Prevalence of Immunoglobulin Deficiency Among Patients Screened for Celiac Disease: A Retrospective Cohort Study

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Abstract

Objectives: Selective immunoglobulin A deficiency (SIgAD) is characterized by an isolated deficiency of serum immunoglobulin A (IgA) while Immunoglobulin G (IgG) and Immunoglobulin M (IgM) remain normal. Symptoms range from being asymptomatic to recurrent infections. We examine the prevalence of low IgA as well as SIgAD among patients screened for celiac disease in Oman. ***Methods:*** A retrospective cohort study was conducted at Royal Hospital, Oman, between 2005 and 2022. Omani citizens aged > 1 year who were screened for celiac disease using anti-tissue transglutaminase (anti-TTG) IgA and analyzing IgA cut-offs were included.We applied a logistic regression model to the variables. ***Results:*** A total of 9,615 patients underwent screening for celiac disease. After exclusion, 114 individuals (1.2%) had SIgAD, based on age-dependent IgA levels. Of these 34% had confirmed SIgAD (normal IgG and IgM levels) while the remaining 66% had no further IgG and IgM testing. Among the 114 patients, 57% were over 14 years old, followed by 53% of the cases between 6-14 years. The prevalence of IgA deficiency was 1.2%. Patients between 6-14 years (p=0,003) and > 14 years (p<0,001) were significantly more likely to have IgA deficiency than those aged 1-2 years. Of the 39 patients with selective IgA deficiency, 11 underwent further testing with anti-TTG IgG antibody, with only 1 testing positive for celiac diseaseconfirmed by oesophageal gastroduodenoscopy (OGD) and histopathology. The remaining 28 patients did not undergo further celiac disease workup, including anti-TTG IgG antibody, OGD or genetic testing. ***Conclusions:*** The prevalence of IgA deficiency was substantial, and most patients with SIgAD and negative celiac disease were not subjected to IgG anti-TTG tests or an OGD biopsy to verify the existence of the illness. Referral to an Immunologist is recommened, particularly when IgG and IgM are low, or when the patient reports recurrent infections, to rule out immunodeficiency.

Keywords: Immunoglobulin A Deficiency; Selective Immunoglobulin A deficiency; SIgAD; Inborn errors of immunity; Celiac Disease; Panhypoglobulinemia; Oman

Introduction

Immunoglobulin A (IgA) deficiency is characterized by low serum IgA. This could be selective (sIgAD), where patients have low IgA while the rest of the immunoglobulins, immunoglobulin M (IgM) and Immunoglobulin G (IgG), remain normal or associated with other immunoglobulin deficiencies.[1] SIgAD is one of the most common inborn errors of immunity. Studies have demonstrated that one in every 500 caucasian people has SIgAD.[1] Indeed, the rate at which SIgAD occurs varies depending on the ethnic group.[2] SIgAD is defined as an isolated serum IgA

deficiency in the presence of normal immunoglobulin M (IgM) and immunoglobulin G (IgG).[3] The majority of patients with SIgAD are asymptomatic; less than one-third of patients present with recurrent infections, such as sinopulmonary infections, gastro-intestinal infections commonly associated with giardiasis, autoimmune conditions, allergic disorders, or anaphylactic transfusion-related reactions.[1,4,5]

The most significant risk factor for having IgA deficiency is a family history of either IgA deficiency or the more profound defect in antibody function, common variable immunodeficiency (CVID). Affected individuals' first-degree relatives are 50 times more likely to experience the disease themselves. Affected mothers are more likely to transmit the disease to their offspring.[1]

