literature, it is known that patients who are positive for the RF have a worse prognosis for the course of the disease. However, the RF phenotype has two significant limitations. First, the specificity of this test for RA is rather low: RF is found in about 5% of healthy people, in 5-25% of elderly people, as well as in a significant number of patients with chronic diseases. Secondly, the presence of RF is not stable. The frequency of RF detection depends significantly on the duration of the disease. The results of one of the domestic studies showed that in the first 6 months it is detected only in 15-43% of patients with RA, subsequently, some RF-negative patients become RF-positive. Under the influence of treatment, the

reverse transformation is also possible. With a disease duration of up to one year, 43% of patients were seropositive in the RF, and 57% were seronegative. In the group of patients with RA duration of less than 3 months, RF was detected in 27%, and with an increase in the duration of the disease, its indicator increased to 62%. ACCP was determined in 80% of the examined patients with a disease duration of up to 3 months, by 12 months of illness, on average, in 90.6% of patients, this indicator turned out to be positive 14-3-3 η protein was determined in all (100%) examined patients, regardless of the duration of the disease. A direct correlation was established between the duration of the disease and the frequency of detection of ACCP, while in patients the correlation between the duration of the disease and the frequency of detection of the 14-3-3 η protein was not established. In patients with long periods of disease duration (7.0 ± 0.9 months), high diagnostic titers of ACCP were revealed (47.1 ± 6.1), in contrast to other groups. A 14-3-3 η protein was determined in all patients regardless of the duration of the disease. This indicates that with an increase in the duration of the disease, the diagnostically significant ACCP figures increase. It should be noted that 80% of patients with a disease duration of up to 3 months were seropositive for ACCP, 100% for 14-3-3 η protein, while the percentage of RF detection in these patients was only 31.2%. By 12 months of illness, the detection of ACCP increased to 90.6%, RF to 37.5%, and the initial results of 14-3-3 η protein did not change (100%). Thus, the determination of the 14-3-3 η protein was significantly superior in sensitivity to ACCP and RF.

Conclusion The debut of RA is observed mainly in middle age. Among the forms of arthritis, polyarthritis is leading with simultaneous damage to small and large joints. The metacarpophalangeal joints are more often involved in the pathological process. In the onset of RA, the mono-oligo-articular nature of the articular syndrome, the defeat of the first metacarpophalangeal joint and the asymmetric damage to the joints are noted. The average duration of morning stiffness continued with an increase in the duration of the disease. Patients with RA onset had

Original Medicine. Volume 2 Issue 1 2023
ISSN 2729-8043
Impact Factor Search 5
https://www.original-medicine.eu/
II degree of activity according to DAS28. The average score of the HAQ index in the examined patients was 1.05 ± 0.03 and this was assessed as moderate functional disorders of the joints. The maximum indicator according to the Ritchie index, which includes the number of painful and swollen joints, was recorded in patients with a high degree of disease activity. Patients at an early stage of RA were diagnosed with FC II of joint insufficiency. At an early stage of RA, seronegativeness was more marked. In patients with RA in the early stages of 14-3-3 η, the protein in the blood is determined much more often than ACCP and RF, which indicates the high importance of this immunological method for the diagnosis of early RA.

Keywords: early rheumatoid arthritis, articular syndrome, clinical features, diagnostics, anticyclic citrulline peptide,14-3-3η protein

Introduction. Representing one of the rheumatological diseases occurring with articular syndrome, rheumatoid arthritis (RA) is characterized by damage to functionally important joints, which leads to disability of patients, especially among young and middle-aged people, which determine the social significance and urgency of the problem. It was found that about 70% of cases of erosive and destructive changes in the joints develop during the first 3-6 months from the onset of the disease, which determines the unfavorable prognosis of its course [4].

Currently, the concept of early stage of RA is interpreted ambiguously. Various authors define it as periods of time from several months to several years. Some experts identify the first 3 months of the disease as a very early stage. Scientific research, which is carried out in the framework of the problem of early arthritis, is devoted primarily to the solution of two closely related issues. Firstly, the possibilities of establishing a reliable diagnosis are being studied, and secondly, approaches to prescribing the optimal therapy option for a given period of the disease are being worked out [1].

