



The Role of Childhood Traumas in Adult Hashimoto's Thyroiditis

Erişkin Hashimoto Tiroiditinde Çocukluk Çağı Travmalarının Rolü

Uğur Aydoğan¹, Hüseyin Demirci², Ebru Aydoğan³

¹Ankara Etlik City Hospital, Clinic of Intensive Care, Ankara, Türkiye

²Ankara Etlik City Hospital, Clinic of Endocrinology and Metabolism, Ankara, Türkiye

³Hacettepe University Hospitals, Clinic of Public Health, Ankara, Türkiye

ABSTRACT

Objective: Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease. There are studies suggesting that childhood traumas cause hypothalamic-pituitary-adrenal axis dysfunction in adulthood, which predisposes patients to autoimmune diseases. Our study aimed to investigate the relationship between HT and childhood trauma.

Methods: In our study, we included 52 patients diagnosed with HT and 31 healthy controls and evaluated the Turkish Childhood Trauma Questionnaire (which evaluates childhood traumas retrospectively) in both groups. The diagnosis of HT was confirmed using anti-thyroid peroxidase (anti-TPO) levels and thyroid ultrasonography.

Results: The childhood emotional neglect score (10.79±3.90) was significantly higher in patients with HT than in the control group (p=0.04). However, no significant difference was observed between the two groups regarding other components. In addition, a significant positive correlation was found between anti-TPO levels and emotional neglect score (p=0.02; r=0.26).

Conclusion: The significantly higher emotional neglect score in patients with HT compared with the control group and the positive correlation between childhood emotional neglect score and anti-TPO level suggest that childhood traumas may play a role in the etiology of adult HT. Further and large-scale studies are needed to elucidate all aspects of this subject.

Keywords: Autoimmune thyroiditis, Hashimoto's thyroiditis, childhood traumas

ÖZ

Amaç: Hashimoto tiroiditi (HT) en sık görülen otoimmün tiroid hastalığıdır. Çocukluk çağı travmalarının yetişkin dönemde hipotalamus-hipofiz-adrenal aks bozukluğuna sebep olduğuna ve bu durumun otoimmün hastalıklara zemin hazırladığına dair çalışmalar bulunmaktadır. Çalışmamızın amacı HT ile çocukluk çağı travmaları arasındaki ilişkiyi incelemektir.

Yöntemler: Çalışmamıza 52 HT tanılı hasta ve 31 sağlıklı kontrol grubu alınarak, her iki grupta Çocukluk Çağı Travma Ölçeği Anketi değerlendirildi. HT tanısı için anti-tiroid peroksidaz (anti-TPO) pozitifliği ve tiroid ultrasonografi kullanıldı.

Bulgular: HT hastalarının çocukluk çağı duygusal ihmal puanı, kontrol grubuna göre anlamlı olarak yüksek saptandı (p=0,04). Diğer bileşenler açısından anlamlı farklılık görülmedi. Anti-TPO düzeyinin duygusal ihmal puanı ile anlamlı pozitif korelasyon gösterdiği bulundu (p=0,02; r=0,26).

Sonuç: HT tanılı hastalarda kontrol grubuna göre duygusal ihmal puanının anlamlı olarak yüksek saptanması ve çocukluk çağı duygusal ihmal ile anti-TPO düzeyinin pozitif korelasyon göstermesi, erişkin HT etiyolojisinde çocukluk çağı travmalarının rolünün olabileceğini düşündürmektedir. Konunun tüm yönleriyle aydınlatılabilmesi için daha fazla ve geniş ölçekli çalışma-lara gerek vardır.

Anahtar Sözcükler: Otoimmün tiroiditi, Hashimoto tiroiditi, çocukluk çağı travmaları

Address for Correspondence/Yazışma Adresi: Uğur Aydoğan MD, Ankara Etlik City Hospital, Clinic of Intensive Care, Ankara, Türkiye

E-mail / E posta: aydoganuur@gmail.com

ORCID ID: orcid.org/0000-0002-8942-9991



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Received/Geliş Tarihi: 16.10.2023

Accepted/Kabul Tarihi: 23.11.2023

INTRODUCTION

Hashimoto's thyroiditis (HT) is considered the most prevalent autoimmune thyroid disease (1) and is believed to arise from a combination of genetic, endogenous, and environmental factors. Environmental factors contributing to its development include viral infections, sex hormones, diet, and stress (2). Several studies have proposed that childhood traumas can lead to hypothalamic-pituitary-adrenal (HPA) axis dysfunction in adulthood, which in turn predisposes individuals to autoimmune diseases (3-6). Exposure to adversities is considered a major condition for enduring alterations in HPA axis biology and increased sensitivity to trauma-related symptoms (7). Given that the HPA stress response axis undergoes maturational changes throughout childhood and adolescence, it may be particularly sensitive to childhood adversity, resulting in long-term and persistent dysregulation of the HPA pathway (8,9).

