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Diagnostic Significance of 14-3-3 η (Eta) Protein and MRI of Joints in Early Stage of Rheumatoid Arthritis

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Abstract The aim of our study was to study the sensitivity of 14-3-3 η (Eta) protein in the blood and conducting of MRI (magnetic resonance imaging) of the joints of the hands in the diagnosis of rheumatoid arthritis (RA) in the early stages of disease. The study included 68 patients aged 19 to 74 years (mean age 44.2 ± 3.2 years) with RA onset (meeting the EULAR / ACR criteria, 2010) with a disease duration of up to 1 year (from 6 to 52 weeks.), in the I clinic of TMA for the period 2019 - 2020. All patients underwent a general clinical and biochemical blood test, immunological blood test (rheumatoid factor (RF), anticyclic citrulline peptide (ACCP) and 14-3-3η (Eta) protein in the blood). Also, radiography (RG) of the hands was carried out, as well as MRI of the joints of the hands. Determination of 14-3-3η (Eta) protein and MRI of joints have a sensitivity comparable to that of RF, ACCP, RG and are highly effective methods for diagnosing early RA, which, in combination with other research methods, helps to establish a diagnosis of the disease at an early stage, which contributes to the timely the appointment of an adequate basic treatment.

Keywords Early rheumatoid arthritis, Rheumatoid factor, Anticyclic citrulline peptide, 14-3-3η (Eta) protein, Magnetic resonance imaging, Radiography

1. Introduction

The prevalence of RA in the population, according to the World Health Organization (WHO) from 0.5 to 1% and economic losses from RA are comparable with coronary heart disease [1]. At the same time, in the first 3 years of illness, 37.5% of patients lose their ability to work and after 5 years, more than 50% of patients with RA could not continue working. These facts indicate that, course of RA is especially aggressive in the first few years from the onset of the disease [2,9]. It has been established that about 70% of cases of erosive-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 [7]. Life expectancy of patients with RA is lower than general population: by 3 years in women and by 7 years in men. In recent years, it has been clearly demonstrated that only timely diagnosis and early active treatment of RA patients can improve the prognosis and outcomes of the disease [13].

Evaluation of laboratory parameters of inflammation – erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and protein fractions - are secondary importance in the diagnostic process, and the absence of their changes should not prevent the diagnosis [6]. In the first 2-3 months, the values of these parameters in at least 50% of patients do not go beyond normal values. In addition, changes in acute phase parameters are completely nonspecific for RA [3]. Detection of RF in blood in diagnostic titers is of much greater importance. However, the phenotype of RF has two significant limitations. First, the specificity of this test for RA is rather low: RF is found in 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 [8]. The frequency of detection of RF depends significantly on the duration of the disease: in the first 6 months, it is detected only in 15-43% of patients with RA, and subsequently some RF-negative patients become RF-positive. Reverse transformation is also possible under the influence of treatment [4,11].

Determination of ACCP is the most important laboratory parameters in the diagnosis of RA in the early stages. Determination of ACCP has a sensitivity comparable than RF and significantly exceeds RF in specificity. But at the same time, ACCP can be negative in patients with RA and positive in patients with other autoimmune diseases. It means that, the test is not more sensitive and specific for RA. In addition, ACCP is considered an expensive diagnostic method for detecting RA [15]. Seronegativeness in both early and established RA remains the main obstacle for both ACCP and RF, which underlines the need for new additional markers that will improve diagnostic sensitivity [16]. It is necessary to develop new markers for RA so that patients can be correctly classified into different risk groups. Current markers estimate only about thirty percent of the total diversity in predicting disease outcome [18]. Protein 14-3-3η

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is a new biomarker for the detection of RA [10]. 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 many intracellular proteins, thereby controlling many biological processes, including protein synthesis, cellular metabolism, protein transport, and cytoskeleton transport [11]. 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 [10,19]. In the extracellular environment, soluble 14-3-3η has ligand activity, preferentially activating cells of the innate immune system [10]. 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) [11]. Levels of 14-3-3 η in serum 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 [20,22].

In addition, elevated levels of 14-3-3η protein in serum 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 [21].

2. Purpose of the Study

Evaluation of diagnostic value of 14-3-3 η (Eta) protein in serum of patients and MRI of joints in the early stage of RA.

