Received: 20 Feb 2023 | **Accepted:** 22 Dec 2023 **Genel Tıp Derg. Volume** 33/**Issue** 6 (December), 683-688
DOI: 10.54005/geneltip.1253549

ORIGINAL ARTICLE

Distribution, Clinical Features and Laboratory Findings of Hashimoto's Thyroiditis in Prepubertal and Pubertal Patients

Prepubertal ve Pubertal Hastalarda Hashimoto Tiroiditi'nin Dağılımı, Klinik Özellikleri ve Laboratuvar Bulguları

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How to cite ?

Kılınç Uğurlu A, Bitkay A. Distribution, Clinical Features and Laboratory Findings of Hashimoto's Thyroiditis in Prepubertal and Pubertal Patients. Genel Tıp Derg. 2023;33(6):683-8.

ABSTRACT

Aims:Hashimoto's thyroiditis (HT) is the most common cause of acquired hypothyroidism in childhood. This disease, which develops on an autoimmune basis, often appears in adolescence. However, in recent years, cases diagnosed with this disease in prepubertal, and infant period have been reported. This is thought to be related to early exposure to environmental factors that disrupt the endocrine system and trigger autoimmunity. We aimed to evaluate the distribution, clinical features and laboratory findings of our patients diagnosed with Hashimoto's thyroiditis in prepubertal and pubertal periods in our clinic.
Material and Method:In the study, the cases diagnosed with Hashimoto's Thyroiditis between August 2019 and May 2022 were divided into two groups as prepubertal (Tanner stage 1) and pubertal (Tanner stage 2-3-4-5). These two groups were compared retrospectively in terms of clinical, laboratory and ultrasound findings.
Results: The mean±SD of 134 patients diagnosed with HT was 12.4±3.4 years. While 25% (n=33) of the cases were prepubertal, 75% (n=101) were pubertal. The cases' female/male ratio (F/M) was 4.1/1, F/M: 2.3/1 in the prepubertal period, and F/M: 5.3/1 in the pubertal period. According to thyroid function tests performed at the time of diagnosis, euthyroidism was most common in all cases. In the prepubertal group, the rates of euthyroidism and subclinical hypothyroidism were similar and had the highest rates. In contrast, euthyroidism was observed most frequently in the pubertal group. When we compared the prepubertal and pubertal groups, subclinical hypothyroidism (36.4%) and hypothyroidism (21%) were more frequent in the prepubertal group compared to the pubertal group (22.8% and 10.9%). However, subclinical hyperthyroidism and hyperthyroidism were more common in the pubertal group (p=0.17).
Conclusion: In our study, HT is more prevalent in boys at the prepubertal stage than in the pubertal stage. While the patients in the prepubertal period applied in the hypothyroid phase, it was remarkable that the pubertal group had hyperthyroidism on their admissions.

Keywords: Hashimoto's Thyroiditis, prepubertal, pubertal, euthyroid phase, female/male ratio

