AUTOIMMUNE DISEASES ACCOMPANYING HASHIMOTO THYROIDITIS IN PEDIATRIC PATIENTS

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AIM: Hashimoto thyroiditis (HT) is the most common cause of goiter and acquired hypothyroidism in children and adolescents living in iodine-sufficient regions. In this study, we aimed to investigate the coexistence of other accompanying autoimmune diseases in patients aged 5–18 years who were diagnosed and followed up at the Pediatric Endocrinology Clinic of our hospital.

MATERIAL AND METHODS: A total of 220 patients aged 5–18 years who were diagnosed with HT at the Pediatric Endocrinology Clinic of the University of Health Sciences Ankara City Hospital. Patient' age at admission, sex, family history, complaints at admission, comorbidities, physical examination and laboratory findings, and clinical follow-up information were retrospectively reviewed.

RESULTS: Of the 220 patients, 77.7% were female and 22.2% were male, with a mean age of 13.8±3.3 years. Of the 51.4 had euthyroidism, 40.4% had subclinical hypothyroidism,and 8.2% had overt hypothyroidism, respectively. Anti-thyroid peroxidase antibody was detected in 97% of patients and anti-thyroglobulin antibody (anti-Tg) was detected in 74% of patients. There was a family history of autoimmune disease in 36.4% of the patients. Autoimmune disease were present in 45 patients (20.4%). The most common autoimmune diseases in the patients were type 1 diabetes mellitus (T1DM) (14%), celiac disease (5%), skin diseases (2.7%), and rheumatologic diseases (1.3%). No statistically significant differences were found between the sex, age at diagnosis, current age, family history of autoimmune disease and thyroid function status of patients with HT and T1DM.

The mean age of the patients followed up with HT with and without additional autoimmune disease was similar (p=0.644). In both groups, female sex was dominant. However, the number of male patients (35.6%) in the group with additional autoimmune disease was statistically significantly elevated than the group without autoimmune disease (19.9%) (p=0.016). The rate of subclinical hypothyroidism was statistically significantly elevated in the group without additional autoimmune disease (p<0.001). A statistically significant relationship was found between elevated Anti-Tg and additional autoimmune disease (OR=2.32 (95% CI; 1.16–4.56). The prevalence of additional autoimmune disease was increased 2.32 times in patients with elevated anti-Tg levels.

There was no statistically significant correlation between the sex of the patients, their thyroid function status and thyroid autoantibodies (p=0.507). However, the prevalence of celiac disease was statistically significantly elevated in female patients (43.5%) than in male patients (6.7%) (p=0.014). In addition, the prevalence of T1DM was found to be statistically significantly elevated in males (93.8%) compared to females (52.2%) (*p*=0.007). 13.3% of patients with additional autoimmune disease were under the age of 10 and 64.4% were above the age of 10, this was statistically significant (*p*<0.01). T1DM was the most common autoimmune disease in both groups.

CONCLUSION: As shown in our study, autoimmune diseases, especially T1DM and celiac disease, are associated with HT. It should be kept in mind that there is an increased risk of autoimmune disease in HT that affects both sexes and increases with age. In particular, regular follow-up of HT patients with elevated anti-Tg levels in terms of autoimmune disease development is important in terms of earlier diagnosis of diseases and reducing their morbidity.

KEYWORDS: Hashimoto thyroiditis. Autoimmune disease. Type 1 diabetes mellitus. Anti-thyroid peroxidase antibody. Anti-thyroglobulin antibody.

INTRODUCTION

HT is the most common cause of goiter and acquired hypothyroidism in children and adolescents in regions where iodine exists at sufficient amounts. Although autoimmunity plays roles in the pathogenesis, genetic predisposition and environmental factors are also important [1].

Patients are diagnosed with the presence of goiter and increased thyroid autoantibodies in sera. The application to a physician may be because of clinical findings based on decreased thyroid functions e.g. goiter, weakness, dry skin, constipation, decreased academic performance or non-thyroid causes e.g. alopecia, vitiligo, atopy, and depression. In HT, clinical manifestation may range from euthyroidism to overt hypothyroidism and hyperthyroidism [2].

