The frequency of celiac disease in children with autoimmune thyroiditis

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Abstract

Backgrounds/Aims : **Although the presence of autoimmune thyroiditis (AT) in celiac disease (CD) has been well documented among adults, CD in AT has been less reported in children. We aimed to investigate the frequency of CD in children with AT.**

Materials and Methods : **This prospective study was carried out from October 2015 to August 2016 and included 66 patients with AT. Firstly, total IgA and tissue transglutaminase antibody (tTG) IgA levels were measured. Those with increased level of tTG IgA were tested for anti-endomysium IgA antibodies (EMA). Patients with positive EMA underwent gastroduodenoscopy for a definitive diagnosis of CD.**

Results : **Sixty-six patients with AT (52 female) with mean age of 14.68 ± 3.18 years were enrolled. IgA deficiency was found in four patients. Only three of 66 patients (4.5%) were positive for tTG IgA. Patients positive for tTG IgA were then tested for EMA, and only one of them (1.5%) had positive EMA antibodies. Gastroduodenoscopy was performed in this patient. The result of pathological investigation was compatible with CD. Furthermore, one patient with AT had been diagnosed with CD previously.**

Conclusions : **Two (3.0%) of 66 patients with AT were found to have CD. According to the results, we assume that there is a close relationship between CD and AT disease. However, there is a need for multicentric, prospective studies that would support our findings.** (Acta Gastroenterol. belg., **2018**, 81, **5-8**).

Keywords : autoimmune thyroiditis, celiac disease, children, intestinal biopsy.

Introduction

Celiac disease (CD) is an immune-mediated systemic disease characterized by various degrees of intestinal villous damage triggered by gluten intake in genetically susceptible individuals (1).

Autoimmune thyroiditis (AT) comprises various clinical forms such as Hashimoto's thyroiditis (HT) and Graves' disease (GD). The most common cause of thyroiditis in childhood is HT (2).

The prevalence of CD is estimated to be 0.5-1% in all parts of the world. However, the risk of developing CD is higher in patients with diabetes, with autoimmune disorders and in the relatives of celiac patients, because of sharing the same HLA types (3).

The association between AT and celiac disease may be explained by common HLA antigens. HT is shown to be associated with HLA-DQ2/DQ8 and GD has been related to HLA-DQ2 (4,5). Also, it has been reported that both diseases have been associated with cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) encoding gene (candidate gene which predisposes thyroid autoimmunity) (6).

Although the presence of AT in CD has been well documented, there is lack of studies on frequency of CD in autoimmune thyroiditis, especially in children (4,7-9). The prevalence of CD has increased dramatically in the last 20 years, partially due to facilitated diagnostics enabling timely diagnosis. However, approximately only 10% of celiac disease patients are symptomatic. Despite the CD screening being recommended in risk groups, a majority of asymptomatic patients remains undiagnosed (10).

In a meta-analysis including 27 studies, the prevalence of biopsy-confirmed CD was determined to be 1.6% in patients with AT. It was higher comparing to data from screening studies of the general population (11). Also, the prevalence of CD was found to be higher in children with AT (6.2%) than in adults (2.7%). The authors suggested that the patients with AT should be screened for CD due its increased prevalence (11). For this reason, in this study we aimed to assess the prevalence of CD in children with AT.

Materials and Methods

This prospective study was carried out from October 2015 to August 2016 in Pediatric Endocrinology and Gastroenterology Outpatient Clinics. Sixty-six patients with AT were included in the study. Age at diagnosis, presenting symptoms, family history, and laboratory values of the patients were recorded.

The diagnosis of AT was based on clinical symptoms, biochemical tests, antithyroglobulin (TG) and/or thyroid peroxidase antibodies (TPO) positivity and/or diffuse or irregular hypoechogenicity of thyroid gland on ultrasonography (4,12).

Patients having incomplete information in files at the time of diagnosis, and patients refused to participate in the study were excluded. All of the patients had at least

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a six-months follow-up period. Patients were evaluated in terms of clinical and laboratory findings of CD.

Sample collection and measurements

A venous blood sample was taken from patients, and serum samples were stored at -80 °C until analysis. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) updated criteria in 2012 for initial screening of the CD include total IgA and tTG IgA as a reliable tests (1). Anti-endomysium IgA antibodies tests and small intestinal biopsy are suggested in cases with positive anti tTG IgA. In patients with IgA deficiency, tTG IgG and EMA IgG are helpful in making a decision for the intestinal biopsy (13). When used in combination, EMA and tTG antibodies have a specificity and sensitivity of 95% (14).

