

Visual Evoked Potentials in Euthyroid Hashimoto's Thyroiditis

Hashimoto Tiroiditinde Görsel Uyandırılmış Potansiyeller

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ABSTRACT

Objective: Hashimoto's thyroiditis (HT) is an autoimmune disease in which neurological involvement is not uncommon. This study aimed to explore the presence of visual evoked potential (VEP) changes as an indicator of subclinical central nervous system involvement in euthyroid HT patients without obvious neurologic findings.

Methods: Thirty HT patients with normal neurological examination and thirty healthy controls were included. VEPs were recorded by using pattern-reversing black and white checkerboard with monocular testing. P100, N75 and N135 (ms) peak latencies, and P100 amplitudes of right (R) and left (L) eyes in each group were compared.

Results: There was no significant difference between the groups for age. The mean of the P100 (R: 108.13±4.3, L: 108.2±4.4 ms), N75 (R: 79.23±6.03, L: 80.2±5.78 ms) and N135 (R: 141.8±11.2, L: 142.4±10.2 ms) latencies, and the P100 amplitude (R: 6.71±4.16, L: 6.6±3.9 µV) in the HT group were not significantly different from P100 (R: 107.2±3.8, L: 107.7±4.36 ms), N75 (R: 79.9±5.5, L: 78.9±6.17 ms), N135 (R: 140.3±8.4, L: 141.9±9.7 ms) latencies and P100 amplitude (R: 8.20±3.32, L: 6.9±2.9 µV) in the control group. Also, there was no significant correlation between P100 latencies and thyroid specific antibody levels in the HT group.

Conclusion: This result may be due to the fact that HT does not significantly affect the optic nerve and visual pathways, or that VEP is an inadequate technique to demonstrate possible involvement.

Keywords: Hashimoto's thyroiditis, visual evoked potentials, P100, N75, N135

ÖZ

Amaç: Hashimoto tiroiditi (HT), nörolojik tutulumun eşlik edebildiği otoimmün bir hastalıktır. Söz konusu tutulumun ötiroid hastalarda subklinik olarak ortaya çıkabileceği öne sürülmektedir. Bu çalışmada, objektif nörolojik bulgusu olmayan ötiroid HT hastalarında merkezi sinir sisteminin (MSS) olası tutulumunun bir göstergesi olarak, görsel uyarılmış potansiyellerdeki (VEP) değişikliklerin varlığı incelenmiştir.

Yöntemler: Nörolojik muayenesi normal olan 30 HT ve 30 sağlıklı kontrol çalışmaya dahil edilmiştir. VEP kaydı dama taşı "patern reversal" kullanılarak yapılmış, her iki grubun, sağ ve sol göz P100, N75 ve N135 dalgalarının tepe latansları ve P100 amplitüd değerleri karşılaştırılmıştır.

Bulgular: Gruplar arasında yaş açısından anlamlı fark bulunmamıştır. Dahil etme kriterlerine uygun erkek hasta mevcut olmadığından, kontrol grubu da sadece kadınlardan oluşturulmuştur. HT grubunun P100 (R: 108.13±4.3, L: 108.2±4.4 ms), N75 (R: 79.23±6.03, L: 80.2±5.78 ms), N135 (R: 141.8±11.2, L: 142.4±10.2 ms) tepe latansları ve P100 amplitüdü (R: 6.71±4.16, L: 6.6±3.9 µV) ile kontrol grubunun P100 (R: 107.2±3.8, L: 107.7±4.36 ms), N75 (R: 79.9±5.5, L: 78.9±6.17 ms), N135 (R: 140.3±8.4, L: 141.9±9.7 ms) tepe latansları ve P100 amplitüdü (R: 8.20±3.32, L: 6.9±2,9 µV) arasında anlamlı fark bulunmamıştır. Tiroid spesifik antikorlar ile P100 tepe latansları arasında da anlamlı bir korelasyon saptanmamıştır.

