ÖZGÜN ARAŞTIRMA ORIGINAL ARTICLE

Hashimoto's Thyroiditis Can Occur Not Only in The Adolescence Period But also in Children Under Five Years of Age

Hashimoto Tiroiditi Sadece Ergenlik Döneminde Değil Beş Yaşından Küçük Çocuklarda da Görülebilir

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Abstract

Introduction: Hashimoto's thyroiditis (HT) is one of the most common autoimmune endocrine disorders in the pediatric age group. In this study, it was aimed to retrospectively examine our cases, who were children and adolescents diagnosed with HT.

Materials and Methods: We retrospectively examined 119 patients between the ages of 1 and 18, who were diagnosed with HT. In all of the cases, physical examination findings, thyroid function tests, anti-thyroid peroxidase (anti-TPO) and antithyroglobulin (Anti-Tg) antibodies, thyroid ultrasonographies and accompanying autoimmune diseases were evaluated.

Results: The female/male ratio was 3.5/1. In our cases, the median age at the time of diagnosis was 12.29 years and 10 (8.4%) of the cases were under the age of five. At the time of diagnosis, 37% of the cases were euthyroid, 21.8% had overt hypothyroidism, 34.5% had subclinical hypothyroidism, 2.5% had subclinical hyperthyroidism and 4.2% had overt hyperthyroidism. At the time of diagnosis, 102 cases (85.7%) had anti-TPO and 82 cases (68.9%) had anti-Tg positivity. The Anti-TPO levels at the time of admission were found to be significantly higher in the hypothyroid group compared to the euthyroid group.

Conclusion: Thyroid function test results of patients with Hashimoto's thyroiditis may vary in the follow-up period. Even though most cases with euthyroidism remain euthyroid, some might progress to hypothyroidism. Although Hashimoto's thyroiditis is most frequently seen in adolescents, approximately 10% of the cases are under the age of five. Therefore, autoimmune thyroiditis should be considered in hypothyroidism occurring in the early stages of life.

Keywords
Autoimmune diseases, hashimoto's thyroiditis, hypothyroidism, thyroid nodules.

Öz

Giriş: Hashimoto tiroiditi (HT), pediatrik yaş grubunda en sık görülen otoimmün endokrin hastalıklardan biridir. Bu çalışmada HT tanılı çocuk ve ergen olgularımızın retrospektif olarak incelenmesi amaçlandı.

Gereç ve Yöntem: 1-18 yaş arası HT tanısı almış 119 hasta retrospektif olarak incelendi. Tüm olgularda fizik muayene bulguları, tiroid fonksiyon testleri, antitiroid peroksidaz (anti-TPO) ve antitiroglobulin (Anti-Tg) antikorları, tiroid ultrasonografileri ve eşlik eden otoimmün hastalıklar değerlendirildi.

Bulgular: Kadın/erkek oranı 3,5/1 idi. Olgularımızda tanı anındaki medyan yaş 12,29 olup, olguların 10'u (%8,4) beş yaşın altındadır. Tanı anında olguların

Anahtar kelimeler
Otoimmün hastalıklar, hashimoto tiroiditi, hipotiroidizm, tiroid nodülleri.

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%37'si ötiroid, %21,8'i aşikar hipotiroidi, %34,5'i subklinik hipotiroidi, %2,5'i subklinik hipertiroidi ve %4,2'si aşikar hipertiroidi idi. Tanı anında 102 (%85,7) olguda anti-TPO, 82 (%68,9) olguda anti-Tg pozitifliği vardı. Hipotiroidi grubunda ötiroid grubuna göre başvuru anındaki Anti-TPO düzeyleri anlamlı olarak yüksek bulundu.
Sonuç: Hashimoto tiroiditli hastaların tiroid fonksiyon testi sonuçları takipte değişkenlik gösterebilir. Ötiroidizmli vakaların çoğu ötiroid kalsa da, bazıları hipotiroidizme ilerleyebilir. Hashimoto tiroiditi en sık adolesanlarda görülse de vakaların yaklaşık %10'u beş yaşın altındadır. Bu nedenle yaşamın erken evrelerinde ortaya çıkan hipotiroidizmde otoimmün tiroidit düşünülmelidir.

