Original Article

Improvement in subclinical cognitive dysfunction with thyroxine therapy in hypothyroidism: A study from tertiary care center

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ABSTRACT

Aim: To evaluate the effect of hypothyroidism (both overt and subclinical) on cognitive function using latencies of P300 auditory evoked potentials (AEPs). P300 latency suggests that shorter latency times are related to better cognitive performance. P300 latencies were also done after thyroxine replacement to see the effect of treatment on cognitive function. **Materials and Methods:** Biochemically proven new onset cases with hypothyroidism (overt and subclinical) were enrolled into the study, AEPs of these two groups when compared with matched controls. After detailed history and physical examination, P300 potentials were recorded at two points Cz and Pz (Cz: On the midline of the head at the vertex, Pz: On the midline of the head between the vertex and occipital protuberance) using a Nicolet Viking Select neuro diagnostic system version 10.0. The study was done in electrophysiology lab in Osmania Medical College. **Results:** A patient characteristics of both cases and controls were comparable. The cases consisted of two groups, overt hypothyroid cases 24, mean thyroid stimulating hormone (TSH) values in them was 94, subclinical cases 21 in whom mean TSH value was 12.3. Mean P300 latencies of all cases at Cz was 342.42 ± 29.5 ms, and at Pz was 345.4 ± 30 ms. Mean P300 latencies of controls at Cz was 296.4 ± 34 ms and at Pz was 297.9 ± 33 ms (difference in $P < 0.001$). Mean P300 values in overt cases were 362.6 ± 32.9 ms at Cz, and at Pz it was 362.5 ± 33.9 ms. Mean P300 values in subclinical cases were 319.3 ± 30.9 ms at Cz, and at Pz it was 316.4 ± 27.9 ms. P300 values in overt cases were highly significant as compared to controls, and P300 values in the subclinical cases versus controls were also significant ($P < 0.001$). **Conclusion:** P300 latency prolongation in both clinical and subclinical hypothyroid cases shows that cognitive function is affected adversely in hypothyroidism including the subclinical hypothyroid cases. Larger studies evaluating the effect of subclinical hypothyroidism on cognitive function are needed with objective means such as the AEPs P300.

Key words: Auditory evoked potentials, central nervous system, hypothyroidism, subclinical hypothyroidism

Introduction

Thyroid hormone is essential for the development of the central nervous system (CNS). Hence, the various neurological manifestations are common in hypothyroidism, these are more severe in congenital hypothyroidism.[1] All intellectual functions, including speech, are slowed in thyroid hormone deficiency. There is a loss of initiative, slow-wittedness, memory defects, lethargy, and somnolence. These neuropsychiatric symptoms tend to improve with treatment and normalization to a euthyroid

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state though the pattern is inconsistent and complete recovery is uncertain.

Cognitive function is the ability of a person to process thoughts. Cognition basically refers to memory, speech, reading comprehension, and ability to learn something new and hypothyroidism impacts aspects of cognitive functioning and mood.[2]

Most of the available tests for cognition are psychometric and include different scales/scores involving particular questionnaire/pictures to which subject's responses are noted. Hence, these tests would invariably be influenced by educational status and intelligence of the subject.[3]

An evoked response potential (ERP) is an electrical potential recorded from the brain following the presentation of a stimulus, as distinct from spontaneous potentials and is detected by electroencephalogram or electromyography (EMG). ERPs are used to study information processing in CNS and neural mechanisms of cognition. ERPs are not affected by psychosocial factors such as education and personality traits, unlike psychometric tests.[4]

Auditory evoked potentials (AEPs) are a subclass of event-related potentials (ERPs). ERPs are brain responses that are time-locked to some "event," such as a sensory stimulus, for AEPs, the "event" is a sound.[3] AEPs (and ERPs) are very small electrical voltage potentials originating from the brain recorded and the scalp in response to an auditory stimulus such as different tones, speech sounds.[4] The P300 wave is an AEP which is used to assess the cognitive function, it is recorded as positive deflection in voltage at latency of roughly 300 ms at 2 points on scalp at Cz (Cz: On the midline of the head at the vertex) and Pz (Pz: On the midline of the head between vertex and occipital protuberance). P300 latency suggests that shorter latency times are related to greater cognitive performance.[4]

There is a scarcity of data on cognitive function with auditory event related potentials (ERPs) in hypothyroid patients.[5] Hence, this study was undertaken to evaluate objectively the effect of hypothyroidism (overt and subclinical) on latencies of ERPs and response to thyroxine replacement.