ÖZ

Giriş: Hashimoto tiroiditi (HT) çocukluk çağında edinsel hipotiroidizmin en sık nedenidir. Otoimmün temelde gelişen bu hastalık sıklıkla ergenlik döneminde ortaya çıkmaktadır. Ancak son yıllarda prepubertal ve infant dönemde bu hastalık tanısı alan olgular bildirilmektedir. Bu durumun endokrin sistemi bozan ve otoimmüniteyi tetikleyen çevresel faktörlere erken dönemde maruz kalınmasından kaynaklandığı düşünülmektedir. Kliniğimizde prepubertal ve pubertal dönemde Hashimoto tiroiditi tanısı alan hastalarımızın dağılımını, klinik özelliklerini ve laboratuvar bulgularını değerlendirmeyi amaçladık.
Gereç ve Yöntem: Çalışmada Ağustos 2019-Mayıs 2022 tarihleri arasında Hashimoto Tiroiditi tanısı alan olgular prepubertal (Tanner evre 1) ve pubertal (Tanner evre 2-3-4-5) olarak iki gruba ayrıldı. İki grup klinik, laboratuvar ve ultrason bulguları açısından retrospektif olarak karşılaştırıldı.
Bulgular: HT tanısı konulan hastaların (n=134) ortalama yaşı 12.4±3.4 yıldı. Olguların %25'i (n= 33) prepubertal iken, %75'i (n=101) pubertaldi. Olguların kız/erkek oranı (K/E) 4,1/1, prepubertal dönemde K/E=2,3/1 ve pubertal dönemde K/E= 5,3/1 idi. Tanı anında yapılan tiroid fonksiyon testlerine göre, tüm olgularda en sık ötiroidizm saptandı. Prepubertal grupta, ötiroidizm ve subklinik hipotiroidizm oranları benzerdi ve en yüksek oranlara sahipti. Buna karşılık, pubertal grupta en sık ötiroidizm gözlendi. Prepubertal ve pubertal grupları karşılaştırdığımızda, prepubertal grupta subklinikhipotiroidi (%36.4), hipotiroidi (%21), pubertal gruba (%22.8 ve %10.9) göre daha sık saptandı. Bununla birlikte, subklinik hipertiroidizm ve hipertiroidizm pubertal grupta daha sık görüldü (p= 0.17).
Sonuç: Çalışmamızda, HT prepubertal evredeki erkek çocuklarda pubertal evredekilere göre daha yaygındır.Prepubertal dönemdeki hastalar hipotiroidi evresinde başvururken, pubertal grubun başvurularında hipertiroidi olması dikkat çekiciydi.

Anahtar Kelimeler: Hashimoto Tiroiditi, prepubertal, pubertal, ötiroid faz, kız/erkek oranı

Introduction

Hashimoto's thyroiditis (HT) is the most common cause of acquired hypothyroidism in childhood (1). It is characterized by the destruction of thyroid follicles due to various cell and antibody-mediated immune processes and lymphocytic infiltration. The pathogenesis of HT typically involves a combination of underlying genetic susceptibility and environmental triggers. Genetic factors have been estimated to contribute to approximately 70-80% of the susceptibility to autoimmune thyroid disease, as indicated by twin studies (2,3). The remaining 20-30% of the disease onset is attributed to various environmental exposures, including infections, stress, iodine intake, smoking, certain medications such as amiodarone and interferon,

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
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Selcuk University Press
Genel Tıp Dergisi | e-ISSN: 2602-3741
https://dergipark.org.tr/tr/pub/geneltip
https://yayinevi.selcuk.edu.tr/

radiation, and environmental toxicants (4–7). It is thought to occur with the effect of environmental factors in individuals with an etiologically genetic predisposition. This disease, which develops on an autoimmune basis, often appears in adolescence. However, in recent years, we have had cases diagnosed with this disease in prepubertal and infant ages (8). This condition may be the result of early exposure to environmental factors that disrupt the endocrine system and induce autoimmunity. Although the disease can present with transient thyrotoxicosis, it typically progresses to subclinical and then overt hypothyroidism due to the complex interaction between the genetic background, existential and environmental factors (9,10). It is aimed to show the distribution, clinical features, and disease phase of the cases diagnosed in the prepubertal and pubertal periods followed up with the diagnosis of Hashimoto's thyroiditis.

Materials and Methods

The research was conducted on a single-center, retrospective case series. Patients diagnosed with Hashimoto's thyroiditis between August 2019 and May 2022 were included in the study.

Physical examination findings, laboratory findings and thyroid ultrasonography findings were recorded by two pediatric endocrinologists from the files of patients diagnosed with Hashimoto's thyroiditis.