Introduction

Hashimoto's thyroiditis (HT) is the most common cause of acquired hypothyroidism and goiter in regions all over the world where there is no iodine deficiency. It is a chronic disease with a prevalence of 1.3% to 9.6% (1). In the physiopathology of HT, there is autoimmunity that develops with cellular and humoral immune mechanisms. Patients develop antibodies against thyroid antigens, most commonly anti-thyroid peroxidase (anti-TPO). Antithyroglobulin (anti-Tg) and TSH receptor blocking antibodies can also be detected in cases with Hashimoto's thyroiditis. These antibodies damage the thyroid tissue and cause fibrosis. This causes inadequate thyroid hormone production over time (2). In Hashimoto's thyroiditis, a definitive diagnosis of is made by detecting lymphocyte infiltration in the biopsy. However, thyroiditis findings detected in the pathologic examinations of the thyroid have been found to be correlated with the level of antibodies. Therefore, anti-TPO and/or anti-Tg positivity has been reported to be diagnostic in Hashimoto's thyroiditis. However, it has been stated that antibody negativity may occur in 10-15% of the cases (3).

Hypoechoic-heterogeneous parenchymal areas and pseudonodular appearance are present in the thyroid ultrasonographies of cases with Hashimoto's thyroiditis. Thyroid function tests performed during the diagnosis may vary. Patients usually present with euthyroid or hypothyroidism clinic. Although it is rare, they may also present with hyperthyroidism. The most common findings among symptomatic patients are goiter and growth retardation (4,5).

HT is an autoimmune disease that may be accompanied by some other autoimmune diseases such as adrenal insufficiency, type 1 diabetes mellitus (DM), Celiac disease, pernicious anemia (3,6). It has also been reported that HT is more common in chromosomal disorders such as Turner and Down syndromes (7). In this study, we aimed to examine the clinical and laboratory features of pediatric and adolescent patients diagnosed with HT in our clinic. Additionally, in the follow-up of the patients, we observed the clinical changes, the autoimmune diseases and thyroid nodules that develop.

Materials and Methods

In the study, 119 cases between the ages of 1 and 18, diagnosed with HT between 2013-2020 in Dicle University Faculty of Medicine Pediatric Endocrinology Polyclinic, were included. The median follow-up duration of the patients was 17 (range: 1-88) months; and the medical records were retrospectively examined. Anti-TPO and/or anti-Tg positivity were used in the diagnosis of Hashimoto's thyroiditis (3).

The cases were clinically classified according to the measured hormone levels: the cases with normal thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels were evaluated as euthyroidism, those with TSH above the normal range but with normal FT4 levels as subclinical hypothyroidism, and those with high TSH and low FT4 levels were evaluated as overt hypothyroidism. High levels of thyroid hormone accompanying suppressed TSH levels was considered as hyperthyroidism, and suppressed TSH and normal thyroid hormone levels were considered as subclinical hyperthyroidism.

The age, gender, height, height standard deviation score (SDS), body weight (BW), BW SDS, body mass index (BMI) and BMI SDS of the cases at the time of admission were measured. Standard reference values of Turkish children were used to calculate these values (8). Cases with chromosomal disorders such as Turner and Down syndromes were excluded from the study. The presenting complaints of the cases, stage of puberty, family history of thyroid disorders, associated autoimmune diseases, TSH, FT4, free triiodothyronine (FT3), anti-TPO, and anti-Tg levels were recorded. Pubertal staging was carried out according to the Tanner scale (9). The volume of the thyroid was calculated

with the formula of length x width x deepness x 0.479 and the values above the 97th percentile according to age were considered as goiter (10,11).

The antibody levels of the cases who were initially euthyroid and had hypothyroidism were compared. The cases who developed thyroid nodules in the follow-up and underwent fine needle aspiration biopsy (FNAB) were recorded. The Electrochemiluminescence Immunoassay "ECLIA" method and the Roche Cobas E601 module were used in the analysis of the serum TSH and FT4, Anti-TPO, Anti-Tg concentrations. The normal range was considered as 0.35-5.5 µIU/ml for TSH and 12.6-21 pmol/L for FT4. For anti-TPO and anti-Tg, values above 60 and 115 IU/ml respectively were considered positive.

The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (date: 04.03.2021, approval number: 2021/174).

Statistical Analysis

The statistical analysis of the results obtained in the study was performed using the SPSS 21.0 (Statistical Package for the Social Sciences - IBM®, Chicago, IL, USA) statistical software package. Whether the variables were normally distributed or not was evaluated using the Shapiro-Wilk test. In the comparison of the data of two independent groups: if the group distribution was normal, the independent samples t test, and if the distribution was not normal, the Mann-Whitney U test was used. In the comparison of the group proportions, the Chi-square test was used. The categorical data were presented as frequency (percentage), while the numerical data were presented as median (the 25th and 75th percentiles) or mean± standard deviation. In the comparison of the groups, a p value of <0.05 was considered statistically significant.

