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Original Article

Respiratory System Involvement in Patients with IgA Deficiency

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Abstract

Background: Selective IgA deficiency (SIgAD), is known as the most common antibody deficiency. This study, investigated the respiratory disorders among these patients.

Method: In this retrospective descriptive study, the data of patients with SIgAD in "Iranian Primary Immunodeficiency Registry" were extracted. Then, demographic characteristics, frequency and type of respiratory disorders, in addition to immunologic findings were gathered and analyzed by SPSS software.

Results: One hundred and twenty three patients with SIgAD (78 males/45 females), with the mean age of 18± 9.6 years old were investigated. Respiratory complications (recurrent cold, chronic cough and pneumonia), were the first presentation in 45% of the patients, and respiratory system involvement was detected among 66 patients (54.1%). The prevalence of pneumonia, otitis media and sinusitis, were 33.3%, 12.5% and 20.7%; respectively; which were significantly reduced after the diagnosis ($P<0.05$). Bronchiectasis had also been found in five patients (4.1%).

Conclusion: Respiratory problems were shown to be common presenting disorders in SIgAD. Early diagnosis and appropriate therapy could be crucial for better protection, and avoidance of severe respiratory complications in these patients.

Keywords: IgA Deficiency; Antibody Defect; Respiratory Infection; Primary Immunodeficiency

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Introduction

Selective immunoglobulin A deficiency (SIgAD), is defined as low levels of serum IgA (<7mg/dl) in the presence of normal IgG and IgM serum levels, in subjects who aged older than five years old (1, 2). The incidence of SIgAD varies regarding ethnic backgrounds, from 1/143 to 1/185000 in different geographic regions (1, 3). Its frequency among 13022 healthy blood donors of Iranian population, was reported to be 1/651 in one survey, while another study in north west part of Iran showed that five cases from 250 healthy and diabetic individuals had SIgAD (4, 5). The exact pathogenesis of the disease has not been well reasearched yet. However, the heterogeneous mechanism, and its association with known genetic loci were illustrated. Impairment of the terminal B-cell maturation, switching to IgA producing plasma cells and some monogenic defects in SIgAD had been identified in these patients (1, 2, 6, 7). Whereas, SIgAD patients are generally asymptomatic. However, they are more susceptible to frequent infections, allergic disorders and autoimmune diseases (8). One of the problematic issues in SIgAD patients, is the risk of severe and even anaphylactic reactions to infusion of intravenous gamma globulin (IVIG) and blood products, from which physicians and IgAD patients should be aware, and the transfusion of these products should be done with caution. (1, 4).

Recurrent pulmonary infections, are the most common diseases associated with SIgAD. Previous studies showed that about 40–90% of the symptomatic IgA-deficient patients present recurrent infections as the only or predominant manifestation, at the time of diagnosis (3, 9). The aim of this study was to investigate the respiratory presentations in patients with SIgAD, registered in the PID network of Iran.

Methods

This study was done on enrolled SIgAD patients, detected by expert clinical immunologists, registered in the Iranian primary immunodeficiency registry (IPIDR) databases, and was followed up at the children's medical center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran), between 1999 and 2019. The patients' information was extracted from their medical records, that were filled by expert physicians (10).The characteristics and demographic findings including age, gender, age of symptoms onset, age at the time of diagnosis, and the delay of diagnosis were assessed. The laboratory findings; including serum level of IgG and IgG subclasses, IgM, IgE, specific antibody titers to diphtheria, tetanus and streptococcus pneumonia, before and 3 weeks after vaccination (by enzyme-linked immunosorbent assay and nephelometry), and the T Cell and B Cell subsets (by flow cytometry analysis) were assessed (11, 12). The patients' first clinical presentations, family history, consanguinity, upper and lower respiratory manifestations before and after diagnosis, were also investigated. These informative data were saved in Excel (Microsoft, USA), and due to ethical regards, patients' names had been changed to codes. These data was converted to SPSS file and analyzed by SPSS 16 software (SPSS Inc, Chicago, USA). Chi square test was administered to compare the frequency of complications before and after treatment.

