Turkish Journal of Medical Sciences

Volume 47 | Number 2 Article 33

1-1-2017

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TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2017) 47: 592-598
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doi:10.3906/sag-1605-50

Allergic and autoimmune disorders in families with selective IgA deficiency

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Received: 07.05.2016 • **Accepted/Published Online:** 02.10.2016 • **Final Version:** 18.04.2017

Background/aim: IgA deficiency is the most common human primary immunodeficiency. The prevalence of allergic disorders and autoimmunity is thought to be increased in selective IgA deficiency (sIgAD). However, it is currently unclear if these disorders coincide within these families. We aimed to evaluate the frequency of allergic and autoimmune disorders in children with sIgAD and their first-degree relatives (FDRs).

Materials and methods: The study included 81 children diagnosed with sIgAD and 274 of their FDRs. The presence of allergic and autoimmune disorders was evaluated and serum antithyroglobulin and antithyroid peroxidase levels were measured in both patients and their first-degree relatives.

Results: The mean age of the patients was 9.9 ± 3.9 years. Among the patients with sIgAD, 45.7% of them had at least one allergic disorder and 17.3% of them had at least one autoimmune disorder. The frequencies of asthma, allergic rhinitis, and eczema in the FDRs of sIgAD patients were 10.9%, 9.1%, and 7.7%, respectively. Among their FDRs, 14.6% had autoimmunity, compared to an estimate of 5% in the general population.

Conclusion: Increased frequency of allergic and autoimmune disorders in patients with sIgAD and their FDRs suggests a possible common predisposing genetic component for sIgAD and autoimmunity in these families.

Key words: allergy, autoimmunity, children, first degree relative, selective IgA deficiency

1. Introduction

Selective immunoglobulin A deficiency (sIgAD) is the most common primary immunodeficiency, the incidence of which varies from 1:163 to 1:18,500, depending on the population screened and the definition of sIgAD applied (1). Most affected individuals are asymptomatic, whereas approximately one third of patients suffer from recurrent mucosal infections, allergies, and autoimmune diseases (2–4). Secretory IgA, which is present in mucosal secretions, has a broad protective function, and in the case of sIgAD the mucosa appears to be less protected and more vulnerable to enteric toxins and pathogenic microorganisms (5). It has been postulated that secretory IgA plays a protective role against allergic disorders as well by eliminating allergens at the mucosal level. Although an increased frequency of allergic disorders has been reported in patients with sIgAD, some studies have failed to demonstrate an increase compared to the general population (6,7).

Autoimmune disorders occur more frequently in patients with sIgAD, with an estimated prevalence of 7%–36% compared to 3%–5% in the general population (8–11). The most common autoimmune conditions that have been reported in association with sIgAD are idiopathic thrombocytopenic purpura, hemolytic anemia, juvenile rheumatoid arthritis, thyroiditis, celiac disease, and type 1 diabetes mellitus (T1DM) (1,12,13). Although the genetic susceptibility behind sIgAD has not been well-defined, pedigrees of IgA-deficient individuals show familial clustering with no distinct Mendelian inheritance pattern (14). Data on the prevalence of autoimmune disorders in first-degree relatives (FDRs) of patients with sIgAD are limited (15).

In the present study, we evaluated the prevalence of allergic and autoimmune disorders in both IgAD individuals and their FDRs and aimed to investigate if sIgAD is associated with increased frequency of these

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disorders in FDRs, which may be indicative of a possible genetic link.

2. Material and methods

2.1. Patient selection

This study was undertaken in Ankara Children's Hematology Oncology Education and Research Hospital between April 1995 and July 2011 with the approval of the local ethics committee. Individuals with sIgAD who were followed-up at the Immunology Clinic were recruited consecutively. Selective IgA deficiency was defined as a serum IgA level <7 mg/dL with normal or elevated levels of serum IgG and IgM levels in children over 4 years old.

2.2. Clinical evaluation

Clinical evaluations of participants with sIgAD and their FDRs (sibling(s) and parents) were carried out by a Pediatric Allergy and Immunology fellow. Demographic and clinical characteristics were obtained for each participant from regular medical records. History of presenting symptoms during the diagnosis of sIgAD and presence of recurrent infections were taken. Three or more infection episodes in a year were accepted as recurrent infection.

2.3. Allergic disease in patients with sIgAD

Asthma: The diagnosis of asthma was made according to the Global Initiative for Asthma guidelines (16): Briefly, patients older than 5 years with a history of multiple episodes of wheezing and at least a 12% improvement in forced expiratory volume in 1 s following bronchodilator therapy were regarded as having asthma; patients 5 years old or younger with a history of recurrent wheezing episodes and a history of at least one allergic disease (asthma, atopic dermatitis, food allergy, allergic rhinitis) in FDRs were regarded as having asthma.

