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Changes in Cognitive Functions Caused by Acute Hypothyroidism During Withdrawal of L-Thyroxine in Patients with Differentiated Thyroid Carcinoma

ABSTRACT

Objective: Chronic hypothyroidism is associated with significant neurocognitive deficits. However, present data about the effect of acute hypothyroidism on cognitive functions are limited. This study aimed to investigate the cognitive functions of patients with differentiated thyroid carcinoma (DTC) in acute hypothyroidism caused by L-thyroxine withdrawal (THW) using auditory event-related potentials (AERPs).

Methods: Twenty-three patients with DTC and fifteen healthy subjects (group 1) were involved in the study. AERPs were recorded using the standard auditory "Oddball" paradigm from the Fz, Cz, Pz, and Oz regions. P300 waves were analyzed. The first records were obtained from group 1 and DTC patients under thyroxine treatment (group 2a). In the patient group, AERP recordings of the patients were repeated approximately 1 month after the withdrawal of thyroid hormone (THW) when the patients became hypothyroid (Group 2b).

Results: P300 latencies were found to be significantly longer in group 2a in the Cz ($P < .01$), Pz ($P < .001$), and Oz ($P < .001$) regions compared to group 1, except for Fz. Group 2b P300 latencies were also longer than group 1 Cz ($P < .009$), Pz ($P < .001$), and Oz ($P < .001$) regions, except Fz. When comparing group 2a and group 2b, the P300 latency of group 2b was longer in the Pz region ($P < .05$).

Conclusion: In this study, it was shown that cognitive functions in patients with DTC had a slower cognitive function in the state of acute hypothyroidism induced by 1-month THW than in both healthy individuals and during L-thyroxine treatment.

Keywords: Acute hypothyroidism, cognitive functions, P300, differentiated thyroid carcinoma

Introduction

Long-standing hypothyroidism profoundly affects a large part of the body, leading to cardiovascular illness, neuropsychiatric disease, metabolism, and oxidative stress.[1-3] Hypothyroidism is associated with an important cognitive deficit.[4,5] Few studies show that L-T4 suppression therapy may affect cognitive functions, and the results are controversial.[6-8]

Differentiated thyroid carcinoma (DTC) is a common endocrine cancer. DTC treatment is generally total thyroidectomy and radioiodine (131I). These treatments are administered following thyroid stimulating hormone (TSH) suppression with levothyroxine.[9,10] Acute hypothyroidism caused by withdrawal of thyroid hormone (THW) is used as an important model for investigating cognitive function and similar dysfunctions.[11] Current data about the relation between acute hypothyroidism and cognitive functions are limited.

Event-related potentials (ERPs) are brain responses associated with various physiological events such as cerebral blood flow, eye movement, or cognitive functions such as recognition of target stimuli, and are objective parameters reflecting cognitive functions.[12] The P300 component of ERP is derived from an electrical signal from the brain, and it reflects multiple aspects of information processing in humans performing cognitive tasks.[13] P300 is a positive wave approximately 300 ms after a rarely presented target stimulus. One of the methods used to create the P300 is the auditory oddball paradigm.[14] In P300 wave analysis, the amplitude and latency of the wave are generally evaluated. It is reported that P300 amplitude is an indicator of updating working memory content, and P300 latency is an indicator of stimulus evaluation speed.[15,16] Studies are reporting a prolongation of P300 wave latency in Parkinson's disease, Alzheimer's disease, dementia, and growth hormone deficiency.[17-19]

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This study aimed to investigate the changes that may occur in cognitive functions in patients with differentiated thyroid carcinoma (DTC) in cases of acute hypothyroidism due to thyroid hormone (L-thyroxine) withdrawal, using auditory event-related potentials (AERPs).

Materials and Methods

Study Groups and Inclusion Criteria

Twenty-three (3 males and 20 female) patients with DTC participated in the study from the Department of Endocrinology, Erciyes University Medical School. Fifteen (12 males and 3 female) age-matched healthy subjects served as a control group. Ethical approval was obtained from Erciyes University, Faculty of Medicine, Ethics Committee for Clinical Research 11 (approval number: 2014/500, date: 2014). Informed consent was obtained from all participants and the study was conducted following the Helsinki Declaration. In both groups, individuals between the ages of 18 and 65 who did not have a neuropsychiatric disease, did not smoke, were not pregnant, did not drink alcohol, did not use antidepressant and hyposedative drugs, and did not have a systemic disease or malignancy were included in the study.

