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ORIGINAL ARTICLE

The frequency and related factors of primary headaches in patients with Hashimoto thyroiditis

Hashimoto tiroiditi hastalarında primer baş ağrısının sıklığı ve ilişkili faktörler

Rabia Gökçen GÖZÜBATİK ÇELİK,[1] Derya ULUDÜZ ULU,[2] Esra HATİPOĞLU,[3] Yalçın HACIOĞLU,[4] Bengi Gül ALPASLAN TÜRK,[2] Mehmet Ali SUNGUR,[5] Baki GÖKSAN,[2] Sabahattin SAİP,[2] Aksel SİVA[2]

Summary

Objectives: The purpose of this study was to evaluate the incidence of primary headache and potential biomarkers in patients diagnosed with Hashimoto thyroiditis.

Methods: Patients with Hashimoto thyroiditis referred to the outpatient endocrinology clinic were included in the study. The demographic data, thyroid function test results, and autoantibody titers were recorded. The headache's clinical characteristics were also determined. The same researcher used the visual analog scale for headache severity rating in all patients.

Results: 155 patients with Hashimoto thyroiditis were included the study. There were 95 (61.3%) cases diagnosed with headache consisting of 20 (21.1%) migraine cases, 17 (17.9%) tension type headaches (TTHs), and 20 (21.1%) new daily persistent headaches (NDPHs). 38 of 155 (24.5%) had hypothyroidism related headaches (HRHs). There was no statistically significant relationship between the headache type and a high blood antibody level anti thyroid peroxidase antibody (p=0.135), while a positive correlation was found with thyroid stimulating hormone (TSH) (p<0.001). Hashimoto patients with migraine (n=14, 70.0%) were found to have higher blood antibody levels, while these ratios were found as 86.8% (n=33) in HRH-patients, 76.5% (n=13) in TTH-patients, and 60.0% (n=12) in NDPH-patients. 86 of 155 (55.5%) patients reported new onset headaches after a Hashimoto's thyroiditis diagnosis, and the headaches persisted without hormone therapy in 48 (84.2%) of these patients. These patients diagnosed with primary headache and this was interpreted as demonstrating comorbidity between Hashimoto's disease and primary headaches.

Conclusion: Detection of only the relationship between TSH level and headache suggested that different mechanisms play a role in the pathophysiology. In the diagnosis of primary headache, it is important to look into secondary reasons.

Keywords: Autoimmunity; comorbidity; hashimoto thyroiditis; primary headaches; thyroid stimulating hormone.

Özet

Amaç: Bu çalışmanın amacı, Hashimoto tiroiditi tanısı alan hastalarda primer baş ağrısı insidansını ve potansiyel biyobelirteçleri değerlendirmektir.

Gereç ve Yöntem: Endokrinoloji polikliniğine başvuran Hashimoto tiroiditi olan hastalar çalışmaya dahil edildi. Demografik veriler, tiroid fonksiyon test sonuçları ve otoantikor titreleri kaydedildi. Baş ağrısının klinik özellikleri de belirlendi. Aynı araştırmacı, tüm hastalarda baş ağrısı şiddeti derecelendirmesi için görsel analog ölçeği (VAS) kullandı.

Bulgular: Primer baş ağrısı olan 95 (%61,3) hastadan 20'si (%21,1) migren, 17'si (%17,9) gerilim tipi baş ağrısı (TTH) ve 20'si (%21,1) yeni günlük kalıcı baş ağrısı (NDPH) tanısı aldı. Yüz elli beş kişiden 38'inde (%24,5) hipotiroidizme bağlı baş ağrısı (HRH) tespit edildi. Baş ağrısı tipi ile yüksek kan antikor düzeyi (anti-TPO) arasında istatistiksel olarak anlamlı ilişki bulunmazken (p=0,135), tiroid uyarıcı hormon (TSH) ile pozitif korelasyon saptandı (p<0,001). Migrenli Hashimoto hastalarında (n=14, %70,0) daha yüksek kan antikor düzeyleri bulunurken, bu oranlar HRH'de %86,8 (n=33), TTH hastalarında %76,5 (n=13), NDPH hastalarında %60,0 (n=12) olarak saptandı. Elli yedi hasta Hashimoto tanısı aldıktan sonra yeni bir baş ağrısı tanımlarken, hormon tedavisi sonrası baş ağrısı devam eden hasta sayısı 48 idi. Bu da primer baş ağrısı ve Hashimoto hastalığı komorbiditeyi göstermekteydi.