In HT, the positivity of thyroid autoantibodies is one of the most important laboratory findings (10). Autoantibody levels were found to be higher in children with traumatic experiences than in the control group. Therefore, trauma-related immune dysfunction is thought to cause a predisposition for the development of autoimmune disease (11). Traumatic events have been linked to changes in the immune system (12), and some studies have found higher rates of a variety of autoimmune diseases in individuals with posttraumatic stress disorder (13,14). The aim of our study was to investigate the relationship between HT and childhood trauma.

MATERIALS AND METHODS

Written approval for the study was obtained from the Kırıkkale University Faculty of Medicine Local Ethics Committee (approval number: 15/06, date: 12.05.2014) and was conducted in accordance with the Helsinki Declaration. The study included 52 patients with HT admitted to the Internal Medicine outpatient clinic of Kırıkkale University Faculty of Medicine. As a control group, 31 healthy volunteers without HT were included. Participants and sample sizes were randomly selected. Informed consent was obtained from all participants. The study excluded patients with other autoimmune diseases (rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, autoimmune hepatitis, Crohn's disease, Celiac disease, ulcerative colitis, type 1 diabetes, etc.) those who had taken antidepressants or antipsychotics within the past six months, individuals with psychiatric illnesses that could affect their ability to comply with the study requirements, and those under 18 years or over 70 years of age.

Diagnosis of HT employed positive thyroid peroxidase antibodies (anti-TPO) and thyroid ultrasonography. The Roche E-170 system (Hitachi, Tokyo, Japan) using a chemiluminescent measurement method was used for anti-TPO detection. To determine thyroid function status, free thyroxine (fT4), free triiodothyronine (fT3), and thyroid-stimulating hormone (TSH) levels were measured using the original kits of the Abbot-Architect analyzer (Toshiba, Chicago, IL, USA) using a chemiluminescent measurement method. Thyroid ultrasonography was conducted by a radiologist unaware of the purpose of the study and the laboratory data using a Hitachi HI Vision Preirus color Doppler ultrasound system (Hitachi, Tokyo, Japan).

The Turkish Childhood Trauma Questionnaire (CTQ) was applied to the patient and control groups. The original English version of

the questionnaire was developed by D.P. Bernstein in 1995 and adapted into Turkish by Şar et al. (15) in 1996. This study aims to evaluate childhood traumas retrospectively. It includes questions assessing physical, sexual, and emotional abuse as well as emotional and physical neglect in childhood. There are also three deceptive minimization questions added to assess the results more accurately. Response options are 1= never, 2= rarely, 3= occasionally, 4= often, and 5= very often. Each question is scored between 1 and 5. It allows the calculation of separate traumatic experience subscales and total scores. Each subscale scores between 5 and 25 points. The total score to be obtained from the scale is between 25 and 125. It is considered that exceeding 5 points for sexual and physical abuse (answering yes to any of the questions, even at the lowest level) should be counted as a positive report. This limit was accepted as 7 points for physical neglect and emotional abuse, 12 points for emotional neglect, and 35 points for the total score (16).

Statistical Analysis

SPSS statistical software (SPSS for Windows, version 15.0, Inc., Chicago, IL, USA) was used for statistical analysis. The distribution of the data was evaluated using the Kolmogorov-Smirnov test. For the display of parametric quantitative data, mean \pm standard deviation; for non-parametric quantitative data, the median is IQR; number of cases (n) and percentile (%) were used to display qualitative data. Student's t-test was used in the analysis of parametric data, Mann-Whitney U was used in the analysis of non-parametric data, Pearson's chi-square and Fisher's exact tests were used in the analysis of qualitative data, and $p < 0.05$ was considered significant. While investigating the relationship between two numerical variables, Pearson's correlation analysis was used for those that fit the normal distribution, and Spearman's correlation analysis was used for those that did not fit the normal distribution.

