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Research Article

Retrospective Analysis of Hashimoto's Thyroiditis in Children and Adolescents: A Single Center Experience

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Hashimoto Tiroiditinin Çocuklarda ve Ergenlerde Geriye Dönük Analizi: Tek Merkez Deneyimi

ABSTRACT

Objective: *Hashimoto's thyroiditis is an organ-specific autoimmune disease and the most common cause of goiter and acquired hypothyroidism in children and adolescents in regions devoid of endemic iodine deficiency. In this study, it was aimed to examine the epidemiological, clinical and laboratory features of Hashimoto's thyroiditis and autoimmune diseases accompanying Hashimoto's thyroiditis in children and adolescents.*
Methods: *We retrospectively examined thyrotropin, free thyroxin, thyroid autoantibodies (thyroid peroxidase and thyroglobulin antibodies), immunoglobulin A (IgA), anti-tissue transglutaminase antibodies (IgA-tTG), and thyroid ultrasonography findings of 108 cases aged 5-18 years with positive anti-thyroid antibodies.*
Results: *The female/male ratio was 80/28 and 68% of the patients were adolescents. The most common admission complaint was goiter. At the time of diagnosis, the cases had euthyroidism (44.4%), subclinical hypothyroidism (35%), overt hypothyroidism (16.6%), and hyperthyroidism (3.7%). Goiter was detected in 58 (53.7%) cases by thyroid ultrasonography. During the follow-up, overt hypothyroidism developed in 6 patients who had subclinical hypothyroidism and subclinical hypothyroidism developed in 8 patients who had euthyroidism. All patients with hyperthyroidism became euthyroid. Levothyroxine treatment was administered to 47 (43.5%) patients. Celiac disease was detected in 2 and type 1 diabetes mellitus in 1 patient.*
Conclusions: *The prevalence of Hashimoto's thyroiditis increases with age both in childhood and adolescence, and thyroid functions tend to deteriorate over time. Therefore, close follow-up and appropriate treatment are important. Although the prevalence of celiac disease is higher in children and adolescents with Hashimoto's thyroiditis compared to healthy children, the true prevalence of autoimmune diseases accompanying Hashimoto's thyroiditis will be revealed in studies to be conducted in larger patient populations.*

Keywords: *Hashimoto's thyroiditis, children and adolescents, thyroid function, goiter*

ÖZ

Amaç: *Hashimato tiroiditi, organa özgü otoimmun bir hastalık olup çocuk ve ergenlerde endemik iyot eksikliğinin bulunmadığı bölgelerde guatr ve kazanılmış hipotiroidinin en sık nedenidir. Bu çalışmada çocuk ve ergenlerde Hashimato tiroiditinin epidemiyolojik, klinik ve laboratuvar özellikleri ve en sık eşlik eden otoimmun hastalıkları irdelemek amaçlandı.*
Yöntem: *Tiroid otoantikorları (tiroid peroksidaz ve tiroglobulin antikorları) pozitif olan 5-18 yaş arası 108 olgunun tirotropin, serbest tiroksin, doku transglutaminaz Ig A antikoru (dTG-igA) ve tiroid ultrasonografi bulguları retrospektif olarak incelendi. Tiroid fonksiyon durumuna göre gruplandırılan olgular karşılaştırıldı.*
Bulgular: *Bu çalışmada olguların %68'i ergen ve kadın/erkek oranı 80/28 idi. En yaygın başvuru şikayeti guatr idi. Tanı anında vakaların %44,4'ünde ötiroidizm, %35'inde subklinik hipotiroidizm, %16,6'sında aşıkar hipotiroidizm ve yaklaşık %3,7'sinde hipertiroidizm saptandı. Olguların 58'inde (%53,7) tiroid ultrasonografi (US) ile guatr tespit edildi. Takip sırasında, ötiroidisi olan 8 hastada subklinik hipotiroidi ve subklinik hipotiroidisi olan 6 hastada aşıkar hipotiroidi gelişti. Hipertiroidili tüm hastalar takipte ötiroid hale geldi. Olguların %43,5'i (n=47) levotiroksin tedavisi alıyordu. Hashimato tiroiditli 2 hastada çölyak hastalığı, 1 hastada tip 1 diabetes mellitus eşlik ediyordu.*
Sonuç: *Çocukluk ve ergenlik döneminde Hashimato tiroiditi prevelansı yaşla birlikte artarken, tiroid fonksiyonları zamanla bozulma eğilimindedir. Bu nedenle bu hastalarda yakın takip ve uygun tedavi önemlidir. Hashimato tiroiditli çocuk ve ergenlerde çölyak hastalığı prevalansı sağlıklı çocuklara göre daha yüksek saptanmakla birlikte Hashimato tiroiditine eşlik eden otoimmün hastalıkların gerçek prevalansının belirlenmesi, daha geniş katılımlı çalışmalar ile mümkün olabilecektir.*

