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Allergy in Patients with Selective IgA Deficiency

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Abstract

Background/objectives: SIgAD is the most frequent of the primary antibody deficiencies. Patients with IgAD can be either symptomatic or asymptomatic. Symptomatic patients suffer from a wide range of manifestations including allergy, malignancy, and autoimmunity. The prevalence of allergic diseases is assumed to be increased in IgAD patients. In this study, we aimed to evaluate the frequency of allergic disorders in IgAD patients as well as a comparison between these patients and IgA deficient patients without allergy.

Methods: The present cohort study included 166 IgAD patients who were diagnosed at the Research Center for immunodeficiencies in children's medical Center. To compare clinical data and laboratory records, all IgAD patients were classified into two groups as follows: patients with allergic diseases and patients without allergic diseases.

Results: Among 166 patients with IgA deficiency, allergy was seen in 33 patients (19.8%). In this study, respiratory tract infections were the most common clinical presentation in all patients (47.6%). Among the infectious manifestations, pneumonia and sinusitis were significantly higher in patients with allergy compared with patients without allergy (respectively 48.5% vs 26.3%; $p = 0.013$, 48.5% vs 20.3%; $p = 0.001$). Based on the laboratory data, the number of platelet and B cells (CD20+) were significantly higher in patients with allergy in comparison to patients without allergy (respectively, $p = 0.025$, $p = 0.44$).

Conclusions: The relation between IgAD disease and allergy could lead to severe clinical complications. Thus, these allergy disorders should be considered as an important feature for suitable management and enhancing the life quality in patients with IgAD.

Keywords: selective immunoglobulin A deficiency, allergy, primary immunodeficiency disorders, autoimmunity.

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Introduction

SIgAD is the most common primary immunodeficiency disease with several presentations ranging from asymptomatic to severe manifestations (1). The incidence rate of this disorder varies from 1:163 to 1:18,500 in different ethnic groups (2). SIgAD is considered a heterogeneous group of diseases thus expected that diverse processes are interfered in its pathogenesis. The exact underlying etiology has not yet been recognized (1), although the defect in terminal differentiation of B cells and switching to IgA-producing plasma cells are believed to be responsible (3). Even though most of IgA deficient cases are asymptomatic, one-third of patients are symptomatic, presented by allergies, autoimmune diseases as well as recurrent sinopulmonary infections (3, 4). Secretory IgA in mucosal secretions has a protective function against enteric allergens, toxins and pathogenic microorganisms; SIgAD deficient patients, as a result, are more vulnerable to these agents (5, 6). In some cases, IgE levels could be increased in patients with IgA deficiency that may be due to a useful mechanism for low secretory IgA level and lack of IgM compensation, especially in atopic individuals (7). Many patients with SIgAD (estimated between 25 to 50%) present their first and/or only clinical manifestation through allergies (1, 8). In some studies, the most common manifestation of allergy is asthma, followed by allergic rhinitis and conjunctivitis, urticaria, atopic dermatitis, and food allergies (3). In this study, we evaluated the prevalence of various allergic disorders in IgA deficiency patients who were referred to the Children's Medical Center.

Materials and methods

Study population

The present retrospective cohort study included 166 symptomatic patients with verified SIgAD, who were referred to the Research Centre for Immunodeficiencies at the children's medical center (affiliated to Tehran University of Medical Sciences) during 1999-2020. The diagnosis of SIgAD was made based on newest ESID criteria including (a) at least one of the following manifestations: increased susceptibility to infection, autoimmune manifestations and affected family members, (b) serum IgA level <7 mg/dL with normal serum levels of IgG and IgM, (c) exclusion of secondary causes of hypogammaglobulinemia, normal IgG antibody response to all vaccinations, individuals older than 4 years of age, and (f) exclusion of patients with T-cell defects.

Data collection

A detailed questionnaire was completed by medical records which contain the demographic data, sex, age at the time of the study, age of onset and diagnosis, family history, mortality and consanguinity, clinical presentations such as allergy, respiratory infections, gastrointestinal and, laboratory data including IgA, IgM, and IgG serum level, and complete blood count (CBC). Patients were divided into two groups including SIgAD patients with asthma and allergic diseases (group A) and SIgAD patients without asthma and allergic diseases.