Materials and Methods

This case-control study was conducted at Department of Endocrinology, Osmania general hospital, Hyderabad, in subjects diagnosed to have hypothyroidism (both subclinical and overt).

Biochemically proven 45 new onset cases of hypothyroidism, age group of 12–45 years were randomly selected and included in the study after careful exclusion. Of which 24 were overt cases and 21 were subclinical cases. Thirty-three age and sex matched controls selected randomly from the hospital staff was taken as a comparative group. Any conditions known to have an effect on P300 were excluded from both the groups. Conditions excluded were hypertension, chronic alcoholism, smoking, or tobacco usage in any form, neurological and psychiatric illnesses, significant head injury in the past, cerebrovascular accidents, insomnia which can adversely affect P300. Since the auditory stimulus was used to elicit P300, individuals having hearing impairment were also excluded. Informed consent was taken from all patients, and this study was approved by the ethical committee.

Methodology

A detailed history and physical examination were carried out in these subjects. Thyroid profile ordered before and after treatment which was done by quantitative chemiluminescence immunoassay.

The P300 wave is an AEP which is used to assess cognitive function, it is recorded as positive deflection in voltage at latency of roughly 300 ms at two points on scalp at Cz (Cz: On the midline of the head at the vertex) and Pz (Pz: On the midline of the head between vertex and occipital protuberance) using a Nicolet Viking Select Neurodiagnostic system version 10.0. The study was done in electrophysiology lab in Osmania Medical College.

The measurements of P300 were done in the hypothyroid subjects before starting thyroxine supplementation. Later on at follow-up once they were found to be euthyroid biochemically repeat assessment of the P300 was done the duration posttreatment at 8 weeks.

Recording electrodes for evoked response potential P300

The volume conducted evoked responses were picked up from the scalp by using disc type of $Ag/AgCl_2$ electrodes. Two reference electrodes was attached to the left and right mastoid, designated as A1 and A2, respectively, one active electrode on vertex labeled as Cz and one as a ground electrode to forehead termed as Fpz. All the electrodes were plugged to a junction box. The impedance between skin and electrode was monitored and kept below 5 K ohms. Recommended montages for ERP p300 were Channel 1: Cz - A1, Channel 2: Cz - A2, and Ground: Fpz.

Procedure for P300

A three stimuli "odd-ball" paradigm is designed to carry out the P300 study.[6] One frequent event and remaining two are being rare events. Target or rare tone and nontarget

or frequent tone of 70 dB was applied on both ears simultaneously through headphones applied to ears of the subject. Rare tone and the frequent tone was of 2 KHz, and 1 KHz, respectively. Rare tone stimuli were given in 20% and frequent tone stimuli in 80% frequency in random. Stimulus frequency was 1 stimulus per 2 s. Total numbers of stimuli given were 160. The signals were picked by electrodes and were filtered, amplified, averaged, displayed on the screen of RMS EMG EP MK2, and recorded. Latency and amplitude of P300 wave were measured.

Statistical analysis

Differences between patient groups were assessed for statistical significance using the Student's *t*-test for independent variables among the groups, analysis of variance (ANOVA) was used for comparisons of P300 values in three groups and differences in P300 latencies within the groups before and after Rx were compared using paired samples *t*-test.

The analysis had done by using Windostat Version 8.6. All results were expressed as means ± standard deviation (SD), where *P* value of 0.05 or below considered as statistically significant.

Results

A total number of 78 patients were studied. Forty-five cases, 33 controls, in cases there were two groups, 24 had overt hypothyroidism, and 21 had subclinical hypothyroidism. Patient characteristics (i.e. age, sex, body mass index [BMI]) of both the cases and controls were comparable [Table 1].

