

Evaluation of peripheral vestibular system in Hashimoto thyroiditis

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Ethics Committee Approval

The study was approved by the Baskent University Research Committee of Medical and Health Sciences and Ethics Committee (Project no: KA18/33).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Hashimoto thyroiditis (HT) is a common autoimmune thyroid disease that may have systemic effects on any organ, including the inner ear. Increased frequency of autoimmune thyroid disease in patients with Meniere's disease and benign paroxysmal positional vertigo (BPPV) has been found, and autoimmunity was implicated in the etiopathogenesis of both diseases. The aim of this study was to evaluate vestibular functions and the effect of levothyroxine (LT4) therapy in patients with Hashimoto's thyroiditis.

Methods: The study included 61 men and women with HT diagnosis (group I: 31 patients who did not receive treatment; group II: 31 patients on LT4 treatment) and 30 healthy individuals (control group) between 18 and 60 years of age. Free T3, free T4, TSH, anti-TPO, and anti-Tg levels of all individuals were measured, and Cervical vestibular evoked myogenic potentials (cVEMPs), ocular vestibular evoked potentials (oVEMP), and video head impulse test (vHIT) tests were performed.

Results: In the cVEMP results, a 20% VEMP wave was not obtained in the group with HT on LT4 treatment. However, no significant difference was found in the statistical results between the groups. There was no significant difference in vHIT and oVEMP tests between groups. Vestibular tests of patients with hypothyroidism (TSH >4.9) were compared with those of euthyroid patients. The altered frequency in the cervical VEMP test of the left ear was higher in hypothyroid patients ($P=0.042$). The oVEMP test results were similar for both ears in both groups. The groups were similar in terms of VOR gain in the vHIT test.

Conclusion: In euthyroid HT patients, vestibular tests were normal. Progression of vestibular dysfunction might be induced by hypothyroidism rather than autoimmune thyroid diseases.

Keywords: Hashimoto thyroiditis, vestibular evoked myogenic potentials, video head impulse test, peripheral vestibular system

Introduction

Autoimmune thyroid diseases are common and affect 1-5% of the general population. Hashimoto thyroiditis (HT) is the most frequent organ-specific autoimmune disorder and arises from an immune response against thyroid antigens that is triggered by environmental factors in genetically predisposed individuals [1,2]. HT is known to cluster with a wide spectrum of autoimmune disorders ranging from organ-specific diseases to systemic diseases [3]. Dizziness affects 15% to over 20% of adults yearly according to large population-based studies, and vestibular vertigo has a prevalence of 5% and an annual incidence of 1.4%. Its prevalence rises with age and is greater in women than in men. The most common vestibular diseases are Meniere's disease (MD) and benign paroxysmal peripheral vertigo (BPPV) [4].

Peripheral vestibular disorders result from vestibular labyrinth or vestibular nerve pathologies. Vestibulospinal and vestibulo-ocular reflexes are evaluated by a vestibular evoked myogenic potential (VEMP) test and the video head impulse test (vHIT). VEMP tests are non-invasive electrophysiological test methods that measure the reflex arc resulting in muscle contraction as a result of stimulation of the peripheral vestibular organs. Cervical vestibular evoked myogenic potentials (cVEMPs) involve the saccule and inferior vestibular nerve [5], and ocular vestibular evoked potentials (oVEMP) involve the utricle and superior vestibular nerve reflex arc responses [6]. The vHIT is based on the examination of eye movements that develop in response to repeated rapid head pushing movements to measure the integrity of the vestibulo-ocular reflex (VOR). It is especially useful for the differential diagnosis of peripheral vestibular diseases and diseases originating from the central nervous system.

