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Original Article

Prevalent Autoimmunities in Patients with Selective IgA Deficiency

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Abstract

Introduction: Among primary immunodeficiency (PID), selective immunoglobulin A deficiency (SIgAD) is the most prevalent type. SIgAD patients can be either asymptomatic or symptomatic. Symptomatic patients suffer from a wide range of manifestations including infections, allergy, autoimmunity, and malignancy. SIgAD patients are more susceptible to some autoimmune diseases, while the exact mechanisms behind this association are not found yet. Therefore, this study was conducted in order to evaluate the possible association between autoimmune disease and specific clinical records or immunological data in SIgAD patients.

Methods: The present cohort included 166 SIgAD patients who were diagnosed at the Research Centre for Immunodeficiencies at the children's medical Centre. A comprehensive history, demographic information, clinical manifestations, laboratory data were obtained from all patients to assess the autoimmune complications.

Results: Autoimmunity was seen in 16 patients (9.6%, 10 males and 6 females). The most common autoimmunity types were juvenile idiopathic arthritis, vitiligo and alopecia (18.8%). 9 patients (6.5%) had a PID family history. Significant data that were higher in patients with autoimmunity were the mean age at the study time (p=0.019), rheumatoid problem (p=0.043), liver problem (p=0.031), IgG level (p=0.006) and IgE level (p=0.004).

Conclusion: The association between SIgA deficiency and autoimmunity could lead to severe clinical complications. So, it is better for immunologists to aware of these problems.

Keywords Agammaglobulinemia, Autoimmunity, Primary immunodeficiency disorders (PIDs).

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Introduction

Among different types of primary immunodeficiency (PID), selective immunoglobulin A deficiency (SIgAD) is the most prevalent entity that is observed almost 1:700 individuals. This disorder is characterized by absent or less than 0.07 g/L IgA serum level in individuals after the age of 4 years old along with normal IgG and IgM serum level (1). Although the exact mechanisms contributing to the disease pathogenesis are not fully known, B cell maturation defects and cytokine production impairment seem to be associated (2-4). The most of individuals with SIgAD are identified without clinical symptomatic and are accidentally diagnosed in the blood or immunologic profiling (5), however some patients manifest different clinical manifestations such as respiratory and gastrointestinal tract infections (6-8), autoimmunity (9), allergy and atopy (10) and malignancies (11). Some SIgAD cases can progress into a more severe type of PID which is called common variable immunodeficiencies (CVID) (12, 13).

The prevalence rate of autoimmune diseases in SIgAD patients ranges from 7-36% in the symptomatic population (9, 14). A recent study suggested that rate of autoimmune diseases in SIgAD patients is almost 11% (5). Among the autoimmune diseases, the systemic lupus erythematosus (SLE), thyroiditis, rheumatoid arthritis, type 1 diabetes mellitus, Graves' disease, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and celiac disease are more frequent in individuals with SIgAD (9). Several mechanisms underlying the autoimmunity development in SIgAD have been introduced. Secretory IgA plays a protective role in mucosal surfaces; thus, environmental antigens can penetrate to the mucosa in IgA deficiency situations, and molecular mimicry and self-antigen cross-reaction will result in auto-reactive antibodies production, as increased level of autoantibodies is seen in SIgAD patients as expected (15-17). Also, T cell abnormalities (especially regulatory T cells abnormalities) can breakdown the SIgAD patients' tolerance and increase their susceptibility to autoimmune disease (18, 19). Regarding the pathogenesis of SIgAD, the presence of an association between human leukocyte antigen (HLA) haplotypes (including HLA-A1, -DR3, -DQ2, and –B8) and autoimmune diseases has been reported for SIgAD patients (9). However, the exact etiology of autoimmunity in SIgAD does not fully understand.

Hence, this study was conducted to evaluate demographic data, the clinical manifestations and laboratory data of symptomatic SIgAD patients with and without autoimmune presentations.

Materials and methods

Patients

The present retrospective cohort study was conducted on the obtained data of 166 SIgAD patients who were referred to the Research Centre for Immunodeficiencies at the children's medical Centre during 1999-2019. SIgAD patients were diagnosed based on newest ESID criteria including increased susceptibility to infection, diagnosis after exclusion of transient form (>4 years of life), low or undetectable serum IgA (when measured with nephelometry <0.07 g/L) but normal serum levels of IgM and other switched Igs (measured at least twice), exclusion of T-cell defects and secondary causes of hypogammaglobulinaemia as well as normal IgG antibody response to all vaccinations (http://esid.org/Working_Parties/Registry/Diagnosis-criteria). All patients or their parents filled out the informed consent.