Allergic rhinitis: Presence of allergic rhinitis was only accepted if it was diagnosed by a physician.

Food allergy: Skin prick tests and serum **s**pecific IgE measurements were performed for the suspected food in patients with a history of food allergy. Serum specific IgE was measured using the Immuno-CAP system (Phadia, Uppsala, Sweden). Food allergy diagnosis was confirmed with an oral food challenge test.

Atopic dermatitis: This was diagnosed according to fulfill Hanifin and Rajka's criteria (17).

2.4. Allergic disease in FDRs

For their FDRs, life-time prevalence of physician-diagnosed asthma, allergic rhinitis, and atopic dermatitis was obtained from the parents of each patient. A diagnosis of allergic disorder was only accepted if it had previously been made by a physician with a compatible history.

2.5. Autoimmune disorders in patients with sIgAD

In patients with sIgAD, autoimmune diseases were diagnosed by a physician specialized in that particular subspecialty (pediatric endocrinology or pediatric rheumatology or pediatric gastroenterology or pediatric hematology).

2.6. Autoimmune disorders in FDRs

A detailed history of autoimmune disorders for FDRs was obtained from the parents of each patient. The diagnosis of autoimmunity was only accepted if it had previously been made by a physician with a compatible history for the corresponding form of autoimmunity.

2.7. Skin prick test

Epidermal prick tests was performed on all IgAD patients on the volar aspect of the forearm with common airborne allergens including house dust mites (*D. pteronyssinus*, *D. farinea*), cat and dog danders, *Alternaria alternata*, and mixed tree, mixed grass, and *Parietaria officinalis* pollens (Stallergenes, SA Antony, France). Histamine (10 mg/mL) and normal saline were simultaneously used as positive and negative controls, respectively. The test was considered positive if the mean diameter of the wheal was at least 3 mm greater than the negative control test after 15–20 min. Atopy was defined as the presence of at least 1 positive skin test response.

2.8. Laboratory measurements

Serum IgA, IgG, IgM, antithyroid peroxidase (anti-TPO) antibody, and antithyroglobulin (anti-Tg) antibody levels were measured for sIgA patients and their FDRs, while levels of serum antigliadin IgG, antiendomysium IgG, and antitissue transglutaminase IgG were only evaluated in patients with IgAD.

Serum IgA, IgG, and IgM levels were measured by nephelometry (Beckman Coulter IMMAGE 800). Serum anti-TPO, anti-Tg, antigliadin IgG, antiendomysium IgG, and antitissue transglutaminase IgG levels were measured by the enzyme immunoassay (ELISA) method.

2.9. Statistical analysis

All calculations were made using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as absolute numbers and percentage or mean ± standard deviation (SD), where applicable. Categorical variables were compared using the chi-square test. A P-value of < 0.05 was considered indicative of statistical significance.

3. Results

3.1. General characteristics

A total of 81 patients with sIgAD with a mean age of 9.9 ± 3.9 (ranging from 4.2 to 20.4 years of age) were enrolled in the study. Recurrent infections were found in 60 (74.1) patients and it was also the most commonly encountered presenting symptom of the patients with sIgAD (Table 1).

The 81 sIgAD individuals had in total 274 FDRs (112 of which were siblings) with a mean age of 26.9 ± 13.5

Table 1. General characteristics and presenting symptoms of patients with sIgAD (n = 81).

Variable		Result N (%)
Age (years)*		10.4 ± 3.9
Age at diagnosis (years)*		6.7 ± 2.8
Follow-up period (years)*		3.7 ± 3.0
Consanguinity		14 (17.3)
Recurrent infections		60 (74.1)
Presenting symptom		
	Recurrent infections	47 (58.0)
	Asthma	22 (27.2)
	Celiac disease	4 (4.9)
	Family screening for sIgAD	3 (3.7)
	Type 1 diabetes	2 (2.5)
	Others$^{\Omega}$	3 (3.7)

*Values provided as mean ± standard deviation, $^{\Omega}$Others: acute urticaria, pulmonary hemosiderosis, short stature

years. Among the FRDs 8 (2.9%) had sIgAD (1 mother, 2 fathers, 5 siblings). Among the 8 FDRs with sIgAD, three had recurrent infections, two of them had asthma, and one had thyroiditis. None of the FDRs had other forms of hypogammaglobulinemia. The demographic and clinical characteristics of the study population are summarized in Table 2.

