



ORIGINAL RESEARCH

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Prevalence of celiac disease in children with type 1 diabetes mellitus and the accuracy of serological tests

Hulya Ozdemir¹, Tufan Kutlu², Mehmet Ozdemir³, Pinar Isguven⁴, Tulay Erkan², Figen Cullu Cokugras², Sergulen Dervisoglu⁵

¹Marmara University Pendik Training and Research Hospital, Department of Pediatrics, Division of Neonatology, Istanbul, Turkey

²Istanbul University Cerrahpaşa Faculty of Medicine, Department of Pediatrics, Pediatric Gastroenterology, Division of Hepatology and Nutrition, Istanbul, Turkey.

³Goztepe Training and Research Hospital, Department of Pediatric Allergy, Istanbul, Turkey.

⁴Sakarya University Faculty of Medicine, Department of Pediatric Endocrinology, Sakarya, Turkey

⁵Istanbul University, Cerrahpasa Medical Faculty, Department of Pathology, Istanbul, Turkey

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Abstract

In children with type 1 diabetes mellitus (DM), prevalence of some autoimmune diseases like celiac disease (CD) has been increased. It is also reported that CD often can be asymptomatic and only serologically evident in patients with type 1 DM. In our study, we aimed to investigate the prevalence of asymptomatic CD and the specificity and sensitivity of anti-gliadin antibodies (AGA), anti-endomysium (EMA) and tissue transglutaminase (tTG) antibodies that used for diagnosis of CD in these patients. Anti-gliadin-IgA, AGA-IgG, EMA, tTG-IgA levels were evaluated. Small-intestine biopsies were applied to the children that parents were positive for at least one of AGA-IgA, AGA IgG, EMA and tTG-IgA. A total of 268 Type 1 DM children were included in the study. Of these sixty-four children who had at least one serological positive underwent small intestine biopsies and in five children (1.9%) CD was diagnosed. Anti-endomysium and tTG-IgA positivity were detected in all cases with Celiac disease, and sensitivity was 100% for both and 95% and 86% for specificity, respectively. The sensitivity and specificity of anti-endomysium and tTG-IgA antibodies were considered to be the most reliable indicator because of their higher specificity than other serological tests. Our results, which support current guidelines, suggest that children with Type 1 DM can be screened with tTG-IgA and EMA, which are the most sensitive and specific tests to detect asymptomatic CD in these patients.

Keywords: Asymptomatic celiac disease, prevalence, type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (DM) is an autoimmune disease that occurs frequently in children and characterized by destruction of the pancreatic beta cells [1]. The incidences of the other autoimmune diseases are increased in children with type 1 (DM) and the best known among these is Celiac disease [2]. There is strong evidence indicating that the incidence of Celiac disease is increased in children with type 1DM [3,4]. The prevalence of coexistence of these two diseases has been reported to range between 0.6% and 16.4% in different studies [5]. Association of Celiac disease and type 1 DM based on autoimmune pathogenesis has been associated with common HLA DR3-DQ2/HLA DR/-DQ2 tissue antigens [6].

It has reported that typical gastrointestinal system findings including diarrhea and abdominal distention occur rarely and atypical findings including anemia, short stature and delayed puberty are observed more commonly in type 1 DM patients who develop Celiac disease. In addition, Celiac disease may be asymptomatic or latent in these patients and may be manifested with serologic markers [7,8]. Although tissue transglutaminase (tTG) IgA and anti-endomysial antibodies (EMA) among serological markers have been shown to be more reliable compared to anti-gliadin antibodies (AGA), it is known that there is no serological marker with 100% sensitivity and specificity [9]. Currently, guidelines recommend measurement of tTG-IgA or EMA levels for screening CD in type 1 DM patients [10,11].

In our study, we aimed to investigate the frequency of asymptomatic celiac disease in children with type 1 DM and the value of AGA, EMA and tTG-IgA that are used in the diagnosis of celiac disease as screening tests.

