ASSESSMENT OF THE ANTIBODIES INVOLVED IN ISCHEMIC HEART DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

Mirela Parvu¹, Lia Georgescu¹, Mariana Tilinca²

¹ DEPARTMENT OF RHEUMATOLOGY, UMPH TARGU MURES, ROMANIA
² DEPARTMENT OF CELLULAR AND MOLECULAR BIOLOGY, UMPH TARGU MURES, ROMANIA

Summary

A high number of patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular disease, and increased cardiovascular mortality. That may not always be related to the presence of traditional cardiovascular risk factors. The aim of this study was to evaluate if antibodies are associated with cardiovascular diseases in patients with RA and which of them are most important. Different antibodies such as rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti CCP), antinuclear antibodies (AAN) and anticardiolipin antibodies (anti ACA) were determined by Elisa method in serum samples, at 106 patients with a diagnosis of RA. We studied the relationship between these antibodies and the ischemic heart disease (IHD). We also performed Framingham Score for all patients using the Joint National Committee on Blood Pressure and the National Cholesterol Education Program models. We found positive antibodies, anti CCP in 87 patients (82%), RF in 86 patients (81%), AAN in 39 patients (36, 8%), anti ACA in 32 patients (30, 2%). There was no association between RF and anti CCP antibodies and ischemic heart disease, but anti ACA and AAN are associated with electrocardiographic changes. Multivariable analysis showed that IHD is independently associated with positive AAN p= 0, 0001, and positive anti ACA p=0, 0001. In conclusion, specific antibodies in patients with RA are independently associated with the development of IHD. AAN and anti ACA are associated with ischemic changes and this finding supports a rational for measuring them in RA especially at patients who had high cardiovascular risks.

Keywords: rheumatoid arthritis, coronary heart disease, antibodies

mariana.tilinca@umftgm.ro

Introduction

Rheumatoid arthritis, a chronic inflammatory systemic disease, with unknown etiology and autoimmune pathogenesis is characterized by articular destructions, functional incapacity, deterioration in quality of life and increased cardiovascular morbidity and mortality (Nurmohamed, 2008). RA is considered an independent risk factor for cardiovascular events, ischemic heart disease or congestive heart failure and is responsible for 40% of death (Nurmohamed, 2008; Del Rincon et al, 2001; Maradit-Kremers et al, 2005). Severe extra-articular manifestations are associated with a higher risk of development of cardiovascular events. However in patients with RA, the traditional and nontraditional cardiovascular risk factors have been reported, which do not contribute to the development of their cardiovascular changes (Del Rincon et al, 2001, Gonzales et al, 2008).

Specific or non specific RA markers include antibodies that predict poor clinical outcome and/or radiologic severity (Gonzales et al, 2008). Raised levels of serum cytokine were associated with the presence of antibody response, which together with clinical features are predictive of a more severe disease course, or extra-articular manifestation. The relationship between these antibodies and cardiovascular comorbidity in patients with RA has not been well defined (Eular/European news, 2005; Edwards et al, 2007; Lopez-Longo, Oliver-Minarro, 2009).
This study was performed to determine the association between the antibodies detected at patients with RA, and especially the electrocardiographic changes of ischemic heart disease.

**Materials and methods**

106 patients admitted at University Clinic of Rheumatology Targu Mures were assessed in this study, patients diagnosed with RA according to ACR 1987 criteria; RA patients seen during this period and who had diabetes mellitus (fasting overnight plasma concentration>109mg/dl), hypothyroidism, gout, significant concomitant diseases (including cancer, liver cirrhosis, fatty liver, neurological, pulmonary, cardiologic, renal disease), or other inflammatory autoimmune diseases and obesity (body mass index >30kg/m²) severe dyslipidemia (total cholesterol and triglyceride levels in fasting plasma >300mg/dl and 250mg/dl respectively), severe anemia hemoglobin <8mg/dl, hematocrit <24%, serious infections were excluded.

**Clinical Assessment**

Patients were assessed according to a standardized clinical interview, physical examination, laboratory tests, and (in patients) chart review; we noted all the patients who had treatment for high blood pressure (HTA). History of coronary disease or HTA was defined; all changes appeared after the patients have been diagnosed with RA. Height and weight were measured, and body mass index was calculated using the ratio of weight (in kilograms)/height (in square meters). Blood pressure was recorded after 10 minutes of supine rest, the average of two measurements was used taken at an interval of 5 minutes. For antibodies we used Elisa method, different kits: QuantaLite™ CCP3 IgG Elisa, for anti CCP; HYCOR Autostat™ ACA IgG for anti ACA IgG; HYCOR Autostat™ AAN for AAN, on TECAN device, and for RF latex method. Normal value was considered under 23UI/ml for anti CCP and under 10UI/ML for AAN and anti ACA.

**Framingham Score (FS)**

The composite simplified coronary prediction model built on the blood pressure and cholesterol categories proposed by the Joint National Committee on Blood Pressure and the National Cholesterol Education Program were used.

**Ischemic heart disease (IHD)**

All subjects underwent a clinical interview, family history of coronary disease, ECG and were classified in: level 0 - absent- without ECG change, without clinical interview of angina, without myocardial infarction before, level 1 - minimal- with ischemic change on ECG, without angina or myocardial infarction, level 2 - moderate- with ischemic change on ECG, with angina on clinical interview, without myocardial infarction, level 3 - severe- with myocardial infarction before.