Anahtar kelimeler: *Hashimato tiroiditi, çocuk ve ergenler, tiroid fonksiyonu, guatr*

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INTRODUCTION

Hashimoto's thyroiditis is an organ-specific autoimmune disease associated with other autoimmune diseases. It is the most common cause of goiter and acquired hypothyroidism in children and adolescents in the regions where there is no endemic iodine deficiency [1]. Although the prevalence of Hashimoto's thyroiditis varies from region to region, it occurs in 3% of children aged 6-18 years. The female/male ratio is 2-9/1 in children and adolescents and 9/1 in adults. It is most common in the pediatric age group in early and middle adolescence and peaks in girls in the pubertal age group [2].

The etiology of Hashimoto's thyroiditis is multifactorial and occurs under the influence of environmental and genetic factors. The fact that it occurs in more than one member of the same family and is more common in monozygotic twins than dizygotic ones in twin studies points to the presence of genetic factors. In Hashimoto's thyroiditis, cellular and humoral responses play a role in the pathogenesis; lymphocytic infiltration of the thyroid gland progresses with fibrosis and leads to increased tissue hardness [3]. In the families of 23-46% of children and adolescents affected by Hashimoto's thyroiditis, history of either Hashimoto's thyroiditis or other autoimmune disease has been reported [1-2]. The most common clinical finding in Hashimoto's thyroiditis is goiter. Hashimoto's thyroiditis is the most common cause of acquired goiter in children and adolescents. Hashimoto's thyroiditis accounts for 40% of goiters found in adolescents. Affected children may be asymptomatic or present a wide variety of complaints. Thyroid function in Hashimoto's thyroiditis can range from euthyroidism to hypothyroidism or in rare instances to hyperthyroidism [4].

Thyroid is the most frequently affected organ in autoimmune diseases. Hashimoto's thyroiditis, an autoimmune disease, may accompany other autoimmune diseases such as alopecia, vitiligo, celiac disease, Addison's disease, type 1 diabetes and polyglandular syndromes [5].

The aim of this study is to evaluate clinical, epidemiological and laboratory findings in children and adolescents with Hashimoto's thyroiditis and to determine the prevalence of autoimmune diseases accompanying Hashimoto's thyroiditis.

MATERIAL and METHODS

A total of 108 patients aged 5-18 years who were followed up with the diagnosis of Hashimoto's thyroiditis in the pediatric endocrinology outpatient clinic from 2017 to 2020 were included in the study. The diagnosis of Hashimoto's thyroiditis was made with increased levels of anti-thyroglobulin (anti-TG) and/or anti-thyroid peroxidase (anti-TPO) autoantibodies. Age, complaints at presentation, family history, body weight, height, body mass index (BMI) and laboratory findings of all subjects were recorded retrospectively from the medical records. Body weight and height of all subjects were measured by the same physician (S.T.) using a digital scale (sensitive to 10 grams) (Densi GL 150) with automatic measurement of the height. Body mass index was calculated by dividing body weight by the square of height in meters. Body weight, height and BMI standard deviation scores (SDSs) were obtained using national database [6].