RESULTS

The mean age in the patient group with HT was 39.46 ± 12.93 years and in the control group was 34.71 ± 12.37 years ($p = 0.09$). The patient group with HT consisted of 41 women (78%) and 11 men (22%); the control group consisted of 20 women (65%) and 11 men (35%) ($p = 0.15$). Among the patients with HT, 38 (73%) were receiving thyroid hormone (L-T4) replacement.

Patients with HT had anti-TPO and TSH levels of 311.5 ± 207.9 IU/mL and 5.14 ± 7.56 μ U/mL, respectively, whereas the control group had levels of 12.7 ± 6.6 IU/mL and 2.10 ± 0.77 μ U/mL, respectively. Anti-TPO and TSH levels were significantly higher in patients with HT than in the control group ($p = 0.001$ and $p = 0.03$ respectively).

In the patient group diagnosed with HT, the levels of fT3 and fT4 were found to be 2.97 ± 0.55 pg/mL and 1.22 ± 0.29 ng/dL, respectively, whereas in the control group, they were 3.09 ± 0.39 pg/mL and 1.24 ± 0.21 ng/dL, respectively. However, there was no statistical difference in the levels of fT3 and fT4 between the HT and control groups ($p = 0.19$ and $p = 0.80$, respectively), as presented in Table 1.

Childhood emotional neglect scores of HT patients (10.79 ± 3.90) were higher than those of the control group (9.13 ± 3.22) ($p = 0.04$). The physical abuse and neglect, emotional abuse, and sexual abuse scores of patients with HT in childhood showed no statistical difference from the control group ($p = 0.20$, $p = 0.75$, $p = 0.66$, and

$p=0.75$, respectively). In addition, between the two groups, there was no significant difference in the total score evaluation of the CTQ ($p=0.26$) (Table 2).

In patients diagnosed with HT, there was no significant difference in physical abuse and neglect, emotional abuse and neglect, sexual abuse, and total CTQ scores between those who received L-T4 replacement therapy and those who did not (Table 3).

The results showed a significant positive correlation between the anti-TPO level and emotional neglect score ($p=0.02$, $r=0.26$) but not with the total scores or other CTQ subscales. However, age, TSH, fT4, and fT3 levels did not correlate with the total score and subscales of the CTQ, as presented in Table 4.

DISCUSSION

This study examined the frequency and types of childhood traumas in patients with HT and in the control group. This study holds significant importance as it is the first of its kind to explore the association between childhood trauma and HT in polyclinic patients. Experimental observations from psychoanalytic,

psychotherapeutic, and general psychiatric perspectives have consistently demonstrated that childhood maltreatment can have long-lasting effects on an individual's health in adulthood. This includes higher health expenditures and an increased risk of various physical and mental health problems (17,18). Numerous recent clinical and epidemiological studies have provided further evidence to support these findings. In addition, advances in basic and clinical neuroscience have enabled a closer examination of potential mechanisms of pathogenesis related to childhood maltreatment and its long-term effects on physical and mental health (19).

Our study found that patients diagnosed with HT were more frequently exposed to emotional neglect in childhood compared with the control group. Emotional neglect has been reported to have the highest prevalence rate among the different types of childhood trauma in the United States compared with other forms of childhood trauma (20). Our study revealed a positive correlation between childhood emotional neglect and anti-TPO levels, which are considered to be the most significant biochemical indicator of HT. In a study on childhood trauma, depression, anxiety, stress, and quality

Table 1. Demographic and laboratory data of the study groups

	Hashimoto's thyroiditis, (n=52) Mean \pm SD	Control, (n=31) Mean \pm SD	p
Age (years)	39.46 \pm 12.93	34.71 \pm 12.37	0.09
Female/male (n)	41/11	20/11	0.15
Anti-TPO (IU/mL)	311.5 \pm 207.9	12.7 \pm 6.6	0.001*
TSH (μ U/mL)	5.14 \pm 7.56	2.10 \pm 0.77	0.03*
fT3 (pg/mL)	2.97 \pm 0.55	3.09 \pm 0.39	0.19
fT4 (ng/dL)	1.22 \pm 0.29	1.24 \pm 0.21	0.80

Anti-TPO: Anti-thyroid peroxidase, TSH: Thyroid-stimulating hormone, fT3: Triiodothyronine, fT4: Thyroxine, SD: Standard deviation, * $p<0.05$.