Sonuç: Baş ağrısı ile ilişkili tek faktörün TSH düzeyi olması patofizyolojide farklı mekanizmaların rol oynadığını düşündürdü. Primer baş ağrısı tanısında tedavi edilebilen sekonder nedenlerin detaylı araştırılması önem taşımaktadır.

Anahtar sözcükler: Otoimmünite; komorbidite; hashimoto tiroiditi; primer baş ağrısı; tiroid uyarıcı hormon.

[1]Department of Neurology, University of Health Sciences, Bakırköy Training and Research Hospital for Psychiatry and Neurological Disorders, İstanbul, Türkiye
[2]Department of Neurology, Istanbul University, Cerrahpasa Faculty of Medicine, İstanbul, Türkiye
[3]Department of Internal Medicine, Istanbul Çam Sakura City Hospital, İstanbul, Türkiye
[4]Department of Family Medicine, Istanbul Training and Research Hospital, İstanbul, Türkiye
[5]Department of Biostatistics and Medical Informatics, Düzce University Faculty of Medicine, Düzce, Türkiye

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Correspondence: Dr. Rabia Gökçen Gözübatik Çelik. Sağlık Bilimleri Üniversitesi, Bakırköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, İstanbul, Türkiye.
Phone: +90 - 554 - 937 00 87 **e-mail:** gokcen3@hotmail.com

Introduction

Headaches and thyroid dysfunction are common medical complaints. Primary headache is a very common neurological condition and needs to be classified into migraine, tension-type headache, trigemino-autonomic headache, and other primary headaches. The most common subtypes of primary headaches are migraine and tension-type headache (TTH), affecting around 11% and 42% of the general population, respectively.[1,2] Epidemiological studies indicate that the prevalence of primary headache, including migraine and TTH, is 90%.[3]

The incidence of thyroid dysfunction in the general population is 4.8–9%.[4] The most common form of hypothyroidism is the autoimmune type known as Hashimoto thyroiditis. The pathophysiology of Hashimoto's thyroiditis is thought to involve immunological mechanisms as anti-thyroid antibodies are present in 90% of the subjects.[5] Patients with thyroid stimulating hormone (TSH) levels below 10 micro-U/L can be asymptomatic. Subclinical and overt hypothyroidism are found in 22% and 7.2% of patients with primary headache, respectively, while the headache rate in patients with hypothyroidism varies between 14% and 73% in multiple studies.[6,7] Regarding these results, hypothyroidism may be a risk factor for persistent regular headache and may aggravate the headache in certain patients. However, the role of thyroid dysfunction in headache pathogenesis is still unclear.

Headache due to hypothyroidism can be identified with at least one of the following characteristics: Persistent, bilateral and non-pulsatile; hypothyroidism found by testing; the headache occurring after 2 months of hypothyroidism; and the headache lasting <3 months after the hypothyroidism diagnosis.[8,9]

Migraine and hypothyroidism, as mentioned in literature, can be identified as comorbid conditions. An attempt has been made to explain this comorbidity with an autoimmune mechanism. However, the borderline hypothyroidism diagnosis is often accompanied by a drastic change in headache management in migraineurs with subclinical hypothyroidism.[9–11] Nonetheless, headache due to hypothyroidism can be misdiagnosed as another types of headaches in undiagnosed hypothyroid patients or when the patients have subclinical hormone levels.

Our research aimed to assess the incidence and clinical symptoms of headaches in patients with hypothyroidism and to determine the comorbidities and misdiagnosed headache types in subclinical Hashimoto's disease patients, in addition to evaluating the association between antibody prevalence, thyroid gland tests in blood sample, and headache frequency. This study contains the first article on this subject in our country and is the first work in the world to evaluate relevant erroneous diagnoses.

Material and Methods

Clinical material and trial

A review of the patients with Hashimoto thyroiditis referred to the outpatient endocrinology clinic during the 2019–2020 periods was conducted to determine the incidence and frequency of hypothyroid related headache and primary headaches in this group. One hundred fifty-five Hashimoto patients were screened from archives and monitored for 1 year for the occurrence of headache prospectively. The age range was 18–70 years. For all patients, those with at least 6 months of clinical follow-up by neurologist and endocrinologist in terms of both headache and/or Hashimoto diagnosis were included in the study on a voluntary basis. All the new/old headaches of the patients were recorded by the same researcher prospectively.