Methods

A complete questionnaire was completed by reviewing medical records including (i) demographic data (such as the age at the study time, age of onset, age at diagnosis, delay diagnosis, follow up, sex, family history, mortality and consanguinity); (ii) clinical presentations (including respiratory infections, allergy, enteropathy, gastrointestinal problems, autoimmunity, types of autoimmunity and lymphoproliferative disorders; and (iii) laboratory tests (such as IgA, IgM, and IgG serum level, complete blood count (CBC) plus differentiation and the subsets of lymphocytes. The enzyme-linked immunosorbent assay (ELISA) was utilized for evaluation of antibody responses to polysaccharide (unconjugated pneumococcal vaccines) and protein (tetanus and diphtheria vaccines) (20). Based on clinical presentation including biopsy results, colonoscopy, endoscopy, and laboratory tests data for example direct coombs test, anti-nuclear antibody (ANA), fluorescent anti-nuclear antibody (FANA), anti-double-stranded DNA (anti-dsDNA), and other para-clinical complementary tests, and radiology investigations according to national criteria, the autoimmune diseases were diagnosed. The autoimmunity diagnosis was checked for every patient by a clinical immunologist and an expert specialist depends on the affected organ. To compare clinical and laboratory data, all patients were categorized into two groups SIgAD patients with and without autoimmunity.

Statistical analysis

Statistical analyses were performed using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). We utilized the Kolmogorov-Smirnov test to estimate whether data were normally distributed and data was analyzed based on parametric or nonparametric values. Chi-square test plus Fisher's exact test was conducted for 2 × 2 categorical variable comparisons, while Mann-Whitney U and Kruskal-Wallis H test and the parametric equivalent of the categorical comparisons were utilized in order to compare the numerical variables.

Results

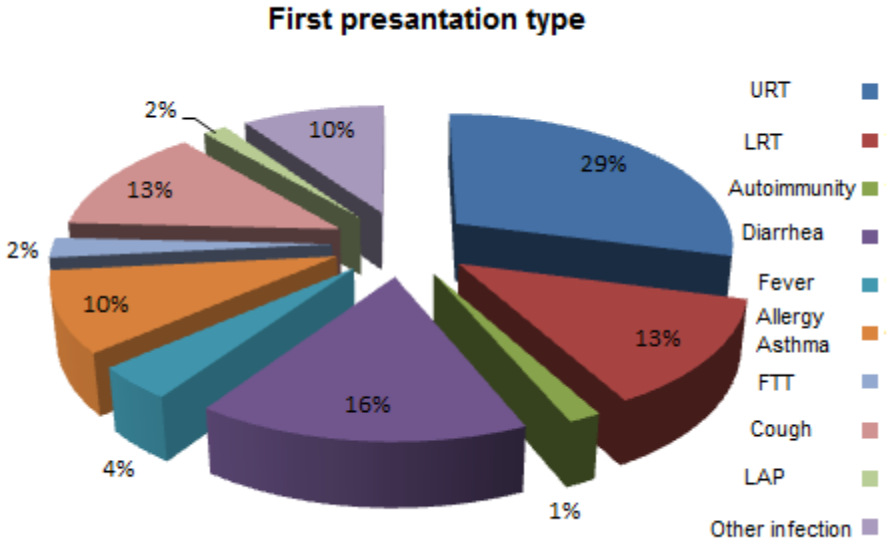
The population of study composed of 166 SIgAD patients (103 males and 63 females; mean age at diagnosis, 4 years). Demographic data of all SIgAD individuals are provided in **Table 1**. The most common clinical manifestation among all SIgAD patients was respiratory tract infections (47.6%) (**Table 2**). Among the first presentations, upper respiratory tract infection (36 cases, 29 %) and diarrhea (16.1%, 20 patients) were the frequent presentations in all SIgAD individuals (**Figure 1**).