Globally, the prevalence varies significantly depending on ethnic backgrounds. In the Arabian Peninsula, the incidence is approximately 1 in 143 individuals, while in Spain, it is 1 in 163. In Nigeria, the incidence is approximately 1 in 252, whereas in England and Brazil, it's 1 in 875 and 1 in 965, respectively. Interestingly, the incidence is notably lower among Asian populations, ranging from approximately 1 in 2,600 to 1 in 5,300 in China and from 1 in 14,840 to 1 in 18,500 in Japan.[6] A study published in 2002 reported that the prevalence of IgA deficiency in patients with celiac disease ranges from 2 to 3%, representing a 10- to 15-fold increase compared to the general population.[7] Similar findings were observed in a study conducted on the Spanish population, where the incidence was equally prevalent among both adults and children.[8] Likewise, a study by E. Valleta in Italy reported a prevalence of 2.6%.[9] A study conducted in Saudi Arabia reported a prevalence of IgA deficiency of 700/100,000 (0.7%).[10]

Two studies on Primary immunodeficiency in Oman reported the prevalence of selective IgA deficiency in their cohorts of patients. Al Temimi et al. found that only one patient out of 90 with primary immunodeficiency had selective IgA deficiency.[11] The second study by Al Farsi et al. showed that selective IgA deficiency was found in 2 of 239 patients with immunodeficiency (0.9%).[12] Nevertheless, no other research has been conducted in Oman that specifically studied the prevalence of IgA deficiency in the general population. Due to the increase in referrals related to low IgA levels detected incidentally on celiac screening, we decided to investigate the prevalence of IgA deficiency in Omani patients undergoing evaluation for celiac disease in Oman. Celiac disease screening involves testing for anti-tissue transglutaminase (anti-TTG) IgA and assessing total blood IgA levels in the same patient. Those with low IgA should have an alternative tests such as anti-tissue transglutaminase IgG (anti-TTG IgG) and/or duodenal biopsy as the gold standard. Due to the geographical variation in the prevalence of IgA deficiency with the lack of prevalence data in Oman, we aimed to look at the prevalence of IgA deficiency in Oman. This information will be of value in counseling patients about this result and for allocating resources such as creating an action plan when such individuals are identified on routine celiac screening. This may include a reflex test to screen for all other immunoglobulins, and if the results are normal to inquire about recurrent infections with a referral to Immunology when other Immunoglobulins are low and or when there is a history of recurrent chest, sinus, and/or ear infections. This will also help raise awareness amongst physicians who request immunoglobulins, especially IgA, for other various reasons such as blood transfusion-related reactions.

Methods

A retrospective cohort study was conducted at the Royal Hospital, a tertiary hospital in Muscat, Oman, spanning the period between January, 2005 to December, 2023.

The study recruited Omani citizens in Oman over the age of 1 year who were screened for celiac disease using anti-tissue transglutaminase (anti-TTG) IgA and total IgA levels. We excluded all patients younger than 1 year of age due to the possibility of transient hypogammaglobulinemia in infancy, as well as patients already diagnosed with panhypogammaglobulinemia (low IgA, IgG, and IgM).

Demographic, clinical and laboratory data were extracted from the electronic medical records including age group [1-2 years, 2-6years, 6-14years and > 14years], gender, comorbidities [Celiac disease, Inflammatory bowel disease, irritable bowel syndrome, diabetes mellitus (DM), thyroid diseases, chronic anemia], anti-TTG IgA, IgA levels [cut off values were age dependent, 0.33 g/L, for age < 2 years; 0.37 g/L for age 2-6 years; 0.58g/L for age 6-14 years and 0.71g/L for those older than 14 years] according to Caliper Paediatric Reference Intervals (seventh edition) edited by Steven Soldin et al.,[13] and the Immunoglobulins Immunoglobulin G and M according to the cut-off value for age [Table 1]. All patients known to have pan-hypogammaglobulinemia, defined as a reduction in 2 or more immunoglobulin levels, IgA, IgG, and IgM, were excluded from the study.