All the patients were diagnosed with thyroid cancer with clinical and laboratory measurements confirmed by histopathologic examination. All patients with DTC had a total thyroidectomy and then were receiving continuously the same therapy (L-thyroxine). Patients who needed whole-body scans (WBS) and stimulated serum thyroglobulin measurements were involved in the study.

AEPs were recorded from healthy subjects (group 1) and patients treated with L-thyroxine (group 2a) as baseline recordings. Approximately 1 month after thyroid hormone withdrawal (THW) in the patient group, in a hypothyroid state and with elevated TSH, the AEP recordings of the patients were repeated on the WBS day in the same patient group, group 2b.

Biochemical Analysis

The serum thyroid hormone levels, TSH, glucose, blood urea nitrogen (BUN), creatinine, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lipid panels were analyzed from the fasting blood sample. Using chemiluminescent technology, serum levels of free triiodothyronine (FT3), free T4, and TSH were measured with Siemens' ADVIA Centaur®XP immunoassay system kits.

AERP Recording Procedure and Techniques

AERP recordings were taken in the morning and from rested participants. Ag/AgCl electrodes were filled with electrode gel. Recording electrodes were placed in the frontal (Fz), central (Cz), parietal (Pz), and occipital (Oz) electrode regions according to the 10/20 international system. The reference electrode was placed on the right earlobe, and the ground electrode was placed on the left earlobe.

Signals from the brain were amplified with a bioelectric amplifier (AB-621 G, Nihon Kohden). Digital filters between 0.3 Hz and 100 Hz were used.[20] The sampling rate was 1000 Hz. Waves were filtered with automatic artifact rejection (> 50 μV or <–50 μV). Thus, the recordings of 2 patients and 1 healthy participant were excluded from the study due to artifactual recording. The study continued with 23 patients and 15 healthy subjects.

Stimuli: The auditory oddball paradigm was used as the stimulus model. Participants listened to the standard stimulus at a frequency of 2000 Hz for 1000 ms and the target stimulus at a frequency of 1000 Hz for 1000 miliseconds through pairs of headphones. A total of 160 stimuli were presented regularly, with the target stimulus having a probability of .20.

Procedure: After the participant was informed about the experiment, they sat on a chair in the isolated room, and electrodes were placed. During the 5-minute adaptation period, target and standard stimulus samples were played. They were asked to keep their eyes open as much as possible, not to make sudden eye and body movements, and to count silently when they heard the target stimuli by looking at a fixed point on the wall.[21]

ERPs were corrected according to the baseline interval. After presenting the target and standard stimuli, positive peaks between 280 and 500 msec were evaluated as the P300 wave. By creating an average recording of each participant's P300 responses to standard and target stimuli, peak-to-peak P300 amplitude and P300 latencies were measured from the beginning of the stimulus to the beginning of the P300 response.

Statistical Analysis

Data showing normal distribution was presented as mean ± SEM. Otherwise, it was presented as median (25%-75%). Paired and unpaired *t-tests* were used to compare parametric variables, while the Mann–Whitney *U* and Wilcoxon tests were for non-parametric variables. Univariate analysis of variance was used to correct variables according to age. P < 0.05*P* < .05 was considered statistically significant.

Results

The mean age of the patients was 39.9 ± 11.1 (range 21-54 years), and the mean age of the healthy subjects was 34.1 ± 12.1 (range 24-56 years). We found significantly decreased serum thyroid hormone levels and increased TSH after THW in group 2 (Table 1).

When we compared group 1 and group 2a, mean P300 latencies were significantly prolonged under L-thyroxine treatment in group 2a at Cz (271.9 ± 10.2; 263.1 ± 9.7, *P* < .01), Pz (270.5 ± 8.5; 259.7 ± 6.3, *P* < .001), Oz (278.4 ± 12.6; 261.3 ± 11.3, *P* < .001) regions for the target stimulus, except at the Fz region.

