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ORIGINAL ARTICLE

Evaluation of serum IgA levels in Iranian patients with type 1 diabetes mellitus

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Abstract An increased prevalence of immunoglobulin (Ig) A deficiency has been documented in a number of autoimmune diseases; however, its association with type 1 diabetes mellitus (DM1) is a subject of debate. This study was performed to evaluate serum IgA levels in a group of pediatric patients with DM1. Three hundred patients with mean age of 12.6 ± 6.7 years were enrolled in this study. Serum IgA and other immunoglobulins levels were measured using enzyme-linked immunosorbant assay. Mean serum IgA level of patients was 271.0 ± 141.4 mg/dl. Only two patients had IgA deficiency (IgA < 10 mg/dl), who were two boys with ages of 9 and 10 years. Although associated autoimmune disorders were found in a number of patients with DM1, no other autoimmune disorder was detected in these two patients with IgA deficiency. Serum levels of all other immunoglobulins were normal. Serum IgA levels did not significantly differ by grouping the patients according to age variation, sex distribution, disease duration, and associated disorders. There was no significant correlation between IgA levels and hemoglobin A1c. This study showed the prevalence of IgA deficiency in Iranian patients with DM1 as 0.7% (1:150), which is much higher than reported prevalences in general populations. Further studies are needed for better understanding the possible etiologies of increased IgA deficiency in DM1 and its effects on diabetes control.

Keywords Autoimmunity · IgA deficiency · Diabetes mellitus

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Introduction

Immunoglobulin (Ig) A deficiency is the most common primary immunodeficiency disease that its prevalence varies within different geographical regions, ranging from 1 in 23,255 in Japanese population to 1 in 169 in the Spanish children [1–5]. The prevalence of IgA deficiency in Iran is estimated about 1 in 651 patients [6]. More than half of cases with IgA deficiency are asymptomatic, whereas recurrent infections in the respiratory and gastrointestinal tracts, autoimmune diseases and allergy are the most common manifestations in symptomatic patients [7]. High prevalence of IgA deficiency in autoimmune diseases, such as systemic lupus erythematous and rheumatoid arthritis, is well documented [8]. However, its association with type 1 diabetes mellitus (DM1) is still a subject of debate.

Although an association of IgA deficiency and celiac disease was reported [8], celiac itself could be associated with DM1 as well [9], whereas exact prevalence of IgA deficiency in DM1 is unknown. Autoimmune antibodies against beta cells, tyrosine phosphatase and glutamic decarboxylase are believed to be responsible for inflammation in pancreatic islets of patients with DM1, but 10%

of diabetic patients do not have these antibodies, which could point out an undetermined role of humoral immunity in DM1 [8, 10, 11].

As of increased susceptibility to infections in individuals with either diabetes mellitus or IgA deficiency, association of these two conditions could significantly increase the risk of infections. Therefore, identifying of IgA deficiency in diabetic patients and long-term monitoring of their immune system and appropriate treatment could decrease morbidity and mortality in this group of patients. This study was performed to evaluate serum IgA levels in a group of pediatric patients with DM1.

Patients and methods

This is a cross-sectional study in the Children's Medical Center, Pediatrics Center of Excellence in Iran. Three hundreds consecutive patients with DM1, aged $\geq$ 4 years, were enrolled in this study during the year 2009. The patients with type 2 DM, patients with diabetes due to pancreas exocrine disorders or drugs, patients with long-standing diabetes with silent initiation of disease and who were suspected to have maturity-onset diabetes of the young (MODY), patients with neonatal onset diabetes, and patients with other genetic syndromes associated with diabetes mellitus were excluded from this study.

Measurement of IgA and other immunoglobulins were taken using enzyme-linked immunosorbant assay (ELISA) method. In the first step, 5 cc of blood from all patients was taken for IgA measurement. If serum IgA level was less than 10 mg/dl, the test was repeated; after confirming the IgA deficiency, measurements of all other serum immunoglobulins levels, including IgM, IgE, IgG, IgG1, IgG2, IgG3 and IgG4 were taken. If needed, other laboratory tests, such as hemoglobin (Hb) A1c, thyroid function tests and tissue transglutaminase (tTG) IgA, were also performed; tTG IgA level of more than 20 U/ml was considered for making the diagnosis of celiac disease.

Statistical analysis was done using SPSS statistical software (version 15). Results were expressed as frequency, Mean $\pm$ SD. Comparison of IgA levels between groups performed by t-test and one-way ANOVA. *P*-value of less than 0.05 was considered significant.

Results

Patients' characteristics

Three hundred patients (125 men and 175 women) with mean age of 12.62 $\pm$ 6.65 years were investigated in this study. Mean interval between first symptoms and diagnosis of DM1 was 22.02 $\pm$ 11.7 (range 7–60) days, whereas mean duration of diabetes was 37.4 $\pm$ 46.4 months. Mean daily insulin doses was 0.83 $\pm$ 0.22 (range 0.05–1.8) IU/kg. Mean HbA1c level was 8.8 $\pm$ 1.9% (3.9–14%).

