Immunol Genet J, Vol. 4, No. 2, June 2021, pp.109-118 **DOI: https://doi.org/10.18502/igj.v4i2.9987**

Original Article

Descriptive Study of 123 Symptomatic Patients with IgA Deficiency: A Retrospective Case Series Study

Mohammad Hassan Bemanian[1], Saba Arshi[1], Mohammad Nabavi[1], Morteza Fallahpour[1], Sima Shokri[1], Ali Alimohammadi[2], Nahid Chezanisharahi[3], Fatemeh Atashrazm[1], Vahid Bakrani[1], Javad Nazari[4*]

[1] *Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran*
[2] *Department of Forensic Medicine, School of Medicine, Arak University of Medical Sciences, Arak, Iran*
[3] *Arak University of Medical Sciences, Arak, Iran*
[4] *Department of pediatrics, school of medicine, Arak University of Medical Sciences, Arak, Iran*

Received: 07 May 2021; Accepted: 13 June 2021

Abstract

Background: IgA deficiency (IgAD) is the most common primary immunodeficiency, which is caused by a defect in IgA antibody production. Most of the patients are asymptomatic. However, patients can present various manifestations. This study was designed to assess the clinical and laboratory manifestations of symptomatic patients with IgA deficiency.

Method: A group of 123 patients with IgA deficiency referred from all over the country to the national immunodeficiency registration center were entered and followed in this study. The data including demographic characteristics, clinical manifestations and laboratory findings recorded at the registry and also the follow-up visits were extracted.

Results: The mean age of studied patients was 17.1 years old. Regarding gender, 45 patients (36.5%) were female. The most common clinical presentations included upper respiratory tract infections in 22 (17.9%), enteropathy in 9 (7.9%), allergic rhinitis in 11 (8.9%), sepsis in 4 (3.3%) patients. Four cases of leukopenia with white blood cell (WBC) <4,000/µl and 21 cases of leukocytosis with WBC> 10,000/µl were observed based on the laboratory results. Moreover, IgG2 and IgG4 in 2 and 11 patients were less than normal rate for their age, respectively.

Conclusion: Although IgA deficient patients are almost always asymptomatic, clinical manifestations such as recurrent sinopulmonary infections, multiple autoimmune diseases, allergic respiratory and skin disorders, gastrointestinal diseases, and rarely severe life-threatening infections could occur.

Keywords: IgA Deficient Patients; Primary Immunodeficiency Disorder; Clinical Manifestations; Laboratory Results

***Corresponding Author:** Javad Nazari, MD
Department of pediatrics, school of medicine, Arak University of Medical Sciences, Arak, Iran
E-mail: javadnazari1972@gmail.com

How to cite this article
Bemanian MH, Arshi S, Nabavi M, Fallahpour M, Shokri S, Alimohammadi A, et al. Descriptive Study of 123 Symptomatic Patients with IgA Deficiency: A Retrospective Case Series Study. Immunology and Genetics Journal, 2021; 4(2): 109-118. DOI: https://doi.org/10.18502/igj.v4i2.9987

Introduction

IgA deficiency (IgAD) is the most common primary immunodeficiency, caused by a defect in IgA antibody production. This disorder which was firstly described in children with ataxia-telangiectasia was later identified as an isolated disease of immunoglobulin deficiency in the general population. The main pathology is a defect in the last parts of the lymphocyte differentiation. The global prevalence of this disease varies in different countries with distinct races, for example, the reported prevalence in Iran which is 1:651. However, most studies express this epidemiological index with a prevalence of 1 in 500 (1, 2).

Though a large number of IgA deficiency subjects are often asymptomatic, some individuals show clinical manifestations including recurrent infections, allergies and autoimmune disorders (3). Patients can present various manifestations such as mild recurrent sinopulmonary infection, gastrointestinal infection, disorders such as celiac disease, allergies, autoimmunity disorders like Grave's disease and systemic lupus erythematous. Moreover, the patients are prone to progress in common variable immunodeficiency (CVID) and malignancies with a higher incidence (1, 2, 4).