Comparison of group 2b in hypothyroid status and off-treatment period and group 1 showed that mean P300 latency (ms) was also significantly prolonged under the off-treatment period at Cz (274.2 ± 13.4; 263.1 ± 9.7, *P*< .009), Pz (276 ± 14.0; 259.7 ± 6.3, *P* < .001), Oz (279.9 ± 16.1; 261.3 ± 11.3, *P* < .001) regions for the target stimulus except at the Fz region.

MAIN POINTS

- Withdrawal of thyroid hormone (THW) therapy before diagnostic or therapeutic intervention in patients with differentiated thyroid carcinoma (DTC) results in acute hypothyroidism.
- The P300 component of event-related potentials is derived from an electrical signal from the brain and reflects human cognitive performance.
- In DTC patients, a decrease in cognitive function was observed in acute hypothyroidism caused by 1 month of THW.

Table 1. Thyroid Profiles of the Study Groups

Parameters	Reference Range	Controls (n = 15)	Patients (n = 23)	
			On L-thyroxine Treatment	Off L-thyroxine Treatment
TSH (μIU/mL)	0.35-5.50	1.9 (0.7-3.6)	0.4 (0.1-2.2)*	79.7 (29.5-137.5)#,·
Free T4 (ng/dL)	0.89-1.76	1.3 ± 0.1	1.9 ± 0.3*	0.3 ± 0.1#,·
Free T3 (pg/mL)	2.3-4.2	3.6 ± 0.4	3.3 ± 0.5	1.1 ± 0.2#,·

Data are presented as mean ± SEM or median (25%-75%) where appropriate. Statistical comparison: The controls vs on L-thyroxine treated patients (*P< .05), The controls vs off L-thyroxine treated patients (#P < .05), on L-thyroxine vs off L-thyroxine treated patients (·P< .05)

Table 2. Mean P300 Amplitudes (mV) in the Patients and Control Subjects

Recorded Brain Regions	Controls (n = 15)	Patients (n = 23)	
		On L-thyroxine Treatment	Off L-thyroxine Treatment
Fz	11.8 ± 5.0	14.0 ± 5.0	12.4 ± 4.6
Cz	14.1 ± 4.4	16.0 ± 5.0	14.4 ± 3.8
Pz	10.8 ± 2.8	11.8 ± 4.1	10.6 ± 3.8
Oz	5.9 ± 2.4	5.0 ± 2.4	5.3 ± 2.4

Data are presented as mean ± SEM.

In the comparison of group 2a and group 2b, mean P300 latencies (ms) were significantly prolonged in group 2b (276 ± 14.0; 270.5 ± 8.5, P < .05) only at the Pz region for the target task.

No statistically significant difference in P300 amplitude (μV) between the groups for all tasks (Table 2).

Discussion

Cognitive functions can be assessed with the P300 wave, an ERP component.[22] P300 waves became more practical for quantitatively evaluating cognitive functions in different diseases. P300 latency shows an indirect indication of the onset of the process involved in stimulus discrimination, while P300 amplitude, which is influenced by several variables, indicates an index of the intensity of the energetic activation or arousal involved.[23]

Although it is well known that chronic overt hypothyroidism has detrimental effects on cognition in adults, it is not known exactly what happens in acute hypothyroidism. In this study, we evaluated cognitive functions using auditory ERPs in patients with DTC who had L-thyroxine treatment and after 1 month who had acute hypothyroidism during L-thyroxine withdrawal. This is the first study in the literature regarding patients with acute hypothyroidism due to thyroid hormone withdrawal in DTC.

Overall, from the clinical point of view, the most striking finding in this study is that patients under L-thyroxine replacement and also during the acute hypothyroid periods both have negative effects on cognitive functions assessed with P300 ERPs.

Our study did not find any difference in P300 amplitude between groups for all tasks. According to our results, mean P300 latency was prolonged in the hypothyroid status compared to patients under L-thyroxine treatment and the control group. Some authors showed prolonged P300 latency in chronic hypothyroidism, consistent with our results. It was found that there was a significant increase in P300 latency compared to control subjects in 75 patients with overt hypothyroidism.[5] In another study, overt hypothyroidism revealed a markedly delayed P300 wave that normalized after euthyroidism was established.[24] According to Dejanovic et al[25] studies, the P300 latencies in patients with subclinical hypothyroidism were significantly longer than those of the control group, which decreased after 6 months of treatment. In our study, the effect of THW on prolonging P300 latency, that is, slowing down cognitive functions, was seen only in the Pz region. Although our patients had overt/severe hypothyroidism that occurred within a month, cognitive status was affected only in the Pz region. Compared to healthy individuals, THW slowed down cognitive functions in all regions except the Fz region in patients with acute hypothyroidism. Our results suggest that the severity of thyroid dysfunction, the duration of hypothyroidism, and the areas where thyroid hormones act on the brain (perhaps thyroid hormone or thyroid-stimulating hormone receptors) may affect cognitive functions.[26]

