Autoimmunity in Patients With Selective IgA Deficiency

Abolhassani H1,2, Gharib B1, Shahinpour S1, Masoom SN1, Havaei A1, Mirminachi B1, Arandi N1, Torabi-Sagvand B1, Khazaei HA3, Mohammadi J4, Rezaei N1, Aghamohammadi A1

1Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
2Division of Clinical Immunology, Department of Laboratory Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden
3Department of Immunology and Hematology, Zahedan Medical Sciences University, Zahedan, Iran
4Department of Life Science, Faculty of New Science and Technology, University of Tehran, Tehran, Iran

Abstract

Background and Objective: Selective immunoglobulin A deficiency (SIgAD) is the most common primary antibody deficiency. Patients with SIgAD have a greater risk of concomitant autoimmune disorders than healthy individuals. The exact mechanism underlying the relationship between autoimmunity and SIgAD is not fully understood. The aim of this study was to evaluate potential associations between autoimmunity and specific clinical or immunological findings in patients with SIgAD.

Methods: The study population comprised 57 symptomatic patients (65% males) with confirmed SIgAD who were referred to our center. Demographic data and history of autoimmunity were recorded both for patients and for their relatives. Comprehensive clinical and laboratory examinations were performed to investigate autoimmune complications in all the patients.

Results: Autoimmune disorders were documented in 17 cases (29.8%; 9 males and 8 females). The most common manifestations were thyroiditis, vitiligo, and hemolytic anemia (3 cases each). Ten patients (17.5%) had a family history of autoimmunity. Significant associations were detected between autoimmunity and increased duration of follow-up (P=.003), serum level of IgM (P=.01), regulatory T-cell count (P=.03), and class-switched memory B-cell count (P=.01). Four cases of autoimmune SIgAD (23.5%) progressed to common variable immunodeficiency during the follow-up period (P=.006).

Conclusions: Autoimmune disorders, autoimmune cytopenia, and Ig subclass deficiency can lead to severe clinical manifestations in patients with SIgAD. Therefore, immunologists and pediatricians should be aware of these conditions.

Key words: Selective IgA deficiency. Autoimmunity. Immunologic characteristics. Switched memory B cell. Regulatory T cells.

Resumen

Fundamento y objetivo: La deficiencia selectiva de IgA (SIGAD) es la inmunodeficiencia primaria de anticuerpos más frecuente. Se conoce que los pacientes con SIGAD tienen un mayor riesgo de padecer trastornos autoinmunes asociados, en comparación con la población normal. Sin embargo, no se encuentra aún esclarecido el mecanismo exacto de la relación entre la autoinmunidad y el SIGAD. El objetivo de este estudio ha sido evaluar las asociaciones entre la autoinmunidad y los hallazgos clínicos o inmunológicos en los pacientes con SIGAD.

Métodos: Han sido estudiados cincuenta y siete pacientes sintomáticos (65% varones), con diagnóstico confirmado de SIGAD. Se registraron sus datos demográficos y los antecedentes, personales y familiares, de enfermedades autoinmunes, y se realizaron múltiples exámenes clínicos y de laboratorio.

Resultados: Se documentaron enfermedades autoinmunes en 17 casos (29,8%; 9 hombres y 8 mujeres), siendo la tiroiditis, el vitíligo y la anemia hemolítica, las manifestaciones autoinmunes más comunes, con 3 casos para cada trastorno. Diez pacientes (17,5%) contaban con antecedentes familiares de autoinmunidad. Se encontraron asociaciones significativas con el desarrollo de enfermedades autoinmunes en estos pacientes con SIGAD: un prolongado período de seguimiento (p=0,003), el nivel sérico de IgM (p=0,01), la cuantificación de las linfocitos T reguladores (p=0,03) y el cambio de isotipo de los linfocitos B de memoria (p=0,01). Cuatro casos de SIGAD, con enfermedad autoinmune asociada (23,5%), evolucionaron hacia una inmunodeficiencia variable común, durante el período de seguimiento (p=0,006).