*Corresponding Author: Hulya Ozdemir, Marmara University Pendik Training and Research Hospital, Department of Pediatrics, Division of Neonatology, Istanbul, Turkey E-mail: hulyaakdenizozdemir@gmail.com

Materials and Methods

Patients who were diagnosed as having type 1 DM and were being followed up in Istanbul University, Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Endocrinology and Göztepe Education and Research Hospital, Division of Pediatric Endocrinology were included in the study. Before initiation of the study, it was retrospectively interrogated if the patients had been diagnosed as having Celiac disease and the patients who had been diagnosed as having Celiac disease were excluded from the study. Presence of the symptoms and signs suggesting Celiac disease, the time of onset of type 1 DM, degrees of metabolic control and long-term diabetes complications were recorded. The antigliadin-IgA, AGA-IgG, EMA, tTG-IgA and HbA1c levels of the patients who were included in the study were evaluated. Among serological markers, AGA-IgA and IgG were evaluated using the ELISA method (Lut Labmaster, Turku, Finland) (a value above 25 AU was considered positive for both markers), anti-endomysial antibodies were evaluated using indirect immunofluorescence method (Immun Diagnostics, AB, Uppsala, USA) (Test result +/-) and tTG-IgA was evaluated using the ELISA method (QUANTA Lite tTG, INOVA Diagnostics, Inc. San Diego, CA 92131) (>30 U positive). Small intestinal biopsy was performed in the children who had at least one positive marker among the markers AGA-IgA, AGA IgG, EMA and tTG-IgA after obtaining informed consent from the families. Small intestinal biopsy was performed in Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Gastroenterology using Olympus pediatric video-endoscopy device such that at least four biopsy samples were obtained from the second part of the duodenum. The diagnosis of Celiac disease was made in accordance with The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria in the patients included in our study [2]. The biopsy samples were assessed in Istanbul University, Cerrahpaşa Medical Faculty, Department of Pathology and it was investigated if villus atrophy, crypt hyperplasia and increased intraepithelial lymphocytes were present.

Statistical Analysis

In this study, statistical analyses were performed using SPSS 10.0 (SPSS Inc, Chicago, IL) package program. In assessment of the data, independent t test was used for comparison of two groups and chi-square and Fisher exact tests were used for comparison of quantitative data in addition to descriptive statistical methods (mean, standard deviation). The results were evaluated at a significance level of $p < 0,05$.

Results

A total of 268 children with type 1 DM that 138 female (51.5%) and 130 male (48.5%) were included in our study. Eleven of the patients had been newly diagnosed, while 257 had been diagnosed before and the mean age and the mean time of disease onset were found to be 12.0 ± 4.3 and 7.6 ± 3.7 , respectively. The demographic features of all our patients are shown in Table 1. The serum AGA-IgA, AGA-IgG, EMA and tTG-IgA levels were evaluated in our type 1 diabetes patients for screening asymptomatic Celiac disease. Anti-gliadin-Ig A was found to be positive in 49 patients (17%), AGA-IgG was found to be positive in 21 patients (8%), EMA was found to be positive in 8 patients (3%) and tTG-IgA was found to be positive in 13 patients (Table 2). The serum IgA value was found to be within the normal limits in all patients.

Table 1. Demographic and clinical characteristics of the patients

Number of patients (n)	268
Age (years)	12.1±4.3
Gender (Female) n (%)	138 (51.5)
Age at the time of the diagnosis of type 1 DM* (years)	7.6±3.7
Mean ± standard deviation	
Duration of type 1 DM (years) Mean ± standard deviation	4.3±3.4
Age at the time of diagnosis of Celiac disease (years)	11.2±5.6
Mean ± standard deviation	
Number of patients who were diagnosed as having Celiac disease n (%)	5 (1.9)
* Diabetes mellitus	