Thyroid stimulating hormone (TSH), free thyroxine (fT4), thyroid autoantibodies (anti-TG and anti-TPO) and findings of thyroid ultrasonography (US) performed considering autoimmune thyroiditis were recorded. The tissue transglutaminase IgA (dTG -A) and serum total IgA levels measured considering accompanying autoimmune diseases were recorded. Thyroid volume measured with thyroid US was calculated using the formula; {(R1 x R2 x R3 x 0.5) / 1000} + {(L1 x L2x L3 x 0.5) /1000}.

Note: R's and L's indicate right, and left thyroid lobes, from right to left side, respectively.

Values above the 97th percentile were accepted as goiter [7]. Serum fT4 and TSH levels were measured using the electro chemiluminescence method (Cobas 6000 Roche). Patients whose serum TSH and fT4 levels within normal reference values (fT4: 0.9-1.67 ng/dL, and TSH: 0.6-4.9 µIU/ml, respectively) were

accepted as euthyroidism. Elevated TSH, but decreaed fT4 were considered as hypothyroidism while elevated TSH but normal fT4 levels as subclinical hypothyroidism [8]. Patients with large goiter accompanied by either overt or subclinical hypothyroidism, or even normal thyroid hormones received levothyroxine treatment in case of globus and/or compression findings. Serum anti-TPO and anti-TG levels were measured using the electro chemiluminescence method (Cobas 6000 Roche). The normal reference range was considered as 0-13 IU/mL for anti-TPO and 0-38 IU/mL for anti-TG.

Serum dTG-IgA was studied by micro ELISA method and 0-10 RU/mL was considered the normal reference range. Serum IgA was studied by immunoturbidimetric method using AU5800 autoanalyzer. Normal reference intervals were determined by age and gender. The cases were divided into groups according to the thyroid functions at admission (euthyroidism, subclinical hypothyroidism, hypothyroidism, hyperthyroidism). Ethics committee approval was obtained for this study.

Statistical analysis

SPSS 21.0 package program was used for all statistical analysis. Kolmogorov- Smirnov and Shapiro-Wilk tests were used to determine the normal distribution. Descriptive statistics were used. Mean (± SD) values of continuous, and categorical variables were calculated. Student's t-test was applied for comparing two groups and Anova test was applied for comparing more than two groups. The chi-square test was used to compare percentages. A p value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 108 patients including 80 girls (74%) 28 boys (26%), of whom 68% were pubertal. Sixty-four patients (59%) had a family history of autoimmune thyroid disease. The mean age at diagnosis was 12.2±2.8 years. The mean height SDS was 0.39±0.98 and mean BMI SDS was 0.34±1.2. In our study, the most common complaint at presentation was swelling in the neck, followed by weight gain, weakness and fatigue, dry hair, muscle weakness and intolerance to cold. Fifteen percent of the cases were referred from other clinics due to impaired thyroid function tests with an accompanying goiter in 25% of them (n=4). The complaints of the cases at admission are summarized in Table 1.

Anti-TPO was positive in 95%, and anti-TG in 87% of the cases. At the time of diagnosis, the patients had euthyroidism (n:48; 44.4%) had, 38 (35%) subclinical hypothyroidism (n:38; 35%), overt hypothyroidism (n:18; 16.6%) and hyperthyroidism (n:4; 3.7%). Goiter was detected in 47 (43.5%) cases by physical examination, and in 58 (53.7%) cases by thyroid US. In 88% (n=95) of the cases, the thyroid parenchyma was heterogeneous due to fibrosis and

Table 1. Complaints of patients with Hashimoto's thyroiditis.

Complaints	n	%	Complaints	n	%
Swelling in the neck	49	43.5	Hair loss	16	15
Fatigue-weakness	42	39	Thyroid dysfunction	16	15
Increased weight	38	35	Loss of appetite	15	14
Dry hair	25	23	Decreased academic success	14	13
Muscle weakness	24	22	Constipation	13	12
Intolerance to cold	17	16	Nervousness	11	12
Dry skin	16	15	Easy nail splitting	9	8.3

Table 2. Comparison of the groups according to thyroid function status.