It is already known that cellular and humoral immune response play roles in the etiopathogenesis of HT, and in its association with other autoimmune diseases [3]. There are few studies reporting that HT may be associated with non-thyroid autoimmune diseases. Most studies, which investigated the coexistence of HT and other autoimmune diseases, were conducted in the adult patient population, and examined the prevalence of HT in nonthyroid autoimmune diseases [4, 5].

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In the present study, the purpose was to investigate the coexistence of other accompanying autoimmune diseases in patients with HT.

MATERIALS AND METHODS

Study Method

A total of 220 patients who were aged 5–18 years, diagnosed with HT in the Pediatric Endocrinology Clinic of the University of Health Sciences Ankara City Hospital, were included in the study. The age at admission, sex, family history, complaints at admission, co-morbidity, physical examination, laboratory findings, and clinical follow-up data of patients were reviewed retrospectively in their files.

Ethics statement: The study was approved by the Health Sciences University Ankara City Hospital Clinical Research Ethics Committee as the subject of the thesis on 27.06.2019 (account decision: 2019-216).

Inclusion Criteria and Conduction of the Study

The autoimmune disease symptoms and laboratory findings in patients with HT were recorded as pernicious anemia, autoimmune hepatitis, T1DM, celiac disease, arthropathies, connective tissue diseases, skin diseases, Addison Disease, multiple sclerosis, and inflammatory bowel disease. Patients with missing file data and those with chromosomal abnormalities were not included in the study.

The diagnosis of HT was made with anti-TPO and/or anti-Tg positivity; and sT4, TSH, and thyroid autoantibodies, hemogram, fasting blood glucose, AST, ALT, and LDH values were examined in all cases. Anti-tissue transglutaminase IgA and serum IgA positivity were also investigated; and thyroid ultrasonography (US) results of all patients were evaluated.

The positivity and numerical values of the anti-TPO (>60 U/mL) and anti-Tg (>4.5 IU/mL) antibodies of the patients were also recorded. The positivity of one of the two antibodies was sought for the diagnosis of HT. Clinically, according to the thyroid hormone levels, euthyroidism was classified as [sT4 normal (N) (0.86–1.4 ng/dL), TSH N (0.64–6.27 mU/L)], subclinical hypothyroidism (sT4 N (0.64–6.27 mU/L)]. 86–1.4 ng/dL), increased TSH (>6.27 mU/L)), overt hypothyroidism (sT4 low (<0.86 ng/dL), increased TSH (>6.27 mU/L), and hyperthyroidism (sT4 increased (>1.4 ng/dL)), and TSH suppressed (<0.64 mU/L)).

Those who had signs of thyroiditis on thyroid ultrasonography (increased thyroid gland size or atrophy, hypoechogenicity, nodularity separated with echogenic septa in the parenchyma, pseudonodules with lymphocytic infiltration and irregularity in gland contours, increased or decreased vascularization) were recorded.

Statistical Analysis

The data analysis was performed with the SPSS (Statistic Package for Social Sciences, Chicago, IL, USA) 22.0 package program. Descriptive statistics were presented as mean ± standard deviation for continuous variables, and numbers and percentages for categorical variables. Whether the distribution of the continuous variables complied with the normal distribution was evaluated with the Kolmogorov-Smirnov Test. When there was a normal distribution, the means were evaluated with the Independent Samples T-test, and the Chi-Square Test or Fisher's Exact Test was used to compare the categorical variables. Factors associated with autoimmune disease were analyzed with the Logistic Regression Analysis, and the results were considered statistically significant at $p < 0.05$.

Table 1. Demographic, Clinical, and Laboratory characteristics of patients diagnosed with HT

	(n=220)
Age (years)	
Mean±SD (min-max)	13,8±3,3 (5–18)
Sex	
Male	49 (22,2%)
Female	171 (77,7%)
Presence of Family History	80 (36,4%)
Function Status	
Hypothyroidism	18 (8,2%)
Subclinical	89 (40,4%)
Euthyroidism	113 (51,4%)
TSH	7,6±11,6
T3	4,06±1,9
T4	1,27±0,3
Anti-Tg	716,9±3017,6
Anti-TPO	3039,1±4602,1

TSH: Thyroid Stimulant Hormone, T3: Triiodothyronine, T4: Thyroxine, Anti-Tg: Anti-Thyroglobulin Antibody, Anti-TPO: Anti-Thyroid Peroxidase Antibody.
The data are shown as Mean±SD, numbers (%).