Anti-TTG IgA was measured using ELISA (Euroimmun, Germany) with cut-off determined as 20 U/ml. The quantification of immunoglobulin A was performed at the biochemistry laboratory at the Royal Hospital in Oman using the Polyethylene Glycol (PEG)-enhanced immunoturbidimetric method. The analytical system employed for this purpose utilized the Abbott assay (Abbott, USA) until 2019 and the Siemens Atellica assay (Siemens, Germany) from 2020 to the end of the study period in 2022. The PEG-enhanced immunoturbidimetric method offers a sensitive and accurate measurement of IgA levels, ensuring reliability and consistency in our analysis. The cutoff values were determined based on age groups according to the Caliper Paediatric Reference Intervals (seventh edition) edited by Steven Soldin et al.[13]; for individuals under 2 years old, the cutoff was set at less than 0.33 g/L, for ages 2 to less than 6 years it was 0.37 g/L, for ages 6 to less than 14 years it was 0.58 g/L, and 0.71g/L for those older than 14 years [Table 1].

Table 1: Immunoglobulin IgA in (g/L) reference intervals (both gender) based on the age group

Age	**IgA Normal Range (g/L)**
1 to 2 years	<0.33 - 1.7
2 to <6years	0.37 - 1.78
6 to <14 years	0.58 - 2.51
>14years	0.71 - 3.35

Data were analyzed, and only patients with IgA deficiency were included in the calculation, while those with panhypogammaglobulinemia were excluded. In addition, an analysis of variation across different age groups and genders was conducted. The collected data were subjected to comprehensive statistical analysis using SPSS (version 23.0, IBM Corp., Armonk, NY), including descriptive statistics and, where applicable, inferential statistics.

The Royal Hospital Ethical Committee (MoH/CSR/23/27616) approved the study which was conducted in accordance with ethical standards. We strictly maintained patient confidentiality and privacy throughout the research process. This study also adehered to the Declaration of Helsinki.

Results

A total of 9,615 patients underwent screening for celiac disease,of which 114 individuals (1.2% of the total) had low IgA levels based on their age-dependent IgA levels. Of these, 39 (34%) had confirmed selective IgAD (normal IgG and IgM levels), while the remaining 75 patients (66%) had no further IgG and IgM testing done. [Figure 1] Of the 114 patients, more than half half (57% of the cases) were over 14 years old and 53% were 14 years old or younger. There was no significant gender disparity among these cases, with 63 (55%) females and 51 (45%) males affected. 22 (13%) patients were between 1 and 2 years, 17 (15%) individuals were between 2-6 years, 23 (20%) people were between 6-14 years, and the vast majority of the cases were above 14 years of age [59 (52%) cases] [Table 2].

