Prevalence of IgA deficiency in adult Systemic Lupus Erythematosus and the study of the association with its clinical and autoantibody profiles

Ana Paula França Mantovani¹, Mariel Perini Monclaro¹, Thelma L Skare²

ABSTRACT

Introduction: IgA deficiency (IgAD) is the most common primary immunodeficiency, which can cause frequent infections. The association of IgA deficiency with systemic lupus erythematosus (SLE) is very important because of the high morbidity and mortality rates of infections in patients with this disease. Objectives: To study the prevalence of IgA deficiency in SLE patients from southern Brazil and to compare the clinical and autoantibody profiles of SLE patients with and without IgA deficiency. Patients and Methods: One hundred and eighty-nine SLE patients were submitted to serum IgA measurement by nephelometry. Levels of IgA below 50 mg/dL were considered to be IgAD. Demographic data, clinical profile (presence of arthritis, psychosis, seizures, stroke, serositis, hemolytic anemia, leucopenia, thrombocytopenia, and nephritis) and autoantibody profiles (ANA, anti-Ro, anti-La, anti-Sm, anti-DNA, anti-RNP, lupus anticoagulant, and anticardiolipin IgG and IgM) were obtained from reviewing medical records. As control, we used literature data from another study performed in the same geographical area. Data were analyzed through contingency and frequency tables, applying the Chi-square, Fisher, and Mann Whitney tests.

Results: IgA deficiency was found in 11 (6.17%) patients (P < 0.001 in relation to controls). The association between IgA deficiency and clinical or autoantibody profile was not significant.

Conclusion: We concluded that a higher prevalence of IgA deficiency was observed in lupus patients than in controls. Deficiency of IgA did not have any particular laboratory or clinical effects on this population.

Keywords: IgA deficiency, systemic lupus erythematosus, primary immunodeficiency.

INTRODUCTION

Immunoglobulin A (IgA) is the second most abundant immunoglobulin in the body and two forms can be identified: IgA1 and IgA2. The first is found mainly in the serum, in the monomeric form and it cannot be transported to mucous secretions.1,2 IgA2 (dimeric) is the main immunoglobulin found in exocrine secretions and in the mucous defense systems (secretory IgA, IgAS) and is found in the saliva, tears, colostrum and nasal and gastrointestinal secretions, among others. Its function is to protect mucous membranes against infections by activating the alternative pathway of the complement and prevent binding of virus to epithelial cells of the respiratory, gastrointestinal and urogenital tracts. Therefore, it has an important antiviral activity.1 One can infer that the objective of IgAS is to limit the infectious process at its entrance site.

IgA deficiency (IgAD) is the most common among all primary immunodeficiencies.1,2 It has a variable prevalence, according to the ethnic profile of the population, ranging from 1/500, in Caucasians,1 to 1/18,500, in Asians.2 The majority of the patients with IgAD does not have any apparent disease, but
some can develop repetitive infections, atopies, gastrointestinal disorders, autoimmune diseases, neoplasias, transfusion reactions and other less common manifestations.\textsuperscript{1}

IgA deficiency is defined as a serum level below 0.05 g/L in individuals older than four years.\textsuperscript{3,4} It can be congenital or acquired and the acquired form is related with exposure to drugs, congenital rubella infections, Epstein-Barr virus, Hepatitis C virus, acquired immunodeficiency virus, splenectomy and bone marrow transplant from IgA-deficient donor.\textsuperscript{1,6} Autoimmune disorders are more common in individuals with IgAD. One study with 126 Brazilian individuals with IgAD showed a prevalence of 19\% of autoimmune disorders, with thyroidopathy being the most common of them.\textsuperscript{6} Other entities that have been described in association with this immunodeficiency include systemic lupus erythematosus (SLE), rheumatoid arthritis, ankylosing spondylitis, scleroderma, psoriasis, vitiligo, Henoch-Schönlein purpura, celiac disease, myasthenia gravis and diabetes mellitus.\textsuperscript{1,6}

As the defective production of IgA is an element that predisposes to infections, the study of this type of deficiency in SLE patients, in whom infections are among the main cause of death, is imperative. The objective of the present study was the determine whether the incidence of IgAD in individuals with SLE in Southern Brazil is the same as that found in the international literature and whether there is some way to recognize these patients based on their clinical or autoantibody profile. This study also intends to investigate, comparatively, the cumulative damage index in SLE patients with and without IgAD.