Sonuç: HT ve kontrol gruplarına ait VEP değerleri arasında anlamlı bir fark bulunmamasının, HT'nin optik sinir ve görsel yolları belirgin şekilde etkilememesinden, yahut VEP tekniğinin hastalardaki olası MSS tutulumunu göstermede yeterli hassasiyete sahip olmamasından kaynaklanıyor olabileceği düşünülmüştür.

Anahtar kelimeler: Hashimoto tiroiditi, görsel uyarılmış potansiyeller, P100, N75, N135

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INTRODUCTION

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis may be associated with various neurological disorders, presenting as central and/or peripheral nervous system involvement (1-3). The detection of an increase in serum anti-thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) levels in this autoimmune disease is important for making the diagnosis. Hashimoto's encephalopathy (HE) is the most remarkable example of a central nervous system (CNS) involvement linked to HT (3). It has been shown that demyelinating lesions similar to multiple sclerosis (MS) and single-photon emission computed tomography abnormalities can be seen in HT (4,5). Furthermore, brain function abnormalities such as cognitive and affective disturbances have also been reported in euthyroid HT patients with subtle neurological symptoms (6).

In many diseases of the CNS, particularly in demyelinating diseases, the visual system can be affected sub-clinically (7,8). Visual evoked potential (VEP), a gross electrical signal recorded from the visual cortex in response to a changing visual stimulus on the check-board pattern (pattern onset/reversal VEP), is one of the methods used to demonstrate the overt or subtle dysfunctions of the visual system (9).

This study aimed to explore the presence of VEP changes as an indicator of subclinical CNS involvement in euthyroid HT patients without obvious neurologic findings.

METHODS

The participants of the patient group (HT group) were randomly selected (by simple randomization according to their protocol numbers) from the patients (over 18 years old) who were admitted to the neurology outpatient clinic from January to March 2019 with nonspecific complaints and an HT diagnosis confirmed by an endocrinologist. All the patients had high TPOAb (>34 IU/mL) and TgAb (>115 IU/mL) levels, reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography, normal thyroid function tests, and no objective finding on the neurological examination. The control group consisted of healthy volunteers. The participants with ocular diseases that could affect the VEP test, such as glaucoma, were excluded from the study. None of the participants had visual complaints.

All participants underwent neurologic examination, and visual acuity was measured using a Snellen chart. Thyroid stimulating hormone (TSH), free thyroxine (fT4), TPOAb, and TgAb levels in the last three months were obtained retrospectively from the patient records.

VEPs were performed by the same technician, in the neurophysiology laboratory, using the 10/20 system monocular reverse pattern VEP method, with Keypoint G4 (Natus Medical Incorporated Alpine Biomed Apps Skovlund, Denmark). The VEP study protocol was based on the recommendations of the International Society for Clinical Electrophysiology of Vision on

performing VEPs (10). The active electrode (Oz) was placed in the midoccipital line, 5 cm superior to the inion. The reference VEP has been used in clinical neurology, for the electrode (Fz) was in the mid frontal line and the grounding electrode was at the vertex (Cz). Visual stimulation was provided by a pattern generator monitor with a mean luminance of 50 cd/m², full field size 15°, and each check subtended 60' and 15'. The mean luminance in the test room was kept at 80 cd/m², the contrast between the black and white squares was 85%. The sweep speed, sensitivity and sweep duration and bandpass filters were 30 ms/division, 5 microV/division, 300 ms, and 2-100 Hz, respectively. The subjects were asked to sit on a chair at a distance of 100 cm from the monitor, close one eye at a time while looking at a fixed point in the middle of the monitor, and relax. The rate of pattern reversal was 2 Hz and an average of two sets of 200 responses was recorded. Both eyes were separately tested.

Latencies (ms) of the major positive component (P100) and negative peaks (N75 and N135) and P100 amplitudes (µV) were determined. Abnormal P100 latencies were normally considered when the latency exceeding 2.5 to 3 SD beyond the mean, or beyond the 95th to 99th percentile. The laboratory values for P100 latency, determined previously in 28 healthy, 21-to 63-year-old controls, is 101.3±6.2 ms (mean ± standard deviation), and therefore, the normal limit is <116 ms (unpublished data). The VEP tests of the participants were evaluated by the same investigator who was blinded to the groups.