The cochlear-vestibular system might be affected by autoimmune diseases, and vertigo could be more common in patients with autoimmune disorders [7]. Autoimmune inner ear disease is rare and is a syndrome of progressive hearing loss and/or dizziness, which is caused by antibodies or immune cells attacking the inner ear [8]. Autoimmunity may be responsible for several forms of frequently seen vestibular diseases, such as MD and BPPV [9,10]. The increased prevalence of systemic autoimmune diseases in patients with MD than the general population, the elevated levels of immunocomplexes, the association between MD and HLA-types, and good response to glucocorticoid treatment are considered to support possible autoimmune etiology in MD [11]. Although this association between autoimmune disorders and vertigo has led to the hypothesis that autoimmune mechanisms might also be involved in the pathogenesis of benign paroxysmal positional vertigo (BPPV), studies show conflicting results [12].

Based on clinical observations of increased vestibulocochlear symptoms in patients with thyroid dysfunction and possible role of autoimmunity in vestibular disorders, certain studies have investigated the relationship between vestibular disorders as MD benign paroxysmal positional vertigo [13,14]. Studies investigating the relationship between vestibular disorders and autoimmune thyroid diseases revealed inconsistent results and were unable to demonstrate a direct cause-effect

relationship, and the role of thyroid dysfunction remains unclear. The aim of this study was to investigate the association between HT and vestibular function and the possible effect of levothyroxine (LT4) treatment on vestibular function.

Materials and methods

Patients

This study examined 91 adult subjects. 61 patients with HT were referred from the outpatient clinic of Başkent University, Department of Endocrinology and Metabolism. This study was approved by the Başkent University Research Committee of Medical and Health Sciences and Ethics Committee (Project no: KA18/33). Written informed consent was obtained from all the participants. The inclusion criteria were an absence of a complaint or history of vertigo, no previous use of medication that might affect the vestibular system in the last 2 weeks, no history of head trauma or previous ear surgery, absence of disorders related to cervical vertebra or the neck, absence of problems with vision or the eyes, normal ear examination, and normal spontaneous nystagmus records. Subjects not meeting any of these criteria were excluded from the study.

The study examined 3 groups. Group I comprised 31 patients who were diagnosed with HT but did not receive treatment, group II comprised 31 patients with HT who were on LT4 treatment, and the control group comprised 30 age and sex-matched healthy individuals. For power analysis, G-power 3.1 software were used. The three independent groups were compared using the power test F test and one-way ANOVA. The effect size was 0.42, type 1 error was taken as 0.05, and the power of the study was 95%.

None of the subjects had vestibular or hearing complaints. All subjects underwent a complete thyroid evaluation, including physical examination and measurement of serum free T4 (FT4), free T3 (FT3), TSH, and anti-thyroid peroxidase (anti-TPO) autoantibodies. Blood samples were drawn after an overnight fast and studied immediately. Serum concentrations of TSH (normal ranges: 0.35–4.94 μ U/mL), FT4 (normal range: 0.7–1.48 ng/dL), FT3 (normal range: 2.3–4.2 pg/mL), and anti-TPO antibodies were determined by chemiluminescence immunoassay using an Abbott-Architect analyzer (Chicago, IL). Anti-TPO <35 U/mL was considered as negative.

Procedure

Pure tone audiometry, tympanometry, VEMP, and vHIT analyses were performed for all patients and the control group. Audiologic tests were conducted using an AC40 Clinical Audiometer audiometric device (Interacoustics A/S, DK-5610, Assens, Denmark). The air and bone conduction hearing thresholds were determined by routine audiologic analyses with air conduction thresholds for values between 0.125 and 8 kHz and bone conduction at 0.5, 1, 2, and 4 kHz. Hearing thresholds greater than 20 dB at two or more frequencies were accepted as sensorineural hearing loss.

Video head impulse test (vHIT)

The vHIT was performed using the Otosuite Vestibular computer program and goggles with a camera attached (GN Otometrics, Taastrup, Denmark). The head was leaned forward

30° and then thrust right and left randomly in the horizontal plane (head velocity ~100-250°/sec) to induce lateral semicircular canals. The head was thrust forward and backward randomly in the sagittal plane (head velocity ~50-250°/sec) to induce vertical semicircular canals (LARP and RALP). Twenty impulses given true were accepted for the evaluation of each canal.