The accurate pathogenesis of IgA deficiency remains unknown, but it is presumed that impaired immunoglobulin class switching to IgA in lymphocytes or maturational failure in producing IgA might play a role (5). Studies have shown that there are two subclasses for IgA. IgA1 is the main subclass and IgA2 is seen in two forms, serum and secretory IgA. Serum IgA is the monomer form of IgA which circulates in the bloodstream, while dimers are secreted and known as IgAs which were found in the mucosa of the respiratory, intestinal and genitourinary systems (6, 7).

IgA deficiency is known by a defect in serum IgA level <2 standard deviations (<2SD) (8) in patients older than 4 years old who have normal levels of other immunoglobulins. Moreover, other immunodeficiency diseases including hypogammaglobulinemia, T-cell defects and antibody production impairment are excluded. Nonetheless, sometimes it might be associated with non-prominent T cell defects (6). Deficiencies in the function of helper and suppressor T cells in these IgAD patients can also be observed. In addition, defects in some parts of the cytokine system have been suggested (9).

There is no specific treatment for this disease. Different modalities for treatment have been taken into account including education, antibiotic prophylaxis, prescribed for cases with an increased incidence of infection, also the administration of polyvalent pneumococcal vaccines and finally, intravenous or subcutaneous immunoglobulin replacement therapy due to immunomodulatory effects of IVIG. There are some cases of IgAD, who have IgE against IgA antibody and may develop anaphylaxis after transfusion of blood products (1).

Given the high prevalence of IgAD and the fact that sometimes this disorder is associated with very severe manifestations, this study was carried out to assess clinical and laboratory manifestations of patients with IgAD and help in the subsequent care and monitoring of these patients.

Materials and Methods

This survey was performed on 123 patients with symptomatic IgA deficiency, aged between 1.5 and 48 years old, identified in various academic centers across the country by physicians experienced in evaluating immune-compromised patients and referred to the Iranian PID Network (IPIN). The data of these patients had been collected in the database of the center and their follow-up had done periodically. IgA deficiency was diagnosed as a complete or severe deficiency in serum IgA. Patients who did not sign the informed consent nor had been regularly followed at the research center for immunodeficiency were excluded from the study.

In addition to collecting data from the registry system, a comprehensive questionnaire, designed by the authors, was completed for all patients at the time of diagnosis. The data collected included the patients' age and gender, the date of first symptoms appeared, the duration between the onset of symptoms and the final diagnosis, family history of the immunodeficiency diseases and unexplained deaths. The first manifestations of the disease in the patients were identified and classified into the groups of respiratory diseases, gastrointestinal diseases, skin lesions and others. The last group included those who presented with

Table 1. Demographic characteristics of IgA deficiency disease patients

Parameters	Total patients
Sex ratio, M/F (%)	78(63.4%)/45(36.5%)
Family history (n=99)	8(8.1%)
Consanguinity (n=101)	42(41.6%)
Dead (%)	2 (1.62%)
Current age (y), Mean(SD)	17.1 (10.1%)
Range (n=123)	(1.5- 48.0)

M, male; F, female; y, year; n, number

serious and severe infections that did not fit any of the groups. Besides, the recurrence number of otitis, pneumonia and sinusitis in the group who experienced frequent sinopulmonary infections, was recorded.

All symptoms, signs, manifestations, as well as the diagnosis of any clinical problems, reported by the patients or physicians, were recorded at each follow-up visit. Moreover, para-clinical data documented in the registry database, including complete blood count (CBC), IgG2, IgG4 tests were surveyed and compared.

Statistical Analysis

Descriptive statistics were used to describe the basic features of the data, including frequency, mean and standard deviation (SD), minimum and maximum (10). All analyses were carried out using SPSS 22.0 software.

Results

Demographic data

A total number of 123 patients were enrolled in the project. At the time of the study, two of them had died and the rest were alive. The mean age of the 121 patients, who were alive, was 17.1 years (between 1.5 to 48 years old and SD 10.14). Regarding gender, 78 (63.4%) patients were male and 45 (36.5%) were female. Totally, 8 patients had a family history of a similar illness, and 42 (41.6%) had a history of parental consanguinity (**Table 1**).