Statistical analysis

Statistical analyses were done by using the SPSS software package, version 22 (SPSS Inc., Chicago, IL, USA). Parameters' broadcast of these two groups was done by the Kolmogorov-Smirnov test. Chi- square test plus Fisher's exact test were 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 performed in order to compare the numerical variables.

Results

Among all registered SIgAD patients, 166 (103 males and 63 females; median (IQR) age at the time of the study, 156 months) were included to this study. The median age of the diagnosed patients was 48 months

and the prevalence of parental consanguinity was noted in 57 patients (40.7%). The demographic data of all SIgA patients is shown in **Table 1**. Overall, the principal manifestation in SIgAD patients was respiratory tract infections (47.6%) and the frequencies of pneumonia, sinusitis and recurrent infection were higher among other infections in our patients.

Dermatologic problems and multiple site complications were also reported in 24.7% and 25.9% of patients, respectively. The detailed information on clinical manifestations and organ involvements is presented in (**Table 2**).

Although the age at the time of the study and delay diagnosis was slightly higher in patients with allergy than patients without allergy, no significant difference was found in the two groups. The age at diagnosis was not significantly different between patients with allergy than patients without allergy (p = 0.66). Our results indicated that patients with allergy were from 9 consanguineous families (30%), whereas patients without allergy were from 48 consanguineous families (43.6%), but this difference was not significant (p = 0.178) (**Table 1**).

Among the infectious manifestations, pneumonia and sinusitis were significantly higher in patients with allergy than patients without allergy (respectively, 48.5% vs 26.3%; p = 0.013, 48.5% vs 20.3%; p = 0.001). Also, the rate of respiratory tract infections was significantly higher in patients with allergy than patients without allergy (p = 0.001).

While the frequencies of dermatologic problems and multiple site complications were higher in patients with allergy than patients without allergy, the difference between these groups was not significant (**Table 2**). Based on laboratory data, the median of platelet count was significantly higher in patients with allergy than patients without allergy (358000 vs. 301000 cell/µL; p = 0.025). Moreover, the median of CD20+ lymphocytes was significantly lower in patients with allergy thanpatients without allergy (7 vs. 21.5 cell/µL; p = 0.044) **(Table 3**). Other laboratory features are mentioned in (**Table 3**). Some of thedemographic data, clinical manifestations and laboratory information of 33 SIgAD patients with allergy presentations are shown in (**Table 4**).

Table 1. Demographic data of SIgAD patients with and without allergy

Parameters	Total patients (n=166)	With allergy (n=33)	Without allergy (n=133)	*p*-value
Age at the study time, m (IQR)	156 (84-264)	192 (138-252)	144 (82.5-264)	0.273
Age at diagnosis, m (IQR)	48 (17-96)	48 (24-96)	51 (12-96)	0.669
Delay diagnosis, m (IQR)	12 (0.875-48)	19.5 (10-38.25)	12 (0.05-48)	0.230
Course of disease, m (IQR)	108 (24-187)	108 (84-210.25)	96 (24-184)	0.118
Sex, N (%)				0.541
Male	103 (61.3)	22 (66.7)	81 (60.9)	
Female	63 (37.5)	11 (33.3)	52 (39.1)	
Consanguinity, N (%)	57 (40.7)	9 (30)	48 (43.6)	0.178
Family history, N (%)	9 (6.5)	2 (6.3)	7 (5.3)	1.000
Mortality, N (%)				0.731
Alive	85 (50.6)	18 (54.5)	67 (50.4)	
Dead	2 (1.2)	0 (0)	2 (1.5)	
Unknown	81 (48.2)	15 (45.5)	64 (48.1)	

Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.
*p-value <0.05 have been regarded as significant.