Introduction

Selective immunoglobulin A deficiency (SIgAD) is the most frequent primary immunodeficiency (PID), with a prevalence that ranges from 1:142 to 1:965 in Caucasian populations [1-3]. It is less frequent among Asians (1:2600 to 1:19 000) [4-7]. The frequency of SIgAD in healthy Iranian adults is 1:651 [6]. The disorder is defined by decreased serum levels of IgA (<7 mg/dL) with normal serum IgM and IgG levels in an individual aged more than 4 years, after other causes of immunodeficiency have been ruled out [8,9]. The main defect in SIgAD is thought to be caused by failure of B cells to differentiate into plasma cells or apoptosis of plasma cells. The ability to reconstitute IgA secretion with CD40/CD40ligand interaction and IL-10, as well as induction of caspase-1 inhibitor and inhibitor of apoptosis-2, suggests that there could be a cytokine-dependent process associated with the inability to generate IgA-producing B cells in these patients [10-11]. However, defects at the transcriptional or posttranscriptional level and functionally defective helper T activity or excessive T-suppressor cell activity have also been reported to form the molecular basis of SIgAD [12-13].

Previous studies have shown a greater risk of concomitant autoimmune disorders in patients with SIgAD than in healthy individuals [9,10]. The prevalence of autoimmune disorders in these patients, especially hematologic autoimmunity, varies from 7% to 36% depending on the population [14]. Although most patients with SIgAD are asymptomatic, autoimmune diseases in selected symptomatic patients raise the suspicion of a unique molecular mechanism underlying the phenotype [11,13]. Furthermore, since SIgAD patients are at increased risk of developing autoimmunity in middle age, long-term follow-up is required to detect autoimmune manifestations and enable early treatment and timely management [15,16].

The aims of this study were to investigate the prevalence of autoimmune disorders in Iranian individuals with symptomatic SIgAD and to evaluate the probable associations between autoimmunity and other clinical and immunological findings in patients with SIgAD.

Patients and Methods

Patients

The study population comprised 57 symptomatic patients with confirmed SIgAD, who were referred to our center, the Children’s Medical Center, also known as the Pediatrics Center of Excellence in Iran, which is affiliated to the Tehran University of Medical Sciences and is a referral center for both pediatric and adult patients with PID. The diagnosis of SIgAD was confirmed according to the criteria of the Pan-American Group for Immunodeficiency [9] and the European Society for Immunodeficiencies [17]. These criteria include a serum IgA level <7 mg/dL with normal serum levels of IgG and IgM in an individual older than 4 years of age. The decreased IgA level should be confirmed in at least 2 consecutive tests, and other causes of immunodeficiency must be ruled out. Informed consent was obtained from patients or their parents or legal guardians and the study was approved by the Ethics Committee of Tehran University of Medical Sciences.

Methods

A detailed questionnaire was completed for all patients to record demographic data, clinical and laboratory data, family and personal history of documented autoimmunity, recurrent and chronic infections, and other complications. At diagnosis, serum levels of IgG, IgA, and IgM and lymphocyte subsets were measured using standard immunochemical assays as defined in our previous study [12]. All patients underwent sampling for measurement of CD4/CD45+FoxP3 regulatory T cells and CD27– IgD+ switched memory B cells. Patients diagnosed with SIgAD before 2008 were recontacted and assessed. Fewer than 0.4% of peripheral blood lymphocytes belonged to the CD19/CD27/IgD cell population and were considered to have a class-switch recombination defect [12,18]. The diagnosis of autoimmune disorder was based on clinical and complementary laboratory findings and standard criteria [19,20]. The criteria for inclusion in the autoimmunity group were development of autoimmune disorder during disease course (before or after diagnosis of PID). This diagnosis was confirmed either by an immunologist involved directly in the patient’s clinical care or by a related subspecialist at this referral hospital.

Statistical Analysis

The statistical analysis was performed using SPSS version 16.0 (SPSS Inc). A 1-sample Kolmogorov-Smirnov test was used to estimate whether data were normally distributed. Parametric and nonparametric analyses were performed based on the findings of this test. A P value of .05 or less was considered significant.