An important issue is that patients on L-thyroxine treatment have mild subclinical hyperthyroidism since there is a propensity to suppress TSH levels in patients with DTC. Patients with low serum TSH values were recruited from the patient pool throughout their outpatient visits. Thyroid hormone replacement is a dynamic process, and physicians and patients frequently face hormone fluctuations, including normal or over-suppressed serum TSH values. Jaracz et al[7] investigated executive functions, working memory, and attention in 31 patients with subclinical hyperthyroidism in the course of suppressive treatment with levothyroxine in patients with DTC and showed neurophysiological impairment in those patients. Similarly, Münte et al investigated the effect of experimentally induced subclinical hyperthyroidism on cognitive functions in 24 healthy young men by giving 300 μg of levothyroxine for 2 weeks. The authors found that no alteration in the overt behavioral effects could be demonstrated. However, ERP recordings demonstrated significant impacts on P300 by thyroxine treatment compared to the control condition.[27] Our results suggest that cognitive functions were not only affected by THW-induced overt hypothyroidism but also by long-term treatment with supraphysiological doses of levothyroxine. This paradox is not surprising because it has been previously shown that patients with overt hypothyroidism demonstrated earlier P300 wave recovery than patients with subclinical hypothyroidism.[24]

In our study, P300 latency was prolonged in Cz, Pz, and Oz (except Fz) regions, but latency prolongation was seen especially in the Pz region. In the studies conducted on patients with hypothyroidism, ERPs were usually recorded from the Cz region (5), or they did not write differences among Fz, Cz, Oz, and Pz regions.[24,25,27,28] There was no literature to discuss our study since such a study has not been done previously. P300 latency is more pronounced in the Pz region due to decreased perfusion observed in hypothyroidism.[29] The most common hypoperfusion in the posterior brain regions[30,31] and the parietal lobe in hypothyroidism support our findings.[32] Hypothyroidism has been associated with reduced synthesis of the

main neurotransmitters and receptors. This can also be a reason for the reduced cerebral responsiveness in hypothyroid subjects compared to euthyroid subjects.[33] In their study of hypothyroid individuals, Krausz et al[30] (2004) observed a deficit in cerebral blood flow to the brain regions mediating attention, motor speed, memory, and visuospatial processing. Mishra et al[28] claimed that decreased cerebral blood flow may be an important reason to explain the prolonged P300 latency. In light of all these studies, it can be said that cognitive slowing in hypothyroidism is due to multifactorial reasons. Our study did not observe a prolongation of P300 latency in the Fz region. There is no literature to compare our results. Further studies are needed to determine why there is no elongation in the P300 latency in the Fz region. The lack of elongation in the P300 wave may be related to the release of neurotransmitters from this region.

There are some limitations to this study. The lack of more detailed investigations, such as hemodynamic brain activity using functional magnetic resonance, being one of the study's limitations. Additionally, although the patients were investigated during a hypothyroid period, the study could not completely exclude the effects of their previous/earlier iatrogenic subclinical thyrotoxicosis on the study outcomes. A new study evaluating the impact of acute hypothyroidism on cognitive functions may be conducted in the preoperative period of thyroid carcinoma patients (as a euthyroid period) and then approximately 1 month of thyroid hormone withdrawal for radioactive iodine therapy.

In conclusion, P300 latencies are impaired in patients with acute hypothyroidism compared to healthy subjects. These results indicate that acute hypothyroidism negatively affects cognitive function compared to healthy subjects. However, subclinical hyperthyroidism, which is frequently seen in patients treated for DCT, is not an innocuous situation, and similar cognitive dysfunction is seen in those patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of Erciyes University (date/approval number: 2014/500).

Informed Consent: Verbal and written informed consent was obtained from the patients who agreed to participate in the study.

Peer-review: Externally peer-reviewed.

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