RESULTS

Demographic Characteristics

Among the 220 patients who were included in the study, 77.7% were female, and 22.2% were male, and had a mean age of 13.8±3.3 years. There was a family history of autoimmune disease in 36.4% of the patients. It was found that 51.4% of the patients were euthyroidism. Thyroiditis findings in thyroid ultrasonography were present in 210 (95%) of the patients. Anti-TPO was detected in 97% of the patients, and anti-Tg was positive in 74%. The mean anti-TPO antibody level was found to be 3039.1±4602.1 U/mL, and the mean anti-Tg level was 716.9±3017.6 IU/mL. The demographic, clinical, and laboratory characteristics of the patients are given in Table 1.

A total of 8.2% of the patients had overt hypothyroidism (elevated TSH, low sT4), 40.4% had subclinical hypothyroidism (elevated TSH, normal sT4), and 51.4% had euthyroidism (normal TSH and sT4).

Admission Complaints of Patients Diagnosed with Hashimoto Thyroiditis

The most common complaint of the patients was swelling in the neck at a rate of 15.1%, weakness 12.7%, weight gain 9.1%, paleness 9.1%, tremor 6.8%, chest pain 5.5%, loss of appetite 5%, palpitation 5%, irregular menstruation 5%, hair loss 4.5%, headache 3.6%, shortness of breath 2.7%, constipation 2.7%, and short stature 2.7%, respectively. There were no complaints in 23 patients (10.5%), and they were diagnosed during routine screening tests.

Autoimmune Diseases Accompanying Hashimoto Thyroiditis

Additional autoimmune disease was present in 45 (20.4%) of the 220 patients who were examined with Hashimoto Thyroiditis. The most common autoimmune disease T1DM in the patients was with 14%, celiac disease with 5%, skin diseases with 2.7%, and rheumatologic diseases with 1.3%.

The mean age of the group with and without additional autoimmune disease was similar (p=0.644). Female sex was dominant in both groups. However, the number of male patients (35.6%) was statistically significantly elevated in the group with additional autoimmune disease than in the group without (19.9%) (p=0.016) (Table 2).

The thyroid function status of the patients was similarly euthyroidism in the group with and without additional autoimmune disease. However, although 66.6% patients with additional autoimmune disease were found to be euthyroidism, 47.4% of them without additional autoimmune disease were euthyroidism (p<0.001). The rate of subclinical hypothyroidism was elevated at a statistically significant level in the group without additional autoimmune disease (p<0.001). No significant relations were detected between elevated anti-TPO and presence of additional autoimmune disease (OR=0.13 (95% CI; 0.01–1.03)). However, statistically significant relations were detected between elevated anti-Tg and additional autoimmune disease (OR=2.32 (95% CI; 1.16–4.56). The prevalence of additional autoimmune disease increased 2.32 times in patients with elevated anti-Tg levels (Table 2).

Among the patients who had additional autoimmune disease, 35.6% were male, and 64.4% were female. The mean age of the female patients was 13.1±3.7, and that of the male patients was 13.9±3.0 years.

The prevalence of celiac disease was elevated at a statistically significant level in female patients (43.5%) than in males (6.7%) (p=0.014). The prevalence of T1DM was elevated in males (93.8%) and females (52.2%) at statistically significant levels (p=0.007) (Table 3).

A total of 13.3% of the patients who had additional autoimmune disease were under the age of 10, and 64.4% were above the age of 10, which was found to be statistically significant (p<0.01). The female sex was dominant in both groups. Similarly, thyroid function status was dominated by euthyroidism in both groups. No statistically significant differences were detected between thyroid autoantibodies, diabetes autoantibodies, and celiac autoantibodies. T1DM was the most common autoimmune disease in both groups, and there were no statistically significant differences in the prevalence of T1DM, rheumatologic disease, skin disease, and celiac disease. The relations between autoimmune disease and age in patients who had a diagnosis of HT are shown in Table 4.