Table 2. Clinical manifestations and organ involvements of SIgAD patients with and without allergy

Parameter	Total patients (n=166)	With allergy (n=33)	Without allergy (n=133)	p-value
Pneumonia, N (%)	51 (30.7)	16 (48.5)	35 (26.3)	0.013 *
Sinusitis, N (%)	43 (25.9)	16 (48.5)	27 (20.3)	0.001 *
Bronchiectasis, N (%)	5 (3)	1 (3)	4 (3)	1.000
Clubbing, N (%)	2 (1.2)	0 (0)	2 (1.5)	1.000
Oral ulcer, N (%)	10 (6)	2 (6.1)	8 (6)	1.000
FTT, N (%)	10 (6)	0 (0)	10 (7.5)	0.214
Recurrent diarrhea, N (%)	16 (9.6)	2 (6.1)	14 (10.5)	0.741
Chronic diarrhea, N (%)	29 (17.5)	5 (15.2)	24 (18)	0.695
Recurrent infection, N (%)	43 (25.9)	8 (24.2)	35 (26.3)	0.808
Otitis, N (%)	25 (15.1)	6 (18.2)	19 (14.3)	0.59
Splenomegaly, N (%)	5 (3)	1 (3)	4 (3)	1.000
Hepatomegaly, N (%)	5 (3)	0	5 (3.8)	0.584
LAP, N (%)	12 (7.2)	1 (3)	11 (8.3)	0.463
Malignancy, N (%)	1 (0.6)	0 (0)	1 (0.8)	1.000
BCGosis, N (%)	5 (3)	0 (0)	5 (3.8)	0.584
Respiratory tract infections, N (%)	79 (47.6)	25 (75.8)	54 (40.6)	0.001*
Urinary tract problem, N (%)	9 (5.4)	3 (9.1)	6 (4.5)	0.384
Heart problem, N (%)	3 (1.8)	1 (3)	2 (1.5)	0.488
Hematologic problem, N (%)	5 (3)	0 (0)	5 (3.8)	0.584
Anemia, N (%)	13 (7.8)	3 (9.1)	10 (7.5)	0.724
Neutropenia, N (%)	8 (4.8)	3 (9.1)	5 (3.8)	0.196
Leukopenia, N (%)	1 (0.6)	1 (3)	0 (0)	0.199
Pancytopenia, N (%)	1 (0.6)	0 (0)	1 (0.8)	1.000
Gastrointestinal problem, N (%)	40 (24.1)	7 (21.2)	33 (24.8)	0.665
Autoimmunity, N (%)	17(10.2)	2 (6.06)	15(11.2)	0.5
Rheumatoid problem, N (%)	9 (5.4)	0 (0)	9 (6.8)	0.207
Skeletal problem, N (%)	3 (1.8)	0 (0)	3 (2.3)	1.000
Neurologic problem, N (%)	11 (6.6)	4 (12.1)	7 (5.3)	0.232
Dermatologic problem, N (%)	41 (24.7)	11 (33.3)	30 (22.6)	0.199
Liver problem, N (%)	8 (4.8)	0 (0)	8 (6)	0.359
Endocrine problem, N (%)	2 (1.2)	0 (0)	2 (1.5)	1.000
Multiple sites problem, N (%)	43 (25.9)	12 (36.4)	31 (23.3)	0.125

Abbreviations: y; year, LAP; Lymphadenopathy, FTT; failure to thrive.
Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.
*P-value <0.05 have been regarded as significant.