	Euthyroidism n=48	Subclinical hypothyroidism n=38	Overt hypothyroidism n=18	Hyperthyroidism n=4	p
Mean (±SD) age (years)	12.1±2.5	12.6±2.1	13.3±1.8	12.5±2.2	0.620
Sex(female/male)	38/10	30/8	14/4	3/1	0.340
Pubertal status (%)	67%	63%	64%	66%	0.165
Goiter (PE) (n)	21 (43.7%)	16 (42%)	8 (44.4%)	2 (50%)	0.324
Goiter (US)	26 (54%)	20 (52.6%)	10 (55.5%)	2 (50%)	0.850
anti-TPO (IU/mL)	114±91	482±123	774±226	561±109	0.018

PE: physical examination, US: ultrasonography.

hypoechogenic areas, and in 12% (n=13) of the cases it was homogeneous. Moreover, with US, pseudonodular appearance was detected in 90 (83%), and true nodules (13 solitary, 5 multinodules) in 18 (17%) cases. The patients with thyroid nodules had euthyroidism (n:10; 55.5%), subclinical hypothyroidism (n:5; 27.7%), and overt hypothyroidism (n:3; 16.6%). Thyroid receptor antibody (TRab) was negative in all patients with hyperthyroidism. The characteristics of the cases grouped according to thyroid functions are shown in Table 2. The mean age, gender and pubertal status of the cases were similar in both groups (p=0.620, p=0.340, and p=0.165, respectively). There was no statistical difference between the groups in terms of prevalence of goiter detected by both physical examination and thyroid US (p=0.324, and p=0.85, respectively). The patients were compared according to the presence of goiter detected by ultrasound (Table 3). There was no significant difference between the groups in terms of anthropometric, clinical and laboratory parameters according to the presence of goiter. Mean serum TPO-ab titer was higher in patients with overt/subclinical hypothyroidism and hyperthyroidism than in patients with euthyroidism (mean values: 774±226, 561±109, 482±123, and 114±91 IU/ml, ρ=0.018, respectively). After 3 years of follow-up, while 15.7% (n=6) of the patients who had subclinical hypothyroidism at presentation developed overt hypothyroidism, 8 patients with euthyroidism developed subclinical hypothyroidism. All patients with hyperthyroidism became euthyroid during follow-up. These patients are still being followed up. While 47 (43.5%) cases included in the study were receiving levothyroxine treatment, the mean levothyroxine dose to reach euthyroid state was 1.62±0.53 µg/kg/day. When other accompanying autoimmune diseases were evaluated, celiac disease was detected in two, and type 1 diabetes mellitus in one patient.

Table 3. Comparison of the groups according to the presence of goiter.

	Goiter (+) n=58	Goiter (-) n=50	p
Mean age (years)	12.8±2.6	11.9±2.4	0.323
Female/male (n)	36/22	30/20	0.816
BMI SDS	0.28±0.9	0.24±1.1	0.160
Pubertal / prepubertal (n)	33/25	28/22	0.620
Anti-TPO (IU/mL)	642±113	581±99	0.265
Thyroid function status (n)			
Euthyroidism	26	22	0.920
Subclinical Hypothyroidsm	20	18	0.625
Overt hypothyroidsm	10	8	0.720
Hyperthyroidism	2	2	-

BMI: Body mass index, SDS: standard deviation score, Anti-TPO: anti-thyroid peroxidase.

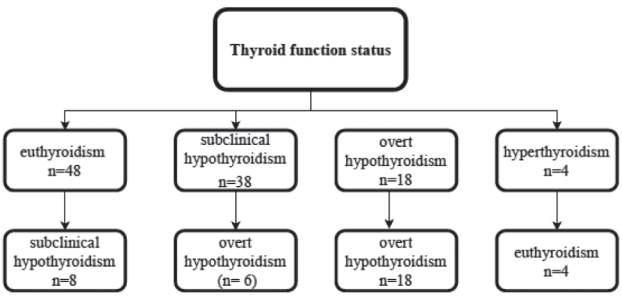

Figure. Thyroid functions of patients with Hashimoto thyroiditis at baseline and follow-up.