Table 1. Demographic data of SIgA patients with and without autoimmunity

Parameter	Total patients (n=166)	AID (n=16)	No AID (n=150)	*p*-value
Age at the study time, y (IQR)	13 (7-22)	20 (12.5–26.75)	12 (6.5-21)	0.019*
Age at diagnosis, y (IQR)	4 (1.41-8)	8 (2.37-13.5)	4 (1.22-8)	0.115
Delay diagnosis, y (IQR)	1 (0.07-4)	1 (0.19-6.75)	1 (0.04-3.81)	0.424
Follow up, y (IQR)	9 (2-15.58)	10.10 (7.25-18.37)	8.75 (2-14.2)	0.104
Sex, N (%)				0.969
Male	103 (61.3)	10 (62.5)	93 (62)	
Female	63 (37.5)	6 (37.5)	57 (38)	
Consanguinity, N (%)	57 (40.7)	7 (46.7)	50 (40)	0.619
Family history, N (%)	9 (6.5)	1 (6.3)	8 (6.5)	1.000
Mortality, N(%)				0.051
Alive	85 (50.6)	5 (31.3)	80 (53.3)	
Dead	2 (1.2)	1 (6.3)	1 (0.7)	
Unknown	81 (48.2)	10 (62.5)	69 (46)	

*p-value <0.05 have been regarded as significant.
Abbreviations: AID; autoimmune disease, No AID; no autoimmune disease, Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N; Count

Figure 1. First presentation type in SIgAD patients



Abbreviations: URT; Upper respiratory tract infection, LRT; Lower respiratory tract infection, FTT; Failure to thrive, LAP; Lymphadenopathy

Table 2. Clinical manifestations and organ involvements of SIgA patients with and without autoimmunity

Parameter	Total patients (n=166)	AID (n=16)	No AID (n=150)	*p*-value
Pneumonia, N (%)	51 (30.7)	2 (12.5)	49 (32.7)	0.152
Sinusitis, N (%)	43 (25.9)	5 (31.3)	38 (25.3)	0.563
Bronchiectasis, N (%)	5 (3)	0 (0)	5 (3.3)	1.000
Clubbing, N (%)	2 (1.2)	0 (0)	2 (1.3)	1.000
Respiratory Infectious only, N (%)	25 (15.1)	0 (0)	25 (16.7)	0.134
Oral ulcer, N (%)	10 (6)	0 (0)	10 (6.7)	0.600
FTT, N (%)	10 (6)	0 (0)	10 (6.7)	0.600
Recurrent diarrhea, N (%)	16 (9.6)	1 (6.3)	15 (10)	1.000
Chronic diarrhea, N (%)	29 (17.5)	1 (6.3)	28 (18.7)	0.310
Recurrent infection, N (%)	43 (25.9)	6 (37.5)	37 (24.7)	0.366
Otitis, N (%)	25 (15.1)	4 (25)	21 (14)	0.268
Allergy, N (%)	33 (19.9)	1 (6.3)	32 (21.3)	0.200
Splenomegally, N (%)	5 (3)	2 (12.5)	3 (2)	0.074
Hepatomegally, N (%)	5 (3)	1 (6.3)	4 (2.7)	0.401
LAP, N (%)	12 (7.2)	3 (18.8)	9 (6)	0.094
Malignancy, N (%)	1 (0.6)	0 (0)	1 (0.7)	1.000
BCGosis, N (%)	5 (3)	0 (0)	5 (3.3)	1.000
Respiratory tract infections, N (%)	79 (47.6)	8 (50)	71 (47.3)	0.839
Urinary tract problem, N (%)	9 (5.4)	1 (6.3)	8 (5.3)	1.000
Heart problem, N (%)	1 (1.8)	1 (6.3)	2 (1.3)	0.264
Hematologic problem, N (%)	5 (3)	0 (0)	5 (3.3)	1.000
Anemia, N (%)	13 (7.8)	1 (6.3)	12 (8)	1.000
Neutropenia, N (%)	8 (4.8)	0 (0)	8 (5.3)	1.000
Leukopenia, N (%)	1 (0.6)	0 (0)	1 (0.7)	1.000
Pancytopenia, N (%)	1 (0.6)	0 (0)	1 (0.7)	1.000
Gastrointestinal problem, N (%)	40 (24.1)	3 (18.8)	37 (24.7)	0.764
Rheumatoid problem, N (%)	9 (5.4)	3 (18.8)	6 (4)	0.043*
Skeletal problem, N (%)	3 (1.8)	0 (0)	3 (2)	1.000
Neurologic problem, N (%)	11 (6.6)	0 (0)	11 (7.3)	0.603
Dermatologic problem, N (%)	41 (24.7)	7 (43.8)	34 (22.7)	0.073
Liver problem, N (%)	8 (4.8)	3 (18.8)	5 (3.3)	0.031*
Endocrine problem, N (%)	2 (1.2)	0 (0)	2 (1.3)	1.000
Multiple sites problem, N (%)	43 (25.9)	6 (37.5)	37 (24.7)	0.366