In the presence of headache, the patients were divided in two groups. The medical criteria for primary headache and hypothyroid related headache are based on the third edition of the International Headache Society List (ICHD-3), taking the history and clinical review into account.[9–11] For the diagnosis of hypothyroid related headache, the following characteristics were briefly sought: (A) The headache is constant, bilateral, and/or non-pulsatile; (B) hypothyroidism is confirmed by suitable testing; (C) the headache begins within 2 months after the onset of hypothyroidism; and (D) headache lasts <3 months after effective treatment of hypothyroidism.

The demographic data, thyroid function tests, and autoantibody titers were noted. The headache's clinical characteristics were determined. The group without headache and the group with headache are related to demographic and laboratory charac-

teristics. The same researcher used the visual analog scale analog scale for rating headache severity from 0 (no pain) to 10 points as follows: mild, 1–3; moderate, 4–7; and extreme.[8–10]

Statistical analysis

The data were analyzed using the SPSS v.22 statistical package. Pearson Chi-square, Fisher's exact tests or Fisher-Freeman-Halton test was used for analysis of categorical variables, as appropriate. Kolmogorov–Smirnov test was used to examine normality assumption. The independent samples t-test or Mann-Whitney U test was used to compare groups in terms of numerical variables. Spearman correlation analysis was used to examine correlation. Descriptive statistics were given as frequency and percentage for categorical variables, and as mean±standard deviation or median (min-max) for numerical variables, according to the distribution. Statistical significance level was considered as 0.05.

The Ethics Committee was received from the competent institution on September 18, 2020 with Decision No. 2523 concerning the work permit.

Results

A total of 155 adult subjects were included with Hashimoto thyroiditis in this study. The mean age was 43.4±11.5 (range, 19–70) years and 145 (93.5%) were female. The median disease duration was 8 (range, 4–34) years. On average, patients were treated within 8 years of their report of hypothyroidism and had been suffering from headache for more than 5 years (media n=5, range, 1–40) years. Thirty (32.3%) of the patients started having headaches 1–2 months after initial signs of hypothyroidism. There was a negative and weak correlation between the duration of the disease and the intensity of the headache (r=–0.230 and p=0.027).

Ninety-five of 155 Hashimoto patients had headache (61.2%), 60 (38.8%) had no headache. Of the 95 patients describing headaches, 38 of them were hypothyroid related headache (HRH) (24.5%), 57 of them were diagnosed with primary headaches (36.7%). Among primary headache diagnosis (n=57), there were 20 (21.1%) migraines, 17 (17.9%) tension type headaches (TTH), and 20 (21.1%) new daily persistent headaches (NDPH) (Table 1).

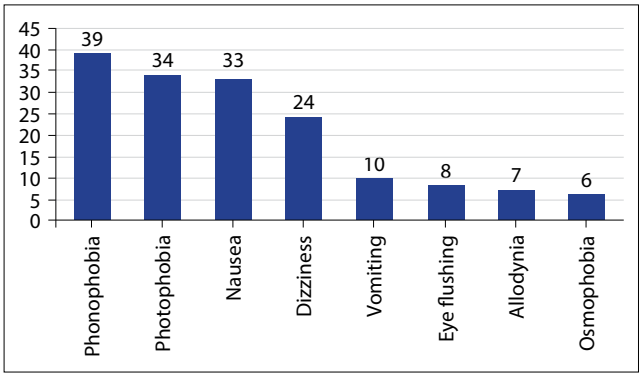

Figure 1. Additional symptoms in Hashimato patients with headache.

We found no difference between the prevalence of migraine and tension-type headaches in Hashimoto patients (p>0.05). In addition, when the other headache subgroups were compared among themselves, no demographically significant result was found (p>0.05).

The headaches had the following characteristics: Frontal-orbital position, 42%; temporal, 40%; posterior portion of the brain, 13%; unilateral, 45%; pulsatile, 67%; moderate to extreme, 84.2% (n=80); 4–72 h, 72.6% (n=69); and nausea/vomiting, 34.7% (n=33). There was no association between gender and the type of headache (p=0.934). Other headache features are summarized in Figure 1.