**PATIENTS AND METHODS**

This study was approved by the Ethics Committee of the Sociedade Evangélica Beneficente under protocol number 2624/2008, and patients signed an informed consent. One hundred and eighty-nine patients of both genders, older than 18 years of age, with at least four classification criteria for SLE of the America College of Rheumatology (ACR)\textsuperscript{7} were included in this study. The cohort consisted of all patients treated at the Rheumatology outpatient clinic from June 2008 to June 2009 and who agreed to participate in this study. Patients included in this study were not on medications associated with acquired IgA deficiency (gold salts, sulfasalazine, D-penicillamine, or phenytoin),\textsuperscript{1} or had infections by the acquired immunodeficiency virus or hepatitis C virus. As for the medication at the moment of IgA evaluation, 162 were on chloroquine, 192 on prednisone (5 to 60 mg), 28 on azathioprine, 22 on methotrexate, 5 on mofetil mycophenolate, 4 on intravenous cyclophosphamide, one on cyclosporine, one on danazol, and one on dapsone. Three patients who had undergone kidney transplants were on rapamycin and tacrolimus.

Blood for measurement of IgA by nephelometry was collected from all patients, and levels from 70 to 400 mg/dL were considered normal. Patients with IgA levels below 50 mg/dL were considered to be IgA deficient.\textsuperscript{2,4}

The medical charts of the patients were reviewed, and the following were recorded: demographic data (gender, age, time since the diagnosis of SLE), presence of articular and extra-articular manifestations (butterfly erythema, discoid lesion, photosensitivity, oral ulcers, serositis, psychosis, seizures, stroke, hemolytic anemia, leukopenia, thrombocytopenia, and nephritis). Levels of leukocytes < 4,000 /mm\textsuperscript{3}, in two or more occasions were considered leukopenia and thrombocytopenia was considered when platelets levels were < 100,000/mm\textsuperscript{3} in two or more occasions in the absence of thrombocytopenia-inducing drugs. The presence of nephritis was confirmed by renal biopsy. In 147 patients, the cumulative damage was determined by the SLICC/ACR index (Systemic Lupus International Collaborative Clinics/American College of Rheumatology),\textsuperscript{8} which measures the degree of irreversible damage secondary to persistent SLE activity and that can vary from zero to 46 points.

A retrospective analysis of the laboratory data was undertaken by reviewing the medical charts and it included autoantibodies levels: antinuclear antibody (ANA), anti-DNA, anti-Sm, anti-Ro/SSA, anti-La/SSB, anti-RNP, antcardiolipin (aCL) IgG and IgM and lupus anticoagulant (LAC). For aCL, levels above 15 GPL (for aCL IgG) and 15 MPL (for aCL IgM) were considered positive.

As control, data from a study with 11,576 healthy Brazilians (blood donors and healthy gravidas), which showed a prevalence of IgAD of 1 in 965 individuals, was used.\textsuperscript{9}

The data was studied by frequency and contingency tables. The Chi-square and Fisher tests (for nominal parameters) and the Mann-Whitney test (for numerical parameters) for association tests were used with the help of the Graph Pad Prism 4.0 software. The level of significance of 5\% was adopted.

**RESULTS**

Of the 189 SLE patients, seven (3.7\%) were males and 182 (96.3\%) females. Their age ranged from 15 to 64 years (mean of 36.2 ± 11.4) and the time of the disease ranged from 0.2 to
36.0 years (mean 6.6 ± 5.8). The age at the diagnosis of SLE ranged from 10 to 63.5 years (mean 29.6 ± 10.9).

Table 1 shows the clinical profile of the study population.

Table 2 summarizes the autoantibody profile of this population.

Deficiency of IgA was present in 11 (6.71%) patients. When comparing this prevalence with the literature data, which showed an incidence of IgA deficiency of 1:965 for the Brazilian population, a P < 0.0001 was observed.

Gender and the age of onset of the disease of SLE patients with and without IgAD were not statistically different (P = 1.0 and 0.71, respectively).

When analyzing the clinical data of patients with and without IgAD, a difference was not observed, as can be inferred from the data on Table 3.

As for the autoantibody profile in populations with and without IgAD, differences were not observed between the two groups, as shown in Table 4.

The SLICC/ACR was applied to 147 patients and scores of 0 to 5 (mean 1.02 ± 1.15) were observed. The mean score of the population without IgAD was 1.04 ± 1.18, whereas that with IgAD was 0.70 ± 0.67 (P = 0.61).

DISCUSSION

Although we used data from the literature as control, the investigation of this cohort clearly demonstrated an increase in IgAD rates in Brazilian SLE patients.

The association of SLE and IgAD was first described in 1962 by West et al.10 and, later, in 1965 by Bachmann et al.11 in a 15-year-old girl with SLE whose sister, who also had SLE, had normal serum IgA levels. More recent studies by Jesus et al.12 and Cassidy et al.13 demonstrated a frequency of 5.2% and 2.6% of this association in patients with the juvenile type of the disease. Rankin and Isenberg1 observed five patients with IgAD among 96 SLE patients. Riffle et al.14 demonstrated the presence of this deficiency in three out of 72 SLE patients, a percentage a little higher than 4%, confirming the results obtained in the other mentioned studies. In the present study, we observed an incidence of 6.17%.