The problem of accurate early diagnosis of RA, which is inextricably linked with the study of the immediate and distant outcomes of the disease, is currently especially relevant, in connection with the possibility of slowing down the development of the disease with the help of modern methods of treatment, if therapy is started early [3]. It is now widely accepted that early identification of RA, assessment of disease severity at diagnosis, and implementation of an effective treatment strategy can significantly improve patient prognosis. Recognizing this, in 2010, criteria for the classification of RA were established, aimed at defining the disease by its early signs. Although the diagnosis of RA is made mainly on the basis of clinical data, an immunological examination plays a significant role in the diagnosis of this disease, which makes it possible to establish the inflammatory activity of the process, as well as to detect a wide range of serological markers. The detection of autoantibodies in RA not only allows to confirm the diagnosis in case of an unclear clinical picture, but is also one of the methods for determining the prognosis of the disease. Effective treatment of RA depends on early identification, followed by timely invention and proper monitoring of treatment responses, which remain challenges for rheumatologists due to the lack of biomarkers of high sensitivity and specificity. Seronegativeness in both early and steady-state RA remains the main obstacle for both ACCP and RF, which underlines the need for new additional markers that will improve diagnostic sensitivity [5,6]. It is necessary to develop new markers for RA so that patients can be correctly classified into different risk groups. Current markers only estimate about thirty percent of the total diversity in predicting disease outcome [2]. Protein 14-3-3η is a new biomarker for the detection of PA [7]. There are seven forms of the 14-3-3 family of intracellular proteins. They have about 50% amino acid similarity to each other and interact with a variety of intracellular proteins, thereby controlling many biological processes, including protein synthesis, cellular metabolism, protein transport, and cytoskeleton transport [8]. In general, isomers, only 14-3-3η were present in synovial fluid with

high levels (at least 5 times higher than their corresponding sera), suggesting that the joint is a likely source of 14-3-3η [9, ten]. In the extracellular environment, soluble 14-3-3η has ligand activity, preferentially activating cells of the innate immune system [9]. Soluble 14-3-3η acts through signaling cascades as extracellular kinase and the P38 pathway, which leads to upregulation of some pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin 1β. (IL-1β), matrix metallopeptidase 9 (MMP-9) and activator of the nuclear factor-κB ligand receptor (RANKL) [7]. Serum 14-3-3 levels may be high in patients with RA but not in other conditions such as osteoarthritis, osteoporosis, gout, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes, systemic lupus erythematosus, primary Sjogren's syndrome , scleroderma and multiple sclerosis [8]. Early diagnosis of RA can minimize irreversible joint damage [1]. In addition, elevated serum 14-3-3η protein levels were associated with more severe joint erosion and poorer treatment outcomes. Here, we have summarized new knowledge about the role played by 14-3-3η in RA and its clinical implications as a surrogate for diagnostic, prognostic and therapeutic responses, as well as a potential drug target for RA.

Purpose of the research: To study clinical features and diagnostic significance of 14-3-3η protein in the blood of patients at the early stages of disease.

Material and methods: The study included 68 patients with RA (meeting the EULAR / ACR criteria, 2010) aged 19 to 74 years (mean age 44.2 ± 3.2 years) with a disease duration of up to 1 year (from 6 to 52 weeks), who underwent inpatient treatment in the departments of cardio-rheumatology, rheumatology and were registered in the arthrology department of multidisciplinary clinic of TMA for the period 2019 - 2020. By sex, the patients were distributed as follows: 63 women (93%) and 5 men (7%) (F: M = 12: 1). The average duration of the disease was 8.6 ± 0.7 months.

To determine RA activity, the following indicators were used: the severity of pain in joints, assessed by the patient on a visual analogue scale (VAS), the total

activity of the disease was assessed according to the recommended EULAR index DAS28 and ESR (mm / h) according to Westergren with the release of 3 main degrees and CRP in serum blood. To assess the functional capabilities of the patient, the definition of the functional class was used. The functional status of the patient was determined by the Stanford Health Assessment Questionnaire (HAQ, 1980) and Richie. Laboratory examination included general clinical and biochemical blood tests. Diagnostics of autoantibody panels included quantitative determination of RF by the Waaler-Rose method, as well as ACCP and 14-3-3η protein by enzyme-linked immunosorbent assay.

Table 1.

Clinical characteristics of patients with RA (n = 68)

Groups		Gender		Average age	Average duration of the disease (in months)
		Man	Woman		
I group (n=16)	абс.	2	14	44,5±2,8	4,6±0,8
	%	12,5	87,5		
II group (n=17)	абс.	1	16	50,4±2,8	5,5±0,9
	%	5,9	94,1		
III group (n=16)	абс.	-	16	38,1±3,3	5,9±0,9
	%	-	100		
IV group (n=19)	абс.	2	17	43,8±3,7	7,0±0,9
	%	10,5	89,5		

Statistical analysis of the results was carried out using Microsoft Excel (2007). To describe the distribution of the analyzed indicators, the frequency of occurrence

for discrete variables or parameters for continuous ones were calculated using the standard representation M ± m, where M is the arithmetic mean, am is the statistical error of its determination (standard deviation of the group mean), as well as other parameters, including percentiles.