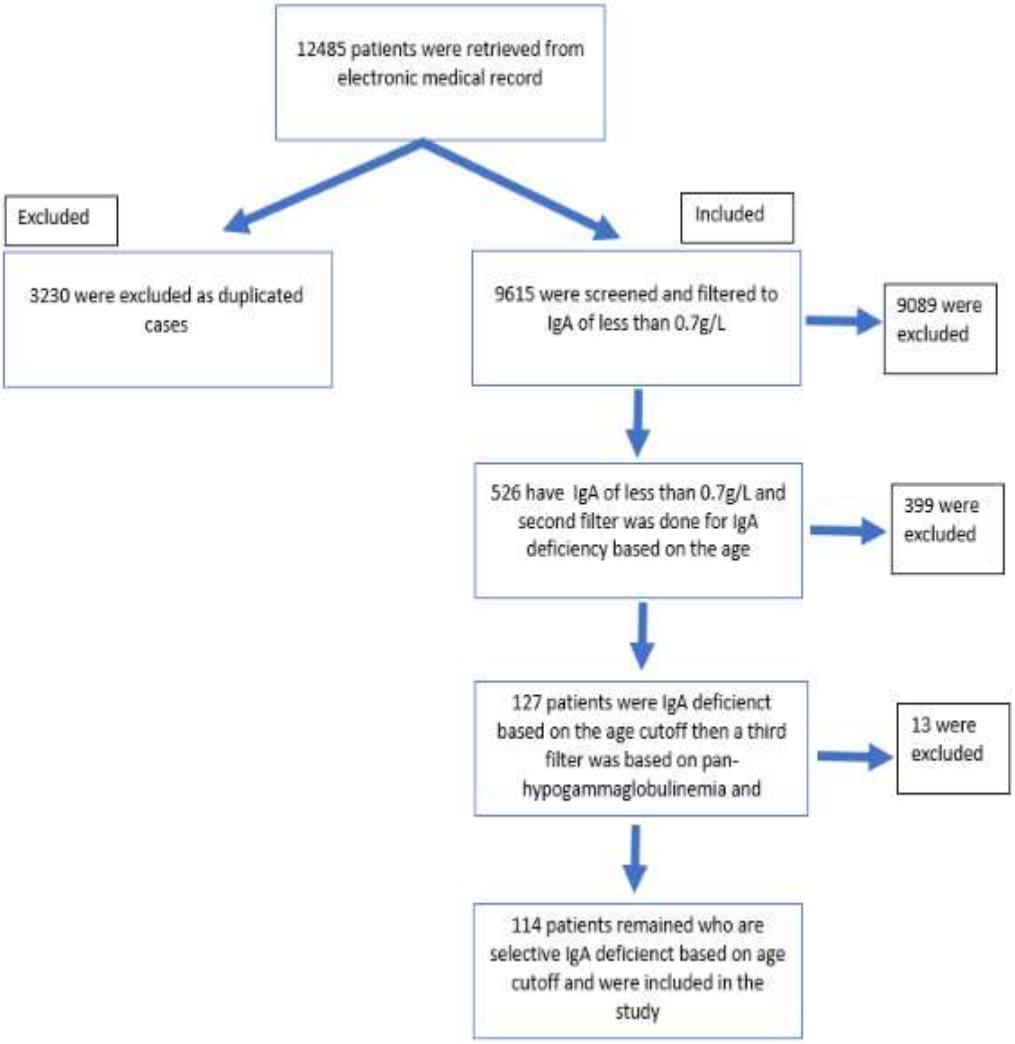

Figure 1. Guiding the Selection Process for Screened Patients

Table 2: Demographic characteristics of the patients with IgA deficiency

Gender	**Male n(%)**	**Female n(%)**	**Total n(%)**
Total	51(45)	63 (55)	114 (100)
Age distribution based on gender			
1- 2years	5 (4)	10 (9)	15 (13)
2 – 6years	10 (9)	7 (6)	17 (15)
6 – 14years	10 (9)	13 (11)	23 (20)
>14years	26 (23)	33 (29)	59 (53)
Investigations			
Hypogammaglobulinemia	6 (5)	7 (6)	13 (11)
Confirmed Celiac Disease	2(2)	3 (3)	5 (4)
Reflexive Anti-Tissue IgG	6 (5)	5 (4)	11(10)
OGD	2 (2)	2 (2)	4 (4)
Biopsy	2 (2)	2 (2)	4 (4)

OGD: OesophagoGastroDuodenoscopy, IgG: Immunoglobulin G

The prevalence of IgA deficiency was 1.2 per 100 individuals, with a confidence interval ranging between 1% to 1.4%. Patients between 6-14 years ($p = 0.003$) and those above 14 years ($p < 0.001$) were significantly more likely to have low IgA than patients 1-2 years of age. There were no significant differences ($p > 0.05$) between males and females with and without IgA deficiency. However there was a significant difference in age categories