Results

The study population comprised 57 patients with SIgAD (37 males and 20 females; mean age at diagnosis, 8.4 [5.6] years). Patients were followed-up for a total of 297 patient-years (mean, 5.3 [2.2] patient-years). The mean age at onset of symptoms was 4.3 (4.0) years, and the mean diagnostic
delay was 3.9 (3.7) years. Nineteen patients (33.3%) were children of a consanguineous marriage (Figure 1). A history of autoimmunity was documented in the first and second-degree relatives of 10 cases (17.5%). The most common presentation among family members of patients with SIgAD was autoimmune thyroiditis (7 cases, 70%). Twelve patients (21.0%) had a positive family history of PID (Figure 2). The most prevalent first presentation in these patients was

**Figure 1.** Pedigree of all symptomatic SIgAD patients with a history of parental consanguinity except P3, P5, P6, P17, P25, P38, and P41, who are represented in Figures 2 and 3.

**Figure 2.** Pedigree of 12 symptomatic SIgAD patients from 11 separate families with a history of primary immunodeficiency. AIHA indicates autoimmune hemolytic anemia; CVID, chronic variable immunodeficiency; ALPS, autoimmune lymphoproliferative syndrome.
pneumonia (33 patients, 57.9%), although only 14 patients (24.5%) showed recurrent infections during the course of the disease. Bronchiectasis, as a sequela of recurrent respiratory tract infections, was seen in 8 patients (14.0%). Allergic disorders were the second most common clinical manifestation (32 patients [56%]).

Autoimmune disorders were documented in 17 patients (29.8%), 5 of whom had >1 autoimmune disorder during follow-up. Eight out of 20 female patients (40%) and 9 out of 37 male patients (24.3%) had an autoimmune manifestation (Figure 3). Although autoimmunity was more frequent in female SlgAD patients, this difference was not significant ($P = .21$, Table 1). The mean follow-up periods differed significantly between patients with nonautoimmune manifestations (4.1 [1.0] years) and patients with autoimmune manifestations (6.8 [3.8] years; $P = .003$).

In this survey, the most common autoimmune manifestations were autoimmune thyroiditis, vitiligo, and autoimmune hemolytic anemia (AIHA) (3 cases each), followed by celiac disease, juvenile rheumatoid arthritis, dermatomyositis, autoimmune alopecia, and type 1 diabetes mellitus (2 cases each). We also detected 1 case each of Crohn disease, ulcerative colitis, myasthenia gravis, and autoimmune lymphoproliferative syndrome (Table 2).

Other characteristics of patients with autoimmune disorders are shown in Table 1. Although patients with autoimmunity were more likely to be children of a consanguineous marriage (47.0%) than nonautoimmune patients (28.9%), this relationship was not significant ($P = .13$). Furthermore, a positive family history of autoimmunity or PID could not significantly predict the presence of autoimmunity in SlgAD patients ($P = .63$ and $P = .48$, respectively).

Thirteen out of 17 patients with autoimmunity (76.4%) developed lower respiratory tract infections, while only 50% of patients without autoimmunity had pneumonia ($P = .083$). A negative relationship was also detected between the presence of allergy and autoimmunity, although this correlation was not significant ($P = .3$, Table 1).

During the follow-up period, 4 autoimmune patients progressed toward common variable immunodeficiency (CVID) and were treated with intravenous immunoglobulin (3 AIHA and 1 thyroiditis). Bronchiectasis was documented in all 4 patients during the course of the disease ($P = .006$, Table 2).

Table 1 also presents immunologic data for children with SlgAD according to whether or not they had autoimmunity. The mean serum level of IgM was significantly higher in patients with concomitant autoimmune disorders than in patients without autoimmune disorders (103.1 [45.7] vs 69.4 [28.4]; $P = .01$). The regulatory T-cell count (2.03 [1.12] vs 2.91 [1.76], $P = .03$) and switched memory B-cell count (0.90 [0.44] vs 1.75 [0.46]; $P = .01$) were significantly lower in patients with autoimmunity (Table 1). Indeed, 15 of all SlgAD patients presented a class-switching defect, which was complicated by autoimmunity in 13 patients (86.6%). IgG2 subclass deficiency at diagnosis of SlgAD was documented in only 2 patients (11.7%) in the autoimmunity group. Moreover, 2 patients (5%)...
without autoimmunity lacked IgG3. Both patients with subclass deficiency had bronchiectasis and progressed to CVID in the long term (P = .08).

