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Original article

Analysis of four serum biomarkers in rheumatoid arthritis: association with extra articular manifestations in patients and arthralgia in relatives

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ABSTRACT

Objectives: To evaluate the frequency of four serum biomarkers in RA patients and their relatives and identify possible associations with clinical findings of the disease.

Design and methods: This was a transversal analytical study. Anti-cyclic citrullinated peptide (anti-CCP), anti-mutated citrullinated vimentin (anti-MCV) and IgA-rheumatoid factor (RF) were determined by ELISA and IgM-RF by latex agglutination in 210 RA patients, 198 relatives and 92 healthy controls from Southern Brazil. Clinical and demographic data were obtained through charts review and questionnaires.

Results: A higher positivity for all antibodies was observed in RA patients when compared to relatives and controls ($p < 0.0001$). IgA-RF was more frequent in relatives compared to controls (14.6% vs. 5.4%, $p = 0.03$, OR = 2.98; 95% CI = 1.11–7.98) whereas anti-CCP was the most common biomarker among RA patients (75.6%). Concomitant positivity for the four biomarkers was more common in patients (46.2%, $p < 0.0001$). Relatives and controls were mostly positive for just one biomarker (20.2%, $p < 0.0001$ and 15.2%, $p = 0.016$, respectively). No association was observed between the number of positive biomarkers and age of disease onset, functional class or tobacco exposure. In seronegative patients predominate absence of extra articular manifestations (EAMs) ($p = 0.01$; OR = 3.25; 95% CI = 1.16–10.66). Arthralgia was present in positive relatives, regardless the type of biomarker.

Conclusions: A higher number of biomarkers was present in RA patients with EAMs. Positivity of biomarkers was related to arthralgia in relatives. These findings reinforce the link between distinct biomarkers and the pathophysiologic mechanisms of AR.

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Análise de quatro marcadores sorológicos na artrite reumatoide: associação com manifestações extra-articulares no paciente e artralgia em familiares

R E S U M O

Palavras-chave:

Artrite reumatoide
Fator reumatoide
Anti-CCP
Anti-MCV
Biomarcadores

Objetivos: Avaliar a frequência de quatro marcadores sorológicos em pacientes com AR e familiares e identificar possíveis associações com achados clínicos da doença.

Métodos: Estudo analítico transversal. Determinaram-se os níveis de anticorpos antipeptídeo citrulinado cíclico (anti-CCP), anticorpos antivimentina citrulinada-mutada (anti-MCV) e fator reumatoide (FR) IgA por Elisa e de FR-IgM por aglutinação em látex em 210 pacientes com AR, 198 parentes e 92 controles saudáveis do sul do Brasil. Coletaram-se dados clínicos e demográficos por meio da revisão de prontuários e questionários.

Resultados: Observou-se maior positividade para todos os anticorpos em pacientes com AR em comparação com os familiares e controles ($p < 0,0001$). O FR-IgA era mais frequente em familiares quando comparados com os controles (14,6% versus 5,4%, $p = 0,03$, OR = 2,98; IC95% = 1,11 a 7,98). O anti-CCP foi o biomarcador mais comum entre pacientes com AR (75,6%). A positividade concomitante para os quatro biomarcadores foi mais comum nos pacientes (46,2%, $p < 0,0001$). Familiares e controles eram positivos em sua maioria para apenas um biomarcador (20,2%, $p < 0,0001$ e 15,2%, $p = 0,016$, respectivamente). Não foi observada associação entre o número de biomarcadores positivos e a idade de início da doença, classe funcional ou exposição ao fumo. Em pacientes soronegativos, predominou a ausência de manifestações extra-articulares (MEA) ($p = 0,01$; OR = 3,25; IC95% = 1,16 a 10,66). A artralgia estava presente em familiares positivos, independentemente do tipo de biomarcador.

Conclusões: Uma maior quantidade de biomarcadores estava presente em pacientes com AR com MEA. A positividade dos biomarcadores estava relacionada com a artralgia em familiares. Esses achados reforçam a ligação entre os diferentes biomarcadores e os mecanismos fisiopatológicos da AR.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that occurs in 0.2–1% of the world population.¹ Its prevalence in first degree relatives of RA patients is of 2–4%, characterizing them as a risk group for RA.^{2–5} In this context, investigation of serological markers in healthy relatives may be of value to identify earlier cases of RA^{6,7} and to understand the pathophysiologic mechanisms underlying the disease process.

Rheumatoid factor (RF) is a classical serological marker used for RA diagnosis, with IgM-RF being the most common isoform. In contrast, IgA-RF has been associated with erosive arthritis and seems to be a better indicator of disease severity than IgM-RF or IgG-RF.^{8,9} Antibodies against citrullinated peptides (ACPAs), such as anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) are considered highly specific markers for RA.¹⁰ Anti-CCP has both diagnostic and prognostic value and can be detected before clinical manifestations of the disease.¹¹ Recently, anti-MCV has also been proposed as a diagnostic marker for early arthritis, with the same specificity but higher sensitivity of anti-CCP.¹² In addition, anti-MCV has been detected in healthy relatives of RA patients¹³ suggesting it as a novel prognostic marker for RA.

Positivity for more than one RA serological marker in the same patient may indicate worse prognosis or, in the case of relatives, early disease onset.^{14,15} In fact, positivity for more than one autoantibody has been reported among unaffected relatives of RA patients, especially in families with multiple cases.^{16,17}

To date, there are no reports considering the simultaneity of these biomarkers in RA patients and their relatives in the Brazilian population. Thus, in the present work we investigated the frequency of anti-CCP, anti-MCV, IgA-RF and IgM-RF in RA patients and their relatives, and tried to identify possible associations between the simultaneity of these biomarkers and clinical findings or diagnosis of RA.

Design and methods

This was a transversal and analytical study approved by the local Ethics Committee in Research. Informed consent was obtained from all subjects.

Subjects

Two-hundred and ten adult RA patients meeting the ACR classification criteria¹⁸ from a single tertiary center were

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