Results

One hundred and twenty three SIgAD patients with the mean age (±SD) of 18± 9.6 years old within the range of: 1.5 -48.5 years old, were investigated. The age for symptoms occurrence, ranged from 1 month to 26 years old. The mean delay time for diagnosis, was 3.3±6 years. Males (n=78, 63.4%), were involved more than females (n=45, 36.6%). A positive family history was found in eight patients (7.8%), and 42 (41.6%) of the patients had consanguineous parents. Respiratory involvement was seen in 66 patients (54.1%) and two patients (1.6%) expired.

Respiratory disorders, especially upper respiratory tract infections (URI) including; otitis media, sinusitis and cold, were the most common first presentations (31 cases). Allergy (eczema, allergic rhinitis and asthma), Gastrointestinal (GI) disorders, pneumonia and cough were the most common first proposed problems among these patients, respectively. About 36 cases (30%), were detected accidentally during a routine checkup, or doing laboratory examinations before surgical procedures. The diagnosis was done in two patients when they were individually evaluated for meningitis (0.08%) and hemolytic anemia (0.08%). (**Figure 1**)

Sixty six patients (54.1%), had respiratory disorder. Age, was found to be significantly associated with respiratory disorders among the study group, which was confirmed by logistic regression analysis (Odds Ratio= 1.05; 1.002-1.09; p value = 0.039). However, gender was not associated with respiratory problems in these patients (p value = 0.377). There was also no significant association between the age of diagnosis, delay of diagnosis, consanguinity and respiratory disorders in the studied population. (**Table 1**). Bronchiectasis was detected in 5

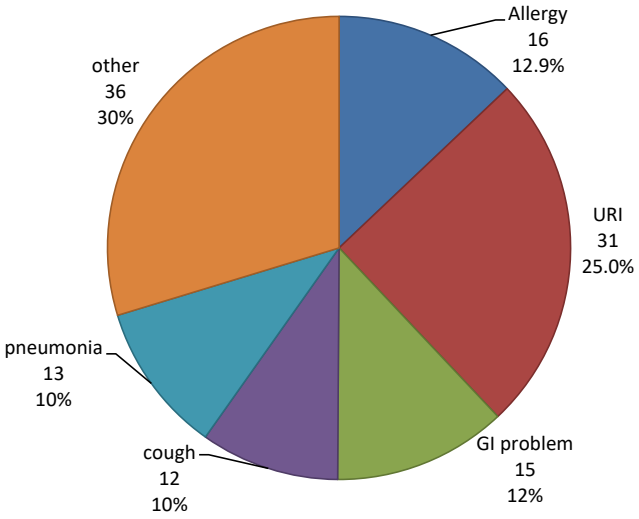

Figure 1. The first symptoms of patients with SIgAD. URI, Upper respiratory infections; GI problem, Gastrointestinal problems

Table 1. Comparison of demographic and immunologic findings of SIgAD patients, based on the respiratory tract involvement