Discussion

SIgAD is thought to be associated with a variety of autoimmune phenomena [21]. We presented the clinical and laboratory features of SIgAD in children treated at our center and compared patients who had autoimmunity and long-term follow-up data with those who did not have this complication. Infectious disorders, especially pneumonia, were the most common presentation in our patients. Pediatric patients with autoimmune SIgAD had a longer follow-up; therefore, the remaining patients should be evaluated in the long term because of the probability of this complication in the future.

SIgAD has been detected in 4% of patients with rheumatoid arthritis, 2% of patients with myasthenia gravis [30], 1.6% of patients with Graves disease, 3.8% of patients with systemic lupus erythematosus, 1.1% of patients with diabetes mellitus type 1, and 2.6% of patients with autoimmune celiac disease [21]. However, we found the diagnostic delay to be similar in both the autoimmune group and the nonautoimmune group. In other words, it is generally accepted that SIgAD is associated with autoimmunity, although most autoimmune patients have not been examined for level of IgA or seen by an immunologist, probably owing to the lack of infectious complications and the lack of awareness of the importance of immunologic screening in patients with autoimmunity.

The percentage of patients with concomitant autoimmune manifestations (29%) is consistent with data reported elsewhere on autoimmune disorders in SIgAD patients (7%-36%) [14,15]. The prevalence of autoimmunity in this study is significantly higher than the estimated prevalence of autoimmune disease in the general population, especially in Iran, where 3% of the population has an autoimmune disease [22]. Given that the
prevalence of autoimmunity in SlgAD patients and their family members is 10-fold and 7-fold higher, respectively, than in the general population, we propose further studies to compare the frequency of autoimmunity in asymptomatic SlgAD patients and to compare SlgAD patients with the healthy population in a case-control study. The frequency of parental consanguinity in SlgAD patients with autoimmunity was higher than in nonautoimmune patients. It could therefore be hypothesized that parental consanguinity is associated with a more severe clinical phenotype in SlgAD patients.

The increased risk of autoimmunity in patients with SlgAD has several possible explanations. First, secretory IgA plays an important role in the protection of mucosal surfaces; therefore, in patients with IgA deficiency, environmental antigens can easily penetrate the mucosa. Molecular mimicry and cross-reaction with self-antigens can lead to formation of autoreactive antibodies [11,23]. An increased frequency of autoantibodies has been observed in patients with SlgAD [11,15]. However, detection of autoantibodies does not predict whether a patient with SlgAD will develop an autoimmune disease [24].

Second, SlgAD could result from shared genetic factors, such as common human leukocyte antigen alleles or haplotypes, which predispose an affected individual to both autoimmunity and immunodeficiency [25]. Fixed haplotypes of major histocompatibility complex genes, including extended haplotype HLA-A1-B8-DR3, are frequently associated with both SlgAD and CVID. In addition, homozygosity for the whole or part of the HLA-B8-DR3-DQ2 haplotype is a risk factor for development of some autoimmune diseases. While not the most common HLA type in Iranian SlgAD patients, the association between these HLA haplotypes and development of autoimmunity is still controversial [26,27]. However, in our study, 4 patients with SlgAD from the autoimmune group (especially with AIHA, bronchiectasis, and Ig subclass deficiency) progressed to CVID, thus supporting a common genetic basis for these 2 disorders, as explained in previous reports [28,29].

The mechanisms that prevent the immune system from responding to self-antigens (elimination or negative selection of self-reactive cells) are believed to be compromised in some patients with PID and in patients with SlgAD [30,31]. This possibility can be seen in the reduced number of regulatory T cells in our investigation. The association between SlgAD and abnormal T-cell regulation, especially in regulatory T cells and reduced switched memory B cells (CD19+/CD27+/IgD- cell population), could also explain the association between SlgAD and autoimmunity [12,18,32].

