



LABORATORY DIAGNOSIS OF RHEUMATOID ARTHRITIS

General Surgery

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ABSTRACT

Summary In this article, the results of a study, conducted in 200 patients with confirmed rheumatoid arthritis and 30 controls, tested for the ESR, CRP, RF, anti-CCP and anti-MCV biomarkers, are presented. The results for the sensitivity, specificity, positive and negative predictive values of the studied tests are presented. The obtained results show higher diagnostic sensitivity and specificity of the anti-CCP and anti-MCV tests. The combination of the two biomarkers, anti-CCP and anti-MCV, and the RF improves the diagnostic and prognostic value.

KEYWORDS

Rheumatoid arthritis (RA), CRP, Anti-CCP, Anti-MCV, rheumatoid factor (RF).

Introduction

Rheumatoid arthritis (RA) is a systemic, autoimmune disease of unknown etiology that causes chronic inflammation of the joints and may affect other periarticular tissues, as well as a number of organs throughout the body. The worldwide incidence of RA is about 1%. In the European countries, it varies between 0.3 and 0.8% (1, 2, 3, 4). Rheumatoid arthritis occurs in all ages, but predominates between 30-55 years of age. It affects mostly women, three times more than men, and reaches over 5% in women after the age of 55 (4, 5, 6). Diagnosis is based on clinical and imaging data and laboratory biomarkers. Most of the used non-invasive serum biomarkers are not pathognomonic for the RA. Some of them, such as ESR and CRP, are more indicative of the extent of the inflammatory process that accompanies RA. The newly introduced antibody tests, anti-CCP and anti-MCV, are expected to be early markers of RA, with high sensitivity and specificity. The selection of anti-CCP, anti-MCV and RF is in line with the 2010 American College of Rheumatology/European League against Rheumatism recommendations that have replaced the 1987 indicators (4, 5). Together with clinical and other indicators, these biomarkers are accepted as criteria for the diagnosis, prognosis and assessment of therapy. We present the results of a study on anti-CCP, anti-MCV, RF, CRP and ESR in 200 patients and 30 controls.

Material and Methods

For the period of one year, 30 controls (men and women, aged 18-65 years) and 200 patients (25 men aged between 18 and 65 years and 175 women aged between 18 and 65 years) were studied, who had been referred by general practitioners and rheumatologists for monitoring of the RA therapy. The controls and patients were studied in the morning in the fasted state. Routine hematological and biochemical examinations were included. In addition, ESR (BD closed system), RF (Quantia RF, turbidimetry, IgG, Abbott Architect c8000), CRP (CRP Vario, turbidimetry, Abbott Architect c8000), anti-CCP (IntiCCR IgG, Immulite 2000System Siemens) and anti-MSV (ELISA-Orgentec Diagnostics GmbH) were monitored, using the following methods.

Results

The obtained results for the sensitivity, specificity, positive and negative predictive values and accuracy are presented in Table 1.

Table 1: Values of the criteria for validation of the studied indicators with the anti-CCP as the "Gold Standard"

Indicator	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Rheumatoid factor (RF)	79	33	92	14	75
Anti-MCV	80	86	90	4	79
Anti-CCP	91	95	95	15	94

ESR	72	33	92	11	69
CRP	42	56	91	9	44

Discussion:

The results of a study of 5 serum biomarkers (anti-CCP, anti-MCV, RF, CRP and ESR) in 30 controls and 200 patients with the clinical diagnosis of rheumatoid arthritis (RA) are presented. Rheumatoid arthritis is characterized by progressive loss of function, systemic complications and early death (1, 2, 3). It is associated with synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction and whole body damage (4, 5, 6). The worldwide incidence of RA is about 1%. In the European countries, it varies between 0.3 and 0.8% (6, 7). Rheumatoid arthritis occurs in all ages, but predominates between 30-55 years of age. It affects mostly women, three times more than men, and reaches over 5% in women after the age of 55. The genotype and environmental factors are important for the occurrence of RA (7, 8, 9). Diagnosis is based on clinical and imaging data and laboratory biomarkers. Although there is no pathognomonic serum biomarker, a panel of indicators for the different autoantibodies will have an important role in the diagnosis, prognosis and assessment of the therapeutic effect (6, 10, 11). Some of these indicators, such as ESR and CRP, are more indicative of the extent of inflammation, while anemia and thrombocytosis are the result of the treatment with NSAIDs. In 2010, the American College of Rheumatology and the European League against Rheumatism proposed the inclusion of anti-CCP, anti-MCV and RF as qualifying criteria for the RA (4, 5, 6), without denying the use of CRP and ESR. The RF is a part of the autoantibody family; it was first described in 1937 by Erik Waaler and is a commonly used test. Although, most commonly, it is of the IgM type, it may also be IgM, IgG, IgA (7, 12, 13). The three isotypes occur at different times: IgM-RF appears positive in the beginning, up to 3.8 years prior to clinical manifestations, followed by IgA-RF (3.2 years) and IgG-RF (0.9 years) (14, 15). The RF is detected in 70 to 80% of the patients with RA, but in less than 50% of the patients with early RA. The two new biomarkers, anti-CCP and anti-MCV, are members of the ACPA family (16). The ACPA are antibodies to citrullinated protein/peptide antigens. Citrullination is a modification of proteins, where the nitrogen in the arginine amino acid is replaced by an oxygen atom and converted to citrulline (Figure 1) (17, 18, 19, 20). The so-modified proteins are perceived by the immune system as antigens and generate an immune response. The detection of these autoantibodies is crucial for the proper diagnosis of RA in the early stages, when the typical symptoms are not presented, but the therapy is most effective. In Bulgaria, the anti-CCP and anti-MCV tests are not yet routinely used. It is argued in the literature, which of the three proposed biomarkers (anti-CCP, anti-MCV or RF) has the best sensitivity, specificity and predictive value (6, 7, 8, 9). In a meta-analysis of 16 studies, the sensitivity, specificity, positive and negative predictive values and the diagnostic odds ratio (DOR) were estimated at 0.77, 0.89, 7.24, 0.28 and 29.66, respectively (2, 7, 8). Most authors find that the sensitivity of anti-MCV is higher than that of anti-CCP, but the

latter is more specific, although other studies do not confirm this (10, 11, 12, 13). In our study, we found the highest values of sensitivity, specificity, positive and negative predictive values and accuracy for the anti-CCP, followed by these for the anti-MCV and RF. In a small proportion (<10%) of the patients, the anti-MCV biomarker was negative and the anti-CCP - positive. The RF was more frequently negative (<15%) than the last two biomarkers. This allowed us to assume that for the diagnosis, prognosis, and effect of the RA therapy, it is necessary to monitor all the three biomarkers (anti-CCP, anti-MCV and RF).

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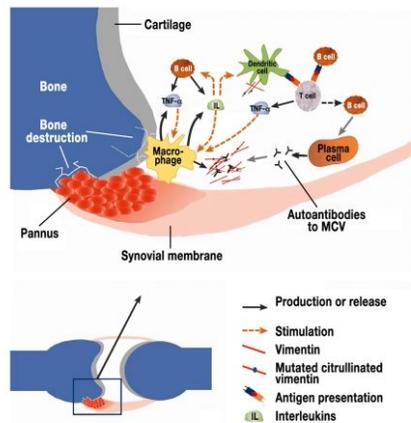


Figure 1. Possible role of the mutated citrullinated vimentin in the pathogenesis of RA (by Egerer, 14)

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