*p-value <0.05 have been regarded as significant.
Abbreviations: AID; autoimmune disease, No AID; no autoimmune disease, y; year, LAP; Lyphadenopathy, FTT; failure to thrive.
Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N; Count

We found that patients with autoimmunity were from 7 consanguineous families (46.7%), whereas patients without autoimmunity were from 50 consanguineous families (40%), but this difference was not significant (*p*=0.619). Moreover, existence of history of PID could not forecast the existence of autoimmunity in SIgAD (*p*=1.000). Autoimmunity was seen in 9.6% (16) patients (in 62.5% males and 37.5% females) (**Table 1**). The mean age at the study time was significantly higher in patients with autoimmunity than patients without autoimmunity (20 vs. 12 years; *p*=0.01). Autoimmunity frequency in SIgAD patients is

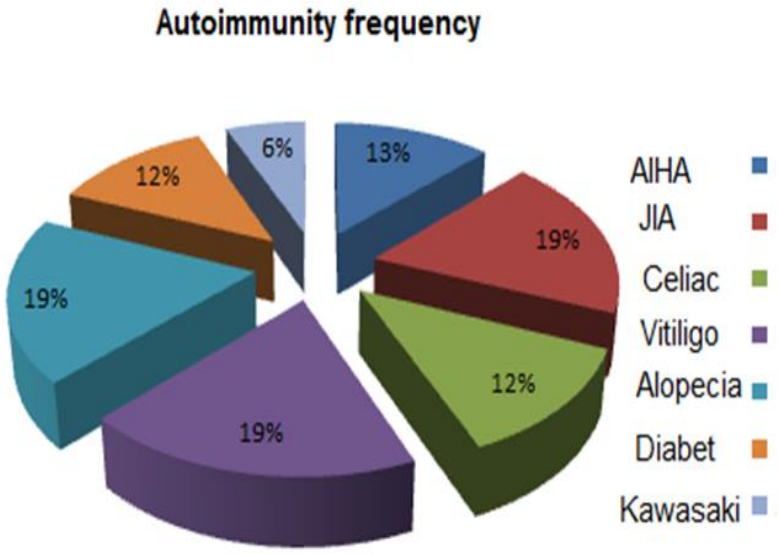
showed in **Figure 2**. The most common autoimmune presentations among SIgAD patients with autoimmunity were rheumatoid arthritis (19%), vitiligo (19%) and alopecia (19%). The rate of rheumatoid problems was significantly higher in patients with autoimmunity than patients without autoimmunity (18.8% vs. 4%; p=0.04). Also, the rate of liver problems was significantly higher in patients with autoimmunity than patients without autoimmunity (18.8% vs. 3.3%; p=0.03). 12.5% of patients with autoimmunity and 32.7% of patients without autoimmunity had pneumonia (p=0.15). There was a negative relationship between autoimmunity and allergy, that was not significant (p=0.2).

Table 3. Laboratory data of SIgA patients with and without autoimmunity

Parameter	Total patients (n=166)	AID (n=16)	No AID (n=150)	*p*-value
WBC, 1000/µL (IQR)	8000 (6485-10000)	7360 (6100-8207.5)	8200 (6520-10120)	0.083
Neutrophil, % of total WBC (IQR)	43.4 (33.65-58.5)	54 (43-60.5)	42 (33-57)	0.062
Lymphocyte, % of total WBC (IQR)	48(32- 57)	41(31-45)	50(31.75-5715)	0.092
Hb, g/dl (IQR)	12.2 (11.3-13)	12 (11.75-13)	12.3 (11.2-13.1)	0.635
Platelet, cell/µL (IQR)	310000 (258750-381500)	253500 (213500-330750)	313500 (263500-386750)	0.097
IgG, mg/dl (IQR)	1116(720-1600)	1571(1042-1915)	1074(650-1551)	0.006*
IgG1, mg/dl (IQR)	789.5(534.75-992.5)	889 (401.6-1215)	535 (763.5-977.5)	0.581
IgG2, mg/dl (IQR)	268(100.25-415.75)	395 (300-550)	207 (98.5-408.5)	0.153
IgG3, mg/dl (IQR)	65(40-96.25)	68 (40-125)	65 (38.5-95.5)	0.929
IgG4, mg/dl (IQR)	26(2-64)	48 (16-102)	17 (2-63)	0.256
IgA, mg/dl (IQR)	5(0.77-9)	5 (0.17-9.75)	5 (1.25-9)	0.818
IgM, mg/dl (IQR)	88(54.75- 138.75)	88 (48-138)	88 (55-141)	0.937
IgE, IU/ml (IQR)	27.5 (7-78)	103 (38-348)	21 (6-71)	0.004*
$CD3^+$ lymphocytes, cell/µL (IQR)	60(50.25–68.75)	57.5 (43.5-69.25)	61 (50.25-68.75)	0.682
$CD4^+$ lymphocytes, cell/µL (IQR)	32.5(26.5–41.25)	35 (31-40.25)	31.5 (25-42.25)	0.520
$CD8^+$ lymphocytes, cell/µL (IQR)	21(17–26.25)	21 (18-24)	21.9 (16.52-27.25)	0.738
$CD56^+$ lymphocytes, cell/µL (IQR)	5.65(3.77–10)	10 (10-10)	5.3 (3.5-9.5)	0.333
$CD19^+$ lymphocytes, cell/µL (IQR)	15(11–19)	16.5 (9.5-21.75)	15 (11-18)	0.597
$CD20^+$ lymphocytes, cell/µL (IQR)	19.5(14.5–24.5)	92 (92-92)	19 (13-23)	0.124