Table 3. Laboratory data of SIgAD patients with and without allergy

Parameter	Total patients (n=166)	With allergy (n=33)	Without allergy (n=133)	*p*-value
WBC, 1000/µL (IQR)	80000 (6485-10000)	7965 (6515-9925)	8000 (6450-10000)	0.990
Neutrophil, % of total	43.4 (33.65-58.5)	45 (36.32-57.75)	42 (33-58)	0.557
WBC (IQR)				
Lymphocyte, % of total WBC (IQR)	48 (32- 57)	50 (30.5-53.45)	48 (32-57.15)	0.710
Hb, g/dl (IQR)	12.2 (11.3-13)	12.15 (11-13)	12.2 (11.5-13.1)	0.561
Platelet, cell/µL (IQR)	310000 (258750-381500)	358000 (312500-447500)	301000 (250000-366000)	0.025*
IgG, mg/dl (IQR)	1116 (720-1600)	1262(764.2-1879)	1063(658-1565)	0.7
IgG1, mg/dl (IQR)	789.5 (534.75-992.5)	802 (622-963)	748 (459-1022.5)	0.85
IgG2, mg/dl (IQR)	268 (100.25-415.75)	235.5 (179-411.5)	286 (79.5-419.5)	0.493
IgG3, mg/dl (IQR)	65 (40-96.25)	65 (59.25-93)	65.5 (36-100)	0.647
IgG4, mg/dl (IQR)	26 (2-64)	28 (2.75-64.5)	19 (1.7-64)	0.808
IgA, mg/dl (IQR)	5 (0.77-9)	4 (0-6.25)	5 (2-9)	0.122
IgM, mg/dl (IQR)	88 (54.75- 138.75)	92 (53-145)	88 (55-138)	0.771
IgE, IU/ml (IQR)	27.5 (7-78)	39 (7-76.5)	23.5(6.52-81.25)	0.580
$CD3^+$ lymphocytes cell/µL (IQR)	60 (50.25–68.75)	55 (46.5-66.5)	61 (54-70)	0.173
$CD4^+$ lymphocytes cell/µL (IQR)	32.5 (26.5–41.25)	33.5 (23-38.5)	32 (28.25-43.6)	0.512
$CD8^+$ lymphocytes cell/µL (IQR)	21 (17–26.25)	20.5 (15.75-28)	21 (18-26)	0.497
$CD56^+$ lymphocytes cell/µL (IQR)	5.65 (3.77–10)	6.5 (3.5-11)	5.65 (3.325-9.75)	0.652
$CD19^+$ lymphocytes cell/µL (IQR)	15 (11–19)	15 (11.75-20)	15 (9-18.5)	0.754
$CD20^+$ lymphocytes cell/µL (IQR)	19.5 (14.5–24.5)	7 (1-13)	21.5 (19-41.75)	0.044*

Abbreviations: 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.
**p*-value <0.05 have been regarded as significant.

Table 4. Data of 33 SIgAD patients with allergy

ID Patients	Sex	Age at diagnosis, y	IgA, mg/dl	IgM, mg/dl	IgG, mg/dl	Family history of PID	Other explanations
1.	Male	72	4	181	1809	No	Recurrent cold, food allergy, hives, blain
2.	Male	24	7	52	505	No	food allergy,sepsis
3.	Male		29	71	299	No	Fever
4.	Male		13	82	769	No	Asthma
5.	Male		18	106	675	No	Recurrent cold
6.	Male	24	0	47	3490	No	allergic rhinitis
7.	Male	72	9	244	1850	No	allergic rhinitis
8.	Male	312	0	50	1813	No	Tonsillectomy
9.	Male	48	5	145	1515	No	Sepsis
10.	Male		3	116	1466	No	Recurrent cold
11.	Female	4		157	921	No	Eczema
12.	Female	36		112	2370	Yes	SAR, recurrent URTI, chicken pox
13.	Female		0.7				Asthma
14.	Female	72		92	2196	No	Asthma
15.	Female	36	0	160	1317	Yes	Asthma, allergic arthritis, aphthous stomatitis, motion sickness, ovarian cysts Blood in urine
17.	Female	240	5	82	1150	No	eczema
18.	Female	24	0	240	480	No	Rickets, conjunctivitis
19.	Male	96	5	53	1089	No	Respiratory infection (5-6 times)
20.	Male	17	9	155	720	No	Asthma, eczema
21.	Male	11	0	1		No	Eye allergy, urticaria
22.	Male	214	5	74	1274	No	Asthma
23.	Male	96	4	87	1971	No	Asthma
24.	Male	18	9	200	1050	No	Asthma, eczema, rhinitis
25.	Male	96	4	134	1186	No	Allergic conjunctivitis
26.	Male	36	4	104	629	No	Eczema, food allergy
27.	Male	48	4	39	1510	No	Asthma, allergic rhinitis, G6PD deficiency, icterus, infantile colic, URTI viral (8 times)
28.	Male	65	0	125	750	No	Asthma
29.	Male	120	6	102	1966	No	Adenoidectomy, tonsillectomy, drug allergy
30.	Male	102	5	48	2096	No	Food allergy
31.	Female	45	0	66	1198	No	seizure, food allergy
32.	Female	36	0	60	1250	No	Asthma, urticaria, eczema, allergic rhinitis, ringed chromosome 18
33.	Female	36	0	52	2000	No	Food allergy, recurrent UTI, Seizure

Abbreviation: SAR, severe acute respiratory syndrome; URTI, upper respiratory tract infection; G6PD, Glucose- 6-phosphate dehydrogenase.