Results

Of the 119 cases included in the study, 93 (78.2%) were female and 26 (21.8%) were male. The female/male (F/M) ratio was 3.5/1. The mean age of the patients at the time of diagnosis was 12.29 (range:1-18).

80 (67.2%) of the cases included in the study presented in the puberty and 39 (32.8%) in the prepubertal period. At the time of diagnosis, 44 (37%) of the cases were euthyroid, 41 (34.5%) had subclinical hypothyroidism, and 26 (21.8%) had overt hypothyroidism. In addition, 5 (4.2%) of the cases had overt hyperthyroidism and 3 (2.5%) had subclinical hyperthyroidism. 7 (15.9%) of the 44 euthyroid patients who were followed-up for an average of 17 months developed hypothyroidism, while 37 (84.1%) remained euthyroid. At the time of diagnosis, 102 of the cases (85.7%) had anti-TPO positivity and 82 cases (68.9%) had anti-Tg positivity. At the time of diagnosis, the median levels of anti-TPO and anti-Tg were 342.15 (103.37-600) IU/ml and 348.30 (105-626.25) IU/ml, respectively. The demographic and laboratory findings of our cases at the time of admission are shown in Table 1. At the time of admission, it was found that the anti-TPO levels of the cases with hypothyroidism were significantly higher than those of the cases with euthyroidism (p=0.01); however, no significant difference was found in terms of the anti-Tg levels (p=0.08) (Table 2).

Table 1. Demographic and laboratory findings of the patients at the time of application

Age (year)	12.29 (range:1-18)
Gender	
Female (n=93)	78.2%
Male (n=26)	21.8%
Height SDS	-0.22(-1.55-0.48)
Weight SDS	-0.34±1.47
BMI SDS	0.02±1.30
Tanner	
Pubertal(n=80)	67.2%
Prepubertal (n=39)	32.8%
Goiter	37.9%
Anti-thyroid antibodies	
Anti-TPO (IU/mL)	342.15 (103.37-600)
Anti-Tg (IU/mL)	348.30 (105-626.25)
TSH (µIU/mL)	6.55(2.60-13.60)
fT4 (pmol/L)	14.42(12.90-16.44)
Hormonal status	
Euthyroidism (n=44)	37%
Subclinic hypothyroidism (n=41)	34.5%
Overt hypothyroidism (n=26)	21.8%
Subclinic hyperthyroid (n=3)	2.5 %
Overt hyperthyroid (n=5)	4.2%

SDS: Standard deviation score, BMI: Body mass index, anti-TPO: Anti-thyroid peroxidase antibodies; anti-Tg: Anti-thyroglobulin antibodies. TSH: Thyroid stimulating hormone; fT4: Free thyroxine

Data are given as mean +/- SD or median (25th–75th interquartile range).

Table 2. Comparison of initial antibody levels of hypothyroid and euthyroid patients

	Hypothyroid (n=67)	Euthyroid (n=44)	p-value
Anti-TPO (IU/mL)	397.85 (183.90-600)	209.30 (64.20-562.20)	0.01
Anti-Tg (IU/mL)	406 (158.15-848.90)	252.50 (78.40-524.60)	0.08

Anti-TPO: Anti-thyroid peroxidase antibodies, AntiTg: Anti-thyroglobulin antibodies
Data are given as median (25-75p).

The most common presenting complaint of the patients was neck swelling (37.9%). Short stature (25.2%), fatigue (11.7%), excessive weight gain (8.4%) and constipation (7.5%) were the other presenting complaints. In 36.1% of the patients, a history of thyroid disorders were present in their mother, father or sibling. Our youngest patient was 1 year old. 10 (8.4%) of the 119 patients included in the study were under the age of five. In 8 (80%) of the cases who were under the age of five and diagnosed with HT, hypothyroidism was present (5 overt + 3 subclinical).

All cases under the age of three had hypothyroidism. Levothyroxine treatment was initiated in all cases in which overt or subclinical hypothyroidism was detected. The average levothyroxine dose, with which these cases became euthyroid was 1.51 mcg/kg. The cases diagnosed with hyperthyroidism mostly presented with the complaint of palpitations. Methimazole treatment was administered to two of the five patients with overt hyperthyroidism.

From the medical records of the patients, it was found that thyroid USG was performed on 108 (90.7%) of the 119 cases included in the study. In 41 (37.9%) of them, thyromegaly was found. Thyroid nodules were detected in approximately 12 patients (11.1%). FNAB was performed on seven of the 12 patients with thyroid nodules. Nodules greater than 1 cm, and growth and calcification appearance in the nodules constituted the indications for FNAB. The biopsy results were evaluated as: chronic lymphocytic thyroiditis in six cases and suspicious for malignancy in one case. The surgical sampling of the patient with suspected malignancy was compatible with papillary thyroid carcinoma.