3. Material and Methods

The study included 68 patients aged 19 to 74 years (mean age was 44.2 ± 3.2 years) with RA onset (meeting the EULAR / ACR criteria, 2010) with disease duration up to 1 year (from 6 to 52 weeks), who underwent inpatient treatment in the departments of cardio-rheumatology and rheumatology and were registered at the arthrological direction of I clinic of the 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 averaged 5.7 ± 0.9 months. To determine the activity of RA disease, the following indicators were used: the severity of pain in the joints, assessed by the patient on a visual analogue scale (VAS), the total activity of the disease was assessed according to the DAS28 index recommended by EULAR. To assess the functional capabilities of the RA patient, the definition of the functional class was used. The functional status of the patient was determined using the Stanford Health Assessment Questionnaire (HAQ, 1980). The laboratory examination included a general clinical and biochemical blood test, an immunological blood test: determination of the concentration of RF, ACCP and 14-3-3 (Eta) protein in the blood. To determine the degree of disease activity, ESR (mm / h) was determined according to Westergren with the release of 3 main degrees and CRP in the blood serum. Diagnostics of autoantibody panels included the quantitative determination of RF by the Waaler-Rose method, as well as ACCP and 14-3-3 (Eta) protein by the enzyme immunoassay.

4. Results and Discussion

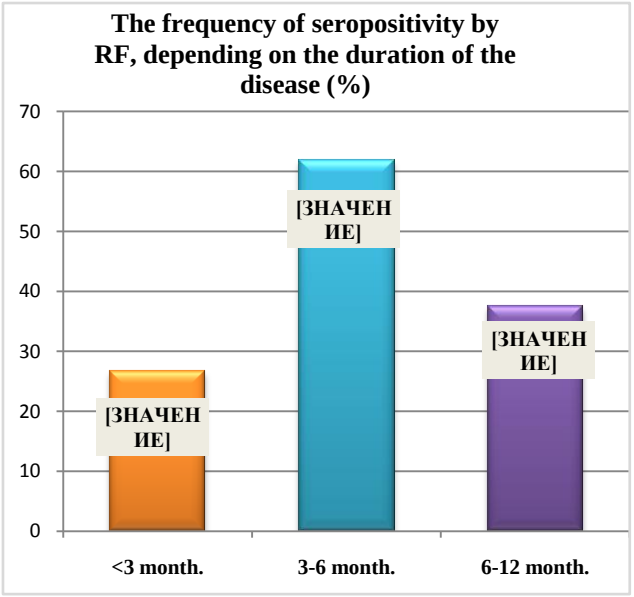
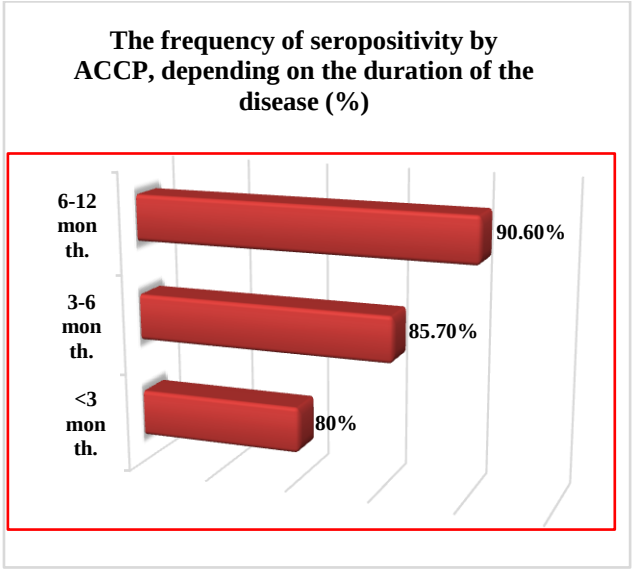


Figure 1



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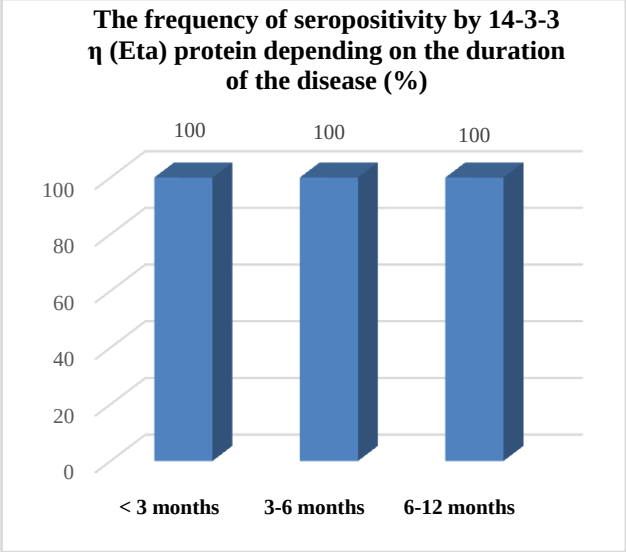