DISCUSSION

Hashimoto's thyroiditis is more common in women, and a female/male ratio varying between 2.1-9.7/1 in childhood and adolescence has been reported [9]. In our study, the female/male ratio was 2.8/1. Hashimoto's thyroiditis is more common in adolescence. In this study, 68% of the cases were between the ages of 12-15 years. In the literature, age peaks similar to our results have been reported [9-12]. Hashimoto's thyroiditis is very rare under 5 years of age. However, rare cases in early childhood have been reported and even in infancy [9-12]. In our study, there were no patients younger than 5 years of age. Euthyroidism is the most common thyroid pattern associated with Hashimoto's thyroiditis (20-80%). Dundar et al. [13] reported euthyroidism in 62.8% of children and adolescents with Hashimoto's thyroiditis, Özen et al. [14] and Tuhan et al. [15] reported euthyroidism in 51.2% and 36.7% of these cases, respectively.

Wasniewska et al. [16] found euthyroidism in 52.1%, SH in 19.2%, and overt hypothyroidism in 22.2% of the cases in a study involving 608 children

and adolescents with Hashimoto's thyroiditis. In our study, the most common thyroid pattern was euthyroidism (44.4%) followed by subclinical and overt hypothyroidism, and hyperthyroidism. The frequency of subclinical hypothyroidism in our study was 35%, which was similar to the rates reported in other studies (26.5%-39.4%) [11,17-20].

It has been reported that thyroid functions in children with Hashimoto's thyroiditis are mainly associated with the age of the cases and the possibility of subclinical and overt hypothyroidism increases with age [9]. Contrarily, it has been reported in the literature that patients with thyroid dysfunction are younger, and this condition has been explained with the view that early onset HT could have a worse prognosis [1,15,16]. However, in our study, no significant difference was found between age and thyroid functions which may be due to the small number of cases in our study population. Initially, thyroid function of the children with Hashimoto's thyroiditis presenting with both euthyroidism and SH tend to gradually worsen [9]. In addition, children and adolescents with SH and underlying Hashimoto's thyroiditis have a higher risk of developing hypothyroidism over time compared to children and adolescents with SH without preexisting thyroid disease [9]. In this study, 15.7% of the patients with SH developed overt hypothyroidism over time during follow-up, while SH developed in 8 cases with euthyroidism.

Although a specific genetic transition has not been identified in Hashimoto's thyroiditis, there is strong evidence that it has a familial inheritance. It has been reported that thyroid antibodies were found to be positive in the first-degree relatives in about half of the cases, and therefore autosomal dominant inheritance was considered. Tuhan et al. [15] reported that the history of thyroid disease in the first degree relatives of cases with Hashimoto's thyroiditis had been revealed in 47.5% of the cases, Wasniewska et al. [16] reported its incidence as 31.6%. In our study, a family history of thyroid disease was detected in 59% of the cases. This result is similar to the rates in the literature and has been evaluated as a finding supporting genetic predisposition for Hashimoto's thyroiditis.

In the literature, it has been stated that the most common complaint of the cases is neck swelling [4,14,21-23]. In a study conducted by Demirbilek et al. [9], 54.9% of the cases with a diagnosis of Hashimoto's thyroiditis had asymptomatic goiter and in a study conducted by Matsuura et al. [24] goiter was detected in 71% of the cases. In this study, asymptomatic goiter was the most common complaint in 45.3% of the cases which was consistent with the literature.