Table 2. Evaluation of CTQ scores between the groups

	Hashimoto's thyroiditis, (n=52) Mean \pm SD	Control, (n=31) Mean \pm SD	p
Physical abuse scores	5.50 \pm 1.02	5.19 \pm 1.08	0.20
Physical neglect scores	7.33 \pm 2.03	7.16 \pm 2.63	0.75
Emotional abuse scores	6.79 \pm 2.18	6.55 \pm 2.68	0.66
Emotional neglect scores	10.79 \pm 3.90	9.13 \pm 3.22	0.04*
Sexual abuse scores	5.13 \pm 0.53	5.10 \pm 0.54	0.75
Total CTQ scores	35.21 \pm 7.80	33.06 \pm 8.99	0.26

CTQ: Turkish Childhood Trauma Questionnaire, * $p<0.05$.

Table 3. Evaluation of CTQ scores in patients with Hashimoto's thyroiditis receiving and not receiving replacement therapy

	Receiving L-T4, (n=38) Mean \pm SD	Not receiving L-T4, (n=14) Mean \pm SD	p
Physical abuse scores	6.95 \pm 2.24	5.31 \pm 2.07	0.42
Physical neglect scores	7.47 \pm 2.00	6.92 \pm 2.22	0.41
Emotional abuse scores	6.95 \pm 2.24	6.46 \pm 2.07	0.50
Emotional neglect scores	10.97 \pm 3.38	10.38 \pm 5.38	0.65
Sexual abuse scores	5.08 \pm 0.36	5.31 \pm 0.86	0.18
Total CTQ scores	35.61 \pm 7.13	34.38 \pm 9.95	0.63

CTQ: Turkish Childhood Trauma Questionnaire, L-T4: L-thyroxine, SD: Standard deviation.

Table 4. Relationship between CTQ scores and thyroid function tests, anti-TPO, and age

		Age	ft3	ft4	TSH	Anti-TPO
Emotional abuse scores	p	0.84	0.59	0.16	0.51	0.15
	r	-0.02	0.06	0.16	0.07	0.16
Physical abuse scores	p	0.65	0.27	0.56	0.58	0.30
	r	0.05	0.12	0.06	0.06	0.10
Physical neglect scores	p	0.44	0.35	0.23	0.94	0.46
	r	0.09	0.10	0.14	0.01	0.08
Emotional neglect scores	p	0.71	0.45	0.45	0.26	0.02*
	r	0.04	0.09	0.08	0.12	0.26*
Sexual abuse scores	p	0.30	0.87	0.82	0.38	0.78
	r	-0.12	-0.02	-0.03	0.10	0.03
Total CTQ scores	p	0.92	0.28	0.25	0.72	0.08
	r	0.01	0.12	0.13	0.04	0.20

CTQ: Turkish Childhood Trauma Questionnaire, Anti-TPO: Anti-thyroid peroxidase, TSH: Thyroid-stimulating hormone, ft3: Triiodothyronine, ft4: Thyroxine, *p<0.05.

of life in women with HT, emotional neglect and overprotection/overcontrol were the most commonly reported childhood traumas (21).

Considering other studies, childhood trauma is likely to cause autoimmune diseases in adulthood (12). One of the most critical parts of the stress response system in humans is the HPA axis (4,7). In contrast to the glucocorticoid levels that increase after the activation of the HPA axis with acute stress, in the case of chronic stress, the organism adapts to the activation of negative feedback in this axis (7). In patients exposed to chronic stress, serum glucocorticoid levels are found to be lower during rest compared with the control group, whereas the concentration of glucocorticoid receptors in the hippocampus increases (4,7). The autoantibody levels were found to be higher in children with traumatic experiences than in the control group. Trauma-related immune dysfunction is thought to predispose children to autoimmune diseases (12-14). The results of our study suggest that the effect of childhood trauma on HT may be associated with anti-TPO activity.