The current study was carried out according to ESPGHAN updated criteria. Firstly, total IgA by immunoturbidimetric method (Roche Diagnostics GmbH, Mannheim, Germany) and tTG IgA (Catalog No. 3503, EESC Diagnostics Gmbh, Wendelsheim, Germany) by ELISA method were measured at the Central Biochemistry Laboratory of Cerrahpasa Medical Faculty. In patients with IgA deficiency, tTG IgG was analyzed. The cut-off value of tTG IgA is 12 U/ml. Patients positive for tTG IgA were then tested for EMA IgA (Inova Diagnostics, Inc. Lubeck, Germany) analyzed by indirect immunofluorescence method at the "Duzen Laboratory Group" in Istanbul, Turkey. Patients with positive EMA antibodies underwent gastroduodenoscopy and small intestinal biopsy for a definitive diagnosis of the celiac disease.

Biopsies

Patients with both tTG IgA and EMA IgA positivity underwent gastroduodenoscopy. Four biopsies from the duodenum, and one biopsy from the bulb was taken. Biopsies were evaluated by the same experienced pathologist according to the Marsh classification criteria for the diagnosis of CD (15).

Statistical analysis

Statistical Package for the Social Sciences 17.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Independent-Samples t-test was used for nominal data with normal distribution. The Mann-Whitney U test was used for statistical analysis of patients not normally distributed variables. Frequency, percentage, and mean ± standard deviation (SD) and median (interquartile range) were used as descriptive statistics. P value was considered statistically significant < 0.05.

Ethical approval

This study protocol was approved by the Institutional Review Board at the Istanbul University, Cerrahpasa Medical School. Before the study, oral and written informed consent was obtained from the patients and their parents.

Results

Of the 66 patients included in the study, 63 were diagnosed with HT and 3 with GD. The mean ages, heights and weights of patients were 14.68 ± 3.18 years, 156.52 ± 15.34 cm (z score -0.19 ± 1.08), and 52.75 ± 14.02 kg (z score 0.10 ± 1.01), respectively. Fifty-two of patients (78.8%) were female.

Table 1 shows the demographic characteristics and laboratory findings of patients with AT.

None of the patients had gastrointestinal symptoms. Three patients (4.5%) positive for tTG IgA were then tested for EMA. Only one of them (1.5%) had positive EMA antibodies (Table 2). Gastroduodenoscopy was performed in the mentioned patient and four biopsy specimens from the duodenum and one biopsy speciment from the bulb were obtained. According to the Marsh classification score, the result of pathology was compatible with stage 3 of CD. As the patient's history was thoroughly evaluated, we learned that he did not have any complaints compatible with CD. One patient with AT had been diagnosed with CD prior to study (Table 2). Four patients had IgA deficiency and no tTG IgG positivity was detected in any of them.

Discussion

Celiac patients may present with gastrointestinal symptoms, extraintestinal symptoms or they can be totally asymptomatic. Approximately 50% of the

Table 1. — **Demographic characteristics and laboratory findings of patients**

	Patients (n=66)
Age (years)*	14.68 ± 3.18
Height (cm)*	156.52 ± 15.34
Weight (kg)**	52.5
Hemoglobin (mg/dL)*	12.75 ± 1.28
Mean corpuscular volume*	81.13 ± 5.07
Thrombocytes (/mm^3)**	264.5
Tissue transglutaminase IgA (U/ml)**	0.55
Total IgA (mg/dl)**	116.0

** Data are presented as mean ± standard deviation. **Data are presented as median (interquartile range).*

Table 2. — **The data of patients who had tissue transglutaminase antibody positivity**

Patient no	tTG IgA (U/ml)	Total IgA (mg/dl)	EMA IgA	Pathology status	Thyroid function
1*	300	126	+	Marsh 3	hypothyroid
2	300	158	+	Marsh 3	euthyroid
3	42.4	120	-	-	hypothyroid
4	16.2	135	-	-	euthyroid

*tTG = tissue transglutaminase, EMA = anti-endomysium antibodies. *The patient diagnosed with Down syndrome.*

celiac patients presents with extraintestinal or atypical symptoms such as anemia, osteoporosis, dermatitis herpetiformis, neurological problems, and dental enamel hypoplasia (16).