DISCUSSION

It was shown in the present study that approximately 20% of the patients who were diagnosed with HT in childhood had additional autoimmune diseases (most commonly T1DM) accompanied by celiac disease. It was also found that male and female patients are at risk in the development of additional autoimmune disease, and the prevalence of additional autoimmune disease increased 2.32 times especially in patients with elevated anti-Tg levels.

There are few studies which show the association of HT with non-thyroid autoimmune diseases [4, 5, 6]. Ruggeri et al. compared the data of 1053 patients of whom 500 adult and 553 child/adolescent patients who had newly diagnosed HT, and showed that female sex was dominant in both groups; however, this was significantly more in adults. Hypothyroidism had an elevated percentage in adults when

Table 2. Characteristics of patients with and without accompanied autoimmune diseases in patients diagnosed with HT

	No additional autoimmune disease (n=175)	Additional autoimmune disease (n=45)	p
Age (years)			
Mean±SD (min-max)	13,9±3,3 (5–18)	13,6±3,2 (5–18)	0,644*
Sex			
Male	33 (19,9%)	16 (35,6%)	0,016**
Female	142 (81,1%)	29 (64,4%)	
Function Status			
Hypothyroidism	13 (7,4%)	5 (11,1%)	0,059**
Subclinical	79 (45,1%)	10 (22,2%)	<0,001**
Euthyroidism	83 (47,4%)	30 (66,7%)	<0,001**
TSH	7,4±9,1	8,2±21,6	0,804*
T3	4,0±2,1	4,1±1,4	0,783*
T4	1,1±0,36	1,1±0,3	0,807*
Anti-Tg	815,3±3651,2	334,1±553,8	0,432*
Anti-TPO	3348,1±4947,4	1837,6±3259,4	0,014*
Thyroid US	169 (96,6%)	41 (91,1%)	0,117**

TSH: Thyroid Stimulant Hormone, T3: Triiodothyronine, T4: Thyroxin, Anti-Tg: Anti-thyroglobulin antibody, Anti-TPO: Anti-thyroid peroxidase antibody, Thyroid US: Thyroid ultrasonography
The data are given as Mean±SD, and numbers (%).
* Independent Samples t-test, ** Chi-Square or Fisher's Exact Test

Table 3. Autoimmune disease and sex relation

	Male (n=16)	Female (n=29)	p
Age (years)			
Mean±SD	13.1±3.7	13.9±3.0	0.418*
Function Status			
Hypothyroidism	2 (12.5%)	3 (10.3%)	
Subclinical	5 (31.3%)	5 (17.2%)	0.507**
Euthyroidism	9 (56.3%)	21 (72.4%)	
TSH	12.6±34.0	5.8±10.0	0.319*
T3	4.1±0.7	4.2±1.8	0.659*
T4	1.2±0.1	1.1±0.3	0.400*
Anti-Tg	207.2±231.3	397.5±654.7	0.338*
Anti-TPO	2403.0±4146.4	1525.69±2683.35	0.394*
Thyroid US	15 (93.8%)	26 (89.7%)	0.644**
Anti-GAD	3.4±7.1	11.5±22.3	0.467*
Anti-tissueTG	4.3±16.7	35.6±67.9	0.044*
Celiac Disease	1 (6.7%)	10 (43.5%)	0.014**
Rheumatologic disease	0 (0%)	2 (6.9%)	0.283**
Skin disease	0 (0%)	4 (13.8%)	0.120**
Type 1 Diabetes	15 (93.8%)	16 (52.2%)	0.007**

TSH: Thyroid Stimulant Hormone. T3: Triiodothyronine. T4: Thyroxine. Anti-Tg: Anti-thyroglobulin antibody. Anti-TPO: Anti-thyroid peroxidase antibody. Thyroid US: Thyroid Ultrasonography. Anti-GAD: Anti-Glutamate Decarboxylase Antibody. Anti-tissueTG: Anti-tissue transglutaminase
The data are given as Mean±SD. and numbers (%).
* Independent Sample t-test
** Chi-Square or Fisher's Exact Test