The normal ranges of the VOR gain for lateral and vertical vHIT were accepted as 0.8-1.2 and 0.7-1.2, respectively. Saccade with an amplitude higher than the peak head velocity was accepted as pathological saccade. A saccade beginning before the end of the head movement was considered as a covert saccade, while a saccade beginning after head movement termination was considered as an overt saccade. In some patients, the saccade amplitude was lower than the peak head velocity in vHIT.

c/oVEMP test technique

The c/oVEMP tests were performed using a Grason-Stadler (GSI) Audera device (Grason-Stadler Inc., MN, USA). All study participants first underwent skin cleansing using alcohol and a peeling gel. Single-use Ag/AgCl (Ambu Blue Sensor N Ref No N-00-S/25) superficial electrodes were used for each test.

oVEMP

Reference electrodes were placed 5 mm below the eye sockets on the inferior oblique muscle. Active electrodes were placed 1–2 cm below the reference electrodes, and the ground electrode was placed on the forehead. Electrode resistances were kept <5 μΩ. During the recording, volunteers in a sitting position were asked to look at objects previously placed 1 m away at 30–40° angles on a horizontal plane with a neutral gaze line for the duration of sound. While giving stimuli via an insert earphone, a recording was made from the contralateral eye. During ear changeover, the individuals were asked to rest with their eyes shut. The apices of the first waveform that was formed after the introduction of the stimulus were designated as N1 and P1. The latency and amplitude values of the waves were then measured.

cVEMP

The surface electromyographic activity of the SCM muscle was recorded using an EP 25 device (Interacoustics Co., Assens, Denmark). The active electrode was put on the upper half of the ipsilateral SCM muscle, and the reference electrode was put on the suprasternal notch. During the recording, the seated patients were instructed to rotate their heads to the side opposite to the stimulated ear to activate the SCM. Background electromyographic activity was monitored visually for consistent tonic contraction.

Short tone bursts (100 dB nHL and 500 Hz each with a 1-ms rise/fall time and a 5-ms plateau time) were delivered monaurally via TDH 49P insert earphones. The stimulation rate was 5 Hz, and the analysis time was 60 ms. In total, 128 responses to stimuli were averaged, and the measurements were repeated twice to check the test wave reproducibility. The latencies of the first positive peak (p13), the next negative peak (n23), and the amplitude difference between the p13 and n23 amplitudes were measured.

Statistical analysis

Analyses were performed using SPSS version 25.0 for Windows (SPSS, Chicago, IL, USA). Continuous data were presented as the mean and standard deviation or the median [minimum–maximum] as appropriate. Comparisons of various numeric parameters among patient and control groups were analyzed with ANOVA and Kruskal–Wallis tests as necessary. Differences were considered to be statistically significant if *P*-values were <0.05.

Results

The demographic and biochemical characteristics of study subjects are presented in Table 1. Groups were similar in terms of age (*P*=0.410) and gender (*P*=0.156). As expected, serum TSH and anti-TPO levels were higher in patients with HT compared with the control group (*P*<0.001). The audiometric examinations of all study subjects were normal.

Table 1: Demographic and biochemical characteristics of study participants.

	Group I (n=31)	Group II (n=30)	Control (n=30)	P-value
Age (years) ^a	38.19 (10.58)	40.93 (10.39)	38.03 (7.26)	0.410
Gender (M/F)	2/29	2/28	6/24	0.156
fT3 (pg/mL) ^a	2.91 (0.52)	2.75 (0.36)	2.79 (0.33)	0.292
fT4 (ng/dL) ^a	1.51 (1.95)	1.05 (0.23)	0.99 (0.12)	0.155
TSH (μU/mL) ^b	2.0 (0.86-7.1)	3.65 (0.03-16.83)	1.16 (0-3.36)	<0.001
AntiTPO (U/mL) ^a	312.96 (298.56)	582.01 (349.02)	0.46 (0.39)	<0.001

a: Mean (SD), b: Median (minimum-maximum), fT3: free T3, fT4: free T4, TSH: thyrotropin stimulating hormone, anti TPO: Anti-thyroid peroxidase antibodies