There were no significant differences between the patients with and without headache as regards demographic data as age, gender and the illness duration (p=0.073, 0.931, and 0.075, respectively). Moreover, the headache was not associated with conditions such as endocrine disease (diabetes), heart disease, asthma, obesity, and smoking in the history (Table 1).

Eighty-six of 155 patients had newly headache, 38 of them had HRH. Among primary headache patients (n=57), 9 of 57 Hashimoto's patients with main headache recalled prior headaches, these new headaches started in 48 of them (84.2%), lasted following hormone treatment, and did not match other diagnostic criteria of HRH. These patients were diagnosed with primary headache.

Ten of 38 HRH-patients were previously followed up in other centers with a diagnosis of primary headache. However, after the diagnosis of Hashimoto, the headaches of these 10 people disappeared after undergo-

Table 1. Demographic characteristics of patients

	Patients with headache (n=95) (61.2%)		Patients without headache (n=60) (38.8%)		p
	n	%	n	%	
Age (years), Mean±SD	42.06±10.73		45.45±12.39		0.073
Disease duration (years), Median (IQR) [min-max]	8 (6) [4–34]		9 (7) [4–34]		0.075
Gender					
Man	6	6.3	4	6.7	0.931
Women	89	93.7	56	93.3	
Type of headache					
HRH	38	40.0			
Migraine	20	21.1			
TTH	17	17.9			
NDPH	20	21.1			
Background					
HT	18	18.9	6	10.0	0.134
DM	6	6.3	0	0.0	0.082
Heart disease	3	3.2	0	0.0	0.284
Depression	13	13.7	1	1.7	0.011
Smoke	20	21.1	3	5.0	0.006

IQR: Interquartile range; HRH: Hypothyroidism-related-headache; TTH: Tension type headaches; NDPH: New daily persistent headaches; HT: Hypertension; DM: Diabetes mellitus.

Table 2. The comparison between thyroid function results and presence of headache in Hashimoto patients

	Patients with headache (n=95) (61.2%)		Patients without headache (n=60) (38.8%)		p
	n	%	n	%	
Abnormal thyroid blood results (T3 and T4)	59	62.1	39	65.0	0.716
TSH	72	75.8	21	35.0	<0.001
High antibody level (anti-TPO)	72	75.8	45	75.0	0.911

TSH: Thyroid-stimulating hormone; anti-TPO: Anti-thyroid peroxidase antibody.

ing hormone treatment for 15 days to 3 months. We reveal that indicating 10 patients misdiagnosed with TTH (n=4), NDPH (n=3) or migraine (n=3).

When the relationship between the presence of headache and the thyroid blood test results was evaluated, there was no association between headache and the T3- and T4 levels (p=0.716), while a positive correlation was found with TSH (p<0.001). While 59 (62.1%) of the 95 patients with headache had abnormal thyroid blood test results, there were 39 (65.0%) such patients in the group without headache. However, there were 72 (75.8%) versus 21 (35.0%) patients with hypothyroid, in groups with and without headache groups, respectively (Table 2).

There was no association between the presence of headaches and the existence of antibodies (75.8% [n=72] vs. 75.0% [n=45], p=0.911). While, antibody

Table 3. The comparison between thyroid function results and headache subgroups in Hashimoto patients

	HRH (n=38)		Migraine (n=20)		TTH (n=17)		NDPH (n=20)		p
	n	%	n	%	n	%	n	%	
Abnormal thyroid blood results (T3 and T4)	29	76.3	10	50.0	9	52.9	11	55.0	0.136
TSH	31	81.6	12	60.0	12	70.6	17	85.0	0.208
High antibody level (anti-TPO)	33	86.8	14	70.0	13	76.5	12	60.0	0.135

HRH: Hashimoto related headache; TTH: Tension type headache; NDPH: New daily persistent headache; TSH: Thyroid-stimulating hormone; anti-TPO: Anti-thyroid peroxidase antibody.

levels were observed to be high in patients with migraine (n=14, 70.0%) diagnosed with Hashimoto's disease, antibodies were high in 13 (76.5%) of 17 TTHs, 12 (60.0%) of 20 NDPHs, and 33 (86.8%) of 38 HRHs. There was no statistically significant relationship between the headache type and high blood antibody level (p=0.135, Table 3).