Table 1: The patient characteristics between cases and controls

Patient characteristics	Overt cases	Subclinical cases	Controls	*P*
Number of patients	24	21	33	
Mean age	26±5.8	25±6.4	24±6.2	0.61
Sex				
Female/male	23/1	20/1	32/1	0.75
Height	153±28.4	151.8±30.3	152.2±21.4	0.69
Weight	68.1±7.6	66.8±8.5	65±9.1	0.58
BMI	29.9±4.1	28.9±4.4	27.9±3.5	0.49
TSH	94.1±15.2	12.3±2.4	2.4±1.1	<0.001
T4	3.36±0.90	7.03±1.67	8.34±1.2	<0.001
T3	0.71±0.25	0.99±0.31	1.2±0.54	<0.001
Mean TSH after Rx	3.1±1.12	2.5±0.87	-	0.2

BMI: Body mass index, TSH: Thyroid stimulating hormone

The mean P300 latencies of all cases at Cz were 342.42 ± 29.5, and at Pz was 345.4 ± 30. Mean P300 latencies of the controls at Cz was 296.4 ± 34 and at Pz was 297.9 ± 33. The difference between cases and controls was highly significant $P < 0.001$. Mean P300 values in overt cases were 362.62 ± 32.9 at Cz, and at Pz it was 362.53 ± 33.9. Mean P300 values in subclinical cases were 319.33 ± 30.9 at Cz, and at Pz it was 316.4 ± 27.9. The P300 values in overt cases were highly significant as compared to controls, whereas the P300 values in subclinical cases versus controls were just significant [Table 2].

There was statistically significant difference in P300 values (at Cz and Pz) before and after treatment in overt ($P < 0.001$) as well as subclinical cases ($P < 0.009$) as compared to controls.

ANOVA of these three groups showed that means of all three groups were different. The mean P300 of controls was 296 (at Cz), 297 (at Pz) with a SD of 33.4. The P300 of overt cases was 362 (at Cz and Pz) with a SD of 32.

The P300 of subclinical cases was 319 (at Cz), 316 (at Pz), with a SD of 30. The difference in P300 latency between overt cases and controls was significant. The difference in means between subclinical cases and controls was significant. The difference between overt cases and subclinical cases was also significant (*P* value was < 0.001). Figures 1 and 2 were showing a graphical representation of a comparison of P300 latencies in these three groups.

Discussion

In our study, AEPs have been used to assess the cognitive status of hypothyroid patients before and after treatment with thyroxine. Our study subjects belonged to an age group range of 12–45 years. This age group was chosen because there are fewer chances of cognitive dysfunction due to other chronic systemic diseases.

Forty-five cases and 33 controls were taken, the controls were age and sex matched. The two groups were similar in age, sex, BMI, and educational status. Female sex predominance was seen as would be expected because thyroid disorders are more common in females.

Table 2: Mean P300 latencies in patients and controls at Pz and Cz

P300 latency	Overt cases		Subclinical cases		Controls	*P* Cases versus controls
	Before Rx	After Rx	Before Rx	After Rx		
Mean at Cz	362.62±32	299.5±50	319.33±30	297.29±36	296.41±34	<0.001
Mean at Pz	362.53±33	310.43±48	316.42±27	299.82±35	297.90±33	<0.001

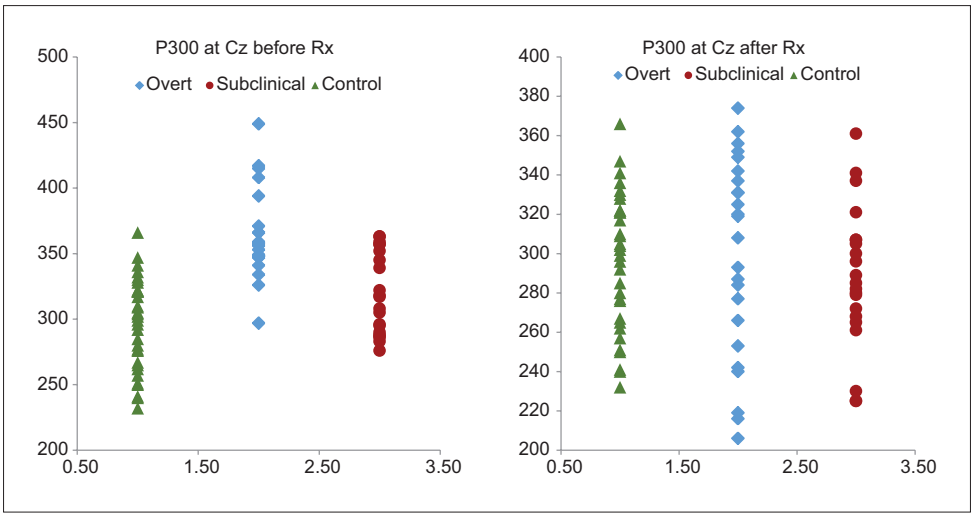

Figure 1: Comparison of P300 latencies of three groups: Overt cases and subclinical cases (before and after treatment) with the controls at Cz