There were no differences between groups for the frequencies of altered cervical and ocular VEMP tests (Table 2). There was no statistically significant difference between the groups in terms of the absence of oVEMP and cVEMP. In cVEMP responses, the number of people with absent VEMP waves in group II was higher, but the difference was not statistically significant (*P*=0.379). In vHIT tests, there was no statistically significant difference between the groups in the mean VOR gain results in each group in all semicircular canals (Table 3).

Table 2: The cervical and ocular VEMP test results of the study participants

		Group I (n=31)	Group II (n=30)	Control (n=30)	P-value
cVEMP	Right Ear (A/P)	2/29	5/25	1/29	0.161
	Left Ear (A/P)	2/29	5/25	0/30	0.357
oVEMP	Right Ear P1 (A/P)	4/27	5/25	5/25	0.895
	Left Ear P1 (A/P)	5/26	7/23	3/27	0.379

cVEMP: Cervical vestibular evoked myogenic potential oVEMP: Ocular vestibular evoked myogenic potentials A: absent P: positive

Table 3: The vestibulo-ocular reflex (VOR) gain results for each semicircular canal of study participants

VOR gain		Group I (n=31)	Group II (n=30)	Control (n=30)	P-value
Left ear	Lateral	0.9 (0-1.3)	0.9 (0.7-1.4)	0.9 (0.6-1.5)	0.998
	Posterior	0.9 (0-1.2)	0.9 (0-1.1)	0.9 (0-1.1)	0.883
	Anterior	0.8 (0-1.2)	0.8 (0.6-1)	0.8 (0-1.06)	0.694
Right ear	Lateral	1 (0-1.3)	1 (0.8-1.3)	1 (0.8-1.5)	0.985
	Posterior	0.7 (0-0.9)	0.8 (0.5-1.1)	0.8 (0-0.9)	0.152
	Anterior	0.9 (0-1.1)	0.9 (0.7-1.2)	0.9 (0-1.2)	0.554

In order to investigate the effect of TSH levels on the vestibular tests, the study subjects were grouped according to their TSH level. There were 22 hypothyroid patients with a median TSH level of 6.0 (4.2-16.4) μU/mL, and 69 were euthyroid with a median TSH level of 1.5 (0.4-3.3) μU/mL. The altered frequency in the cVEMP test of the left ear was higher in hypothyroid patients (*P*=0.042). The oVEMP test results were similar for both ears in both groups (Table 4). The groups were similar in terms of VOR gain in the vHIT (Table 5).

Table 4: The cervical and ocular VEMP test results of hypothyroid and euthyroid participants.

		Euthyroid (n=69)	Hypothyroid (n=22)	P-value
cVEMP	Right Ear (A/P)	4/65	4/18	0.093
	Left Ear (A/P)	1/68	3/19	0.042
oVEMP	Right Ear (A/P)	10/59	4/18	0.737
	Left Ear (A/P)	10/59	5/17	0.509

cVEMP: Cervical vestibular evoked myogenic potential, oVEMP: Ocular vestibular evoked myogenic potentials, A: absent, P: positive

Table 5: The vestibulo-ocular reflex (VOR) gain results for each semicircular canal hypothyroid and euthyroid participants.