First Presentation

The results indicated that the first manifestations among the symptomatic group included a wide variety of clinical symptoms. The most prevalent symptoms were divided into four categories of respiratory diseases, gastrointestinal diseases, skin lesions, serious infections and others. Upper respiratory infections were the most common respiratory manifestations with 19 cases (15.4%). Then, pneumonia with 15 cases (12.2%), nonspecific cough with 11 cases (8.9%), otitis with 4 cases (3.3%), sinusitis with 5 cases (4.1%) and asthma with 2 cases (1.6%) were the other most prevalent problems. Among gastrointestinal manifestations, diarrhea with 15 cases (12.2%) was the most common. Other manifestations in this category included inguinal hernia; blood in stool, appendicitis, and aphthous stomatitis each one with 1 case and oral candidiasis with 1 case. Eczema with 7 cases (5.7%) was the most prevalent skin manifestation in these patients. The most critical initial clinical manifestations were serious infections including 1 case with meningitis (0.8%) and 3 cases with systemic BCG infection (2. 4%) (**Figure 1**).

Another interesting issue was the recurrence of common infections, expected in patients with humoral immunodeficiencies, such as otitis, sinusitis and pneumonia, which could occur frequently when there is isolated IgA deficiency. Investigation of the frequency of infection in the study group showed that some patients experienced numerous infections, up to 3 times and even more in some cases. Among 123 studied patients with IgA deficiency, 40, 30 and 19 people were affected by sinusitis, pneumonia and otitis infections, respectively (**Table 2**).

Clinical manifestations after the onset of disease

The patients were classified based on clinical manifestations into several groups and subgroups. The main groups included respiratory manifestations, gastrointestinal manifestations, allergic disorders, skin manifestations, serious