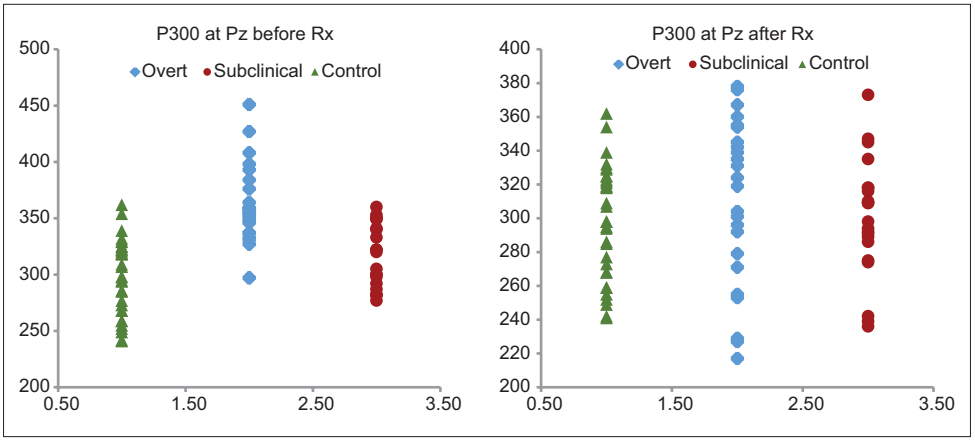

Figure 2: Comparison of P300 latencies of three groups: Overt cases and subclinical cases (before and after treatment) with the controls at Pz

The P300 values at Cz and at Pz are reported differently because they represent waves recorded at different points in the brain. The P300 latencies were significantly prolonged in hypothyroid subjects as compared to the controls ($P < 0.001$). In the study done by Sharma *et al*. P300 latency in case of newly diagnosed clinical hypothyroid patients was significantly increased in comparison to newly diagnosed subclinical cases and control groups.[7]

In the study done by Osterweil *et al*. on the other hand, no difference in P300 latencies was found in hypothyroid patients as compared to the controls.[8] Their study group consisted of elderly (31–99 years, mean 68.6 ± 16.4 years) nondemented hypothyroid patients. The age distribution of the group was highly heterogeneous, this heterogeneity and a relatively elderly group of subjects may have masked the differences in P300 latencies. In a study done by Ozisik and Arman, the mean P300 latencies in hypothyroid patients were prolonged as compared to controls.[9]

Then we analyzed the P300 values in overt and subclinical cases separately, to see if the subclinical cases also had prolonged P300 values as it would have an impact on the treatment of these subjects. When compared to controls even the subclinical cases had prolonged P300 values which were significant. Tütüncü *et al*. quantitatively analyzed the cognitive functions of patients with mild and severe hypothyroidism by measuring P300 latencies before and after treatment, when euthyroidism was achieved.[10] Moreover, the results of our study showed a change in cognitive function in response to treatment both in subclinical and overt cases. There was statistically significant difference in 300 values (at Cz and Pz) before and after treatment in overt ($P < 0.001$) as well as subclinical cases with ($P < 0.009$). In the study done by Tütüncü *et al*. the P300 latency in the subclinical cases and could normalize only after 6 months of euthyroidism.[10] No such delay in normalization of P300 values was noted in our study. Mean time of follow-up at which a repeat P300 was done was 8 weeks in our study.

The P300 AEPs are a reliable and objective method of assessing cognitive function. There are limitations associated with AEP's as with any ERP, especially the lack of wide spread availability. However, they help in the identification of subtle defects in cognition unlike the psychometric tests which can only identify gross defects in cognition. Cognitive dysfunction due to hypothyroidism is an important aspect which needs to be studied, especially in subclinical hypothyroidism because of the magnitude of cases in clinical practice. Large studies involving a greater number of subjects are needed. This test of AEPs P300 will be useful to identify patients with subclinical hypothyroidism that will benefit with treatment as against those who can be followed up.

Conclusion

In our study, P300 latency prolongation in both clinical and subclinical hypothyroid cases shows that cognitive function is affected adversely in hypothyroidism including the subclinical hypothyroid cases. This observation supports another treatment indication for subclinical hypothyroidism. Larger studies evaluating the effect of subclinical hypothyroidism on cognitive function are needed with objective means such as the AEPs P300.

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Conflicts of interest

There are no conflicts of interest.

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