When the relationship of any antithyroid drug with the presence of headache and headache type in patients was questioned, no relationship was found between them (p=0.618 and p=0.102, respectively).

Discussion

In certain research, an increased prevalence of hypothyroidism has been identified in people with headache disorders. The literature has demonstrated that headaches and hypothyroidism can be comorbid but the cause remains unclear.[12]

Subclinical hypothyroidism in 11.2%, and overt hypothyroidism in 1.2% of control group cases, was statistically important in the discrepancies between primary headache and control group was found.[13] In our study, 95 of 155 patients predominantly suffered from headache (61.3%) and 57 of 155 (36.7%) had primary headache. Migraine, NDPH, and TTH were found to be common primary headache types among Hashimoto patients (21.1.1%, 21.1%, and 17.9%, respectively). In retrospective research of 102 subjects, 30% of patients had HRH, while the incidence of headache was 34% in female subjects newly diagnosed with hypothyroidism in a cross-sectional sample.[14] In the current study, HRH was to be more uncommon than reported in the literature. HRH was detected in 38 of 155 (24.5%) Hashimoto patients in our study. Then, no significant results were obtained in the demographic characteristics of the group with and without headache.

Headache due to hypothyroidism is a recent entry into the ICHD-3 and involves persistent, bilateral, non-pulsatile headache in subjects with reported hypothyroidism. The headache starts within 2 months of the onset of hypothyroidism and lasts <3 months following the diagnosis. Moreau et al.[14] reported that these patients had bilateral (80%), non-pulsatile (90%), moderate (89%) headaches, and a migraine history was present in 15.4%. We similarly found that the headache related with hypothyroidism of our patients was usually unilateral (fronto-orbital: 42%; and temporal: 40%), pulsatile (67%), and moderate to extreme in severity (79%).

Our findings have shown that migraine and hypothyroidism can be comorbid conditions, possibly due to an autoimmune process (production of antithyroid antibodies). Similarly, migraines have been more common in people with headaches due to hypothyroidism (53%) than without migraine (38%).[15] In the current study, 21.1% of the 155 hypothyroid patients were diagnosed with migraine. 57 of 155 Hashimoto diagnosed patients had primary headache additionally. The blood tests will indicate the Hashimoto patients with comorbid headache. The treatment of borderline hypothyroidism is also followed by dramatic improvements in the management of the migraine headaches of subclinical hypothyroidism. This was seen as evidence of comorbidity between the condition of Hashimoto and primary headaches. In addition, other autoimmune disorders (except thyroid related) including diabetes were not a risk factor for headache in the Hashimoto cases, like migraine.

Patients with primary headaches or those with Hashimoto thyroiditis may have been misdiagnosed as migraine before being diagnosed with hypothyroidism. Subclinical and overt hypothyroidism was present in 22% and 7.2%, respectively, of patients with primary headache disorders in the literature.[6,16] However, the misdiagnosis of HRH as primary headache or the opposite has not previously been addressed in the literature. In our research, the 10 misdiagnosed patients (3 of 10 with migraine, 3 of 10 with NDPH, 4 of them with TTH) reported that their headaches were relieved after hormone therapy. The clinician should be careful in terms of misdiagnoses of primary headache in the subclinical periods of Hashimoto patients.

Headache severity was significantly related to TSH blood levels ($p<0.001$), while T3 and T4 did not display any association with headache frequency in this study ($p=0.716$). There was no association between the presence of headaches and the existence of antibodies (75.8% [n=72] vs. 75.0% [n=45], $p=0.911$).
There is no significant limitation in our study. Studies that prospectively evaluate more patients with a diagnosis of subclinical Hashimoto could be reveal supportive results for this issue.

Conclusion

Although primary headaches can be comorbid with hypothyroidism, the association of headache with only serum TSH level and not being associated with autoantibodies and T3-T4 levels in serum sample is a surprising result, suggesting that different mechanisms play a role in the pathophysiology. Then, subclinical hypothyroid cases may be misdiagnosed as primary headache. Physicians should therefore employ a multidisciplinary approach when diagnosing primary headaches, monitor these patients on a regular basis after the diagnosis, and continue to re-evaluate certain causes of headache and in particular HRH, during each visit.

Ethical Approval: The study was approved by The Istanbul Training and Research Hospital Ethics Committee (Date: 18/09/2020, No: 18.09.2020).

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