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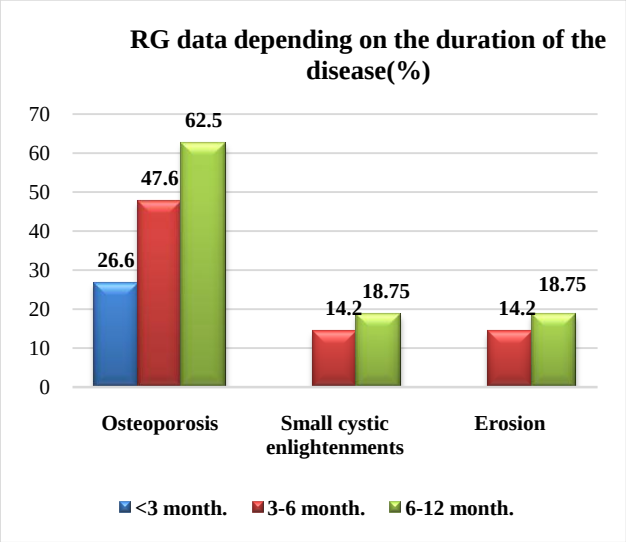

Figure 4

Sero-belonging is of no small importance in the diagnosis of RA; according to the results of this study, seronegativeness was mostly noted at an early stage. 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 have shown that in the first 6 months it is detected only in 15-43% of patients with RA, and 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 RA, 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% (Fig. 1), 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 was positive (Fig. 2.). 14-3-3 (Eta) protein was detected in all (100%) patients examined, regardless of the duration of the disease (Fig. 3.).

According to the results of the study, seropositivity of RA was established in 42.6% of cases, and 26.6% of seropositive patients had a 3-month duration of the disease. In patients with RA duration up to 6 months, RF was detected in 61.9% of cases. From the data obtained, it follows that with an increase in the duration of the disease, the frequency of RF detection increases. The results of the study indicate that seropositivity of RA is unstable, increased detection rates of RF were 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 detected [2,4]. According to the literature data, it was found that ACCP are more specific for RA and at least as sensitive as traditional RF: the sensitivity of ACCP in the diagnosis of RA is 70-80%, the specificity is 98-99%. The sensitivity of the test for patients with early RA ranges between 40 and 70% [5,7]. In our study, during the initial examination, ACCP was detected in the majority of patients with RA than RF (86%). At the same time, 14-3-3 η (Eta) protein was detected in all patients with RA than RF and ACCP. A direct correlation was established between the duration of the disease and the frequency of detection of ACCP, and in patients, the correlation between the duration of the disease and the frequency of detection of 14-3-3 η (Eta) protein was not established. Patients with long periods of disease duration (7.0 ± 0.9 months) showed high diagnostic titers of ACCP (47.1 ± 6.1), in contrast to other groups. 14-3-3 η (Eta) protein was detected in all patients regardless of the duration of the disease. This indicates that with an increase of duration of the disease, the diagnostic significant numbers of ACCP increase also. 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 (Eta) 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 (Eta) protein did not change (100%). Thus, the determination of 14-3-3 η (Eta) protein significantly exceeded ACCP and RF in sensitivity.

As shown in Fig. 4, on radiographs of the hand joints in RA patients with a disease duration of <3 months, osteoporosis was observed only in 4 (26.6%) patients out of 15, in patients under 6 months of the disease, this symptom was detected already in 47, 6% (10 patients). In 3 (14.2%) patients, small cyst-like enlightenments were determined and the same number of patients had erosions. When the disease was up to 12 months old, osteoporosis was observed in 20 patients (62.5%), small cystic enlightenments and erosions had the same number of patients, namely 6, which amounted to 18.8% of patients.

MRI of the hands has the highest sensitivity and specificity compared than RG. MRI of the hand joints in the examined patients revealed the following pathological changes: effusion in the joint cavity (70.5%), tenosynovitis (79.4%), bone marrow edema (52.9%) and erosion (47%) (Fig. 5.).