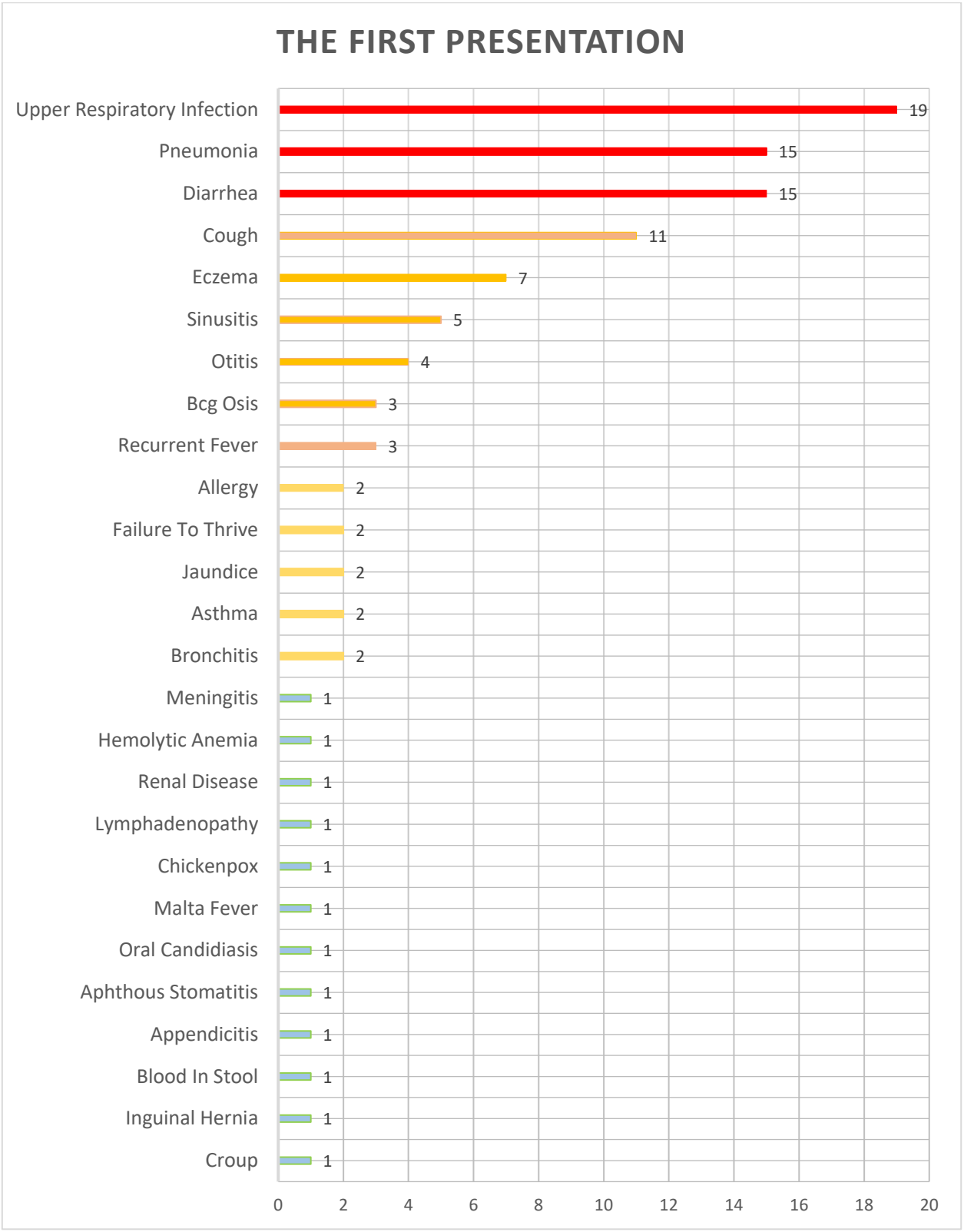

Figure 1. The first presentation of IgA deficiency patients

and severe infections, autoimmune disorders (**Figure 2**). The most prevalent manifestations were reported in the respiratory disorders group, of which 22 individuals (17.9%) had upper respiratory tract infections. The other most common manifestations were enteropathy with 9 patients (7.9%) among the gastrointestinal symptoms group, allergic rhinitis with 11 patients (8.9%) among the allergic disorders, and sepsis with 4 patients (3.3%) among the serious

Table 2. frequency of upper and lower respiratory tract infections in IgA deficiency patients

Parameters	Total patients
Otitis media	
1time	6
2time	3
3time	1
More than 3 times	9
(n=19)	
Pneumonia	
1time	21
2time	3
3time	2
More than 3 times	13
(n=39)	
sinusitis	
1time	22
2time	7
3time	0
More than 3 times	11
(n=40)	

infections group.

Upper and lower respiratory infections and asthma with 22 (17.9), 11 (8.9) and 8 (6.5) cases, respectively, were the most common conditions in the category of respiratory manifestations. In the group with gastrointestinal symptoms, after enteropathy, diarrhea was the most common with 7 cases (5.7%), followed by, jaundice (icterus), infantile colic, oral candidiasis, gastroesophageal reflux and hepatomegaly each one with 3 cases (2.4%) and aphthous stomatitis, blood in stool, celiac, splenomegaly each one with 2 cases (1.6%) and irritable bowel syndrome with 1 case (0.8%) were found.

In the field of allergic manifestations, allergic rhinitis with 10 cases(8.1%) was the most common manifestation and other manifestations including food allergy, allergic conjunctivitis and drug allergy had 11 cases (8.9%). Skin manifestations were seen in 27 cases (22%) of patients including urticaria (hives) as the most common one and then eczema, unclassified cutaneous rash, scaling, skin itching, and erythema. Serious infections with a wide range of manifestations were observed, sepsis with 4 cases (3.3%), followed by pulmonary abscess and septic arthritis each one with 2 cases (6.1%) and then tympanic perforation, cellulitis, liver abscess, TB, osteomyelitis, pseudomonas infection, meningitis, skin abscess, shigellosis and malta fever each one included 1 case (0.8%).

Among autoimmune disorders, autoimmune hemolytic anemia with four cases (3.3%) and then hair loss, diabetes mellitus and vitiligo each with two cases (6.1%) and hypothyroidism with one case (0.8%) were found in patients. Interestingly, in the subsequent follow-up of the patients, it was revealed that several other manifestations such as febrile convulsion and renal disease including nephrotic and nephritic syndrome were seen (**Figure 2**). The results of follow-up visits indicated that some patients showed recurrent upper and lower respiratory tract infections such as sinusitis, otitis and pneumonia. About18 patients had recurrent sinusitis, more than one up to twelve times during their lifetime (**Table 2**). Other clinical manifestations such as noninfectious diseases as well as eczema are shown in detail in **Figure 1**.