Results and Discussions: Patients with a course of RA less than 3 months accounted for 18.7% in Group I, 29.4% in Group II, 18.8% in Group III, and 21% in Group IV. Disease duration up to 6 months in group I was found in 56.3% of patients, in II - in 29.4% of patients, in III - 31.2% and in 10.7% of patients in group IV. The 12-month prescription of the disease was determined in group I in 12.5% of patients, in group II - in 23.6%, in group III - in 25%, and in group IV - in 36.8% of patients.

The average value of morning stiffness in all examined patients was 79.1 ± 19.3 minutes. The duration of morning stiffness in patients of group I averaged 46.6 ± 15.8 minutes, in patients II - 75.6 ± 27.3 minutes, in patients in groups III and IV it averaged 65.6 ± 19.7 and 128, 4 ± 14.5 minutes, respectively, regardless of the duration of the disease. Analysis of the nature of the articular syndrome in patients with RA showed that polyarthritis, as a criterion for RA, was detected in 57.4% of patients, the mono-oligo-articular nature of joint damage was detected in 42.6% of those examined.

The data presented indicate the highest percentage (72%) of hand joints lesions in RA patients, regardless of the duration of its course. In the onset of RA, the pathological process more often involved the joints of the hands (72%), less often - the knee (13.2%), foot joints (2.8%), shoulder (1.5%), elbow (2.9%) and ankle joints (7.6%). Only in 9 patients (13.2%), there was a simultaneous lesion of almost all joints.

The analysis of the degree of activity according to DAS28 showed that in 23.5% of patients in group IV, the average value was 5.31 ± 0.49, which corresponded to the III degree of activity, in 76.5% of patients, on average, 4.8 ± 0.1 (II degree of activity). There were no patients with a low degree of RA activity.

The average score of the HAQ index in the examined patients was 1.05 ± 0.03 and this was assessed as moderate functional disorders of the joints. The minimum functional impairment of the joints was observed in patients of group I (0.99 ± 0.03). In the remaining groups, there was an average degree of functional disorders of the joints according to the HAQ index (1.07 ± 0.03)

The maximum indicator according to the Ritchie index, which includes the number of painful and swollen joints, was recorded in patients of group IV (26.6 ± 0.8), the minimum - in patients of group I (15.6 ± 0.3). The average score of the Richie index in the examined patients was 21.1 ± 0.4. The severity of joint pain according to the VAS showed the highest numbers (77.4 ± 2.1) (severe pain) in patients of group IV, when the lowest score was reached by patients in group I (49.4 ± 2.8) (moderate pain). The average VAS scores in patients of groups II and III were practically the same, which corresponded to 70 ± 2 and 70.6 ± 2.3 (severe pain).

Among the examined patients, FC II was found in 40%, FC I - in 34%, FC III was established in 26% of patients. It should be noted that 74% of patients in group IV had a higher FC, namely FC III. In 81% of patients in group I, FC I was noted.

Seroprevalence is of no small importance in the diagnosis of RA. According to the results of this study, seronegativeness was mostly observed in the early stage of RA. According to the literature, it is known that patients who are positive for the RF have a worse prognosis for the course of the disease. However, the RF phenotype has two significant limitations. First, the specificity of this test for RA is rather low: RF is found in about 5% of healthy people, in 5-25% of elderly people, as well as in a significant number of patients with chronic diseases. Secondly, the presence of RF is not stable. The frequency of RF detection depends significantly on the duration of the disease. The results of one of the domestic studies showed that in the first 6 months it is detected only in 15-43% of patients with RA, subsequently, some RF-negative patients become RF-positive. Under the influence of treatment, the reverse transformation is also possible [6].

With a disease duration of up to one year, 43% of patients were seropositive in the RF, and 57% were seronegative. In the group of patients with RA duration of less than 3 months, RF was detected in 27%, and with an increase in the duration of the disease, its indicator increased to 62%. ACCP was determined in 80% of the examined patients with a disease duration of up to 3 months, by 12 months of illness, on average, in 90.6% of patients, this indicator turned out to be positive 14-3-3 η protein was determined in all (100%) examined patients, regardless of the duration of the disease. The results of the study indicate that seropositivity of RA is unstable, an increase in the frequency of detection of RF was recorded in patients with a long duration of the disease, and it should be noted that during therapy, the RF titer may decrease or not even be determined [2,4].