Table 4. Autoimmune Disease and age relation

	≤10 years of age (n=6)	>10 years of age (n=39)	p
Sex			
Male	3 (50%)	13 (33.3%)	0.427*
Female	3 (50%)	26 (66.7%)	
Function Status			
Hypothyroidism	1 (16.7%)	4 (10.3%)	0.866*
Subclinical	1 (16.7%)	9 (23.1%)	
Euthyroidism	4 (66.7%)	26 (66.7%)	
TSH	25.9±55.8	5.5±8.7	0.414**
T3	3.7±0.8	4.2±1.5	0.534**
T4	1.2±0.1	1.1±0.3	0.896**
Anti-Tg	145.5±174.0	357.6±581.6	0.478**
Anti-TPO	530.6±994.7	2038.6±3443.8	0.297**
Thyroid US	6 (100%)	35 (89.7%)	0.411*
Anti-GAD	0.5±0.7	8.8±17.0	0.528**
Anti-tissueTG	8.2±18.3	25.5±59.1	0.523**
Celiac Disease	1 (20%)	10 (30%)	0.636*
Rheumatologic Disease	0 (0%)	2 (5.1%)	0.570*
Skin disease	1 (16.7%)	3 (7.7%)	0.472*
Type 1 Diabetes	5 (83.3%)	26 (66.7%)	0.412*

TSH: Thyroid Stimulant Hormone. T3: Triiodothyronine. T4: Thyroxine. Anti-Tg: Anti-thyroglobulin antibody. Anti-TPO: Anti-thyroid peroxidase antibody. Thyroid US: Thyroid Ultrasonography. Anti-GAD: Anti-Glutamate Decarboxylase Antibody. Anti-tissueTG: Anti-tissue transglutaminase
The data are given as Mean±SD. and numbers (%).
* Chi-Square or Fisher's Exact Test
** Independent Sample t-test

compared to children/adolescents who had comorbidities (41.5% vs. 26.9%). It was also found that euthyroidism is present in approximately half of the patients [1]. In the study of Shigesi et al., 10–20% of patients who were diagnosed with chronic autoimmune thyroiditis and positive anti-thyroid antibodies in the general population were female, and 1–2% were male [7]. Similarly, a female predominance was detected in the present study, and 51.4% of the patients were euthyroidism at the time of diagnosis. The study supports our article.

Autoimmune diseases represent a family consisting of at least 80 diseases, which share a common pathogenesis, in which the immune system attacks its own body organs [6]. In the study that was conducted by Özsu et al., other accompanying autoimmune diseases in the families of 106 patients that were followed up for HT were examined and it was found that 35.8% of them had autoimmune thyroid disease [8]. In the study of Gopalakrishnan et al., a family history of autoimmune thyroid disease was detected in 18 (18.4%) of 98 patients who had HT, 16 had family history of hypothyroidism, and 2 had hyperthyroidism. There was a family history of rheumatoid arthritis in 3 patients (3.1%) [9]. In the present study, when the family history of 220 patients with HT was examined, it was found that there was a positive family history of autoimmune disease in 36.4% of the patients. This percentage was elevated than in other studies. Similarly, the most common autoimmune disease in the families of our patients was autoimmune thyroid disease.

The circulating antibodies against thyroperoxidase are considered the best serological markers for diagnosing HT, and are found in approximately 95% of HT patients and are rare in healthy controls. Anti-TPO titer correlates well with the number of autoreactive lymphocytes that infiltrate the thyroid and the degree of sonographic hypoechogenicity [10]. The antibodies against thyroglobulin, which is the most abundant protein of the thyroid gland, are less sensitive and less specific than anti-TPO [11]. In the present study, anti-TPO was found in 97% of patients, and anti-Tg was positive in 74%, which means, anti-TPO antibodies were more common and at elevated levels. Also in the present study, a statistically significant relation was detected between elevated anti-Tg and the presence of additional autoimmune disease the prevalence of which was increased by 2.32 times in patients with elevated anti-Tg levels. The same relation could not be shown with elevated anti-TPO.