Clinical manifestations

The first presentations of diabetes were polyuria and polydypsia in 192 cases (64%) and diabetic ketoacidosis (DKA) in 108 cases (36%). There was a history of recurrent infections in 7% of patients. From 87 patients who underwent celiac examinations, celiac disease was confirmed in four cases. Hypothyroidism and hyperthyroidism were documented in 7 and 0.7% of patients, respectively. Three patients had also experienced vitiligo. Autoimmune hepatitis was also documented in three patients. None of the patients had history of Addison disease, pernicious anemia and myasthenia gravis. There was a history of allergic diseases in 6% of patients.

Family history

The rate of consanguineous marriages in the parents of patients was 26.7%. History of DM1 in first-degree and second-degree relatives was positive in 10.3 and 7.75% of the studied patients, respectively. Meanwhile, history of DM2 in first-degree and second-degree relatives was positive in 7.3 and 45.7% of patients' families, respectively. Although none of the families' members had history of recurrent or unusual infections, there was a history of allergy in 3% of the patients' families. There was a history of hypothyroidism and hyperthyroidism in first-degree relatives of 13 and 3.7% of patients, respectively. Five percent of the patients had history of vitiligo in their first relatives, but none of the patients' family members had history of either celiac disease or autoimmune hepatitis.

Prevalence of IgA deficiency

Mean serum IgA level of patients was 271.03 $\pm$ 141.4 (range: 1–490) mg/dl. Only two among 300 studied patients had IgA deficiency (IgA $<$ 10 mg/dl), yielding to prevalence of 0.67%. They were 9 and 10 years old boys with no history of recurrent infections and other autoimmune disorders such as celiac disease, thyroid disorders, autoimmune hepatitis and vitiligo. There was no history of DM 1 and DM2 and other autoimmune diseases in their first-degree relatives. However, the first patient, who was from a consanguine parents, had allergic rhinitis, and there was a history of allergic disease in his family members. Serum levels of all other immunoglobulins were within normal ranges. Characteristics of these two patients are shown in the Table 1.

Table 1 Characteristics and laboratory findings of two patients with clinical features and history of two patients with DM1 and IgA deficiency

	Patient 1	Patient 2
Diabetes status		
Diabetes duration	24 month	Recently
First presentation	Polyuria and polydypsia	Diabetic ketoacidosis
Daily insulin dose	0.5	0.8
HbA1c (%)	5.9 (NR < 7)	7.2 (NR < 7)
Complete cell blood count		
White blood cells ($\times 10^3$/μl)	6.1	6.7
Neutrophil, lymphocyte (%)	54, 43	62, 34
Hb (mg/dl)	11.8	13.3
Platelets ($\times 10^3$/μl)	326	249
Serum immunoglobulins		
IgA (mg/dl)	4 (NR > 10)	1 (NR > 10)
IgM (mg/dl)	130 (NR: 52–242)	138 (NR: 52–242)
IgE (IU/ml)	100.2	125
IgG (mg/dl)	1,431 (NR: 600–1,572)	1,700 (NR: 600–1,572)
IgG_1 (mg/dl)	868 (NR: 280–1,740)	1,050 (NR: 280–1,740)
IgG_2 (mg/dl)	377 (NR: 80–550)	550 (NR: 80–550)
IgG_3 (mg/dl)	62 (NR: 22–320)	40 (NR: 22–320)
IgG_4 (mg/dl)	48 (NR: 10–170)	220 (NR: 10–170)
Lymphocyte surface marker		
CD_3 (%)	70 (NR: 28–77)	54 (NR: 28–77)
CD_4 (%)	46 (NR: 32–62)	31 (NR: 32–62)
CD_8 (%)	23 (NR: 2–36)	21 (NR: 2–36)
CD_{16} (%)	6 (NR: 5–19)	16 (NR: 5–19)
CD_{19} (%)	17 (NR: 3–14)	18 (NR: 3–14)
CD_{56} (%)	5 (NR: 2–20)	14 (NR: 2–20)
CD_4/CD_8	2 (NR: 1–2)	1.4 (NR: 1–2)
Thyroid function tests		
Antithyroglobulin Ab (IU/ml)	15 (NR: 5–100)	23.2 (NR: 5–100)
Anti TPO Ab (IU/ml)	5 (NR < 50)	1.8 (NR < 50)
TSH (mIU/l)	3.2	3.63
T4 (μg/dl)	8.4	7.3
T3 resin uptake (%)	31	32
Others		
Anti insulin Ab	Negative	Negative
Cortisol (mg/dl)	35 (NR: 4.5–22)	18 (NR: 4.5–22)
ACTH (pg/ml)	43 (NR: 7.9–66.1)	35 (NR: 7.9–66.1)
Anti endomysium ab IgG	Negative	Negative

NR Normal range

Comparison of IgA level between groups

Serum IgA levels did not significantly differ, when the patients were grouped by age, sex, disease duration, associated disorders. There was no significant correlation between IgA levels and HbA1c. Based on HbA1c level, the patients were divided into two groups: good control (HbA1c < 7%) and poor control (HbA1c ≥ 7%) [12, 13]. Mean serum IgA level of patients with good control was not significantly different from that of patients with poor control (274.9 vs. 305.5; $P > 0.05$) (Table 2).