According to the literature, it was found that ACCP is more specific for RA and at least as sensitive as traditional RF: the sensitivity of ACCP in the diagnosis of RA is 70-80%, specificity - 98-99%. The sensitivity of the test for patients with early RA ranges between 40 and 70% [7]. In our study, during the initial examination, ACCP was detected to a greater extent than RF in RA patients (86%). At the same time, the 14-3-3 η protein was detected in all patients with RA, in comparison with RF and ACCP.

A direct correlation was established between the duration of the disease and the frequency of detection of ACCP, while in patients the correlation between the duration of the disease and the frequency of detection of the 14-3-3 η protein was not established. In patients with long periods of disease duration (7.0 ± 0.9 months), high diagnostic titers of ACCP were revealed (47.1 ± 6.1), in contrast to other groups. A 14-3-3 η protein was determined in all patients regardless of the duration of the disease. This indicates that with an increase in the duration of the disease, the diagnostically significant ACCP figures increase. It should be noted that 80% of patients with a disease duration of up to 3 months were seropositive for ACCP, 100% for 14-3-3 η protein, while the percentage of RF detection in these patients was only

31.2%. By 12 months of illness, the detection of ACCP increased to 90.6%, RF to 37.5%, and the initial results of 14-3-3 η protein did not change (100%). Thus, the determination of the 14-3-3 η protein was significantly superior in sensitivity to ACCP and RF.

Conclusion

1. The debut of RA is observed mainly in middle age. Among the forms of arthritis, polyarthritis is leading with simultaneous damage to small and large joints. The metacarpophalangeal joints are more often involved in the pathological process. In the onset of RA, the mono-oligo-articular nature of the articular syndrome, the defeat of the first metacarpophalangeal joint and the asymmetric damage to the joints are noted.

2. The average duration of morning stiffness continued with an increase in the duration of the disease.

3. Patients with RA onset had II degree of activity according to DAS28. The average score of the HAQ index in the examined patients was 1.05 ± 0.03 and this was assessed as moderate functional disorders of the joints. The maximum indicator according to the Ritchie index, which includes the number of painful and swollen joints, was recorded in patients with a high degree of disease activity. Patients at an early stage of RA were diagnosed with FC II of joint insufficiency.

4. At an early stage of RA, seronegativeness was more marked.

5. In patients with RA in the early stages of 14-3-3 η, the protein in the blood is determined much more often than ACCP and RF, which indicates the high importance of this immunological method for the diagnosis of early RA.

References:

1. American Intercollegiate of rheumatologists. Recommendations for use of basic anti-inflammation preperations and Biologic agents in rheumatoid arthritis. // Clinical pharmacology and therapy.- 2018.- Vol. 18, N 1. - P. 43
2. Bas S., Genevay S., Meyer O. Anti-cyclic citrullinated peptide antibodies in the diagnosis and prognosis of rheumatoid arthritis. // Rheumatology.-2003.-Vol.42.- P. 677-680.
3. Bijlsma J.W., Wcinblatt M.E. //Optimal use of the methotrexate: the advantages of tight control. Ann Reum Dis. 2017. P.11.
4. Calguneri M., Pay S., Caliskaner Z. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. // Clin. exp. rheumatol.- 2019. Vol. 17. - P. 699-704.
5. Cohen S.B., Emery P.A., Greenwald M.W., Dougados M.K., Furie R.A., Genovese M.C., Keystone E.C., Loveless J.E., Burmester G.R., Cravets M.W., Hessey E.W., Shaw T.T., Totoritis M.C.; Rituximab for rheumatoid arthritis refractory to anti–tumor necrosis factor therapy: Results of a multicenter, randomized, double–blind, placebo–controlled, phase III trial evaluating primary efficacy and safety at twenty four weeks. // Arthritis rheum.- 2016.- Vol. 9, N 54.- P. 2793–2806.
6. Duer-Jensenc A.H., Stewart N.O., Crabbe J.N. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. //Ann. Rheum. Dis.- 2016.Vol.6, N 7.-P.-350.
7. Emery P., Breedveld F. C., Dougados M. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. // Ann. rheum. dis. – 2014. – Vol. 61, N 4. – P. 290–297.
8. Tashpulatova M.M., Nabiyeva D.A., Djuraeva E.R., Sagatova D.R., Askarov N.L. 14-3-3 (eta) protein as a new biomarker in rheumatoid arthritis// International Journal ofAdvanced Science and Technology Vol.29.-№ 5(2020). P. 1871-1877
9. Tashpulatova M.M.,Kasimova M.B., Ziyayeva F.K., Sultonova M.X.,Sharipov Z.A. Enhancement of the diagnosis and treatment of early rheumatoid arthritis//International Journal of Pharmaceutical research 2020.12.02.0031-Vol 12.- Issue 1. P. 221-228