Discussion

The current study was conducted on the extracted data of 166 SIgAD deficient patients who were diagnosed in the Research Centre for Immunodeficiencies at the Children's Medical Centre during 1999-2020. SIgAD patients can be either symptomatic or asymptomatic. The majority of IgA deficient patients are asymptomatic. Symptomatic patients show variable clinical presentations such as autoimmunity, allergy, mild recurrent sinopulmonary infection, and different severe complications (9-12). Due to the importance of allergic disorders in SIgAD patients, we aimed to study allergic complications among the affected patients. Our results demonstrated that most of the patients had typical clinical manifestations including recurrent infections.

The most common clinical presentations in the SIgAD patients were respiratory tract infections (47.6%).

Similar to our findings, respiratory tract infections have been reported as the most common clinical manifestation in some other studies (13-15). The absence of secretory IgA and its protective effects allow pathogens to overcome mucosal defenses, leading to infections in lower and upper respiratory tracts (16, 17). In contrast to our findings, Aytekin et al. have reported allergy followed by autoimmunity as the most common clinical manifestation among their study population(18).

Some studies have shown that IgA deficiency and allergy are correlated and there is a high prevalence of allergic disorders in SIgAD patients (10, 19, 20), while some other studies have reported no association between IgA deficiency and atopy of the childhood (21, 22). In our study, 33 SIgAD patients (19.8 %) had allergic disorders. Several studies have reported various frequencies for allergic disorders in SIgAD. Buckley et al. and Edwards et al. have reported the frequency of atopy in patients with SIgAD to be 58% and 13%, respectively (23, 24), and Aghamohammadi et al. have reported the frequency of allergy disease to be 40% (25). The allergic diseases most commonly associated with SIgAD are allergic conjunctivitis, rhinitis, urticaria, eczema, food allergy and asthma (26). Lattif et al. have reported the most common allergic disorders are allergic conjunctivitis, rhinitis, urticaria, atopic eczema and bronchial asthma and food allergy may be more common in patients with IgA deficiency (19). In an study from Brenninkmeijer, the prevalence of physician-diagnosed asthma, allergic rhinitis, and eczema in children was reported to be 10.7%, 16.9%, and 2.6%, respectively (27). While in our study the most common allergic disease was asthma followed by rhinitis allergic and eczema, these differences in allergy frequency, as well as allergic patterns in different studies, could be due to different underlying genetic defects, ethnicity, and environmental factors. Furthermore, IgE serum levels are often increased in IgA deficient patients that may be due to the compensatory mechanisms for the low secretion of IgA and lack of IgM compensation, especially in atopic patients. Therefore, IgA in mucosal barriers plays a significant role in the prevention of allergy (28, 29). Similar to Shkalim et al. and Koopman et al study, we observed a significantly higher amount of respiratory tract infections (pneumonia and sinusitis) among the allergy-positive group compared to the allergy-negative one (13, 30). It seems that allergic patients are more susceptible to respiratory tract infections.

According to our findings, SIgAD patients without allergy had a higher amount of CD20 lymphocytes compared to the allergy- positive group. However, in the literature, we found no studies about the role of CD20 in IgA deficient patients without allergy and positive groups to compare our results with. Further studies are required to determine whether CD20 has a protective role in the pathogenesis of allergy.

Conclusions

Since allergy is the prominent clinical manifestation of these symptomatic patients, it is advisable to consider SIgAD in individuals with allergy

who have a family history of immunodeficiency or recurrent infections and premature death. Moreover, the primary diagnosis of allergy in patients with SIgAD leads to a decrease in subsequent complications such as recurrent respiratory infections and results in increasing patient's quality of life.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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