between the patients with IgA deficiency versus those without. Patients between 6 and14 years $p = 0.003$) and > 14 years ($p < 0.001$) were significantly more likely to have IgA deficiency than patients 1 to 2 years of age. Only 39 patients out of the 114 (34%) had further testing with other IgG and IgM levels and were normal, confirming selective IgA deficiency while the remaining 75 patients (66%) did not. Of the 39 patients with selective IgA deficiency, 11 underwent further testing with anti-TTG IgG antibody as the recommended serological test for patients with low serum IgA and only 1 was positive for celiac disease and underwent oesophageal gastroduodenoscopy (OGD) and histopathology confirming the diagnosis. The remaining 28 patients had no further celiac disease workup neither with anti-TTG IgG antibody testing, OGD, nor Human Leukocyte Antigen (HLA) DQ2 and HLA DQ8 typing for celiac disease. As for the 75 patients with low IgA and no testing for total IgG or IgM done, anti-TTG IgG antibody was not done. Only 13 of the 75 patients proceeded directly with OGD, and four showed histopathological evidence of celiac disease, while 9 were negative. Overall, the total number of confirmed celiac disease cases in the low IgA group was 5 out of 114 (4.4%); 24 patients out of the 114 (21%) underwent further workup for celiac disease, while the remaining 90/114 (79%) had no further workup. This is concerning as many patients may be missed, largely, due to a lack of awareness regardingthe normal anti-TTG IgA antibody levels in patients with low IgA deficiency and its implication for celiac disease screening. An alert should be raised in the system advising the request for immunoglobulin G and M measurement as well as anti TTG IgG antibody testing in view of the patient's low IgA level. A pathway to guide referral to an immunologist is crucial, particularly when the IgG and IgM levels are low or when the patient reports recurrent infections, to rule out immunodeficiency.

As for the indications for requesting celiac screening, 24 patients (21%) had gastrointestinal symptoms: diarrhea in 15 (21%), abdominal pain without bloating in 4 (4%), abdominal pain with bloating in 2 (2%), vomiting and diarrhea in 1(1%), abdominal pain with vomiting in 1(1%) and constipation in 1(1%), while 21 patients (18%) had celiac screening requested as part of anemia workup. Thirty patients (26%) were screened due to underlying comorbidities. mainly diabetes and thyroid disease. Interestingly, there was no clear indication for screening for celiac disease in 30 patients (26%).

Out of the 114 patients with low IgA, 24 (21%) had underlying type I DM, 8 (7%) had type II DM and an another 8 (7%) had thyroid disease. 4 (4%) patients had chronic anemia, 3 (3%) had inflammatory bowel disease, and 3 (3%) had irritable bowel syndrome [Table 3].

Table 3: Common Comorbidities in Patients with IgA Deficiency

Comorbidities	**Male (n, %)**	**Female (n, %)**	**Total (n, %)**
Type I DM	14(12%)	10 (9%)	24 (21%)
Thyroid disease	2 (2%)	6 (5%)	8 (7%)
Type II DM	3 (3%)	5 (4%)	8 (7%)
Chronic Anemia	3 (3%)	1 (1%)	4 (3.5%)
IBD	2 (2%)	1 (1%)	3 (2.6%)
IBS	1 (1%)	2 (2%)	3 (2.6%)

DM,Diabetes Mellitus, IBD: Inflammatory Bowel Disease, IBS: Irritable Bowel Syndrome

Discussion

IgA deficiency is associated with various autoimmune and inflammatory disorders of the gut. A 10- to 15-fold increased risk for celiac disease in SIgAD has been reported.[7] The link between these diseases may be genetic through shared HLA Haplotypes.[7] Our study revealed that the prevalence of IgA deficiency in Oman is 1.2 per 100 individuals (1.2%), with no observed gender disparity. The higher prevalence of IgA deficiency in our study population is largely due to the large sample size. This was calculated by studying the IgA levels of 9,615 patients not known to have celiac disease and who underwent screening for celiac disease for various indications, such as baseline screening for underlying comorbidities, including type 1 DM and thyroid disease screening (26%), followed by gastrointestinal complaints in (21%) patients and as workup for chronic anemia in 18% of patients. There was no clear documentation for the reason for celiac disease screening in 30 (26%) patients. A total of 114 patients out of 9,615 had low IgA levels. Over half (57%) were older than 14 years, followed by 53% of the cases between 6 and 14 years old. Of the 114 patients, only 39 (34%) had confirmed selective IgAD (normal IgG and IgM levels), while the remaining 75 patients (66%) did not undergo further IgG and IgM testing. Patients between 6-14 years (p=0.003) and > 14 years ($p < 0.001$) were significantly more likely to have IgA deficiency compared to patients 1-2 years of age. Only 24 out of the 114 with low IgA (21%) were properly screened for celiac disease. Of these 24 patients.5 (21%) had celiac disease (21%), confirming that patients with IgA deficiency are at a higher

risk of developing celiac disease. This is of concern as the remaining 90 out of the 114 (79%) did not undergo further testing for celiac disease,increasing the likelihood of missing cases that may be at risk for celiac disease.