Systemic lupus erythematosus is a complex disease with variable course and prognosis, which affects young people and might have important effects on quality of life and survival. Comorbidities can further increase its severity. The demonstration of a higher incidence of IgAD in individuals with SLE should be valued and at least two arguments to justify its importance can be raised.

First, there is the possibility of some factor linked to the etiology of both diseases. It has been documented that autoimmune diseases, and not only SLE, are more common in individuals with IgA deficiency.1 Possible reasons for this association would include the presence of a predisposing genetic terrain common to both diseases or favoring the development of an auto-immune disease by infections (especially viral), which are more common in these patients.1 Several viral infections have been implicated in the development of SLE and, among them, cytomegalovirus,
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Epstein-Barr virus and so forth. Such exposure could be prevented by effective concentrations of IgA. Another explanation would be that serum IgA itself would have an anti-inflammatory effect. The interaction of IgA with the Fcα R1 receptor of the cellular membrane would lead to the activation of ITAM (tyrosine-based activation motif), which would lead to the recruitment of tyrosine phosphatase SHP-1. In turn, SHP-1 would lead to the inhibition of several inflammatory and autoimmune reactions. The lack of IgA would result in the abolition of this inhibitory signal. The second argument is related to the fact that infections are among the greatest causes of mortality in this population and they could be increased in patients with deficiency of IgA.

Table 3

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>With IgAD (n = 23)</th>
<th>Without IgAD (n = 134)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discoid lupus</td>
<td>0/11</td>
<td>23/134 (17.16%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>5/11 (45.45%)</td>
<td>98/136 (72.05%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>6/9 (66.66%)</td>
<td>65/132 (49.24%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Butterfly erythema</td>
<td>3/11 (27.27%)</td>
<td>73/132 (55.30%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Arthritis</td>
<td>4/11 (36.36%)</td>
<td>98/177 (55.36%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Psychosis</td>
<td>0/11</td>
<td>6/175 (3.42%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Seizures</td>
<td>1/11 (9.09%)</td>
<td>16/175 (9.14%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>1/11 (9.09%)</td>
<td>9/178 (5.05%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Serositis</td>
<td>1/11 (9.09%)</td>
<td>32/166 (19.27%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>0/11</td>
<td>12/176 (6.81%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4/11 (36.36%)</td>
<td>47/176 (26.7%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4/11 (36.36%)</td>
<td>37/176 (21.02%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Nephritis</td>
<td>5/11 (45.45%)</td>
<td>78/178 (43.82%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>With IgAD (n = 11)</th>
<th>Without IgAD (n = 178)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA (n = 189)</td>
<td>11 (100%)</td>
<td>177 (99.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-DNA (n = 189)</td>
<td>4 (36.36 %)</td>
<td>45 (25.28%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Anti-Ro (n = 188)</td>
<td>4 (36.36 %)</td>
<td>65 (38.98%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Anti-La (n = 188)</td>
<td>1 (9.09%)</td>
<td>31 (17.51%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Anti-RNP (n = 175)</td>
<td>1 (9.09%)</td>
<td>44 (27.5%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Anti-Sm (n = 176)</td>
<td>0</td>
<td>40 (22.72%)</td>
<td>0.12</td>
</tr>
<tr>
<td>aCl IgM (n = 177)</td>
<td>0</td>
<td>22 (13.25%)</td>
<td>0.36</td>
</tr>
<tr>
<td>aCl IgG (n = 189)</td>
<td>1 (9.09%)</td>
<td>26 (12.51%)</td>
<td>1.00</td>
</tr>
<tr>
<td>LAC (n = 175)</td>
<td>1 (9.09%)</td>
<td>26 (15.85%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

IgAD = IgA deficiency; n = sample investigated; LAC = lupus anticoagulant; aCl = anticardiolipin antibodies.
point of view, regarding the presence of IgAD, although a tendency for patients with IgAD to be less photosensitive and to have a smaller incidence of butterfly rash was observed. Unlike the results of Rankin and Isenberg,4 the present study did not show a significant relationship between IgAD and the presence of anti-Sm or anti-SSB/La. This discrepancy can be justified by the fact that the autoantibody profile of a sample is affected by the genetic background of the study population.17,18 The prevalence of the anti-Sm antibody was higher in the population of the aforementioned study than in the present study. A significant relationship to other investigated autoantibodies was not observed, either.

As this was a retrospective study, it was not possible to obtain data on the prevalence of infections in IgAD patients in relation to the others. Thus, this is an aspect that remains open for future investigations.

To conclude, one can infer that SLE patients from Southern Brazil show a higher prevalence of IgAD than the non-lupus population and that the autoantibody profile, as well as clinical findings and the degree of cumulative damage do not differ in SLE patients with and without IgAD.

REFERENCES