The cases diagnosed with Hashimoto's Thyroiditis were divided into two as prepubertal (Tanner stage 1) and pubertal group (Tanner stage 2-3-4-5) (11). These two groups were compared retrospectively in terms of clinical, laboratory, and ultrasound findings. The pubertal staging was performed according to breast Tanner staging in girls and testicular volumes in boys. Tanner stage 1 was defined as prepubertal and Tanner stage 2,3,4,5 as pubertal (11). Thyroid staging in thyroid examination was evaluated as follows (12);

Stage 0: No visible or palpable thyroid gland,

Stage 1A: No visible thyroid gland, but palpable when the neck is in normal position,

Stage 1B: Presence of an enlarged thyroid gland when the neck is in the extended position,

Stage 2: Presence of visibly enlarged thyroid gland when the neck is in the standard position.

Stages 1A, 1B, and 2 were defined as goiter (12). Height and weight were measured, body mass index (BMI) was calculated using the standard formula weight (kg)/ height2 (m) and the standard deviation score (SDS) was calculated based on local reference data (13). Thyroid gland volume was determined by thyroid ultrasonography (US) using the formula length x width x depth x 0.479 (14). If thyroid volume is ≥1.88 SDS, it is defined as goiter (15). Free T4(fT4) TSH, Anti-Thyroglobulin antibody, and Anti-TPO antibody (Atellica, Siemens) concentrations were measured using immunochemiluminometric assay (ICMA) (Atellica, Siemens). For the diagnosis of Hashimoto's thyroiditis, Anti-thyroglobulin and Anti-TPO antibodies concentrations were defined as being above the reference ranges (16) (Anti-thyroglobulin reference >4.5 IU/ml), (Anti-TPO reference>60 U/ml).

The patients were classified into the following groups concerning thyroid function at initial diagnosis: euthyroid (both fT4 (0.85—1.4 ng/dl) and TSH (1-4.8 mU/L) concentration were within normal limits); subclinically hypothyroid (normal fT4 and TSH: 5 -10 mU/L) hypothyroid (low fT4 and TSH > 10 mU/L) and subclinically hyperthyroid (normal fT4 and suppressed TSH); hyperthyroidism (elevated fT4 and suppressed TSH).

This study was approved by the Ethics Committee of Ankara City Hospital (Approval number/date) E2-22-1988/22.06.2022).

All data analyzes were performed with SPSS 26.0. Descriptive statistics were used to evaluate demographic and clinical characteristics. Data were defined as percent and mean ± standard deviation (SD) or median and categorical data. "Chi-Square" test was used when comparing the ratios of two independent groups; "The Mann-Whitney U" test was used when comparing the medians of two independent groups; "The student t-test" was used when comparing the means of two independent groups, and "Chi-Square" test was used for comparing categorical variables. Statistically, $p<0.05$ was considered significant.

Results

The study included 134 patients diagnosed with Hashimoto's thyroiditis, with a mean age of 12.4±3.4 years. Among the cases, 25% (n=33) were in the prepubertal period while 75% (n=101) were in the pubertal period. The female-to-male ratio (F/M) of all cases was 4.1/1, with a ratio of 2.3/1 in the prepubertal period and 5.3/1 in the pubertal period. The distribution of females and males in the prepubertal and pubertal periods is presented in Figure 1.

Anthropometric measurements did not differ significantly between prepubertal and pubertal cases, as shown in Table 1.

Thyroid Stage 0 was the most common stage observed in both prepubertal and pubertal cases in the physical examinations as indicated in Table 2.

No significant differences were found in fT4, TSH, Anti-Thyroglobulin antibody, and urine iodine levels between prepubertal and pubertal cases ($p>0.05$) as presented in Table 3. The median value of Anti-TPO antibody was 627 U/ml in all patients, with lower median values observed in the prepubertal group (396 U/ml) and higher median values in the pubertal group (831 U/ml). However, there is no difference statistically ($p=0.09$).