Patients with sIgAD had a mean serum IgG level of 1483 ± 383 mg/dL, with levels falling within the normal range for age and sex in almost all patients. Only 6.2% of sIgAD patients had elevated levels of IgG for their age. While 12 sIgAD patients had elevated IgM levels, 16 (19.7%) patients had a serum IgE level greater than 100 mg/dL. Ten of those having IgE levels greater than 100 mg/dL had one or more allergic disorder. They had also similar frequency of recurrent infections with those having IgE levels lower than 100 mg/dL (75.0% and 76.9%, respectively, P = 0.540). The results of the patients with selective IgA deficiency and FDRs are given in Table 3.

3.2. Clinical characteristics

3.2.1. Allergic diseases

In our patient group, at least one allergic disorder was present in 45.7% of children with sIgAD. Overall, 34.6% of the patients had asthma, followed by allergic rhinitis in 27.2% and atopic dermatitis in 11.1%. Following a skin prick test, 22.2% of patients with sIgAD were found to be sensitive to at least one allergen. One patient had a history of physician-diagnosed food allergy. There was no significant difference in the prevalence of allergic disorders between the patients with and without recurrent infections (P = 0.220). The frequencies of asthma, allergic rhinitis, and eczema in the FDRs of sIgAD patients were 10.9%, 9.1%, and 7.7%, respectively (Table 2). The prevalence of asthma and allergic rhinitis was higher in patients with sIgAD compared to their FDRs (P < 0.001 and P = 0.019, respectively), while there was no difference in terms of the frequency of atopic dermatitis (P = 0.939). Overall, 32.1% of the children with IgAD had at least 1 FDR with an allergic disorder, while among the children with a confirmed allergic disorder, 43.2% also had at least 1 similarly affected FDR.

3.2.2. Autoimmune disorders

At least one physician-diagnosed autoimmune disorder was present in 14 (17.3%) of the patients with sIgAD, the most common condition being celiac disease (9.9%), followed by type-1 diabetes mellitus (DM) (3.7%) and thyroiditis (2.5%). Two patients had both celiac disease and thyroiditis and 1 patient had type-1 DM and celiac disease, while 1 patient had FMF and ankylosing spondylitis (table 3). There was no significant difference in the prevalence of autoimmune disorders between the patients with and without recurrent infections (P = 0.358).

Four patients with sIgAD had detectable levels of TPO, whereas three of them were positive for anti-Tg antibodies. Two of the patients with thyroid autoantibody positivity had clinically hypothyroidism (Table 3). Eight patients were eventually diagnosed with celiac disease for having positive titers of antigliadin IgG, antiendomysium IgG, and antitissue transglutaminase IgG antibodies.

Among the FDRs, 24 were positive for anti-TPO and 20 had detectable levels of anti-Tg antibody. In subjects with positive thyroid antibodies, 15 of them had a history of clinical thyroiditis (hypothyroidism) and patients without a compatible clinical history were not considered to have thyroiditis. The individuals with positive thyroid autoantibodies had a mean age of 33.9 ± 9.8 years and 75.8% of them were female. Overall, 14.6% of the FDRs enrolled had a history of at least one physician-diagnosed autoimmune condition, the most frequent being thyroiditis (9.1%) and rheumatoid arthritis (2.6%). The difference between patients with IgAD and their FDRs with regards to the frequency of autoimmune disorders was statistically insignificant (P = 0.554). Overall, 38.3% of the children with IgAD had at least one FDR with an autoimmune disorder, while among the children with a confirmed autoimmune disorder, 42.9% also had at least one similarly affected FDR.

4. Discussion

In this study, we demonstrated a higher frequency of allergic and autoimmune disorders in patients with IgAD compared to the general population, while at the same

Table 2. Demographic characteristics and frequencies of allergic and autoimmune disorders in sIgAD patients and their FDRs.

		sIgAD (n = 81)	FDRs (n = 274)	P
Age (mean ± SD, in years)		10.4 ± 3.9	26.9 ± 13.5	<0.001
Female n (%)		133 (48.6)	141 (51.4)	0.037
Allergic disorders n (%)				
	Asthma	28 (34.6%)	30 (10.9)	<0.001
	Allergic rhinitis	22 (27.2%)	25 (9.1)	0.019
	Atopic dermatitis	9 (11.1%)	21 (7.7)	0.939
	Food allergy	1 (1.2%)	-	-
	>1 allergic disease	17 (21.0)	14 (5.1)	<0.001
Autoimmune disease n (%)				
	Total	14 (17.3)	40 (14.6)	0.554
	Celiac disease	8 (9.9)	1 (0.3)	
	T1DM	3 (3.7)	2 (0.7)	
	Thyroiditis	2 (2.5)	25 (9.1)	
	FMF	1 (1.2)	2 (0.7)	
	Vitiligo	1 (1.2)	2 (0.7)	
	Chronic ITP	1 (1.2)	-	
	Rheumatoid arthritis	-	7 (2.6)	
	Pulmonary hemosiderosis	1 (1.2)	-	
	>1 autoimmune disease	4 (4.9)	-	