Character	Total (n=123)	With respiratory problem	Without respiratory problem	*P*-Value
Male/female	78/45	44/22	33/23	0.377
Age (Month)	215±115	237±107	191±122	0.033*
Age of diagnosis	80±90	87±99	70±75	0.335
Delay of diagnosis	39±71	48±81	28±55	0.150
Consanguinity	42 (41.6%)	26 (42.6%)	16 (38.5%)	0.680
IgG mg/dl (Mean±SD)	1270±608	1283±654	1264±550	0.760
↓IgG1 <360 mg/dl	2(6.9%)	1(4.8%)	1(14.3%)	0.444
↓IgG2 <60 mg/dl	5 (14.3%)	3 (13.6%)	2 (16.7%)	1.000
↓IgG3 <30 mg/dl	2 (6.3%)	0 (0%)	2 (20%)	0.097
↓IgG4 <18 mg/dl	14 (43.8%)	13 (61.9%)	1 (10%)	0.007*
IgM mg/dl (Mean±SD)	112±69	110±73	116±65	0.685
IgE mg/dl (Mean±SD)	123±34	148±430	95±203	0.495
Flowcytometery:				
CD3 % (Mean±SD)	56±14	59±13	50±14	0.044*
CD4 % (Mean±SD)	31±10	33±9	29±12.5	0.230
CD8 % (Mean±SD)	23±8	23±7.8	24±10	0.713
CD19 %(Mean±SD)	15.7±11.4	17±13.2	13.3±5.5	0.370
Anti-diphtheria Ab <0.1 U/dl	5 (10.9%)	3 (11.1%)	2 (11.1%)	1.000
Anti-tetanus Ab <0.1U/dl	4 (8.9%)	3 (11.1%)	1 (5.9%)	0.648
No anti-PPV† Ab rising after vaccine	3 (11.1%)	3 (16.7%)	0 (0%)	0.529

†: 23-valent Pneumococcal Polysaccharide Vaccine (PPV23)

Table 2. The number and frequency of otitis media, sinusitis and pneumonia, before and after diagnosis of SIgAD

Disorder	No	Before diagnosis	After diagnosis	*P*-Value
Pneumonia:	100	32 (33.3%)	11 (11.6%)	
<2		20 (20.8%)	7 (7.4%)	< 0.001
≥2		12 (12.5%)	4 (4.2%)	
Otitis media:	88	11 (12.5%)	3 (3.4%)	
1-2		6 (6.8%)	3 (3.4%)	0.024
>2		5 (5.7%)	0(0%)	
Sinusitis:	82	17 (20.7%)	6 (7.4%)	
<2		10 (12.2%)	3 (3.7%)	0.013
≥2		7 (8.5%)	3 (3.7%)	

No, Total number after excluding the missing data

patients (4.1%) in the study group. It is worth mentioning that bronchiectasis was reported in one of the two SIgAD patients who expired.

No significant association was found between the respiratory involvement and mean serum IgG, IgM or IgE levels. (**Table 1**)

Thirty five patients underwent IgG subclass assessment, among them, 5 cases had IgG2 subclass deficiency. There was no significant association between IgG2, IgG1, IgG3 subclass deficiency and respiratory complications; however, there was a considerable higher respiratory involvement in patients with low serum IgG4 level. (**Table 1**)

Flow cytometry showed that the CD3 marker in patients with respiratory involvement was meaningfully increased (P=0.044). Although, the other T-cell and B-cell CD markers did not significantly change. (**Table 1**)

The specific Ab level against tetanus, diphtheria toxin and streptococcus pneumonia, before and 3 weeks after vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV23), were not found to be considerably different between two groups (with and without respiratory disorder) of SIgAD patients. **(Table 1**)

The frequency of pneumonia, otitis media and sinusitis, were 33.3%, 12.5% and 20%, which significantly reduced after diagnosis. (**Table 2**)

Discussion

The current study was done on the patients with SIgAD, diagnosed and referred by specialists of clinical immunology from multiple centers of IRAN, founded by population screening. Therefore, it is expected that the majority of the evaluated patients were symptomatic. About half of the patients in our study had respiratory involvement, and the first presentation among 45% of the patients, was a symptom related to upper or lower respiratory tract. (Cold: 25%, Cough: 10%, Pneumonia: 10%).

Several studies showed similar findings, and demonstrated that recurrent respiratory infection was the most common problem, and the first presentation among patients with IgAD (2, 8, 9). A cohort study on 2100 SIgAD patients by Ludvigsson et al. showed that these patients are more prone to infections, in comparison to the control group, with the prevalence ratio of 2.4. In the line of our study, the most common disorder was the respiratory tract infection, significantly more prevalent than the control group, with a ratio of 3.2 (13).