A study conducted by Carpenter et al. (22) with 230 healthy adults demonstrated that childhood emotional neglect led to a decrease in cortisol activity in adulthood, resulting in a diminished cortisol response to CRH stimulation tests. The researchers suggest that this could be due to the impairment of stress-related biological mechanisms that weaken the physiological system (22). Other opinions are that chronic adrenal stress hypoactivity develops because of stress-related HPA axis activation or receptor downregulation related to HPA activation (23,24). Because cortisol is a potent anti-inflammatory hormone, cortisol dysfunctions due to childhood trauma are important (25). A limitation of our study is that cortisol levels were not measured in either the patient or control group.

Danese et al. (26) examined the relationship between C-reactive protein (CRP) and childhood trauma, an inflammatory marker believed to contribute to autoimmune diseases. The study found that individuals who experienced childhood trauma had higher CRP levels in adulthood. These results suggest that childhood trauma causes an inflammatory process in adulthood. CRP levels were not among the parameters evaluated in our study.

In a study conducted by Kiecolt-Glaser et al. (27) with 32 healthy adults, interleukin-6 (IL-6) and tumour necrosis factor alpha levels were found to be higher in patients with at least one type of childhood abuse than in those without abuse. IL-6 is effective in differentiating B-cells and stimulating immunoglobulin synthesis and is also a T-cell costimulator. It also acts as a differentiating factor for T-cytotoxic lymphocytes. The T-cells of patients with HT interact with thyroid antigens and peptides composed of these antigens. Activated T-cells stimulate the release of thyroid autoantibodies from B-cells and initiate antibody-dependent cytotoxicity. In addition, T-cells directly induce apoptosis in thyroid gland cells (28,29). These findings suggest that childhood trauma may play a role in the development of HT through its impact on cellular and humoral immune responses. Specifically, T- and B-lymphocytes are believed to contribute to the pathologic process of the disease by exerting a cytotoxic effect and synthesizing immunoglobulins.

In another study by Dube et al. (30) that prospectively evaluated adverse childhood events in a large sample, it was found that those with more than two adverse childhood experiences increased their likelihood of developing immunologic diseases by 70-100% compared with those without. In this study, 8,293 female and 7,064 male patients receiving health care in San Diego, California, the association between childhood trauma and hospitalization for any autoimmune disease was examined. During the follow-up period, 372 patients were hospitalized because of any autoimmune disease. The autoimmune diseases causing hospitalization were type 1 diabetes mellitus (23.1%), rheumatoid arthritis (18.8%), immune thrombocytopenic purpura (16.7%), idiopathic pulmonary fibrosis (9.1%), and systemic lupus erythematosus (8.1%). Because of the study, the frequency of childhood trauma was found to be high in patients hospitalized because of an autoimmune disease. In this study, HT was included among autoimmune diseases, but no significant result was found in terms of HT (30). In our study, a different relationship was found between HT patients without hospitalization and childhood emotional neglect. The fact that HT is not an indication of frequent hospitalization may be the reason for the difference in the results. In addition, when evaluating the

results, it is important to consider the possibility that patients may not have responded truthfully to questions about sexual abuse because of societal value judgments.

Based on these findings, preventing childhood trauma may be an effective strategy for reducing the risk of developing autoimmune thyroid diseases in adulthood and ultimately lowering treatment costs. However, due to the limitations of our study, which was a small, cross-sectional preliminary study without patient profiles from diverse populations and races, as well as being conducted at a single center, it is crucial to refrain from generalizing the results. Furthermore, the self-reported nature of trauma history in our study, as opposed to obtaining information from family or medical records, may have impacted the accuracy of reported trauma rates.

CONCLUSION

In our study, a different relationship was found between HT patients without hospitalization and childhood emotional neglect. Preventing childhood trauma may be an effective strategy for reducing the risk of developing autoimmune thyroid diseases in adulthood. Therefore, further large-scale studies are required to elucidate all aspects of this subject.

Ethics

Ethics Committee Approval: Written approval for the study was obtained from the Kırıkkale University Faculty of Medicine Local Ethics Committee (approval number: 15/06, date: 12.05.2014).

Informed Consent: Informed consent was obtained from all participants.

Peer-Review: Externally peer-reviewed.

Authorship Contributions

Concept: U.A., H.D., E.A., Design: U.A., H.D., E.A., Data Collection or Processing: U.A., H.D., E.A., Analysis or Interpretation: U.A., H.D., E.A., Literature Search: U.A., H.D., E.A., Writing: U.A., H.D., E.A.

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

Financial Disclosure: The authors declared that this study received no financial support.

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