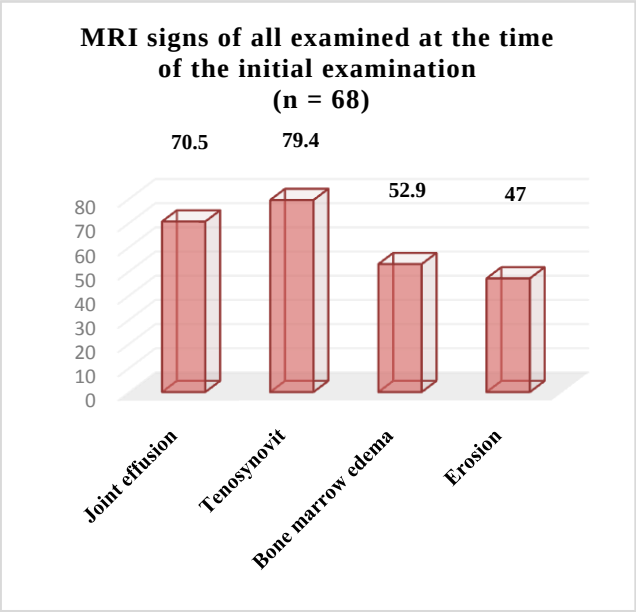

Figure 5

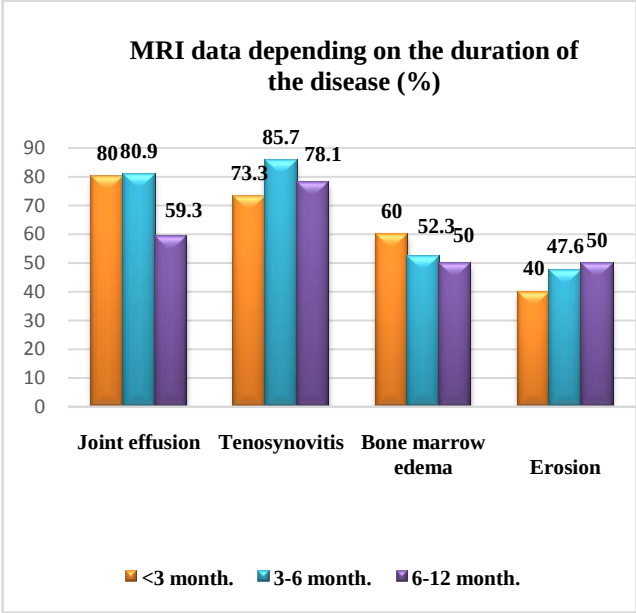

Figure 6

Assessment of results of MRI depending on the duration of the disease is shown in Fig. 6. In the group of patients with RA duration of less than 3 months, MRI of the hands revealed: joint effusion - in 12 (80%) patients, tendosynovitis - in 11 (73.3%), 9 (60%) patients had bone edema. brain, 6 (40%) - erosion. With a disease duration of up to 6 months, 17 patients (80.9%) had an effusion in the joint cavity, 18 (85.7%) had tenosynovitis, 11 (52.3%) had bone marrow edema, and 10 (47.6 %) of patients - erosion. An increase in the duration of the disease up to 12 months was accompanied by the detection of a greater number of changes, namely, in 19 patients (59.3%), an effusion in the joint cavity was detected, tenosynovitis - in 25 (78.1%), bone marrow edema - in 16 (50%), erosion in 16 (50%) patients.

5. Conclusions

In the early stages of the disease, 57.4% of patients were seronegative in the RF, diagnostically significant titers of ACCP were determined in 86% of patients, and at the same time, 14-3-3 η (Eta) protein in the blood was determined in all (100%) patients. When analyzing radiographs of the joints in 51.5% of patients, pathological changes were not revealed, in the remaining 48.5%, certain radiological manifestations of RA were determined at the time of the initial examination. An interesting fact is that the analysis of the results of MRI of the joints in patients with early RA showed the presence of significant pathological changes in contrast than RG. The highest sensitivity and specificity for detecting erosions in RA patients was observed during MRI of the hands (47%) compared with RG (13.2%). In the absence of early erosions, bone marrow edema was determined in 52.9% of patients, which is considered a reliable precursor of erosion. Determination of 14-3-3 η (Eta) protein has a sensitivity comparable to the sensitivity of ACCP and RF, and significantly exceeds them. Compared to radiography, MRI is a highly effective method for diagnosing RA, which, in combination with other research methods, helps to establish a diagnosis of the disease at early stage, which contributes to the timely appointment of an adequate basic treatment.

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