Laboratory results

Regarding the patients' laboratory tests, CBCs showed that the leukocyte count ranged from 1070 to 55000/µl. Leukopenia (WBC <4,000/µl) was diagnosed in 4 cases and 21 cases were classified as leukocytosis (WBC> 10,000/µl). Moreover, the status of lymphocytes

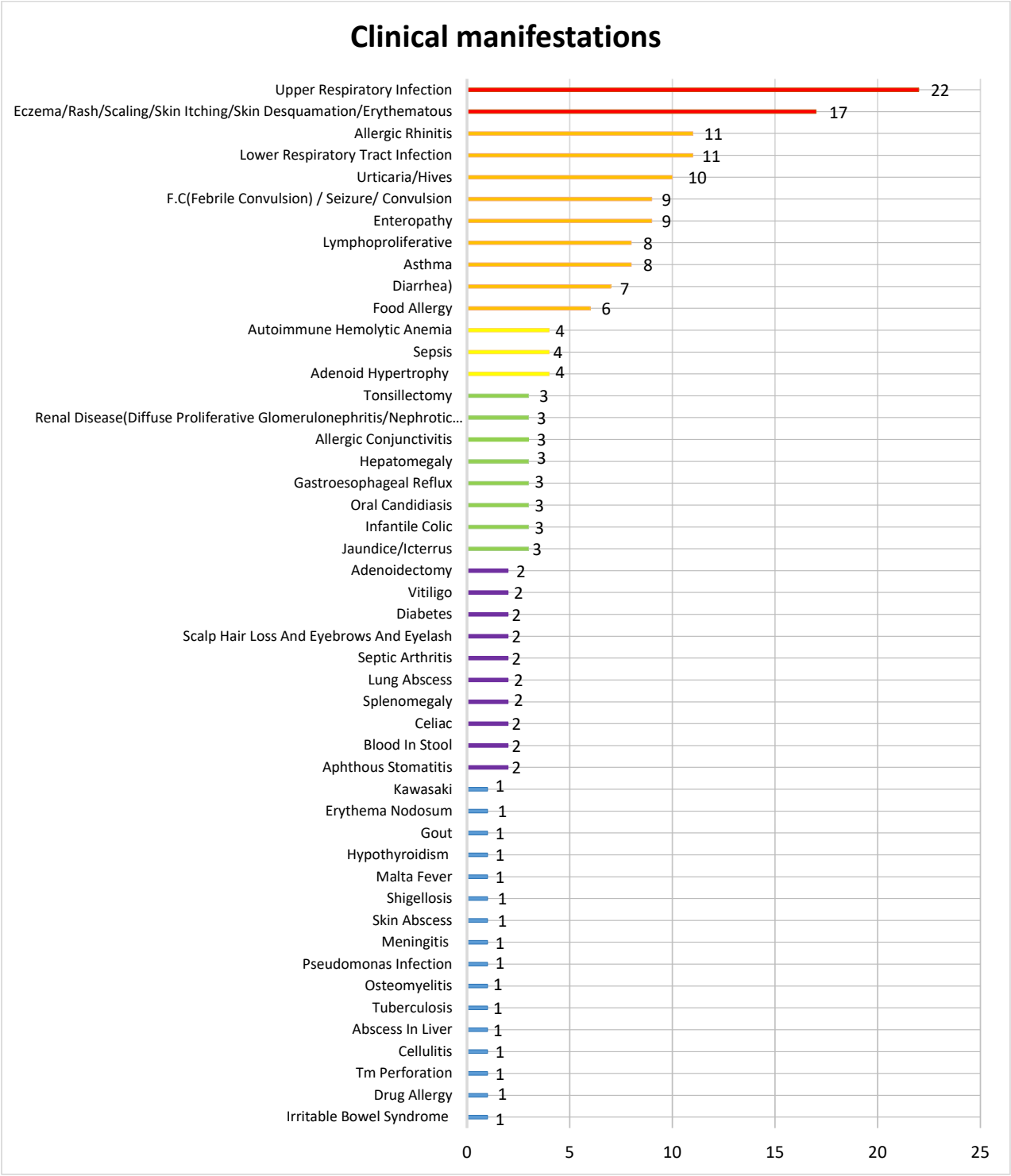

Figure 2. Clinical Manifestations of Patients with IgA deficiency disease.

and neutrophils was determined in this study. Accordingly, lymphopenia (lymphocyte <1500/µl) and neutropenia (neutrophil <1500/µl) were found to be significant in 7 and 4 of the patients, respectively. Also, 6 of the patients had thrombocytopenia (platelets <150,000/µl). The summary CBC results are shown in (**Table 3**).