sIgAD: selective immunoglobulin A deficiency; FDRs: first-degree relatives; T1DM: type 1 diabetes mellitus; FMF: familial Mediterranean fever; mean ± SD: mean ± standard deviation

time showing an increased risk of autoimmunity in their FDRs, again compared to the general population. In fact, in a significant proportion of our patients with IgAD the presenting symptoms were related to an underlying allergic and/or autoimmune disorder.

Although it is widely accepted that allergic diseases occur more commonly in patients with sIgAD, some studies have reported disease frequencies comparable to those of the general population. In an earlier study, Buckley et al. reported the frequency of atopy in children and adults with sIgAD as 58% (18). Edwards et al. later reported a frequency of allergy/asthma of 13% in patients with sIgAD, where they also found a higher prevalence of allergy in younger individuals (10). In a more recent study by Aytekin et al., allergic manifestations including asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, urticaria, drug allergy, and food allergy were noted in 43.2% of children (age range 4–18 years) with sIgAD (4). In our study, 34.6% of the patients with sIgAD had asthma, 27.2% had allergic rhinitis, and 11.1% had eczema, while a further 22.2% were sensitized to at least 1 allergen on a skin prick test. In a recent study from Turkey, the prevalence of physician-diagnosed asthma, allergic rhinitis, and eczema in school-age children was reported as 10.7%, 16.9%, and 2.6%, respectively (19). When our findings are compared to these results, it would seem that asthma and eczema occur more commonly in children with sIgAD.

It is widely thought that the absence of the protective effect of secretory IgA on the mucosal surface, which in turn facilitates the passage of aeroallergens and food allergens in the respiratory and gastrointestinal tracts, is mainly responsible for the increased incidence of allergic diseases associated with sIgAD by increasing the likelihood of sensitization against such antigens (20,21). Although only 1 patient in our study had a physician-diagnosed food allergy, results of a recent study showing an increase in the frequency of food allergies in 4-year-old children support this hypothesis (6). The absence of secretory IgA and its protective effects allows viruses to overcome mucosal defenses, thus leading to upper and lower respiratory tract infections (LRTIs) and it has been shown that viral LRTIs, especially rhinovirus, are related with increased incidence

Table 3. Laboratory findings of patients with sIgAD and their FDRs.

	sIgAD (N = 81) n (%)	FDR (N = 274) N (%)
IgA (<7 mg/dL)	81 (100)	8 (2.9)
IgG (mg/dL)*	1483.5 ± 383.4	1219.3 ± 299.1
IgM (mg/dL)*	113.5 ± 41.5	134.3 ± 76.9
IgE (mg/dL)*	92.0 ± 175.6	59.6 ± 89.9
Anti-TPO, positive	4 (4.9)	24 (8.7)
Anti-TG, positive	3 (3.7)	20 (7.3)
Skin prick test, positive	18 (22.2)	ND
Antigliadin IgG,	8 (9.9)	ND
Antiendomysium IgG	8 (9.9)	ND
Antitissue transglutaminase IgG	8 (9.9)	ND

IgA: immunoglobulin A; IgE: immunoglobulin E IgG: immunoglobulin G; IgM: immunoglobulin M; Anti-Tg: anti-thyroglobulin antibody; Anti-TPO: anti-thyroid peroxidase antibody; ND: not done; sIgAD: selective immunoglobulin A deficiency; FDRs: first-degree relatives; *Values provided as mean ± standard deviation

of asthma (22). These mechanisms related to secretory IgA are more likely to play a role in the development of allergic disorders.

A genetic susceptibility has yet to be identified in association with sIgAD. Although the pedigrees of individuals with sIgAD do show familial clustering, there is no evidence to support Mendelian inheritance (14). In a recent prevalence study from Turkey, Baştürk et al. reported the frequency of sIgAD among school children as 1:188, whereas in our study we observed a frequency of 1:34 among the FDRs of individuals with sIgAD (23). Our findings are suggestive of the presence of a genetic component to disease susceptibility.

