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Original Article

Celiac disease in children and adolescents with Hashimoto Thyroiditis

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Abstract

Aim: The aim of this study was to evaluate clinical and laboratory findings and determine the prevalence of celiac disease (CD) in children with Hashimoto thyroiditis (HT).

Material and Methods: The data of a total of 80 patients with positive anti-thyroid antibodies who were aged between 6 and 17.9 years were retrospectively studied. Age, gender, complaints at the time of presentation, family history of thyroid disorders, clinical and laboratory findings were recorded. The levels of thyrotropin, free thyroxin, thyroid autoantibodies (thyroid peroxidase and thyroglobulin antibodies), immunoglobulin A (IgA), anti-tissue transglutaminase antibodies (IgA-tTG), and thyroid ultrasonography findings were enrolled.

Results: Eighty patients (65 females (81.2%) and 15 males (18,8%)) were included in the study. Family history of thyroid disease was present in 38 (47.5%) patients. The most common complaints at the time of presentation were goiter (%30) and weight gain (%25). Forty three (53.8%), 23 (28.7%), and 14 (17.5%) patients presented with euthyroidism, subclinical hypothyroidism and obvious hypothyroidism. Thirty seven (46.2%) patients had goiter. IgA-tTG was found to be positive after a diagnosis of HT was made in only one patient (1.25%) and the diagnosis of CD was confirmed when intestinal biopsy of this patient revealed villus atrophy, crypt hyperplasia and increase in the intraepithelial lymphocyte count.

Conclusions: In our study, it was found that the most common complaints at presentation in patients with a diagnosis of hashimoto thyroiditis included goiter, weakness and weight gain and the prevalence of celiac diseases was found to be 1.25% (1/80). This study shows that the prevalence of CD in patients with a diagnosis of HT is higher compared to the prevalence in the healthy pediatric population.

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Keywords: Celiac disease, children, hashimoto thyroiditis

Introduction

The most common cause of goiter and acquired hypothyroidism is hashimoto thyroiditis (HT) in children and adolescents especially in regions where endemic iodine deficiency is not found (1). Although the prevalence of hashimoto thyroiditis varies from region to region, it was reported to be 3% in children aged between 6 and 18 years and the female/male ratio was 2/1 (2). It occurs most commonly in the early and middle adolescence in the pediatric age group. Although the most commonly observed clinical finding is goiter, patients may biochemically be euthyroid, hypothyroid or hyperthyroid at presentation (3).

Celiac disease (CD) is a proximal intestinal disease which develops against gluten which is a vegetable protein found in wheat, barley, rye and in a small extent in oat in individuals with genetic predisposition. The clinical picture in celiac disease ranges from asymptomatic state to severe malabsorption and it has been reported that 33-67% of all patients are asymptomatic at the time of diagnosis (4). Currently, the most efficient serological marker in the diagnosis of CD is accepted to be serum anti-tissue transglutaminase (dTG) IgA and its positivity requires investigation in terms of CD (5).

It is known that cellular and humoral response are involved in the etiopathogenesis of hashimoto thyroiditis and it is associated with the other autoimmune diseases (6). In this study, we aimed to evaluate the clinical and laboratory findings in children followed up with a diagnosis of HT (i) and to investigate the prevalence of CD in these patients (ii).

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Material and Methods

The data of 114 patients aged between 6.0 and 17.9 years who presented to our clinic between 2005 and 2014 with the diagnosis of HT (euthyroid, subclinical hypothyroidism, overt hypothyroidism) were enrolled in the study. The patients who had regular file records were examined retrospectively. The subjects whose file records included deficient data (dTG-IgA and serum IgA levels could not be found in the file records of 28 subjects), who received a diagnosis of subclinical hypothyroidism (four subjects), who had selective IgA deficiency (one subject) and/or partial IgA deficiency (one subject) were excluded from the study. The diagnosis of hashimoto thyroiditis was made with increased anti-tiroglobulin (anti-TG) and/or anti-peroxidase (anti-TPO) autoantibody levels. The age, age of onset of complaints, familial history, body weight (kg), height (cm), body mass index (MBI), BMI-standart deviation score (SDS) and laboratory findings of all subjects were retrospectively recorded from the file records. The height was measured by Harpenden stadiometer (Holtain Limited, Crymych, Dyfed, U.K) and the body weight was measured using SECA (GMBH & CO KG Hamburg, Germany) scale with had a sensitivity of 0.1 kg. The body mass index was calculated by dividing the body weight by the square of the height in meters. The body weight SDS, height SDS and BMI SDS values were obtained using the (Centers for Disease Control and Prevention) CDC data. The Thyrotropin (TSH), free thyroxin (fT4) and thyroid autoantibodies (anti-TG and anti-TPO), findings on ultrasonographic examination which was performed considering autoimmune thyroiditis, dTG-IgA and serum IgA levels which were tested considering accompanying autoimmune diseases of 80 subjects who had a diagnosis of HT were recorded. The thyroid volume was calculated on thyroid ultrasonography using the following formula: width x length x 0.523 and the values above the 97th percentile were considered goiter (7). The serum fT4 and TSH levels were measured using DxI800 autoanalyzer (Beckman Coulter Inc, CA, USA) with chemiluminescence immunoassay method. The lower and upper limit values of the measurement method used in the biochemistry laboratory were considered the normal reference range for thyroid function tests (sT4: 0.5-1.51 ng/dL, TSH: 0.34-5.6 uIU/L). The subjects whose serum TSH and fT4 levels were within the normal limits were considered euthyroid, the subjects whose fT4 level was low and/or normal and TSH level was >20 µIU/mL were considered to have hypothyridism and the subjects whose fT4 was normal and TSH was 5.6-20 µIU/mL were considered to have subclinical hypothyroidism. Serum anti-TPO and anti- TG levels were measured with chemiluminescence immunoassay method using Immulite 2500 autoanalyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). The normal reference range was considered 0-9 IU/mL for anti-TPO and 0-4 IU/mL for anti-TG.