Discussion

High prevalence of IgA deficiency in some autoimmune diseases was documented [8]. However, there are not enough reports on association of IgA deficiency and DM1.

Table 2 Comparison of serum IgA level in different groups of DM1 patients

Group	Subgroups	Frequency	Mean ± SD	*P*-value
Sex	Male	125	253.32 ± 164.2	>0.05
	Female	175	283.7 ± 136.9	
Age (years)	0–9	133	267.4 ± 144.7	>0.05
	10–19	122	271.9 ± 134.7	
	20–29	36	289.3 ± 151.6	
	30–39	9	241 ± 154.2	
DM duration	<1 year	134	272.6 ± 143.3	>0.05
	1–5 year	108	276.15 ± 138.8	
	>5 year	58	257.9 ± 143.3	
HbA1c	<7%	34	274.9 ± 141.6	>0.05
	≤7%	201	305.5 ± 141.5	
Recurrent infection	+	21	268.9 ± 139.8	>0.05
	−	279	298.45 ± 169.65	
DM1 in first-degree relatives	+	31	256.16 ± 126.31	>0.05
	−	269	273.72 ± 143.13	
DM1 in second-degree relatives	+	22	256.9 ± 156.2	>0.05
	−	278	273.3 ± 140.4	
Celiac disease	+	4	175 ± 30	>0.05
	−	83	195.8 ± 118.15	

This study was performed in our region for the first time to see the prevalence of IgA deficiency in the patients with DM1.

In this study, some autoimmune disorders such as hypo- and hyper-thyroidism, celiac disease, vitiligo and autoimmune hepatitis were seen in DM1 patients and in some of their relatives, which can emphasize the association of DM1 and other autoimmune disorders in agreement with previous studies [11, 14].

Prevalence of IgA deficiency in our study was 0.7%, which is much lower than that of reported in some studies and higher than some other studies. Cerutti et al. [15] showed that the prevalence of selective IgA deficiency was 7 in 191 Italian DM1 patients (3.7%), which was higher than normal population. In the study by Hoddinott et al. [16], two of 129 investigated patients with DM1, with disease onset of before the age of 15 years, were completely IgA deficient (1.6%). Smith et al. [17] showed that the prevalence of IgA deficiency in diabetes mellitus could be dependant to the age of patients, whereas its prevalence was 2.5% in children with juvenile-onset DM1 (9 in 366) in comparison with 0 in 421 adults patients. In spite of these studies that showed a prevalence of more than 1% in IgA deficiency associated with DM1, Liblau et al. [18] reported a prevalence of 0.38% (1 in 261) for IgA deficiency in the study on French adult patients with DM1. IgA levels did not differ between diabetic and control groups, and serum levels of IgE, IgM, IgG and its subclasses in that IgA-deficient patient were normal. Moreover, in the study by Liberatore et al. [19], no case of IgA deficiency was found in the group of 66 patients with DM1.

Although prevalence of IgA deficiency in DM1 in our study (1 in 150) was different in comparison with other studies on diabetic patients, it is more than four times higher than its prevalence in general population in our region (1 in 651) (0.67% in DM1 vs. 0.15% in general population) [6]. Such prevalence is also much higher than prevalence of IgA deficiencies in other countries [4, 5]. High prevalence of IgA deficiency in DM1 could be due to a common genetic predisposition in both DM1 and IgA deficiency [14]. Both diseases belong to autoimmune polyendocrine syndromes [14], and HLA-DQB1 gene encoding non-Asp residues in position 57 is associated with increased risk of both disorders [18].

IgA deficiency can cause abnormalities in glycemic control of diabetes by inducing various infections. However, in our study, IgA deficiency was not correlated with glycemic control, and there was no correlation between IgA and HbA1c levels. This finding is in agreement with the study by Cortona et al. [20] that indicated IgA deficiency did not correlate with either increased rate of infections or HbA1c level.

Results of this study along with previous studies can be helpful in better determining humoral immunity and autoimmunity in the development of DM1. However, further studies are needed for better understanding the etiologies of increased IgA deficiency in DM1 and its effects on diabetes control.

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