At the time of admission, the most common phase observed in Hashimoto's thyroiditis cases was the euthyroid phase. In the prepubertal group, both euthyroid and subclinical hypothyroidism rates were equally common. In the pubertal group, the euthyroid

phase was observed most frequently. The distribution of cases according to the disease phase periods is provided in Table 4.

When we compared the prepubertal and pubertal groups, subclinical hypothyroidism (36.4%) and hypothyroidism (21%) were more frequent in the prepubertal group compared to the pubertal group (22.8% and 10.9%). Subclinical hyperthyroidism and hyperthyroidism were more common in the pubertal group, but these differences were not statistically significant (p>0.05).

The presence of goiter in Thyroid US was more frequent in the pubertal group compared to the prepubertal group (p>0.05), while cases without goiter were common in both groups. These findings are summarized in Table 5.

Table 1. Age and anthropometric findings of the cases at the time of diagnosis

	Total %100(n=134)	Prepubertal %25(n=33)	Pubertal %75(n=101)	p value
Age at admission(-years)	12.4±3.4 (3.4-18)	7.7±1.7	13.9±2.3	0.001
Weight SDS	0.13±1.4	0.05±0.8	0.16±1.53	0.60
Height SDS	1.3 ±1.2	0.09±1.08	1.69±1.56	0.74
BMI SDS	0.054±1.32	0.56±0.99	0.08±1.41	0.60

Table 2. Thyroid staging of the cases in physical examination

Thyroid stage	0	1A	1B	2	p value
Prepubertal	51% (n=17)	9% (n=3)	9% (n=3)	30% (n=10)	0.65
Pubertal	46% (n=46)	7% (n=7)	20% (n=20)	28% (n=28)	
Total	47% (n=63)	7% (n=10)	17% (n=23)	28% (n=38)	

Table 3. Laboratory findings of the cases

	Total 100%(n=134)	Prepubertal 25% (n=33)	Pubertal 75% (n=101)	p value
fT_4 (ng/dl)	1.12±0.2	1.18±0.36	1.1±0.2	0.25
TSH (mU/L)	4(0.01-713) *	3.833(0.02-713) *	4.1(0.01-150) *	0.86
Anti-Thyroglobulin (IU/ml) †	9.7(5-2000) *	24(5-430)	9(5-2000) *	0.22
Anti-TPO (U/ml) ‡	627(61-13.043) *	396(61-11.460) *	831(61-13043) *	0.09
Iodine (urine) (µg/L)	104±79	80±68	111±84	0.51

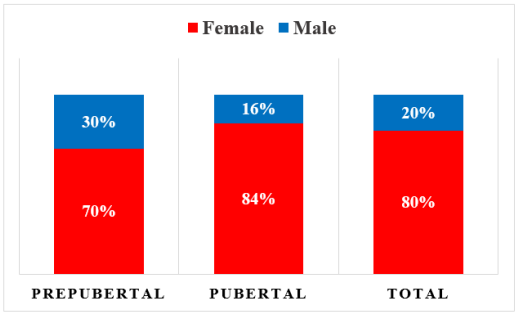
*Median (minimum; maximum), other data as mean ± SD
† (reference > 4.5 IU/ml)
‡ (reference < 60 U/ml)

Table 4. Disease phase periods of the cases

Disease Phase	Euthyroi-dism	Subc-linical Hypoth-yroidism	Hypoth-yroidism	Subc-linical Hyperth-yroidism	Hyperth-yroidism	p value
Pre-pubertal	36.4% (n=12)	36.4% (n=12)	21% (n=7)	6% (n=2)	0%(n=0)	0.17
Pubertal	55.4% (n=56)	22.8% (n=23)	10.9% (n=11)	8.9% (n=9)	2% (n=2)	
Total	50.7% (n=68)	26.1% (n=35)	13.4% (n=18)	8.2% (n=11)	1.5% (n=2)	

Table 5. Goiter according to Thyroid US rates of the cases at the time of admission