*p-value <0.05 have been regarded as significant.
Abbreviations: AID; autoimmune disease, WBC; white blood cells, Hb; Hemoglobin, Ig; Immunoglobulins, CD; Cluster of Differentiation, y; year
Note: For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N; Count

Figure 2. Autoimmunity frequency in SIgAD patients



Abbreviations: AIHA; Autoimmune hemolytic anemia, JIA; Juvenile idiopathic arthritis

The mean of IgG level was significantly higher in patients with autoimmunity than patients without autoimmunity (1571 vs. 1074 mg/dl; p=0.006). Also, the mean of IgE level was significantly higher in patients with autoimmunity than patients without autoimmunity (103 vs. 21 IU/ml; p=0.004). Other laboratory data are provided in **Table 3**. Some of the demographic data, clinical manifestations and laboratory data of 16 SIgAD patients with autoimmunity presentations are mentioned in **Table 4**.

Discussion

The present retrospective cohort study was conducted on the obtained data of 166 SIgAD patients who were diagnosed and submitted in the Research Centre for Immunodeficiencies at the children's medical Centre during 1999-2019. We identified 16 SIgAD patients in this cohort that it indicates 9.6% as rate of autoimmunity in our study.

The presence of autoimmunity in SIgAD patients could be associated with some issues. One of the roles of SIgA is to defend in mucosa, thus, low or lack of SIgA in these patients lead to environmental antigens penetrate to mucosa and immune system reacts with this antigens, and result in production of autoantibodies (15). The existence of autoantibodies in SIgAD patients has been previously reported (15, 16). Furthermore, SIgA deficiency could be associated with genetic factors, such as HLA phenotype or alleles, as these genetic factors predispose SIgA deficient patients to autoimmunity and immunodeficiency (21). Moreover, some mechanisms that prevent immune system from reactive to self-antigens, are knocked down in SIgAD patients (22). Also, IgA is an anti-inflammatory role that down-regulates cell response to chemotaxis and phagocytosis and leads to clearance of pathogens and antigens (23).

Table 4. Data of 16 SIgAD patients with autoimmunity

ID Patients	Sex	Age at diagnosis, y	Autoimmunity type	IgA, mg/dl	IgM, mg/dl	IgG, mg/dl	Family history of PID	Other explanations
1.	Female	8	Celiac disease	5	109			Recurrent infection, chickenpox, respiratory tract, Gastrointestinal and multiple sites problem
2.	Female	22	alopecia	4		1935		Otitis, sinusitis, LAP, respiratory tract, dermatologic and multiple sites problem
3.	Female	2.25	Celiac disease	0.7	25	1679		Anemia
4.	Female		JIA	19	48	972		Rheumatoid problem
5.	Male	9	Vitiligo	9	7	2253		Recurrent infection, Pneumonia, sinusitis, Recurrent diarrhea, respiratory tract, dermatologic, heart, Gastrointestinal and multiple sites problem
6.	Male	2.5	Vitiligo	5	32	926	*	Recurrent infection, Otitis, respiratory tract, dermatologic problem
7.	Female	17	JIA	22	230	1700		Recurrent infection, Otitis, sinusitis, Rheumatoid problem
8.	Female	10	Vitiligo	24	88	1016		Dermatologic problem, rash and cough
9.	Male		AIHA	0	190	1120		Splenomegally, Chronic diarrhea, Gastrointestinal and liver problem
10.	Male	8	alopecia	4	134	1186		Otitis, sinusitis, allergy, respiratory tract problem
11.	Male	0.7	Diabet	6	130	1431		Recurrent cold
12.	Male	8	Diabet	10	138	1700		Recurrent cold
13.	Male	28	alopecia	9	76	820		Recurrent infection, LAP, respiratory tract, dermatologic, liver and multiple sites problem
14.	Male	5	JIA	0	67	2910		Allergy, respiratory tract problem, Rheumatoid and multiple sites problem
15.	Male	0.08	AIHA	0	259	1855		Recurrent infection, Pneumonia, sinusitis, Splenomegally, hepatomegally, LAP, respiratory tract, urinary, dermatologic, liver and multiple sites problem
16.	Female		Kawasaki	0	65	2049		Hive, dermatologic problem