The clinical characteristics of HT include local and systemic symptoms. When the profound and wide-ranging effects of thyroid hormones on most organs and tissues are considered, the symptoms of hypothyroidism are many and varied [12]. In the study conducted by Demirbilek et al. with 162 children and adolescents who had HT, the most common complaint was found to be goiter (54.9%) [13]. In the present study of ours, similar to other studies, the most common complaint of patients was goiter with a rate of 15.1%. The results of the study and other similar studies show the importance of routine thyroid examination in the diagnosis of HT.

In the study that was conducted by Ruggeri et al. to compare the data of 500 adult and 553 pediatric/adolescent patients with 1053 newly diagnosed HT, the epidemiological distribution of patients who had additional HT-related autoimmune disease was significantly different in the two cohorts. The most common comorbidities in adult patients were arthropathies (mostly psoriatic arthritis, rheumatoid arthritis) and connective tissue diseases (mostly Sjögren's Syndrome). However, arthropathies and connective tissue diseases were not found to be significant in the pediatric/adolescent population, but the most common autoimmune comorbidities were found to be celiac disease and T1DM [1]. In the present study, additional autoimmune disease was detected in 45 (20%) patients. The most common autoimmune disease was T1DM with a rate of 14%, similar to the studies mentioned above. T1DM stems from the autoimmune destruction of insulin-producing β cells, and is characterized by the appearance of insulin and the presence of β-cell autoantibodies [14]. The second most common additional autoimmune disease was found to be celiac disease in the present study with a rate of 5%, skin diseases with a rate of 2.7%, and rheumatologic diseases with a rate of 1.3%.

The development of autoimmune diseases is affected by hormones, immunomodulators, and metabolic factors. Increased previous reports show how countries without elevated-calorie diets have a lower predisposition for developing cancer, autoimmune disorders, obesity, and diabetes. There is a clear relation between diet and increased autoinflammatory and autoimmune events [11]. Although the relation between HT and diet was not focused on in the present study, vitamin D deficiency, which is very common in our country, was found to be the most common non-autoimmune disease that accompanied HT at a rate of 26.8%. Also, obesity was detected in 6.8% of patients, and was the second most common non-autoimmune disease that accompanied vitamin D deficiency.

Sex and age may be significant risk factors for the development of autoimmune diseases. In the present study, the mean age of the group with and without autoimmune diseases as well as HT was similar (p=0.644). Female sex was dominant in both groups. However, the number of male patients (35.6%) was statistically significantly elevated in the group with additional autoimmune disease than the group without additional autoimmune disease (19.9%) (p=0.016). In the study that was conducted by Ruggeri et al, adults who had co-morbid HT-related autoimmune disease were more often female and elderly compared to those without. In a previous child/adolescent cohort, no differences were detected in the age between patients with or without additional autoimmune disease; however, the male/female rate was significantly lower in the former (2.8:1 vs 4.9:1; p=0.046), in other words, boys/adolescents were considered to have more risks for additional autoimmune diseases, which is similar to the present study [1]. Although it is already known that autoimmune diseases are more common in women [5], it can be speculated in the light of both our study and other studies supporting this that boys who are diagnosed with HT must be carefully monitored for possible autoimmune diseases.

In the present study, no significant relations were detected between elevated anti-TPO levels and presence of autoimmune disease; however, a statistically significant relation between elevated anti-Tg and presence of autoimmune disease. The prevalence of autoimmune disease was increased 2.32 times in patients with elevated anti-Tg levels. The importance of regular follow-up of HT patients who have elevated anti-Tg levels for the development

of additional autoimmune diseases was shown with this ratio.

In conclusion, HT is an organ-specific autoimmune disorder with environmental and structural factors triggering autoimmune reaction against thyroid antigens in genetically susceptible individuals. As shown in the present study, other autoimmune diseases e.g. T1DM and celiac disease are associated with this disease. It must be kept in mind that there is an increased risk of autoimmune disease development with age in HT, and this affects both sexs. Regular follow-up of HT patients (especially male sex with elevated anti-Tg levels) must be performed in terms of the development of autoimmune diseases.

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