One-third of the patients of our study, had at least one episode of pneumonia, a year before diagnosis, which significantly decreased after the diagnosis. The frequency of sinusitis and otitis media were 20% and 17%, respectively; which also significantly dwindled after the diagnosis. Recurrent and severe or complicated respiratory infections, are the most prevalent indicators of immunodeficiency, which leads to early diagnosis. Appropriate and prompt therapeutic measures might be effective for reducing the period and number of infections in these patients. Even though upper and lower respiratory tract involvement in SIgAD, is generally higher than normal population, it is much lower in our patients compared to other B-cells defects, such as agammaglobulinemia and common variable immunodeficiency (CVID) (14-16). Meanwhile, frequent and repeated respiratory symptoms

could be considered as an important markers of immune defects, and the early diagnosis and appropriate therapy could effectively reduce the period and number of infections. A study by Aghamohammadi et al. showed that about 16.5% of patients with frequent ear, nose and throat infections, had defect in antibody mediated immunity, and 3% had SIgAD (17). Another study by Ozkan et al. showed that the prevalence rate of IgA and/or IgG subclass deficiency, was 25% in patients with recurrent upper respiratory tract infections, and 22% in patients with recurrent pulmonary infections (18). In the current study, we found that patients with respiratory disorders had significantly lower IgG4 subclasses. Thus, it seems that IgG4, might have an important role in the immunity of respiratory tract. Regarding higher numbers of CD3 positive lymphocytes in flowcytometry of SIgAD patients with respiratory tract manifestations, it seems that repeated exposure to infectious agents might have stimulated the immune system and especially T-cells, for a better response.

The IgA antibody, secretory IgA in particular, has an important role in mucosal immunity. Accordingly, increased sino pulmonary infections, in SIgAD patients could be predictable. Nonetheless, appropriate medical treatment and prophylactic antibiotic prescription might be beneficial in controlling these complications. Five patients (4.1%) of our study population, had concurrent IgG2 subclass deficiency. However, no significant association between the respiratory involvement and IgG2 deficiency was found, which was opposite to some other findings, which a more severe phenotype was reported in the coexistence of IgAD and IgG2 subclass deficiency (19, 20). This difference could be explained by the diversity of the study population and ethnicity. Positive family history of immunodeficiency was found in eight cases (7.8%), and about one third of the patients had parental consanguinity. Owing to a common genetic basis for SIgAD and CVID, as well as the similarity of the underlying B-cell defects, their occurrence in members of the same family is probable, and it was reported in some studies (21,22). For this reason, it is highly recommended that the family history, particularly in case of related parents, should be thoroughly assessed for early diagnosis, genetic consulting and even prenatal detection, to improve the management and control of these disorders.

Conclusion

SIgAD is known to be the most common immune deficiency. Although, these patients usually are asymptomatic, they are at a higher risk of infection, especially in the respiratory tract than normal population. So, the measurement of serum IgA level, as the first screening test in patients with recurrent or persistent respiratory symptoms, is highly recommended for the early detection of the antibody defects, appropriate treatment and regular follow up.

Conflict of interest

There is no conflict of interest between authors.