This study was approved by Yeditepe University Faculty of Medicine Local Ethics Committee (approval number: 2019-920, date: 02.01.2019) and written informed consents were obtained from all participants.

Statistical Analysis

The sample size was determined by using the G*Power software within the inputs of α err prob: 0.05, Power (1- β err prob): 0.80, and the effect size $d=0.8$ before the initiation of the study (11). SPSS 22.0 program was used for the analysis. The distribution of the variables was evaluated using the coefficient of variation, skewness-kurtosis, histogram and the Shapiro-Wilk normality test. Independent Samples t-test was used to compare the VEP values (P100, N75 and N135 waves, and amplitude of P100) of two groups (the right eye values of the patients were compared with the right eye values of the control group and the left eye values were compared with the left eye of the other group). The correlation between the P100 latencies and thyroid antibody levels in the HT group was evaluated using the Pearson correlation test. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

Thirty HT patients and 30 control were included. Since all the patients were females, the control group was also composed of female volunteers. The reasons for and frequencies of the referral of the patients to the neurology clinic were as follows: Headache 18 (60%), mild cognitive complaints (forgetfulness,

decreased attention, and difficulty in concentration) 6 (20%), sleep disturbances 3 (10%), fatigue 2 (6.7%) and dizziness 1 (3.3%). There was no significant difference in age between the HT and control groups (38.93±8.73 and 33.80±8.77 years, respectively). The mean duration of HT disease was 11.68±8.89 years.

Mean serum TSH, fT4, TPOAb, and TgAB levels of HT patients were 2.7±1.88 uIU/mL, 1.16±0.21 ng/dL, 349.7±204.9 IU/mL, and 192.09±168.16 IU/mL, respectively. The visual acuities of all participants were 20/20.

Table 1 shows the comparisons of the mean latencies of P100, N75, and N135 waves, and P100 amplitudes of R and L eyes in the HT and control groups. There was no statistical difference between the latencies of the abovementioned waves and amplitudes between the two groups. In the HT group, P100 wave latencies were not significantly correlated with the levels of TPOAb (r=0.08, p=0.71) and TgAb (r=-0.13, p=0.710).

DISCUSSION

Autoimmunity targeting the thyroid gland can also influence the CNS, and this association has been demonstrated by immunohistochemistry and imaging techniques (12-15). Animal models have shown that immune system activation can trigger inflammation in the CNS and influence animal behaviors (16). The effects of immune dysregulation on the CNS can be explained by the altered neural pathway functions and the blood-brain barrier damage as a result of the changes in various cytokines (17,18). Positive glucocorticoid response and histologic findings of perivascular lymphocytic infiltration in HE, the more overt CNS involvement of HT, may support the hypothesis based on the immunological explanation (19). Furthermore, *in vitro* studies showed that various antibodies, such as anti-ganglioside, anti-neural antibodies, and particularly TPOAbs, bind to CNS cells and impair myelin sheath damaging myelinogenesis (6,20). The increased production of monocyte- and T-lymphocyte-derived cytokines in HT patients can also negatively affect some neurotransmitters playing role in various neuronal pathways (6).

In recent years, an increasing number of studies have reported insidious brain function abnormalities, only detected by specific

tests, in euthyroid patients (6,21-23). Immunological mechanisms are the most probable reasons for these abnormalities, as shown by the studies indicating that TPOAb levels are higher in the patients with cognitive deficits than in the other HT patients without abnormalities (6,22,23).

HT, the most common autoimmune thyroid disease, may also coexist with other autoimmune conditions (24,25). In the context of this study, it is important that HT and autoimmune diseases of the CNS affecting the optic nerve and visual pathways, such as MS, are remarkably seen together. Since HE has several features resembling MS, such as common genetic loci, certain deregulated anti-inflammatory responses, elevated CSF oligoclonal bands, and demyelinating lesions on imaging studies, it is included in the differential diagnosis of MS, and both diseases have been suggested to have common similar pathological pathways in CNS involvement (2,5,19,24,26).