In our study, dTG-IgA was studied with ELISA method (Katalog number: EI 1910-9601 A) using Euroimmun analyzer I (Euroimmun Inc, Luebek, Germany) and 0-20 RU/mL was considered the normal reference range. Serum IgA was studied with immunoturbidimetric method using AU5800 autoanalyzer (Beckman Coulter Inc, CA, USA). The normal reference ranges were specified according to age and gender.

Approval was obtained from Dokuz Eylül University School of Medicine Noninvasive Research Ethics Committee for the study (Decision number: 2014/36-05).

Statistical analysis

Statistical analysis was performed using SPPS 16.0.1 (SPSS Inc.; Chicago, IL, USA) program. All data were given as mean±standard deviation (SD). In comparison of the groups, Kruskal-Wallis test which is nonparametric test was used. If a statistically significant difference was found ($p<0.05$), Mann-Whitney U test was used to specify which group the difference was related with. A p value of <0.006 obtained in the Mann-Whitney U test was considered significant (Bonferroni correction). In comparison of multiple groups, multi-sided chi-square test. A p value of <0.05 was considered statistically significant.

Results

Eighty subjects including 65 females (81.2%) and 15 males (18.8%) were included in the study. 72,5% of the subjects were adolescents. A familial history of thyroid disease was present in 38 (47.5%) subjects. The mean age at the time of diagnosis was 10.6±3.4 years. The mean body weight SDS was 0.59±1.17, the mean height SDS was 0.30±1.13 and the mean BMI SDS was 0.40±1.17. Goiter was observed on examination in 37 (46.2%) of the subjects. The complaints at presentation are summarized in Table 1.

At the initial presentation the mean thyroid hormone levels and antibody titers were found to be as follows; fT4: 0.96±0.27 ng/dL, TSH: 17.5±32.0 µIU/mL, anti-TPO: 505.4±425.4 IU/mL, anti-TG: 423.9±825.8 IU/

mL. At the time of diagnosis, 53.8% of the subjects (n=43) had euthyroidism, 28.7% (n=23) of the subjects had subclinical hypothyroidism and 17.5% (n=14) of the subjects had overt hypothyroidism. The distributions of age, gender and goiter (according to thyroid USG and physical examination) by thyroid functions at presentation are shown in Table 2. When the subjects were compared by thyroid function states, no significant difference was found in terms of gender, presence of puberty and presence of goiter (p>0,05). The mean age of the euthyroid subjects was significantly higher compared to the mean age of the subjects with subclincal hypothyroidism (p<0.05).

Anti-TPO was positive in 100% of the subjects included in the study and anti-TG was positive in 82.5%. On thyroid ultrasonography, the thyroid volume was > +2 SDS in 32 of 77 subjects (46.3%). Pseudonodular appearance was found in 37 (46.3%) of the subjects and nodule was found in 6 (7.5%). While 57 (71.3%) subjects included in the study received levothyroxine, the mean dose to reach the euthyroid state was found to be 1.51±0.63 µg/kg/day.

dTG-IgA was found to be positive in one subject (1.25%) who was found to have the complaints of abdominal pain, loss of appetite and abdominal distension in the follow-up and intestinal biopsy of this subject revealed villus atrophy, crypt hyperplasia and increased intraep-

Table 1. Presenting complaints of the subjects who were diagnosed with Hashimoto thyroiditis