Goiter	Absent	Available	p value
Prepubertal	65% (n=20)	35% (n=11)	0.34
Pubertal	55% (n=55)	45% (n=45)	
Total	57% (n=75)	43% (n=56)	



	Prepubertal(n)	Pubertal(n)	Total(n)	p value
Female	23	85	108	0.06
Male	10	16	26	

Figure 1. Gender distribution of the cases in the prepubertal - pubertal period

Discussion

Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) is the most common acquired thyroid disease in children and adolescents. T cell activation, and HLA tissue groups are associated with the development of goiter and thyroiditis. Autoimmunity is clearly associated with female gender and advanced age. In our study, we determined the differences in the clinical features, autoimmune marker concentrations and thyroid function patterns at the time of diagnosis of HT, which is rarer in the prepubertal period, compared to the pubertal period.

The prevalence of Hashimoto's thyroiditis is relatively low in the first three years of life; however, it increases significantly after the age of six and reaches its highest frequency, particularly during adolescence (17,18). Previous studies conducted in our country by Demirbilek et al. (19) and Özsu et al (20) reported the mean age of diagnosis as 11.4±2.97 and 11.5±2.8 years, respectively. Consistent with the existing literature, our study found the mean age of diagnosis as12.4±3.4 years. These findings highlight the trend of Hashimoto's thyroiditis to manifest more frequently in the later stages of childhood and adolescence. The observed consistency in the mean age of diagnosis between our study and previous research suggests a general agreement within the literature regarding the age distribution of this disease. Understanding the age distribution of Hashimoto's thyroiditis is essential for recognizing its patterns of occurrence and facilitating early detection and management.

The incidence of Hashimoto's thyroiditis in the pubertal stage demonstrates a proportional relationship with

the escalating autoimmune burden, resulting in a higher prevalence compared to the prepubertal stage. In our study, the proportion of pubertal cases was 75%, while in another study conducted by Özsu et al. (20) evaluating 106 patients with Hashimoto's thyroiditis from our country, they identified 72% of the cases as pubertal. The proportion of our prepubertal cases was 25%, whereas López a et al. (21) reported a slightly higher rate of 31%. It is worth noting that our study encompassed a smaller proportion of prepubertal cases. Nevertheless, considering the rising prevalence of autoimmune diseases over the past decade, examining rates across prepubertal stage and pubertal stage within the same region becomes crucial for elucidating the impact of environmental factors (22–24).

Existing literature indicates incidence rates ranging from 73.8% to 86% in females, establishing a greater predominance of the disease among females (19,25–27). Our study aligned with these findings, as the female rate was 80%, consistent with previous series. In our investigation, the female-to-male ratio was lower in the prepubertal stage (2.3/1) but increased throughout the pubertal stage (5.3/1). Tang et al. (8) observed a ratio of 1.7/1 in their study on cases of children under three years of age. In another study evaluating a total of 1053 cases involving adults (n=550) and children (n=553), the ratio was 4.3/1 in the pediatric age group and 14.5/1 in the adult age group (27). These findings further emphasize the higher prevalence of Hashimoto's thyroiditis among females, with the female-to-male ratio demonstrating an increase with age.

The results of our study showed that the median levels of Anti-TPO antibody were approximately twofold higher in the pubertal group (831 U/ml) compared to the prepubertal group (396 U/ml). However, it is important to note that this difference did not reach statistical significance. In the research, which involved 8,040 students aged 6 to 14 (28), a rise in positive antithyroid antibody (ATA) levels related to age was noted among girls starting at 11 years old, while no such pattern was observed among boys. A similar outcome was identified in young individuals with type 1 diabetes (29,30), indicating that the occurrence of ATA notably increased only among females after reaching 12 years of age. It is worth noting that both studies lacked an assessment of pubertal stages and solely focused on reporting serum ATA levels. The finding of higher levels of Anti-TPO antibody in the pubertal period suggests a potential association between increased autoimmunity and advanced age and puberty in Hashimoto's thyroiditis(31).