In this study, in addition to IgA level which is less than normal and which is considered as a diagnostic main criterion, two subclasses of IgG2 and IgG4 which are important in these patients were examined. Therefore, it was observed that

Table 3. Laboratory Results with IgA deficiency disease

Parameter	Total patients
WBC range	(1070-55000)
Leukopenia,	4
normal,	74
Leukocytosis	21
Lymphocyte range	(336-32450)
Lymphopenia	7
Neutrophil Lymphocyte range	(364-28609)
Neutropenia	4
Hemoglobin range	?
Normal(Men),	24
Anemia(Men),	33
Normal(Female),	21
Anemia(Female)	3
Platelet range	(10000-633000)
Thrombocytopenia	6
Normal	56
Thrombocytosis	11
IgG2(64-495) range	(3.5-2500)
Under normal	2
Normal	24
Above normal	6
IgG4(11-157) range	(1-412)
Under normal	11
Normal	17
Above normal	3

WBC: Under 4000(Leukopenia), Between 4,000 and 10,000(normal), Above 10000(Leukocytosis)
Lymphocyte: Under 1500 (Lymphopenia)
Neutrophil: Under 1500(Neutropenia)
Hemoglobin: Anemia (Men) (Under 13gr/dl), Anemia (Female) (Under 11gr/dl)
Platelet: Under 150000(Thrombocytopenia), Between 150000 and 450000(normal), Above 450000(Thrombocytosis)
IgG2 (64-495): Under 64(Under normal), Between 64 and 495(normal), Above 495(Above normal)
IgG4 (11-157): Under 11(Under normal), Between 11 and 157(normal), Above 157(Above normal)

IgG2 in 2 cases and IgG4 in 11 cases were less than normal compared to the normal range for these patients' age, which makes other differential diagnoses such as common variable immunodeficiency more likely (**Table 3**).

Discussion

Primary immunodeficiency disorders (PIDs) usually are the result of a genetic defect in the immune system of patients that causes chronic and serious infections and if left untreated, can be life-threatening. About 430 single-gene underlying phenotypes have been described with a spectrum of manifestations such as infection, malignancy, allergy, autoimmunity and autoinflammation. Thanks to the use of the next-generation sequence technique, there has been a dramatic increase in the number of known disorders (11). This trend leads to several new innate immunity errors in one or a few relatives, which may not provide a complete and accurate picture of its prevalence and phenotype (12). IgAD is a relatively common primary immunodeficiency that is associated with some clinically significant complications. Interestingly, infectious diseases, allergic disorders and autoimmune conditions are more common among IgAD populations (13).

IgA deficiency patients are known as individuals whose serum IgA level is less than 2SD, with normal levels of serum IgG and IgM and no other cause for immunodeficiency. There is no exact definition for IgAD in different

societies because IgA levels vary to such an extent with ethnicity and seasons that the prevalence of IgAD drop in winter or IgA levels are also known to be associated with metabolic syndrome, heavy drinking and liver fibrosis. In this survey, serum immunoglobulin concentration was determined. It indicated that all of the patients had a level of IgA less than 50 with normal IgG and IgM, other immunodeficiency syndrome rolled out by more investigation. (Of course, it should be noted that patients' information was based on the data recorded in the registry and could not be further investigated and their additional information was not obtained in subsequent follow-ups.