**Statistical analysis**

Statistical analysis was performed using SPSS, version 17, using chi square test, p<0.05 were considered to be statistically significant.

**Results**

From 106 patients with RA successively evaluated, 18 (17%) were male and 88 (83%) were female, the average ages being 54.14±11.6 years, with a duration of the disease of 6.25 ± 5.2 years. Demographic characteristics and clinical parameters are represented in table 1.
Table 1. Demographic characteristics and clinical parameters

<table>
<thead>
<tr>
<th>Data</th>
<th>RA patients (numbers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years±SD</td>
<td>54.14 ± 11.6</td>
</tr>
<tr>
<td>Genders</td>
<td></td>
</tr>
<tr>
<td>Male (M)</td>
<td>18</td>
</tr>
<tr>
<td>Female (F)</td>
<td>88</td>
</tr>
<tr>
<td>Durations of RA, years±SD</td>
<td>6.25 ± 5.2</td>
</tr>
<tr>
<td>Framingham Score (M/F)</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>4/72</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>5/13</td>
</tr>
<tr>
<td>High risk</td>
<td>1/11</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>86 (81.1%)</td>
</tr>
<tr>
<td>Anti CCP positive</td>
<td>87 (82.0%)</td>
</tr>
<tr>
<td>AAN positive</td>
<td>39 (36.8%)</td>
</tr>
<tr>
<td>Anti ACA positive</td>
<td>32 (30.2%)</td>
</tr>
</tbody>
</table>

The incidence of positive antibodies was represented in figure 1. The patient associated one or more types of antibodies.

Figure 1. The incidence of antibodies at patients with rheumatoid arthritis

- b. anti-cyclic citrullinated peptide antibody
- c. antinuclear antibody
- d. anticardiolipin antibody
Presence of positive antibodies at patients with RA was associated with different types of ischemic heart disease, classified in level 0, 1, 2, 3. The relationship between the antibodies and the electrocardiographic changes of ischemic heart disease was represented in figure 2.

The presence of AAN and anti ACA was significantly associated with different levels of IHD, with p<0.0001. Positive RF was not associated with IHD, p =0.61, and with anti CCP p =0.078.

Patients with high FS, presented ischemic heart disease in level 3, AAN and anti ACA positive. High values of anti CCP, 3 times larger, are important in predictive changes on ECG, for ischemic heart disease. We found a significant correlations between SF and IHD with r =0.51.

**Discussion**

Patients with RA have unusually severe cardiovascular morbidity and higher cardiovascular mortality. Several observational, most retrospective investigations, using administrative databases or questionnaires, have studied the incidence of CVD in large cohorts of
RA patients and some study demonstrate that IHD is more common in patients over 50 years, males being more exposed compared to the female. It is important to realize that RA patient are less likely to report angina and are twice as likely to have a silent myocardial infarction and sudden death. In our study 31% of the patients showed no clinical, anamnastic or ECG changes for IHD (Nurmohamed, 2008). Autoantibody productions are conditions strongly associated with RA. A few auto-antibodies including anti-oxidized low density lipoprotein (ox LDL), RF, anti CCP, AAN, anti ACA are considered autoimmune factors associated with atherosclerosis in autoimmune disease, as well as in the general populations, and the prevalence of these auto-antibodies in RA populations was previously reported (Eular/European news, 2005, Edwards et al, 2007, Peter et al, 2009). Anti CCP are extremely specific for RA-98%, and are detected very early. The potential of citrullination and anticitrulline immune response in pathogenesis of RA was discussed (Eular/European news, 2005, Lopez-Longo, Oliver-Minarro, 2009). We found that more than 50% of patients had over two folds of anti CCP values and these are associated with ischemic changes on ECG and ischemic manifestations. Presence of AAN and anti ACA antibodies, are associated with greater inflammatory activity, higher frequency of extra-articular manifestations and poorer outcomes in early arthritis. Regarding AAN and anti ACA we found strong associations between these antibodies and levels of IHD, especially levels 2 or 3. The risk of IHD is associated with the titers of antibodies. Patients with AAN and anti ACA had more severe RA, extra-articular manifestations and durations of the disease. As it is known cardiovascular mortality at patients with RA is increased, cardiovascular manifestations are now considered extra-articular manifestations of rheumatoid disease (Nurmohamed, 2008). Framingham risk score is important, because FS predicts the presence of coronary atherosclerosis in patients with rheumatoid arthritis (Chung et al, 2006). In this study we demonstrated that patients with high FS presented elevated titers value of antibodies which can be considered poor markers for cardiovascular manifestations.

**Conclusion**

Specific antibodies in patients with RA are independently associated with the development of IHD. AAN and anti ACA are associated with ischemic changes and this finding supports a rational for measuring them in RA especially at patients who had high cardiovascular risk.

**List of abbreviations**

RA = rheumatoid arthritis  
RF = rheumatoid factor  
Anti CCP = anti cyclic citrullinated antibody  
Anti ACA = anticardiolipin antibody  
AAN = antinuclear antibody  
FS = Framingham Score  
HTA = hypertension  
IHD = ischemic heart disease  
ACR = American College of Rheumatology  
ox-LDL = anti-oxidized low density lipoprotein

**References**


