ANTI RO, ANTI LA, ANTI RNP ANTIBODIES AND ELETROCARDIOGRAM’S PR INTERVAL IN ADULT PATIENTS WITH SYSTEMIC LUPUS ERITEMATOSUS

Militino Costa,† Marilia Barreto Gameiro Silva,‡ José Antonio Silva,§ Thelma L Skare*-

ARTIGO ORIGINAL

Methods: PR intervals and the presence of anti-Ro, La and RNP antibodies were studied in 61 SLE patients and compared with 61 controls.

Results: 36.6% of SLE patients were anti-Ro positive, 20% were anti-La and 22.9% were anti-RNP positive. All studied PR intervals were within normal limits (upper limit of 0.2 sec). We did not find any association between PR interval length and the presence of anti-Ro (p=0.54), anti-La (p=0.45) or anti-RNP autoantibodies (p=0.36).

Conclusion: The presence of anti-Ro, La and RNP autoantibodies does not influence PR interval in adult SLE patients.

Keywords: Antigen Antibody Complex; Heart Block; Systemic Lupus Erythematosus.

Introduction

Neonatal lupus is caused by placental transfer to fetus of maternal anti-Ro, anti-La and anti-RNP autoantibodies. Methods: PR intervals and the presence of anti-Ro, La and RNP antibodies were studied in 61 SLE patients and compared with 61 controls.

Results: 36.6% of SLE patients were anti-Ro positive, 20% were anti-La and 22.9% were anti-RNP positive. All studied PR intervals were within normal limits (upper limit of 0.2 sec). We did not find any association between PR interval length and the presence of anti-Ro (p=0.54), anti-La (p=0.45) or anti-RNP autoantibodies (p=0.36).

Conclusion: The presence of anti-Ro, La and RNP autoantibodies does not influence PR interval in adult SLE patients.

Keywords: Antigen Antibody Complex; Heart Block; Systemic Lupus Erythematosus.

Background: Children born from mothers with anti-Ro, La or RNP autoantibodies may develop neonatal lupus. One of the manifestations of neonatal lupus is congenital atrioventricular block.

Objective: To study EKG PR interval in adult systemic lupus erythematosus (SLE) patients with anti-Ro, anti-La and anti-RNP autoantibodies.

Methods: PR intervals and the presence of anti-Ro, La and RNP antibodies were studied in 61 SLE patients and compared with 61 controls.

Results: 36.6% of SLE patients were anti-Ro positive, 20% were anti-La and 22.9% were anti-RNP positive. All studied PR intervals were within normal limits (upper limit of 0.2 sec). We did not find any association between PR interval length and the presence of anti-Ro (p=0.54), anti-La (p=0.45) or anti-RNP autoantibodies (p=0.36).

Conclusion: The presence of anti-Ro, La and RNP autoantibodies does not influence PR interval in adult SLE patients.

Keywords: Antigen Antibody Complex; Heart Block; Systemic Lupus Erythematosus.

Introduction

Neonatal lupus is caused by placental transfer to fetus of maternal anti-Ro, anti-La and, in a lesser degree, anti-RNP autoantibodies. Mothers of babies with neonatal lupus may have systemic lupus erythematosus (SLE), Sjögren’s syndrome or may be asymptomatic carriers of these autoantibodies.1

In the clinical spectrum of neonatal lupus, complete congenital cardiac atrioventricular (A-V) block can be found.1 Other cardiac findings are transient first degree A-V block, prolongation of QTc interval, sinus bradycardia, cardiomyopathy and endocardial fibroelastosis.2

Ro and La antigens are present in cardiac conduction tissues in human fetus.3 One possible explanation for the occurrence of neonatal A-V block is the cytotoxic action of maternal anti-Ro and anti-La antibodies and the influx of inflammatory cells, which injure myocardial and conduction tissue nearby.3 It is very unlikely that such antibodies can penetrate an intact cell. However, Ro and La antigens can be expressed in the cellular membrane of
In adults, anti-Ro antibodies and, less commonly, anti-La antibodies have been associated with subacute cutaneous lupus, antinuclear antibody negative lupus and lupus-like syndrome in patients with homozygotic deficiency of C2 and C4 complement fractions. Data on the effect of such autoantibodies in adult cardiac tissue are controversial. Logar et al found that anti-Ro antibodies were associated with myocarditis and conduction defects in adults with SLE. In patients with polymyositis, Behan et al reported an association of the presence of anti-Ro with cardiac damage. Furthermore, Lazzerini et al found a high prevalence of increased QTc interval in patients with connective tissue diseases that were anti-Ro positive. On the other hand, Gordon et al, studying 19 mothers of neonatal lupus children and 111 SLE patients, could not establish a relationship between the presence of anti-Ro and heart conduction defects.

In this study we looked for possible associations between the presence of anti-Ro, anti-La and anti-RNP antibodies and alterations of the PR interval in adult SLE patients.

**Methods**

This study was approved by the local Ethics Committee and all the enrolled patients gave written consent. Lupus patients attending our clinic between March and June 2007 were invited to participate. The patients had to have at least 4 of the ACR classification criteria for SLE. We excluded patients using class I and II anti-arrhythmic drugs, anti-histaminics, quinolones, macrolides, phenothiazines, cisisaprile, and those with ischemic heart disease, previous cardiomyopathies, lupus carditis or history of cardiac conduction disorders. Individuals with renal failure, diabetes or with any other possibility of hydrouleotylosic disturbance were also excluded.