Complaint	Number	%	Complaint	Number	%
Swelling in the neck	24	30	Cramp	7	8.8
Increased weight	20	25	Easy nail spilliting	6	7.5
Weakness	19	23.8	Tingling in the feet	6	7.5
Intolerance to cold	11	13.8	Hair loss	3	3.8
Dry hair	10	12.5	Swelling in the hands	3	3.8
Constipation	10	12.5	Nervousness	4	5
Dry skin	9	11.3	Dyspnea	2	2.5
Loss of appetite	8	10	Coarse voice	1	1.3
Decreased academic success	8	10			

Table 2. Comparison of the age, gender, puberty and goiter frequency of the subjects by thyroid function status

	Overt hypothyroidism (n=14)	Subclinical hypothyroidism (n=23)	Euthyroidism (n=43)	p
Mean age (years)	9.17±2.84 [a]	9.18±2.70 [b]	11.76±3.46 [a,b]	0.02**
Gender				
Female (81.3%)	10 (%71.4)	18 (%78.3)	37 (%86.1)	0.209*
Male (18.7%)	4 (%28.6)	5 (%21.7)	6 (%13.9)	
Presence of puberty				
Pubertal (72.5%)	8 (%57.1)	14 (%60.9)	36 (%83.7)	0.052*
Prepubertal (37.5%)	6 (%42.9)	9 (%39.1)	7 (%16.3)	
Presence of goiter				
Physical examination				
Goiter present (46.2%)	7 (%50)	10 (%43.5)	20 (%46.5)	0.927*
Goiter absent (53.8%)	7 (%50)	13 (%36.5)	23 (%53.5)	
USG finding				
Goiter present (40%)	8 (%57.1)	10 (%43.5)	14 (%35.0)	0.342*
Goiter absent (60%)	6 (%42.9)	13 (%46.5)	9 (%65.0)	

*Ki-kare testi,

**Kruskal_Wallis test (p<0.05)

[a,b]Mann-whitney U test (p<0.016)

[a]Overt Hypothyroidism-Eutyhroidism (p=0.009), bsubclinical hypothyroidsim-euthyroidism (p=0.002)

ithelial lymphocyte count. The biopsy findings were reported as Marsh grade 3a.

Discussion

Hashimotothyroiditis is observed most commonly in the adolescence and in female gender (2-7/1) (3, 8-10). In our study, 72.5% of the subjects (n=58) were adolescents and the female/male ratio was found to be 4.3/1. These results were considered to be compatible with the literature.

Although no specific genetic inheritance has been identified for hashimoto thyroiditis in the pediatric age group, there is strong evidence that it is familial. It has been reported that thyroid antibodies are positive in first degree relatives in approximately half of the subjects and thus autosomal dominant inheritance is considered. The fact that it is observed more frequently in monozygous twins compared to dizygous twins in twin studies supports this view. In studies conducted up to the present time, immunomodulator genes (HLA-DR, CTLA-4, CD40, PTPN22) and thyroid specific genese (Tg and TSH receptor genes) have been identified (11). In the study conducted by Wasniewska et al. (12) which included 608 subjects with HT, the rate of a positive history of thyroid disease in first degree relatives was found to be 31.6%. In this study of ours, the rate of thyroid disease in the family was found to be 47.5%. This rate was similar to the rates reported in the literature and it was considered a finding which supported genetic predisposition in HT.

When the subjects were classified by thyroid function states in our study, most were found to be in the euthyroid state which was compatible with the literature (1, 12, 13). In our country, 62.8% of the subjects with a diagnosis of HT were found to be euthyroid in a study conducted by Dündar et al. (14) and 36.7% of the subjects with a diagnosis of HT were found to be euthyroid in a study conducted by Özen et al. (9). In this study, 51.2% of the subjects were found to be euthyroid (n=43), 27.4% were found to have subclinical hypothyroidism (n=23) and 16.6% were found to have overt hypothyroidism (n=14). Wasniewska et al. (12) conducted a study with 608 children and adolescents with HT and found that 52.1% of the subjects were euthyroid, 19.2% had subclinical hypothyroidism and 22.2% had overt hypothyroidism similar to our study.

When the subjects were compared according to thyroid functions, it was found that the mean age of the euthyroid subjects was significantly higher compared to the mean age of the subjects who had overt hypothyroidism and subclinal hypothyroidism. In the literature, it has been reported that the subjects who have thyroid dysfunction are younger which is compatible with our study (1). Younger age of the subjects with thyroid dysfunction was explained with the view that early onset HT could have a more severe prognosis (12). When the subjects were compared by thyroid function in our study, no significant difference was found in terms of gender, presence of puberty and presence of goiter. When the subjects with HT were classified by thyroid function in the study conducted by Dündar et al. (14), no significant difference was found in terms of gender in accordance with our study, whereas presence of goiter was found with a higher rate in euthyroid subjects.