The involvement of the optic nerve and visual pathways in autoimmune CNS disorders can be seen sub-clinically, as in MS, and is only demonstrated by special methods such as VEP (7,8). The hypothesis of our study was based on this information. Moreover, it has been shown that patients with recurrent and bilateral optic neuritis have a greater frequency of HT than other optic neuritis patients, despite normal magnetic resonance imaging (MRI) findings (27). In many cases, optic neuropathy in autoimmune thyroid diseases relates not only to thyroid hormones, but also to increased autoantibodies and can be seen in euthyroid patients (28).

VEP parameters, particularly latencies, may be influenced by hypothyroidism and hyperthyroidism. Although this situation is well documented in hypothyroidism, controversial results have been reported in hyperthyroidism (29-31). The prolongation of VEP latencies is the most common change, and it usually returns to the normal after the euthyroid state is achieved with the treatment in hypothyroid patients (32-34). Thyroid ophthalmopathies and exophthalmos are the main reasons of the VEP changes in hyperthyroid patients (29,33,35). While the exact mechanisms remained elusive, compressive optic neuropathy, axoplasmic stasis, ischemia and mechanical stretch due to proptosis,

Table 1. The comparison of VEP latencies (P100, N75, N135) and P100 amplitudes of the HT and control groups

| VEP | SIDE | HT (mean ± SD) | Control (mean ± SD) | p |
|---------------------|------|----------------|---------------------|-------|
| P100 latency (ms) | R | 108.13±4.3 | 107.2±3.8 | 0.412 |
| | L | 108.2±4.4 | 107.7±4.36 | 0.662 |
| N75 latency (ms) | R | 79.23±6.03 | 79.91±5.50 | 0.620 |
| | L | 80.20±5.78 | 78.90±6.17 | 0.438 |
| N135 latency (ms) | R | 141.8±11.2 | 140.30±8.41 | 0.630 |
| | L | 142.4±10.2 | 141.91±9.72 | 0.869 |
| P100 amplitude (µV) | R | 6.71±4.16 | 8.20±3.32 | 0.579 |
| | L | 6.6±3.85 | 6.92±2.90 | 0.709 |

VEP: visual evoked potentials, R: right eye, L: left eye, SD: standard deviation, ms: milliseconds, µV: microvolt, Independent Samples t-test, HT: Hashimoto's thyroiditis

and perineural inflammation have been proposed (33,36). Decompressive surgical approaches and steroid treatment can greatly improve the VEP changes in hyperthyroid patients with ophthalmopathy (37,38).

Our goal was to explore the presence of VEP changes as an indicator of the subclinical effects of HT on optic nerve and visual pathways. The pattern reversal VEP consists of a prominent positive component at approximately 100 ms (P100), followed by negative components (N75 and N135). Dysfunctions of the optic nerve, chiasma, and retrochiasmatal pathways can be assessed using the VEP. Although a delayed P100 component often occurs in association with optic nerve diseases, it should not be considered pathognomonic for optic nerve diseases (29). VEP can be used to detect subclinical optic nerve demyelination. Even after the use of MRI increased, the VEP preserved its value in the diagnosis of demyelination because it has been shown that the specificity of the changes on MRI may be less than originally anticipated in many patients (39).

Study Limitations

We could not find any statistically significant difference between the groups in terms of the latencies of VEP waves and P100 amplitudes. These results may be due to the fact that the optic nerve and visual pathways are not significantly affected in euthyroid HT patients or the sensitivity of VEP is not sufficient (8,40). There are some limitations of this study. The small number of patients and the lack of male euthyroid HT patients are some of our limitations.

CONCLUSION

The results of this study cannot support the hypothesis that VEP can be a screening test for the subclinical involvement of the optic nerve or visual pathways in euthyroid HT patients. As the possible reasons for these results, we suggested that there was no significant involvement in the aforementioned regions of CNS in euthyroid HT patients without visual symptoms and/or the lack of sufficient sensitivity of the VEP method in this regard.

Ethics Committee Approval: This study was approved by Yeditepe University Faculty of Medicine Local Ethics Committee (approval number: 2019-920, date: 02.01.2019).

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