All the enrolled patients performed a standard resting 12 lead electrocardiogram that was read by one examiner. Adopted normal values for PR interval were 0.12 to 0.20 seconds. Charts were reviewed for demographic data, presence of anti-Ro, anti-La and anti-RNP antibodies.

Routine pre-anesthetic electrocardiograms from patients submitted to minor surgeries such as ablation of varicose veins or cataract extraction, without systemic diseases and not on any medication were used as a control.

Obtained values were studied by frequency tables using Student's t test for numerical data and Fisher and chi-square tests for nominal data with the help of the software Graph Pad Prism version 4.0. The significance level adopted was 5%.

**Results**

We studied 61 patients with SLE and 61 controls. The characteristics of the studied population are shown on Table I.

In the SLE group, anti-Ro and anti-La tests were performed in 60 patients, 22 (36.6%) being anti-Ro positive and 38 (63.3%) anti-Ro negative; 12 (20%) anti-La positive and 48 (80%) anti-La negative. Anti-RNP was determined in 48 patients 11 (22.9%) being positive and 37 (77.1%) negative.

PR intervals according to the presence of auto-antibodies are displayed on Table II.

**Table I. Characteristics of the studied population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLE</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>36.57±11.48</td>
<td>37.66±18.18</td>
<td>0.68 (*)</td>
</tr>
<tr>
<td>Gender- men:women</td>
<td>3:58</td>
<td>6:55</td>
<td>0.49 (***)</td>
</tr>
<tr>
<td>PR interval (msec) lower limit</td>
<td>100</td>
<td>100</td>
<td>0.09 (*)</td>
</tr>
<tr>
<td>upper limit</td>
<td>200</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>141.9±19.6</td>
<td>135±20.4</td>
<td></td>
</tr>
</tbody>
</table>

SLE= Systemic lupus erythematosus

(*) Student’s t test

(**) Fisher’s exact test

(***) milliseconds
Discussion

Anti-Ro and anti-La are autoantibodies directed against nuclear and cytoplasmatic small ribonucleoproteins, which can cross the placenta causing neonatal lupus. These antibodies may be responsible for congenital heart blocks, skin rashes, cytopenias and hepatic dysfunction in the newborn. Cardiac A-V block is the most important cause of morbidity and mortality in these children and it is most often detected between weeks 16 and 24 of pregnancy. More than 60% of the affected children require a lifelong pacemaker.

In fatal cases, anti-Ro has been extracted from tissue obtained from the newborn heart as opposed to other fetal organs. In addition, injections of anti-Ro into pregnant mice generated animals with conduction defects. Such observations place these autoantibodies in a central position for the origin of cardiac conduction disturbances.

An interesting observation is that when a mother gives birth to a child with congenital cardiac conduction defect, there is very little chance that the disease recurs in a subsequent pregnancy, even when she remains positive for the autoantibodies. So, it is not enough that the mothers have anti-Ro. The child seems to participate in an active way, probably with a predisposing genetic component.

Why is fetal tissue so sensible to the action of these autoantibodies? One possible explanation is that fetal cardiac tissue has a high index of apoptosis, leading to exposition of intracellular antigens that makes it vulnerable to the action of circulating autoantibodies. When apoptosis takes place, Ro and La antigen of nuclear origin are detected in big apoptotic blebs. Ro antigen of cytoplasmatic origin has been found in small apoptotic blebs.

Increased activity of anti-Ro antibodies caused by apoptotic cells is also found in adults. This activity is clearly demonstrated in cases where ultraviolet light increases skin lesions in SLE patients with this autoantibody. Nevertheless, myocardial tissue apoptosis is a very rare event in adults.

In this study we examined whether anti-Ro (and also anti-La and anti-RNP) antibodies were associated with PR prolongation in adult SLE patients. None of these autoantibodies could be linked to cardiac conduction defects in adults, which is in conformity with the findings by Gordon et al. This shows that mature cardiac tissue is resistant to injury caused by these autoantibodies.

In our sample no patient had primary cardiac lesions, so the possibility that in cases of myocardial necrosis caused by vasculitis (with subsequent exposition of Ro and La antigens) such autoantibodies may amplify the final results still remains.

Some authors observed associations between anti-Ro and anti-La and prolongation of QTc interval. In the present study we chose not to analyze this parameter because it is possible for lupus patients to have increased QTc, despite the autoantibody profile. Cardoso et al have attributed this to a subclinical cardiovascular disease. In addition, most of our patients were using antimalarial drugs, which are known to increase QTc interval.

The authors conclude that anti-Ro, anti-La and anti-RNP antibodies did not interfere with PR interval in adult SLE patients. More studies are still needed to verify the role of these autoantibodies as lesion amplifiers in SLE patients with myocardial lesions.

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References:

Table II. Mean PR interval (in milliseconds) in SLE patients according to the autoantibody profile

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Ro (n=60)</td>
<td>139.1±20.94</td>
<td>143.4±17.43</td>
<td>0.54 (#)</td>
</tr>
<tr>
<td>Anti-La (n=60)</td>
<td>137.9±17.77</td>
<td>142.8±20.19</td>
<td>0.45 (#)</td>
</tr>
<tr>
<td>Anti-RNP (n=48)</td>
<td>144.1±11.14</td>
<td>140.2±20.06</td>
<td>0.36 (#)</td>
</tr>
</tbody>
</table>

SLE – Systemic lupus erythematosus
(#{#}) – Mann Whitney

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Krefeld, Alemanha
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