VOR gain		Euthyroid (n=69)	Hypothyroid (n=22)	P-value
Left	Lateral	0.9 (0-1.5)	0.9 (0-1.2)	0.607
	Posterior	0.8 (0-1.2)	0.9 (0-1.1)	0.791
	Anterior	0.8 (0-1.1)	0.9 (0-1.2)	0.528
Right	Lateral	1 (0-1.5)	1 (0-1.3)	0.433
	Posterior	0.8 (0-1.1)	0.8 (0-0.9)	0.170
	Anterior	0.9 (0-1.2)	1 (0-1.1)	0.199

Discussion

This cross-sectional study showed that there was no difference in vestibular function between patients with HT and the control group in detailed vestibular tests. Studies show an increased prevalence of autoimmune thyroid disease in patients diagnosed with MD and BPPV, and autoimmunity was held responsible in the etiopathogenesis of both diseases. Most studies were designed to investigate thyroid autoimmunity or thyroid dysfunction in patients who have already been diagnosed with a vestibular disease, and some of these studies had no control group [15]. There are limited studies concerning vestibular pathologies in patients with HT.

To address the limitations in the literature, our study evaluated the peripheral vestibular system in patients with thyroid autoimmunity without vestibular complaints. The similar results of vestibular function tests in both patient and control group suggest that thyroid autoimmunity may not have a causal role in vestibular dysfunction. Our study indicates that thyroid autoimmunity might be limited to the thyroid gland alone and not have any systemic effects. However, thyroid autoantibodies are accepted as an indicator for predisposition to other autoimmune diseases [16]. Considering the possible role of autoimmunity in the pathogenesis of peripheral vestibular diseases, we may conclude that patients with HT may be potential candidates for developing peripheral vestibular diseases, especially MD. Further prospectively designed studies are needed to evaluate this.

In our study, the VEMP test results were similar in both control and patient groups. We can conclude that the endolymphatic sac, saccule macula, and inferior vestibular nerve may be affected by these results. Similar to our study, Chiarella et al. [14] found that cVEMP tests were higher in HT patients than the control group. In this study, the ratio of female patients to male patients in the HT group was significantly higher than in the control group. There is a predominance of females among those with MD, and hormonal factors may play a role in its etiopathogenesis. Therefore, the high number of female patients in the HT group in the study by Chiarella et al. [14] may have caused the higher frequency of abnormal VEMP tests. Moreover, in that study, only one SCC was evaluated using a caloric test, whereas in our study, all three SCCs were evaluated with vHIT tests. This increases the strength and reliability of our study.

There was no difference between groups in terms of gain of VOR. vHIT evaluates all three SCCs with a high-frequency impulse. McCaslin et al. [17] showed that vHIT is the most effective way of evaluating horizontal VOR in their study on MD. Chen et al. [18] demonstrated that there are normal vHIT symptoms in the early stages of the disease, but dysfunctions arise in the advanced stages. In light of the results, it was concluded that the immune response that may lead to dysfunction in the cupula in the semicircular canals, afferent cellular system, and vestibular nerve did not occur.

Our study was a cross-sectional study and was performed on asymptomatic patients who had not yet developed the autoimmune changes that cause MD or BPPV, which may be the reason behind the failure to detect the pathology in vertigo-related tests. Thus, prospective studies to investigate the association between thyroid autoimmunity and vertigo in asymptomatic HT patients are required. Approximately half of the HT patients included in our study were under LT4 treatment and were euthyroid. No significant difference was detected between HT patients under LT4 treatment and HT patients not receiving any treatment in terms of vestibular tests. There was an altered frequency in the left ears of patients with hypothyroidism in cervical VEMP tests. Since the patients did not have any symptoms and signs of vestibular dysfunction, we could not interpret the clinical importance of this result. Nevertheless, this may be an early sign of vestibular dysfunction accompanying thyroid dysfunction.

Limitations

This study had the following limitations. Firstly, due to the small number of participants (both with HT and hypothyroidism), some abnormalities in vestibular function may not have been identified, and we may not have tested the exact effect of hypothyroidism on the vestibular system. Secondly, the cross-sectional design of our study did not allow us to follow the patients for the symptoms and signs of vestibular dysfunction.

Conclusion

In conclusion, in our study, we did not find any relationship between HT and vestibular dysfunction, despite the opposite clinical observations and the findings in a relatively small number of studies. For this reason, there is a need for further studies with a prospective design to investigate the course of vestibular function in patients with HT.

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