References

1. Yel L. Selective IgA deficiency. J Clin Immunol. 2010;30(1):6-10.
2. Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA Deficiency: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management. Scand J Immunol 2017;85(1):3-12.
3. Wang N, Hammarström L. IgA deficiency: what is new? Curr Opin Allergy Clin Immunol 2012;12(6):602-8.
4. Saghafi S, Pourpak Z, Aghamohammadi A, Pourfathollah AA, Samadian A, Farghadan M, et al. Selective immunoglobulin A deficiency in Iranian blood donors: prevalence, laboratory and clinical findings. Iran J Allergy Asthma Immunol. 2008;7(3):157-62.
5. Ahmadiafshar A, Mohsenifard MR, Mazloomzadeh S. Evaluation of serum & salivary IgA in patients with type 1 diabetes. PLoS One 2015;10(4):e0122757.
6. Abolhassani H, Aghamohammadi A, Hammarström L. Monogenic mutations associated with IgA deficiency. Expert Rev Clin Immunol 2016;12(12):1321-35.
7. Bousfiha A, Jeddane L, Picar C, Al-Herz W, Ailal F, Chatila T, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol 2020;40(1):66-81.
8. Latiff AH, Kerr MA. The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem 2007;44(pt2):131-9.
9. Yazdani R, Latif AH, Tabassomi F, Azizi G, Rezaei

N, et al. Clinical phenotype classification for selective immunoglobulin A deficiency. Expert Rev Clin Immunol. 2015;11(11):1245-54.
10. Abolhassani H, Kiaee F, Tavakol M, Chavoshzadeh Z, Mahdaviani SA, Momen T, et al. Fourth update on the Iranian National Registry of Primary Immunodeficiencies: integration of molecular diagnosis. J Clin Immunol. 2018;38(7):816–32.
11. Jefferis R, Kumararatne DS. Selective IgG subclass deficiency: quantification and clinical relevance. Clin Exp Immunol. 1990;81(3):357-67.
12. Schauer U, Stemberg F, Rieger CHL, Büttner W, Borte M, Schubert S, et al. Levels of Antibodies Specific to Tetanus Toxoid, Haemophilus influenzae Type b, and Pneumococcal Capsular Polysaccharide in Healthy Children and Adults. Clin Diagn Lab Immunol. 2003;10(2): 202–7.
13. Ludvigsson JF, Neovius M, Hammarström L. Risk of Infections Among 2100 Individuals with IgA Deficiency: a Nationwide Cohort Study. J Clin Immunol 2016;36(2):134-40.
14. Moazzami B, Mohayeji Nasrabadi MA, Abolhassani H, Olbrich P, Azizi G, Shirzadi R, et al. Comprehensive assessment of respiratory complications in patients with common variable immunodeficiency. Ann Allergy Asthma Immunol. 2020;124(5):505-11.
15. Fekrvand S, Yazdani R, Olbrich P, Azizi G, Shirzadi R, Modares iM, et al. Evaluation of respiratory complications in patients with X-linked and autosomal recessive agammaglobulinemia. Pediatr Allergy Immunol. 2020;31(4):405-17.
16. Arshi S, Nabavi M, Bemanian MH, Shakeri R, Taghvaei B, Ghalebaghi B. et al. Phenotyping and follow up of forty-seven Iranian patients with common variable immunodeficiency. Allergol Immunopathol (Madr). 2016;44(3):226-31.
17. Aghamohammadi A, Moin M, Karimi A, Naraghi M, Zandieh F, Isaeian A, et al. Immunologic evaluation of patients with recurrent ear, nose, and throat infections. Am J Otolaryngol. 2008;29(6):385-92.
18. Ozkan H, Atlihan F, Genel F, Targan S, Gunvar T. IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage. J Investig Allergol Clin Immunol. 2005;15 (1):69-74.
19. Domínguez O, Giner MT, Alsina L, Martín MA, Lozano J, Plaza AM. [Clinical phenotypes associated with selective IgA deficiency: a review of 330 cases and a proposed follow-up protocol. An Pediatr (Barc). 2012;76(5):261-7.
20. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, et al. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009; 29(1):130-6.
21. Moise A, Nedelcu FD, Toader MA, Sora SM, Tica A, Ferastraoaru DE, et al. Primary immunodeficiencies of the B lymphocyte. J Med Life. 2010;3(1):60-3.
22. Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, et al. Progression of Selective IgA Deficiency to Common Variable Immunodeficiency. Int Arch Allergy Immunol. 2008;147:87–92.