We found that the prevalence of celiac disease in patients with low IgA is 21% (5 out of 24 patients with low IgA who were fully screened). The incidence, as reported in some studies conducted in other countries, ranges between 2-3%.[13] Studies have also demonstrated that SIgAD is the most common primary immunodeficiency disorder, based on community and blood donor studies.[6]

Other findings from global data provided by the Jeffrey Model Centers Network, 8,437 diagnosed SIgAD patients worldwide have prevalence rates that vary across continents: 5,492 patients in Europe, 1,704 in North America, 1,050 in Latin America, 115 in Asia, and 76 in Africa.[1] A study conducted in Saudi Arabia reported a prevalence of IgA deficiency of 700/100,000.[10] These figures highlight substantial variations in SIgAD prevalence, clearly influenced by ethnic backgrounds and geographical locations.

Two studies conducted in Oman on primary immunodeficiency diseases highlighted that phagocytic disorders were the most common conditions observed, followed by primary antibody deficiency.[11,12] However, it is worth noting that these studies did not specify the prevalence of selective IgA deficiency in the Omani population.[11,12] This high prevalence in the Arabian peninsula could be attributed to the region's high consanguinity. In light of these global comparative statistics, our study not only contributes valuable national data, but also provides insight into the prevalence of Immunoglobulin A deficiency in Oman. The high prevalence seen in our study, when contextualized within this broader global framework, emphasizes the necessity of understanding regional and ethnic variations in immunodeficiency disorders. Healthcare planning, diagnostic strategies, and the development of targeted interventions rely on this knowledge to tailor healthcare services to the specific needs of our diverse population.

The prevalence of IgA deficiency and the associated comorbidities(immunodeficiency, autoimmunity including type 1 diabetes mellitus and thyroid disease as well as autoinflammatory conditions such as inflammatory bowel diseases) are important findings that shed light on the prevalence and demographic nuances of IgA deficiency, not only scientifically valuable but also hold considerable clinical implications and, which can consequently improve patient care and diagnostic approaches. For example, a referral guide can be created advising to screen for other immunoglobulins for those patients found incidentally to have low IgA as well as a reflex test to test for anti-TTG when low IgA is detected, in order to avoid false negative results for celiac disease. In addition, advise including in the clinical details of the referral whether the patient suffers from recurrent infections.. This would speed up the immunological workup for those patients and minimize the number of patients who might have celiac disease but are missed during screening, which could lead to negative health consequences.

Limitations of our study

The population under consideration may have influenced the high prevalence observed in our study. Our study focused on patients who underwent screening for celiac disease using the anti-IgA and anti-TTG tests, potentially introducing selection bias. The lack of a comprehensive immunoglobulin panel screening for nearly two-thirds of the patients diagnosed with low IgA levels poses a significant limitation. This omission raises the possibility of undiagnosed cases of panhypogammaglobulinemia, which could have affected the accuracy of our results. The inclusion of patients with ongoing infections is another potential bias factor to consider.

Conclusion

The prevalence of IgA deficiency was 1.2%. Furthermore, we observed that the majority of patients with IgA deficiency and negative celiac disease did not undergo IgG anti-TTG testing or an OGD biopsy to confirm the presence of the disease. Screening probable cases of celiac disease with a reflex test upfront and reevaluating budget allocation are also recommended.

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Data availability

The data used for this study is available and will be shared by the corresponding author upon request.

Conflict of interest

None declared by the authors

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