Small intestinal biopsy was performed in 64 of 65 patients who had any positive serologic test and total villus atrophy was found in three of the patients who underwent biopsy and crypt hyperplasia and increased intraepithelial lymphocytes together with subtotal villus atrophy were found in two (Table 3). The family of a patient who had positive AGA IgA (150 AU) did not accept small intestinal biopsy. Small intestinal biopsy was performed in 48 of 49 patients who had positive antigliadin IgA and celiac disease was found in three patients (6%). Small intestinal biopsy was performed in all 21 patients who had positive AGA IgG and Celiac disease was found in three (14%) (Table 2). EMA and tTG-IgA were found to be positive in all patients who were found to have Celiac disease, both AGA-IgA and AGA-IgG were found to be negative in one patient, AGA-IgA was found to be negative in one patient and AGA-IgG was found to be negative in another patient (Table 3). Histological findings of celiac disease could not be found in 45 patients (93%) who had positive antigliadin IgA, in 18 patients (85%) who had positive AGA-IgG, in 3 patients (37%) who had positive EMA and in 8 patients (61%) who had positive tTG-IgA. Annual follow-up was planned in these patients who had positive serological markers considering latent celiac disease. In five patients who were diagnosed as having celiac disease, the mean age was found to be 11.2 ± 5.6 years, the mean time of diabetes was found to be 10.5 ± 3.8 years and the mean HbA1c value was found to be 11.4 ± 3.8 and no statistically significant difference was found compared with the patients who were not found to have celiac disease ($p > 0,05$). In our study, the incidence of asymptomatic celiac disease was found to be 1.9% in diabetes patients.

Table 2. Antibody positivity and percentages of performance of small intestinal biopsy

	AGA [†] -IgA	AGA [†] -IgG	EMA [§]	tTG-IgA [‡]
Type 1 DM* n (%)	49 (18.2)	21 (7.8)	8 (2.9)	13 (4.8)
Patients who underwent biopsy n (%)	48 (97.9)	21 (100.0)	8 (100.0)	13 (100.0)
Number of the patients with a diagnosis of Celiac disease confirmed with biopsyn (%)	3 (6.2)	3 (14.2)	5 (62.5)	5 (38.4)
* Diabetes mellitus, [†] antigliadin antibody, [§] antiendomysial antibody, [‡] tissue transglutaminase antibody				

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value and relative efficiency value of the tests, which we used in the diagnosis of Celiac disease. EMA and tTG-IgA positivity was found in all patients who were found to have Celiac disease (sensitivity 100%). Histological findings of celiac disease were not found on small intestinal biopsy in three patients with positive antiendomysial antibodies and in

eight patients who had positive tTG-IgA and the specificities of these two tests were found to be 95% and 86%, respectively. The sensitivities of anti-gliadin-IgA and IgG were found to be lower (60% for both) compared to the other two serological markers and their specificities were found to be 26% and 70% respectively. Anti-gliadin-IgA was found to have the lowest positive predictive value and relative efficiency value (6% and 29%, respectively),

whereas EMA was found to have the highest positive predictive value and relative efficiency value (62% and 95%, respectively). Antiendomysial antibodies were found to have a sensitivity of 100%, a specificity of 95%, a positive predictive value of 62%, a negative predictive value of 100% and a relative efficiency value of 95% and it was considered the most reliable marker among serological markers.

Table 3. Clinical and laboratory findings of the patients who were diagnosed as having Celiac disease with small intestinal biopsy

Patients	Gender	Age	Age at the time of diagnosis of type 1 DM* (years)	Duration of type 1 DM* (years)	Age at the time of diagnosis of Celiac disease (years)	AGA [†] -IgA (AU)	AGA [†] -IgG (AU)	EMA [§]	tTG-IgA [‡] (U)	Histological findings
1	F	4.8	3.8	1.0	4.8	28.8	47.9	+	95	Total villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes
2	F	5.6	4.6	1.0	5.6	121.4	129.9	+	57	Subtotal villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes
3	M	13.5	7.1	6.4	13.5	10.9	26.7	+	255	Subtotal villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes
4	M	15.8	10.3	5.5	15.8	23.4	6.8	+	130	Total villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes
5	F	16.7	10.5	6.4	16.7	152.6	20.6	+	250	Total villus atrophy, crypt hyperplasia, increased intraepithelial lymphocytes

* Diabetes mellitus, [†] anti-gliadin antibody, [§] antiendomysial antibody, [‡] tissue transglutaminase antibody

Table 4. Diagnostic values of AGA[†]-IgA and IgG, EMA[§] and tTG-IgA[‡] in patients

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Relative efficiency (%)
AGA [†] -IgA	60	26	6	89	29
AGA [†] -IgG	60	70	14	95	70
EMA [§]	100	95	62	100	95
tTG-IgA [‡]	100	86	38	100	87