Goiter was found on physical examination at the time of diagnosis in 53% of all cases, 54% of the pubertal group and 48% of the prepubertal group. Thyroid USG revealed goiter in 43% of all cases, 45% in the pubertal group, and 35% in the prepubertal group. Goiter was detected at a lower rate in the prepubertal group. The ratio of goiter in our study was similar to recent researches (21,32).

With the thyroid function tests at admission, we detected euthyroidism and subclinical hypothyroidism more frequently. Thyroid function at presentation may differ among pediatric reports (8,25,26,33,34), ranging from euthyroidism to overt hypothyroidism or, rarely, hyperthyroidism. Subclinical hypothyroidism (19,32,33) or, less frequently, subclinical hyperthyroidism (26,27) are additional pattern of thyroid function recorded in children and adolescents presenting with HT. In the majority of our instances, euthyroidism was the relevant diagnosis. Compared to Ruggeri et al.'s (27) research, the rate of cases presenting with hyperthyroidism was found at a high rate (27). It was noted that hyperthyroidism admissions were more prevalent during puberty. One possible explanation is the fluctuation of autoimmune activity during the course of the disease. Hashimoto's thyroiditis is characterized by the destruction of thyroid tissue due to autoimmune mechanisms. As the disease progresses, there can be periods of increased inflammation and destruction followed by phases of decreased activity. During puberty, hormonal changes and alterations in the immune system may lead to a temporary increase in autoimmune activity, resulting in hyperthyroidism. This transient hyperthyroid phase can occur before the eventual progression to hypothyroidism, which is a more characteristic feature of HT. Another factor to consider is the potential overlap or coexistence of other autoimmune disorders in the pubertal period. Autoimmune diseases often cluster together, and it is not uncommon for individuals with Hashimoto's thyroiditis to develop additional autoimmune conditions such as Graves' disease, which is characterized by hyperthyroidism(35).

In addition, we found admissions in the hypothyroid phase more frequently in the prepubertal period. Hashimoto's thyroiditis is characterized by chronic inflammation of the thyroid gland, leading to its destruction over time. In the prepubertal period, there may be a longer duration of autoimmune attack on the thyroid gland before diagnosis, resulting in more extensive damage and a higher likelihood of developing hypothyroidism. The diagnosis of Hashimoto's thyroiditis can sometimes be delayed, especially in younger children, as symptoms may be nonspecific or attributed to other causes. This delay in diagnosis may result in a longer period of untreated thyroid dysfunction in the prepubertal group, leading to a higher proportion of patients presenting in the hypothyroid phase.

In conclusion, Hashimoto's thyroiditis is more commonly diagnosed during the pubertal period with a higher prevalence in females. Our study showed that the female-to-male ratio increased with age, indicating a greater susceptibility of females to the disease. No significant differences were observed in thyroid function and autoimmune marker concentrations between prepubertal and pubertal cases, suggesting that these factors do not vary significantly based on pubertal stage. In the last decade, Hashimoto's thyroiditis has been detected in the prepubertal period

with increasing exposure to endocrine disruptors and various environmental factors that trigger autoimmunity (7,36). These findings provide valuable insights into the clinical features and characteristics of Hashimoto's thyroiditis in children and adolescents. Further research is needed to explore the underlying mechanisms contributing to the higher prevalence of Hashimoto's thyroiditis in females and its association with puberty. Understanding these factors can help develop targeted interventions and personalized treatment approaches for individuals with Hashimoto's thyroiditis.

Funding: This research received no specific grant from any funding agency.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships

Author Contributions: KILINÇ UĞURLU A: Constructing the hypothesis or idea of research and article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking responsibility for the research/study, Taking responsibility for patient follow-up, collection of data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in writing the study. BİTKAY A: Collection of data management and reporting

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