A second autoimmune disease was detected in nine (7.6%) of 119 patients in the follow-up. Three of these developed vitiligo, two developed type 1 DM, two developed Celiac disease, one developed total alopecia and one developed autoimmune hemolytic anemia.

Discussion

Although the exact etiology of Hashimoto's thyroiditis is not fully clarified, it is stated to be caused by the interaction of genetic, environmental and epigenetic influences (12). It is the most common cause of hypothyroidism in developed countries. Lymphocyte infiltration in the thyroid tissue leads to fibrosis over time and eventually to parenchymal atrophy. Hashimoto's thyroiditis is more common in women. In many studies, the male/female case ratio was reported as 2-9/1 (13-16). In our study, this ratio was found to be 3.5/1, compatible with the literature.

Hashimoto's thyroiditis is most frequently seen in the adolescent age group. In our study, the adolescent cases constituted 67.2% of all of the patients and this finding was consistent with the literature (1,13,17). Although cases under the age of five are reported rarely (18), cases diagnosed with HT in early childhood and infancy have been reported (19-22). Autoimmune thyroiditis is very rare, especially in children under the age of three. It has been stated that the autoimmune thyroiditis occurring in this age group may be a preliminary finding of autoimmune polyglandular syndrome in particular (19). Cases under the age of three are mostly presented in the form of case reports in the literature. Severe hypothyroidism findings were detected in these cases (19-22). There has been no case report regarding patients under the age of three in previous studies conducted in our country (13,14,17,23). In our study, there were 10 (8.4%) cases under the age of five and three cases under the age of three. 8 of the 10 cases younger than 5 years of age had hypothyroidism. In two of the three cases under the age of three, subclinical hypothyroidism was present; and one case had overt hypothyroidism. The newborn screening test results were found to be normal in all three cases. A delayed diagnosis of hypothyroidism in the first three years of life can have negative effects on both intellectual performance and growth. Therefore, it should be kept in mind that patients with normal newborn screening results but with symptoms of hypothyroidism may have autoimmune thyroiditis.

Children and adolescents with Hashimoto's thyroiditis may be asymptomatic or may present with symptoms of goiter and/or hypothyroidism and

rarely with symptoms of hyperthyroidism. Presenting complaints are generally neck swelling or growth retardation. Cases may initially present with symptoms of hyperthyroidism due to an excess of thyroid hormones in the bloodstream as a result of follicular cell destruction associated with autoimmunity. However, later they may exhibit symptoms of hypothyroidism as a result of atrophy of the thyroid tissue. These symptoms can be insidious and variable. Constipation, fatigue, dry skin and weight gain are the early signs of hypothyroidism. Cold intolerance, hypohidrosis, muscle spasms, hair loss, and depression can also occur (24,25). As stated in the literature, the most common presenting complaint in our cases was goiter (37.9%). On the other hand, some of our patients presented with symptoms of hypothyroidism such as short stature, fatigue, weight gain and constipation, whereas the most common symptom in patients presenting with hyperthyroidism was palpitations.

In previous studies, it has been shown that cases with HT are generally euthyroid (26-28). In a study conducted by Valenzise et al. (27), the rates of euthyroid and hypothyroid cases were found to be 52.1% and 41.4%, respectively; while Lee et al. (28) reported these rates to be 47.1% and 45.8% in their study. In our study, contrary to the abovementioned studies, most of the cases were hypothyroid at the time of diagnosis (37% euthyroid, 56.3% hypothyroid). In a study conducted by Radetti et al. (29), 64.8% of the euthyroid patients, and in another study (5), 57.1% of the euthyroid patients were reported to have remained euthyroid at the end of five years. Wang et al. (30) found in their study that 88% of the cases remained euthyroid after an average of 6.4 years of follow-up. In our study, 84.1% of the cases remained euthyroid after an average of 17 months of follow-up. Although, in our study, the follow-up period of euthyroid patients was short, it was observed that the majority of the cases remained euthyroid, consistent with the literature (5,29,30).