Abbreviations: Ig; Immunoglobulins, PID; Primary immunodeficiency, LAP; Lyphadenopathy, y; year, JIA; Juvenile idiopathic arthritis, AIHA; Autoimmune hemolytic anemia

Generally, the prevalence of autoimmune diseases in SIgAD patients varies from 5 to 30%, based on studied populations (5). Our SIgAD patients had 19% juvenile idiopathic arthritis**,** vitiligo and alopecia, 13% autoimmune hemolytic anemia, 12% celiac disease and diabetes as well as 6.3% Kawasaki, indicating juvenile idiopathic arthritis, vitiligo and alopecia were the most common types of autoimmunity in our patients. Previous studies indicated that among the hematologic but not prevalent as other antibody deficiencies such as common vatriable immunodeficiency. Among non-hematologic autoimmune diseases some have been reported to be more common in SIgAD

such as Graves' disease, type 1 diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, and celiac disease (5). In our study, the rate of rheumatoid diseases was significantly higher in patients with autoimmunity than patients without autoimmunity. SIgAD often is associated with rheumatoid diseases, like systemic lupus erythematosus and rheumatoid arthritis. It is due to impairment of immune system of SIgAD patients to defense against infectious pathogens and leads to accumulation of viral complex in tissue (16).

We found that the mean age at the study time was significantly higher in patients with autoimmunity than patients without autoimmunity; however, the delay of diagnosis is similar in both groups. In other word, it is accepted that patients with SIgAD mostly are associated with autoimmunity, but most patients with autoimmunity have not been examined for IgA level (24). The rate of autoimmunity in our study was 9.6%, that was consistent with other studies (7%-36%) (16), (25). The rate of autoimmunity in our study was higher than other studies (3%) (26). It showed that the autoimmunity prevalence in our study is 3 fold higher than another study. However, the rate of autoimmunity in our SIgAD patients was less than previous reported study by Abolhassani et al. that was 16 vs 17 patients or 9.6% vs 29% of patients (24). This lower prevalence could be related to two reasons: 1) the number of our patients are much more than previous study (166 vs 57 patients). 2) There were some patients with autoimmunity that primarily diagnosed as SIgAD, but deep analysis by genetic mutations demonstrated other PID disorders for these patients and these patients were excluded from our study.

The rate of liver problems was significantly higher in our patients with autoimmunity than patients without autoimmunity. Liver problems were seen in other PID like CGD, HIgM and CVID (18), but there is no data about liver problem in SIgAD in other studies, and we could not compare our data with previous study, suggesting the investigation of liver problems in other studies SIgAD patients. Regarding laboratory findings, we found that the mean of IgG level was significantly higher in patients with autoimmunity than patients without autoimmunity. Given that IgG can be autoantibodies, higher the IgG level in our autoimmune patients could be related to the existence of autoantibodies in this group of SIgAD patients. There is no study to be evaluated autoantibodies in SIgAD patients with autoimmunity. We suggest further studies to investigate the existence of autoantibodies (especially IgG class) in SIgAD patients with autoimmunity. Autoimmune disorders could be observed in SIgAD patients, thus knowing autoimmune disorders in

these patients are important.

Based on the correlation between lo IgA deficiency and autoimmune disorders, and the evidence of presence of anti-IgA antibody, receiving blood for some SIgAD patients should be performed with caution due to autoantibodies. In this context, screening these patients for autoantibodies could be helpful for these patients. SIgAD patients with autoimmune manifestations should be followed up longer than patients without autoimmunity. To manage this group of patients, different therapeutic approaches including high doses of Ig administration and immunomodulation with corticosteroids and anti-CD20 agents are recommended.

Conflicts of Interest: There are no conflicts of interest.

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