Therefore, some patients with suspected IgA deficiency were recorded in the initial investigation even with age under 4, when it was sometimes observed that manifestations such as severe infections indicated that additional investigation was needed, but these studies were not available.) Based on a study by Kardar et al. normal IgA level of the Iranian population was about 72–375 mg/dl (8, 13). Of note, a subgroup of IgAD patients with selective IgA deficiency (SIgAD) is diagnosed in patients more than 4 years old, whose IgA level is less than 7 mg/dL and have normal IgG and IgM serum levels in addition to ruling out the other causes of hypogammaglobulinemia. However, in this survey, we did not consider the concepts of SIgAD and we considered the general concept of IgA deficiency including both partial IgAD and SIgAD patients, as described above (14).

A study conducted by Cataldo et al. showed that celiac disease is more common in patients with IgAD and silent forms of celiac are more frequent in children than adults. Moreover, they found that patients with IgAD are more susceptible to infections and allergic diseases (15). In this study, we observed two cases of celiac disease among the 123 examined patients (about 1.6%). The prevalence of celiac disease in the Asian population is between 0.1% up to 3.2%. Therefore, our findings have concordance with its prevalence in the normal population. However, the reason of this low rate is that some patients and not all 123 patients in our study were undergone a thorough investigation for celiac disease. In addition, the seronegative form of celiac that could be found in the endoscopic examination was not ruled out, as endoscopy was not performed for all the enrolled patients in this study (16).

The results indicated that 21 cases (17%) of IgAD patients showed allergic disorders, among which, the most common included allergic rhinitis, food allergies, allergic conjunctivitis and drug allergies, respectively. A study conducted by CelalÖzcan et al. showed that 51.3% of patients with hypogammaglobulinemia had a history of allergic rhinitis, but our patients had 11% allergic rhinitis. It should be noted that this difference could be explained because they checked allergic rhinitis in all patients with humoral immunodeficiency not just IgAD (17). Regarding critical infectious diseases, we found that about 18 patients (14.6%) developed serious infections during the course of their disease, among which, sepsis was the most common, then lung abscess, septic arthritis, and also other infections such as cellulitis, liver abscess, tuberculosis, osteomyelitis, pseudomonas infection, meningitis, skin abscess, shigellosis, and brucellosis were observed in the patients. This was a significant finding because serious infectious diseases are expected to be rare manifestations in patients with IgA deficiency (2).

In a study by Jelena Zivkovich and colleagues, they looked at allergic and respiratory disorders in children with IgA deficiency and indicated that allergic disorders and infectious diseases have a higher prevalence compared with the control group. They indicated that recurrent infections of the respiratory tract were the most common clinical manifestation in IgA deficient patients. Furthermore, there was a higher prevalence of allergic diseases, specifically asthma, allergic rhinitis and atopic dermatitis in children with low serum IgA (18). In the current study, we observed that IgA deficiency often causes mild disease with fewer complications and morbidities. A high rate of pneumonia (57%) has been reported in a study in children affected with low serum IgA. They found recurrent infections in 24.5% and bronchiectasis in 14.0% (19). These findings were in agreement with our study. In comparison, in Ziukovich's study, 12% of upper respiratory infections were reported among their patients, while in our study, the initial manifestations of the disease were about 19 patients (4.15%) and manifestations after the onset of disease were 22 patients (17.9%) with upper respiratory tract infections that were close to Ziokovic's findings.

In a systematic review performed by D. Odineal and Gershwin, they found that recurrent infections were present in 24.5% of patients with IgA deficiency. They indicated that while 17.5% of children with IgAD had recurrent URIs, 11.8% had recurrent otitis, 17.8% had pneumonia, and 6.0% had recurrent pneumonia (13). The results of our study indicated that 26 patients (21.1%) have pneumonia as both initial and subsequent manifestations and 13 patients (10.5%) have recurrent otitis,18 (14.6%) have recurrent pneumonia and 18 individuals (14.6%) have recurrent sinusitis among IgA deficiency patients. In other words, a total of 49 patients (39.8%) had recurrent infections. This indicates that the results of Odineal and Gershwin study were similar to the results of the current study in some items and there are differences in some other cases. This could be explained by the impact of sample size, ethnicity, or the difference in the accuracy of documentation.