Table 2. Characteristics of Patients With Concomitant Autoimmune Disorders

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Diagnosis, y</th>
<th>Autoimmune Disorders</th>
<th>IgA, IgM, IgG, IgG Subclass deficiency</th>
<th>Family History of Autoimmunity</th>
<th>Other Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>4</td>
<td>DM + thyroiditis</td>
<td>0/73/1645/-</td>
<td>-</td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>5</td>
<td>Celiac disease</td>
<td>0/160/1370/-</td>
<td>Celiac</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>4</td>
<td>AIHA</td>
<td>0/110/1470/IgG2SD</td>
<td>-</td>
<td>Bronchiectasis, progress to CVID</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>11</td>
<td>Vitiligo + thyroiditis</td>
<td>6/44/956/-</td>
<td>-</td>
<td>Progress to CVID</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>11</td>
<td>Alopecia universal</td>
<td>7/50/1300/-</td>
<td>Alopecia areata</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>5</td>
<td>AIHA + thyroiditis</td>
<td>0/69/780/IgG2SD</td>
<td>AIHA</td>
<td>Bronchiectasis, progress to CVID</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>9</td>
<td>Celiac disease</td>
<td>0/152/1900/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>4</td>
<td>Vitiligo + myasthenia gravis</td>
<td>5/180/690/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>26</td>
<td>Crohn disease</td>
<td>5/94/921/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>10</td>
<td>JRA</td>
<td>0/23/959/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>9.5</td>
<td>Ulcerative colitis</td>
<td>5/78/992/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>4</td>
<td>Vitiligo</td>
<td>7/99/1176/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>7</td>
<td>AIHA + DM + JRA</td>
<td>6/151/2000/-</td>
<td>-</td>
<td>Bronchiectasis, progress to CVID</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>9.5</td>
<td>Alopecia areata</td>
<td>4/134/1186/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>9</td>
<td>Type 1 diabetes</td>
<td>7/130/1431/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>10</td>
<td>Type 1 diabetes</td>
<td>7/138/1700/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Female</td>
<td>4</td>
<td>ALPS</td>
<td>0/69/780/-</td>
<td>Thyroiditis</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AIHA, autoimmune hemolytic anemia; ALPS, autoimmune lymphoproliferative syndrome; CVID, chronic variable immunodeficiency; DM, dermatomyositis; IgG2SD, IgG2 subclass deficiency; JRA, juvenile rheumatoid arthritis.
IgA also plays an anti-inflammatory role in the immune system. It downregulates cell-mediated responses to chemotaxis and IgG-mediated phagocytosis. Since secreted IgA facilitates clearance of pathogens, SIgAD results in defective antigen clearance, leading to immune complex deposition in the inflamed tissue of various organs [33].

A higher compensatory level of serum IgM was found in patients with autoimmune manifestations than in the other patients. Circulating natural IgM acts as a first line of defense against foreign antigens but may contribute to autoimmunity in different disease models [34,35]. An association between increased levels of serum IgM and development of autoimmunity has been reported in other forms of PID including Wiskott-Aldrich syndrome [36]. Most natural IgM is produced by B-1 cells, which could cross-react with self-antigens to cause autoimmunity [37,38]. Moreover, increased levels of IgM could also indicate a severe defect in the cell switch recombination of autoimmune SIgAD patients; this possibility is compatible with our finding for class-switched memory B cells in this group of patients. In addition to defects in the secretion of IgA, low IgG subclass levels were documented in both autoimmune and nonautoimmune patients. However, IgG2 deficiency was found only in patients with autoimmune diseases; patients without autoimmune diseases only lacked IgG3. Although the present study focused on humoral immunodeficiency and lymphocyte subsets, we suggest that future studies investigate the quality of the cell response in SIgAD patients.

**Conclusions**

Autoimmune disorders are strongly associated with SIgAD and have a higher incidence in patients with severe clinical manifestations and special immunologic characteristics, which should be investigated in selected groups of patients. Screening for hematologic autoimmunity in SIgAD patients with Ig subclass deficiency and bronchiectasis could help to detect possible progression to CVID. Early management with intravenous immunoglobulin could help to eliminate secondary complications.

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**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**


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Asghar Aghamohammadi
Children’s Medical Center Hospital
Dr Qarib St
Keshavarz Blvd
Tehran 14194, Iran
E-mail: aghamohammadi@tums.ac.ir