On thyroid ultrasonography (USG), gland enlargement, diffuse heterogeneity, hypoechoic appearance, micronodular appearance and more rarely nodular formation are observed in patients with Hashimoto thyroiditis (3, 15, 16). When the file records were examined in our study, it was found that thyroid USG was performed in 77 subjects and thyroid volume was found to be >+2 SDS in 41.5% of these subjects which was compatible with the literature (9). When the rates of development of nodule in the literature were reviewed, it was found that rates up to 34.4% have been reported (17). However, thyroid nodule was found in six subjects (7.5%) in our study which is similar to the study conducted by Dündar et al. (14) (nodule in 7% of 78 subjects).

In children with Hashimoto thyroiditis, L-thyroxine treatment is given to the subjects with overt and subclinical hypothyroidism. Treatment is recommended in euthyroid subjects with goiter (11, 18). In the literature, the rate of L-thyroxine treatment in individuals with HT ranges between 40% and 70% (10, 14, 17). In our study, this rate was found to be 71.3% which was compatible with the literature. The mean L-thyroxine dose was found to be 1.51±0.63 µg/kg/day which was also compatible with the literature (9).

In Hashimoto thyroiditis, thyroid gland enlargement and swelling of the neck are reported as the most common complaints in the literature (3, 9, 16, 19). In our study, the most common complaint at presentation was found to be swelling in the neck in accordance with the literature and physical examination revealed goiter in 46,3% of the subjects. In our study, the complaint of swelling in the neck was followed by weakness, increased weight, intol-

erability to cold and dry hair. In the literature, the most common symptoms which follow swelling in the neck include nervousness, increased weight, loss of appetite, dermatological problems and hair loss. In this study, the most common symptoms at presentation after swelling in the neck included weakness (23.8%), increased weight (25%), intolerability to cold (13.8%) and dry hair (xerasia) (12.5%) (9, 11).

Celiac disease is considered one of the most common life-long diseases and is observed with an increasing prevalence worldwide (20). Growth retardation, abdominal distention, chronic diarrhea, vomiting and restlessness which develop with inclusion of gluten in the diet are the classical findings of CD. Short stature, iron deficiency anemia, osteoporosis, delayed puberty, dental disorders, arthritis, chronic abdominal pain and neurological problems have been reported at older ages (21). It has been reported that serologic tests performed for screening purpose are the most valuable methods in celiac disease. dTG-IgA which is one of the antibodies used in serological tests is an antibody produced against transglutaminase (structural protein of the intestinal mucosa). It sensitivity has been reported to be 90-100% and its specificity has been reported to be 95-100%. When cost, technique and reliability are considered, it has been reported to be the most efficient serologic marker (22, 23). However, intestinal biopsy is still the gold standard in the diagnosis of the disease (24). It has been reported in numerous previous studies that the prevalence of autoimmune thyroid disease is increased in individuals with celiac disease (25-27). However, there are a limited number of studies examining the prevalence of CD in children and adolescents with autoimmune thyroid disease. In studies conducted with adults, the prevalence of CD has been reported to be 10.8-3.3% in subjects with autoimmune thyroid disease (28-30). In studies conducted with children, the prevalence of CD has been reported to be 0.3-1.2% in healthy children and 1,3-6,5% in children and adolescents with a diagnosis of autoimmune thyroiditis (31, 32). In a study conducted by Sattar et al. (32) in children, dTG-IgA was found to be positive in 14 (4.6%) of 302 subjects with autoimmune thyroiditis and it was reported that the diagnosis of CD was confirmed with intestinal biopsy in seven of these subjects (2.3%). In our country, it was reported that five subjects (4.9%) were diagnosed with CD in a study conducted by Sarı et al. (31) with children and adolescents with a diagnosis of autoimmune thyroditis. In a study conducted with healthy school age children in Turkey, the frequency of CD was reported to be 1:212 (0.47%) (33). In this study of us, dTG-IgA positivity was found only in one (1.25%) of 80 subjects during the clinical follow-up after a diagnosis of HT was made. The diagnosis of CD was confirmed with intestinal biopsy in this subject. In addition, it was found that this subject had abdominal pain, loss of appetite and abdominal swelling.

The limitation of our study was the fact that it was conducted with a small number of subjects, because it was a retrospective study. More elucidative evidence about the frequency of CD in subjects with a diagnosis of HT will be demonstrated with studies conducted with a larger case group.

In this study, it was found that (I) the most common complaints at presentation in subjects with a diagnosis of HT included goiter (29.8%), weakness (23.8%) and increased weight 25%) and (ii) the frequency of CD was 1.25% (1/80). Although a higher frequency of CD was found in our subjects compared to the frequency in healthy children, studies with a much higher number of subjects are needed to justify screening of CD in subjects with HT.

Ethics Committee Approval: Ethics committee approval was received for this study from Dokuz Eylül University School of Medicine. (Decision No: 2014 / 36-05).

Informed Consent: Written informed consent was not obtained from patients due to the retrospective nature of this study.

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