Conclusion

Although IgA deficient patients almost always are asymptomatic, clinical manifestations such as recurrent sinopulmonary infections, multiple auto-immune diseases, allergic diseases related to the respiratory system, GI diseases, allergic skin diseases and rarely severe life-threatening infections could occur. Upper and lower respiratory diseases, gastrointestinal disorders, allergic diseases, autoimmune disorders and rarely serious bacterial infections were clinical features of patients. More investigations and genetic sequencing are needed for the exact diagnosis of patients with low IgA and suspected of IgA deficiency.

Conflict of interest

There is no conflict of interest.

References

1. 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.
2. Latiff A H,Kerr M A. The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem. 2007;44(Pt 2):131-9.
3. Kumar V, Jarzabek-Chorzelska M, Sulej J, Karnewska K, Farrell T,Jablonska S. Celiac disease and immunoglobulin a deficiency: how effective are the serological methods of diagnosis? Clin Diagn Lab Immunol. 2002;9(6):1295-300.
4. Ludvigsson J F, Neovius M,Hammarström L. Association between IgA deficiency & other autoimmune conditions: a population-based matched cohort study. J Clin Immunol. 2014;34(4):444-51.
5. 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(2):87-92.
6. Bagheri Y, Sanaei R, Yazdani R, Shekarabi M, Falak R, Mohammadi J, et al. The Heterogeneous Pathogenesis of Selective Immunoglobulin A Deficiency. Int Arch Allergy Immunol. 2019;179(3):231-46.
7. Yazdani R, Latif A, Tabassomi F, Abolhassani H, Azizi G, Rezaei N, et al. Clinical phenotype classification for selective immunoglobulin A deficiency. Expert Rev Clin Immunol. 2015;11(11):1245-54.
8. Kardar G A, Shams S H, Pourpak Z,Moin M. Normal value of immunoglobulins IgA, IgG, and IgM in Iranian healthy adults, measured by nephelometry. J Immunoassay Immunochem. 2003;24(4):359-67.
9. Nurkic J, Numanovic F, Arnautalic L, Tihic N, Halilovic D,Jahic M. Diagnostic Significance of Reduced IgA in Children. Med Arch. 2015;69(4):236-9.
10. Moradzadeh R, Nadrian H, Golboni F, Kazemi-Galougahi M H,Moghimi N. Economic inequalities amongst women with osteoporosis-related fractures: an application of concentration index decomposition. Health Promot Perspect. 2016;6(4):190-95.
11. Bousfiha A, Jeddane L, Picard 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.
12. Modell V, Orange J S, Quinn J,Modell F. Global report on primary immunodeficiencies: 2018 update from the Jeffrey Modell Centers Network on disease classification, regional trends, treatment modalities, and physician reported outcomes. Immunol Res. 2018;66(3):367-80.
13. Odineal D D,Gershwin M E. The Epidemiology and Clinical Manifestations of Autoimmunity in Selective IgA Deficiency. Clin Rev Allergy Immunol. 2020;58(1):107-33.
14. Bonilla F A, Khan D A, Ballas Z K, Chinen J,

Frank M M, Hsu J T, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015;136(5):1186-205 e1-78.
15. Cataldo F, Marino V, Ventura A, Bottaro G,Corazza G R. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and "Club del Tenue" Working Groups on Coeliac Disease. Gut. 1998;42(3):362-5.
16. El-Metwally A, Toivola P, AlAhmary K, Bahkali S, AlKhathaami A, AlSaqabi M K, et al. The Epidemiology of Celiac Disease in the General Population and High-Risk Groups in Arab Countries: A Systematic Review. Biomed Res Int. 2020;2020:6865917.
17. Özcan C, Metin A, Erkoçoğlu M,Kocabas C N. Bronchial hyperreactivity in children with antibody deficiencies. Allergol Immunopathol (Madr). 2015;43(1):57-61.
18. Živković J, Lipej M, Banić I, Bulat Lokas S, Nogalo B, Lulić Jurjević R, et al. Respiratory and allergic disorders in children with severe and partial immunoglobulin A immunodeficiency. Scand J Immunol. 2019;90(6):e12828.
19. Dominguez O, Giner M, Alsina L, Martin M, Lozano J,Plaza A, editors. Clinical phenotypes associated with selective IgA deficiency: a review of 330 cases and a proposed follow-up protocol. Anales de pediatria (Barcelona, Spain: 2003); 2012.