Autoimmune disorders are one of the most important clinical manifestations in individuals with sIgAD (24–26). The prevalence of autoimmunity in IgAD individuals has been shown to be highly variable, ranging from 7% to 36% in symptomatic IgAD individuals (27), whereas the prevalence of autoimmune disorders in the general population is estimated to be between 3% and 5% (8,9). Recently, Jacob et al. reported the frequency of autoimmunity as 19% in their sIgAD patients, which is similar to our results (28). In our study, the frequency of autoimmunity was 17.3% in children with sIgAD compared to a frequency of 14.6% in their FDRs, both of which are higher than in the general population. Although data regarding the prevalence of autoimmune diseases in Turkey is lacking, a recent study reported an overall prevalence of 1% for rheumatoid arthritis, whereas the frequency for the same disorder among the FDRs in our study was 3.8% (29). In our study population 1.2% of sIgAD patients and 0.7% of their FDRs had FMF, which were much higher than the prevalence of FMF (0.093%) in the general Turkish population (30).

Celiac disease was present in 9.9% of our sIgAD patients. Several studies in the literature reported a higher prevalence of celiac disease in patients with sIgAD, as well as a higher frequency of sIgAD among patients with confirmed celiac disease (13,31). A recent study from Turkey reported the prevalence of celiac disease as 0.47% in healthy school children, which is much lower than the prevalence in our sIgAD patients (32). The exact nature of the relationship between these two conditions remains elusive. However, human leukocyte antigen alleles and haplotypes such as HLAB8, DR3, DR7, and DQ2 have been shown to occur more frequently in both conditions, suggesting a possible link with human leukocyte antigens (33,34). On the other hand, the absence of mucosal IgA in patients with sIgAD disrupts mucosal clearance of food antigens, and the passage of some molecules into subepidermal and submucosal tissue may facilitate the production of antibodies against these antigens in individuals with a genetic susceptibility for developing celiac disease.

Several hypotheses have been put forth to help explain the relationship between sIgAD and autoimmunity (35). The absence of secretory IgA in the mucosal surfaces compromises mucosal integrity, thus allowing for unhindered passage of environmental antigens into the systemic circulation, and these dietary proteins may result in cross-reactions with self-antigens. Antibodies against cow's milk, among other autoantibodies, have

been detected more frequently in patients with selective IgA. Another hypothesis could be that the decrease in antigen clearance may lead to tissue inflammation via the formation of immune complexes.

Besides the above-mentioned immune mechanisms, it has been postulated that homozygosity for certain haplotypes of the major histocompatibility complex genes could be a risk factor for the development of some autoimmune diseases in patients with sIgAD, with some studies showing a higher frequency of certain MHC haplotypes in individuals with sIgAD and their families (36,37). Recently, the possibility of a link between some non-HLA candidate genes and sIgAD has been reported (38).

It has been well documented that sIgAD is associated with an increased frequency of autoimmune disorders. Moreover, a recent study has also demonstrated the presence of familial clustering for autoimmune disorders (8). The fact that both sIgAD and autoimmune diseases show familial clustering and that sIgAD is associated with an increased frequency of autoimmunity raises a question regarding whether FDRs of patients of sIgAD are also at risk. In a recent study by Jorgensen et al., a higher frequency of autoimmune diseases was reported in FDRs of individuals with sIgAD compared to the general population (15). Our study also produced similar results. Furthermore, we observed that up to 38.3% of children with sIgAD had at least one relative with an autoimmune disorder, with the frequency rising to 42.9% among FDRs of children who had an autoimmune disease themselves. Besides these, antibodies against thyroglobulin and TPO were positive in 3.7% and 4.9% of children with sIgAD, respectively, compared to respective positivity rates of 8.7% and 7.2% in their FDRs. Besides the high frequency of thyroid autoantibodies, 9.1% of FDRs had physician-diagnosed thyroiditis. These findings suggest that selective IgA deficiency is associated with increased autoimmune disorders in the FDRs of these patients.

The main limitation of this study is the lack of a control group. Due to this, we compared our results with those of population-based studies, and the frequencies of allergic and autoimmune diseases were higher in patients with sIgAD and the frequency of autoimmune disorders was higher in their FDR (8,9,29,30,32).

With this study, we demonstrated an increased frequency of autoimmune diseases in the FDRs of patients with sIgAD compared to the general population, a finding that suggests a possible common predisposing genetic component for sIgAD and autoimmunity in these families. Furthermore, besides a history of recurrent infections, a significant proportion of children with sIgAD may present with symptoms related to an underlying allergic or autoimmune condition. A diagnosis of sIgA deficiency deserves consideration in the differential diagnosis in patients presenting with an autoimmune or allergic disorder.

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