Hashimoto's thyroiditis is the most common cause of acquired hypothyroidism in children and adolescents. Its incidence varies between 13-52.4% in different series [17,19,20,25]. The frequency of overt hypothyroidism in our study was 16.6%. In studies on children with a diagnosis of Hashimoto's thyroiditis, Alos et al. [11] reported overt hypothyroidism in 21.2% and Tuhan et al. [15] in 17.5% of their cases. The differences in the frequency of hypothyroidism reported in the literature were explained by dietary iodine intake, female/male ratio, average age of the patients, diagnostic criteria, and the time elapsed between the onset of the disease and its diagnosis. Increasing iodine intake with diet, using higher TSH threshold levels for the diagnosis of the disease, and delay in diagnosis contribute to the increase in the estimated frequency of hypothyroidism [9].

Hyperthyroidism can also be seen at presentation and it is usually mild. However, some patients may present with thyrotoxicosis (Hashitoxicosis). In this study, hyperthyroidism was detected in 4 cases (3.7%). This rate was slightly lower than the previous reports (7.8-11.7%) [9,19,20]. This situation may be due to the small number of cases in our study population.

In the literature, it has been reported that patients with thyroid dysfunction are younger [1,15,16]. The younger age of the patients with thyroid dysfunction has been explained with the view that early-onset Hashimoto's thyroiditis may have a more severe course [16]. However, when the cases in our study were compared according to thyroid function status, there was no difference between the groups in terms of age. Again, in this study, there was no significant difference between the groups in terms of

gender, adolescence and the presence of goiter. Consistent with our study, Tuhan et al. [15] found that there was no difference in terms of gender, adolescence and presence of goiter between the groups that were compared according to thyroid function status. Dündar et al. [13] reported a higher rate of goiter in euthyroid cases.

In the literature, rates of thyroid nodules up to 34.4% have been reported in cases with Hashimoto's thyroiditis [13,15,26]. Dündar et al. [13] reported thyroid nodules in 7% of children and adolescents with Hashimoto's thyroiditis and Tuhan et al. [15] found thyroid nodules in 7.5% of their patients. In our study, true nodules (13 solitary, 5 multinodules) were detected in 17% of the cases. The patients with thyroid nodules had euthyroidism in 55.5%, SH in 27.7% and overt hypothyroidism in 16.6% of the cases.

In children with Hashimoto's thyroiditis, L-thyroxine treatment is given to the subjects with overt and subclinical hypothyroidism. L-thyroxine treatment is also recommended in euthyroid subjects who have large goiter leading to compression and/or tenderness [23,26]. In the literature, the rate of using L-thyroxine in cases with Hashimoto's thyroiditis varies between 40-70% [13,26-28]. In our study, 43.5% of the cases were receiving levothyroxine treatment, while the average L-thyroxine dose to reach euthyroid state was calculated as 1.62±0.53 µg/kg/day in accordance with the literature [14].

As an autoimmune disease Hashimoto's thyroiditis is frequently associated with other autoimmune diseases. In our study, 2 patients had celiac disease and 1 patient had type 1 diabetes. In studies conducted with adults, the prevalence of celiac disease in patients with autoimmune thyroid disease was reported to be 1.8-3.3% [29-31]. In children and adolescents with Hashimoto's thyroiditis, the frequency of celiac disease is between 1.3-6.5% [32,33]. Studies should be conducted with greater number of patients. In studies conducted with children and adolescents diagnosed with Hashimoto's thyroiditis, Sarı et al. [32] found celiac disease in 4.9% of 101, while Tuhan et al. [15] in only one (1.25%) of 80 cases. In another study, Sattar et al. [33], found dTG-IgA positivity in 14 (4.6%) of 302 children and adolescents with Hashimoto's thyroiditis, and celiac disease was diagnosed by small intestine biopsy in half of these cases (2.3%).

As a result, Hashimoto's thyroiditis is more common in women, and its incidence increases with age during childhood and adolescence. Moreover, thyroid functions tend to deteriorate over time. Therefore, close follow-up and appropriate treatment are important. Although the prevalence of celiac disease in children and adolescents with Hashimoto's thyroiditis is higher than in healthy children, the true prevalence of autoimmune diseases accompanying Hashimoto's thyroiditis will be revealed by studies to be conducted in a larger patient population.

Ethics Committee Approval: S.B.U. Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee approval was obtained (05.03.2021/693).

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