[†] Anti-gliadin antibody, [§] antiendomysial antibody, [‡] tissue transglutaminase antibody

Discussion

Type 1 DM that occurs as a result of insulin deficiency due to autoimmune damage of the pancreatic β cells may be observed in association with the other autoimmune diseases [1]. Celiac disease, which is an autoimmune enteropathy, is characterized by intestinal lesions, which occur with gluten intake in sensitive individuals [12]. Association of celiac disease and type 1 DM has been shown in many studies and this association has been associated with common HLA DR3-DQ2/HLA DR/-DQ2 tissue antigens [6]. Following numerous studies conducted in this context, it has been recommended that Celiac disease should be screened by measuring the anti-gliadin-IgA, IgG, tTG-IgA and EMA levels in children with type 1 diabetes even if they are asymptomatic, because type 1 diabetes and Celiac disease have similar underlying genetic properties [2,5]. It has been reported that the prevalence of celiac disease is 20-fold higher compared to the normal population [5]. In the European countries, the incidence of CD in children with type 1 diabetes has been reported to be 6.6% in Italy, 11% in Germany, 1.1% in Finland and 1.6% in France [13-16]. In the other countries, it has been reported to be 16.4% in Algeria and 8.6% in Israel [17,18]. This variable incidence is thought to be

associated with the distribution of HLA genotypes and interaction of environmental and immunological factors [19]. In our study, AGA-IgA and IgG, EMA and tTG-IgA were used as screening tests and small intestinal biopsy was performed in 64 patients (24%) who had at least one positive serological marker. A diagnosis of celiac disease was made in accordance with the ESPGHAN criteria in five patients as a result of examination of the tissue samples obtained and the incidence of celiac disease was found to be 1.9%. In studies conducted so far, the highest prevalence of celiac disease in type 1 DM patients has been reported in Algeria (16.4%) [17]. It is not clear if genetic differences play a role in the high prevalence of association of these two diseases, because there is no information related with HLA tissue groups in Algerian patients.

Currently, noninvasive immunological markers with high sensitivity and specificity are being widely used for screening, because characteristic findings of celiac disease are absent in patients with type 1 DM [2]. A strong body of evidence has shown that anti-gliadin antibodies, antiendomysial antibodies, and anti-tissue transglutaminase antibodies are the most relevant serology tests for Celiac disease screening, diagnosis, and patient follow-up [20-

25]. It is now accepted that both antiendomysial antibodies and tTG antibodies are highly sensitive and extremely specific [20,21]. The European Society for Pediatric Gastroenterology recommends screening with tTG-IgA in patients with type 1 diabetes and endoscopic biopsy in patients who are found to have positive antibody [26]. The most sensitive and specific tests are tTG-IgA and EMA [10,11,27]. In one study conducted in the United States of America, EMA was found to be positive in all 38 patients who had celiac disease and EMA positivity could not be shown in any subject in the control group [27]. It has been reported that atypical findings are more prevalent in type 1 diabetes patients who develop celiac disease and these patients may even be asymptomatic or have latent findings and can be specified with serological markers. Although tTG-IgA and EMA have been shown to be more reliable compared to AGA among serological markers, it is known that no serological marker has a sensitivity or specificity of 100% [28]. The most sensitive and specific tests include tTG-IgA and antiendomysial IgA (EMA). Similar to the literature, EMA and tTG-IgA were found to be more sensitive and specific compared to AGA-IgA and IgG in our study (sensitivity of EMA and tTG-IgA 100%, specificities of EMA and tTG-IgA 95% and 86%, respectively). Antigliadin-IgA and IgG were found to have a sensitivity of 60%. Their specificities were found to be 26% and 70%, respectively.

Conclusion

In our study, the incidence of asymptomatic CD was found to be 1.9% in children with type 1 DM. Our results, which support current guidelines show that celiac disease can be screened with tTG-IgA and EMA that are the most sensitive and specific tests and small intestinal biopsy can be performed in children with type 1 DM.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

The financial support for this study was provided by the investigators themselves.

Ethical approval

Before the study, permissions were obtained from local ethical committee.

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