Over the last 30 years, the clinical presentation of CD has shifted from the malabsorption symptoms in childhood to milder and atypical symptoms in adulthood (17,18). Although it is increasingly being recognized, symptomatic cases constitute only the tip of the iceberg. Most of the CD patients remain asymptomatic and they are diagnosed through either family history or with an incidental screening (19).

The etiology of AT disease is multifactorial, and includes genetic and environmental factors (20). The etiology of AT is also complex; autoimmunity against thyroid antigens develops after exposure to environmental factors in genetically susceptible individuals (21).

It has been suggested that the presence and duration of gluten exposure in patients with CD plays also a direct role as trigger in autoimmunity (22).

The prevalence of CD in adults with AT was reported to be 3.3-4.8 times higher than in general population (23-25). Celiac disease was found to be more prevalent (3.4-7.8%) in patients with AT (especially HT), compared to the general population (25-29).

In a meta-analysis including 27 studies, the prevalence of biopsy-confirmed CD was found to be 1.6% in patients with AT (11).

Guliter *et al*. (30) reported the prevalence of CD in adults with AT to be 5.9% in Turkey. In this study, tTG IgA was measured in all patients and seven of them tested positive. A small intestinal biopsy was performed in six of them and four patients were diagnosed with CD. tTG IgA was found to be positive in eight (7.9%) patients in another study conducted in Turkey among 101 children with AT. Duodenal biopsy was performed in seven of them and five patients (4.9%) were diagnosed with CD (4).

CD was detected in one (1.25%) patient in a retrospective study including 80 children with AT from our country (31).

In a study conducted in United States of America including 302 children, adolescents, and young adults with AT (95% HT, 5% GD), tTG IgA positivity was detected in 14 (4.6%) patients; small intestinal biopsy was obtained from 13 of them and 7 (2.3%) patients were diagnosed with CD (32). tTG IgA positivity and biopsy-proven CD was found higher in AT than the general population (32).

Limiting factors of the previous studies are inadequate patient numbers, and use of the different diagnostic criteria for CD. In addition, AT patients had positive serological test but intestinal biopsies were not routinely performed in most of the studies. A proportion of these patients may have so-called "potential CD" and their diagnosis would only have been made with long-term serologic and histologic follow-up (33,34).

This study was carried out according to ESPGHAN updated criteria from 2012. Total IgA and tTG IgA were analyzed in all patients. Three patients (4.5%) positive for tTG IgA were then tested for EMA. Only one of them (1.5%) had positive EMA antibodies. Gastroduodenoscopy was performed in this patient and the pathologic examination was compatible with Marsh classification 3 of CD. This patient was also diagnosed with Down syndrome, without any complaint compatible with CD. Also, one patient with AT had been diagnosed with CD four years ago. In this study, the prevalence of biopsy-proven CD was 2/66 (3.0%). In a meta-analysis, the prevalence of biopsy-confirmed CD was found to be 1.6% in patients with AT (11). In a multicenter study from Turkey including healthy children between the ages of 6-17, the prevalence of CD was found to be 0.47% (35). According to our results, the prevalence of CD in children with AT was 6 (3.0%) times higher than in the general population of Turkey. One of the two patients diagnosed with celiac disease is a Down syndrome patient, and Down syndrome is also known to be associated with CD.

Universal screening of CD is debated, but not generally advised. However, it has been reported that the cost-effectiveness of CD screening in high-risk groups would be more appropriate. (36,37). Screening for CD in high-risk groups (even if asymptomatic) should be considered due to its potential harmful effects on growth and bone health. AT patients are considered a high-risk group, as had been confirmed by our data.

As a result, the prevalence of CD in children with AT was found to be 6 times higher than in general population. However, prospective, multicentric studies with higher number of patients are needed in order to provide a more reliable and valid data. Furthermore, a case with Down syndrome, who was negative at celiac screening 6 years earlier, tested positive at the time of our study. We suggest that CD screening should be done in children with AT (even if asymptomatic). Serological tests in every 2 to 3 years seem appropriate in screening of CD, to avoid the deleterious effects of unrecognized CD in patients with high-risk groups such as AT patients, and Down syndrome.

Conflict of interest

The authors declared that there is no conflict of interest

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