In the diagnosis of Hashimoto's thyroiditis, particularly anti-TPO and/or anti-Tg positivity are used (3). In a study conducted by Baş et al. (23), the positivity levels of anti-TPO and anti-Tg were found to be 93% and 56%, respectively; and in another study conducted by Yeşilkaya et al. (17), they were found to be 79.4% and 73.2%, respectively. In our study, we found anti-TPO positivity in 85.7% and anti-Tg positivity in 68.9% of the cases with HT at the time of diagnosis, and this was consistent with the literature data. In studies evaluating the relationship between baseline antibody titer and hypothyroidism, conflicting results were found. In some studies, no difference was found between the hypothyroid and euthyroid groups in terms of antibody levels (17,29). However, in a study conducted by Demirbilek et al. (24), it was shown that serum anti-TPO titer was higher in patients with hypothyroidism compared to the euthyroid group. Similar to the study of Demirbilek et al. (24), in our study, the anti-TPO level was significantly higher in the hypothyroidism (subclinical + overt hypothyroidism) group at the time of admission compared to the euthyroidism group, however, no significant difference was found in terms of anti-Tg. Therefore, we believe that in cases with HT, high anti-TPO levels at the time of diagnosis may predict hypothyroidism.

Hyperthyroidism is extremely rare in Hashimoto's thyroiditis. TSH receptor antibodies (TSHRAb) may be present in these cases. These antibodies are usually blocking. However, although rare, there may also be stimulating antibodies in cases with HT, like in Graves' disease. Hyperthyroidism in Hashimoto's thyroiditis is associated with either follicular cell destruction in the onset of the disease or stimulant type TSHRAb (27). The rate of overt hyperthyroidism at the time of admission was reported as 6.5% in the study of Ruggeri et al. (31) and as 8.6% in another study (24). In our study, the rate of overt hyperthyroidism was found to be 4.2%. All of these cases presented with palpitations. In two of the cases with hyperthyroidism, TSHRAb levels were positive and methimazole was administered. Patients who were administered with methimazole went into remission within one year without developing recurrence. Of the five patients with overt hyperthyroidism, overt hypothyroidism developed in four and euthyroidism in one. In the follow-up of our three patients with subclinical hyperthyroidism, euthyroidism developed.

Thyroid nodules are less common in children and adolescents compared to adults. However, malignancy rates of thyroid nodules in children are higher (22-26%) (32). Studies in adults have reported a positive correlation between HT and papillary thyroid carcinoma (PTC) (33,34). In a series of 365 cases involving children and adolescents, it was

stated that the nodule prevalence developing in cases with HT was 31.5% and 9.6% of these nodules were malignant (1). In our study, 11.1% of the cases had thyroid nodules. As a result of FNAB performed on seven of these patients, PTC was detected in one case (8.3%). In another study conducted in our country, it was stated that the rate of thyroid nodules in children with HT was 13%, which was similar to our study, and PTC was detected in 5.12% of them (35). Therefore, it is very important to detect thyroid nodules and follow up the patients regularly in cases with HT.

It is known that the frequency of other autoimmune diseases is increased in Hashimoto's thyroiditis. Diseases such as Celiac disease, type 1 DM, vitiligo and alopecia may occur in the pediatric population (36). In a study consisting of children and adult patients with Hashimoto's, it has been determined that in adults, connective tissue disorders are more common, and in children and adolescents, the most common diseases are type 1 DM and Celiac disease (31). In a study conducted by Özer et al. (13) on cases with Hashimoto's thyroiditis, the rate of autoimmune diseases was found to be 13.9%, and Demirbilek et al. (24) reported this rate to be 14.2% in their study. In these studies, it was stated that the most common accompanying autoimmune disease was type 1 DM (13,24). In our study, the rate of autoimmune diseases was found to be 7.6% and vitiligo was the most common disease. Unlike other studies, cases who were initially diagnosed with Type 1 DM were not included in our study. Therefore, the rate of autoimmune diseases was found to be lower than other studies.

Study Limitations

This study has limitations due to its retrospective nature and the fact that the follow-up period of the cases was short.

Conclusion

In conclusion, Hashimoto's thyroiditis is a lifelong chronic disorder. Its prevalence increases with age, however, as in our study, it is observed that the prevalence of HT gradually increases in younger cases. Since thyroid hormone levels can vary, follow-up is necessary. The presence of high anti-TPO at the time of admission may predict hypothyroidism. Since many autoimmune diseases may accompany Hashimoto's thyroiditis, the cases should also be evaluated in this regard. In addition, close follow-up of the nodules is necessary in terms of thyroid nodules and thyroid malignancies.

Ethics

Ethics Committee Approval: The approval for this study was obtained from the Ethics Committee of Dicle University Faculty of Medicine (date: 04.03.2021, approval number: 2021/174).

Conflict of Interest: No conflict of interest was declared by the authors.

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