

Original article

Cognitive function in subclinical and overt hypothyroidism

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ABSTRACT

Introduction: Neurocognitive deficits in overt hypothyroidism are well documented. But there is a controversy as to if subclinical hypothyroidism is associated with impaired cognition. Our aim was to evaluate the cognitive function in subclinical and overt hypothyroid patients and normal persons, and compare the results.

Materials and methods: The study population consisted of 90 women comparable in age, BMI, education and occupation. allocated into 3 groups of 30 persons in each, on the basis of serum thyroid hormones and TSH assay.

1.Control group 2.Subclinical group 3.Overt group. All the persons in the three groups were subjected to MMSE and Cognitive evoked potential study. The data were analyzed using ANOVA and Tukey post hoc analysis. The mean difference was significant when $p < 0.05$ level.

Results: MMSE score was significantly lower in the overt group. In the subclinical group, it was not significantly different from the control group. The overt group showed significant prolongation of P300 wave latency and significant decrease in P300 amplitude at Cz and Pz when compared to the control group. The overt group showed significant prolongation of P300 wave latency when compared to the subclinical group . In the subclinical group, a significant prolongation of P300 wave latency alone at Cz and Pz was noted when compared to the control group.

Conclusion: There is significant cognitive impairment in both subclinical and overt hypothyroid patients, the overt hypothyroid patients being more affected, as evidenced by cognitive evoked potential study.

Key words: Hypothyroidism, Cognitive evoked potential, P300, MMSE, Cognition.

Introduction

Cognition is the higher intellectual function of the brain. The cognitive decline of the individual results in a great burden on the self, family and community. Symptoms and signs of neurologic deficit may be the presenting features in hypothyroid patients and may result in significant disability. Neurocognitive defects in overt hypothyroidism such as slowed information processing speed, poor learning, poor memory and attention deficit are well documented in various studies.^{1,2,3,4,5} But there is a controversy as to if subclinical hypothyroidism is associated with impaired cognition. In subclinical hypothyroidism, normal measures of cognition have been reported by

certain studies^{3, 6, 7}. But there are studies which have documented cognitive impairment in subclinical hypothyroidism^{8, 9, 10}.

More over in most of the previous studies, they had used neuropsychological battery of tests to assess various domains of cognition. There are only few studies in the literature which have employed electrophysiological tests to quantify cognitive impairment in hypothyroidism .

In the present study, in addition to the *Mini Mental State Examination* (MMSE)¹¹, Cognitive evoked potential study was done to assess cognitive function in the subclinical and overt hypothyroid patients. The possibility of using cognitive evoked potential as

an investigatory tool to detect early cognitive impairment in hypothyroidism was being explored in the present study.

Aim and objectives

1. To evaluate the cognitive evoked potential in subclinical and overt hypothyroid patients and normal persons, and compare the results.
2. To assess cognition using Mini Mental State Examination in subclinical and overt hypothyroid patients and normal persons, and compare the results.

Materials and methods

TYPE OF STUDY Cross Sectional Comparative study

The study was conducted in the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai-3. The ethical clearance was obtained from Institute Ethics Committee.

The study population consisted of 90 women in the age group of 25 to 40 years with comparable BMI, education and occupation level. They were allocated into three groups of 30 persons in each, on the basis of serum thyroid hormones and TSH assay.

- * **CONTROL GROUP:** Healthy women in the age group of 25 years to 40 years, with normal T3, T4 and TSH values.
- * **SUBCLINICAL GROUP:** Newly diagnosed subclinical hypothyroid women (normal T3 and T4 values with an elevated TSH value > 5.5 mIU/L) in the age group of 25 years to 40 years who were not on thyroxine treatment.

- * **OVERT GROUP:** Newly diagnosed hypothyroid women (low T3 and T4 values with an elevated TSH value > 5.5 mIU/L) in the age group of 25 years to 40 years, who were not on thyroxine treatment.

Thyroid assay was done by ELISA method using *ERBA Thyrokit*. The total T3 and T4 are measured by competitive Enzyme immuno assay principle. Serum TSH is measured by ELISA based on sandwich principle. The normal range for total T4 is 40 to 120 nmol/L, total T3 concentrations is 0.8 to 2 ng/ml and normal serum TSH is 0.5 to 5.5 mIU/L

Thirty overt and eighteen subclinical patients were selected by screening the patients attending the Endocrinology outpatient department at Rajiv Gandhi Government General Hospital, Chennai 3. Remaining twelve subclinical hypothyroid patients were incidentally diagnosed while attending the master health check-up at Rajiv Gandhi Government General Hospital, Chennai 3. The Control group persons were selected from the College and Hospital staffs who volunteered for the study. Persons with associated diabetes Mellitus, hypertension, vascular disorders, neurodegenerative disease, hepatic disease, kidney disease, ear disease, vitamin deficiency, any major medical illness at present or within three months, history of drug abuse, overt dementia (MMSE < 24) and persons on psychotropic drug were excluded from the study.

All the persons were explained about the nature and procedures involved in this study. The informed written consent from all the persons involved in this study was obtained. The importance of demographic details is stressed while assessing cognition¹², and so details like education in years and occupational level were carefully recorded. Height and weight were

taken and Body mass index (BMI) was calculated. Vitals like pulse, blood pressure, respiratory rate and temperature were recorded. Complete general and systemic examination was done for all the persons in the study. ENT examination was done to exclude ear disease.

Mini Mental State Examination¹³ MMSE was done to assess cognition of all the persons involved in this study .A total score of 30 points is possible. The score obtained by the individual was calculated and recorded.

Cognitive Evoked Potential study¹⁴ was done for all the individuals in the study with a computerised recorder RMS EMG EP MARK II using the standard auditory odd ball paradigm. Random sequences of two distinguishable auditory clicks were delivered binaurally.It includes frequent stimuli (80%) of 1 KHz frequency and rare stimuli (20%) of 2 KHz frequency.The individuals were asked to raise their finger on hearing the rare stimuli. The intensity of the

stimuli was 60 db above hearing level. The stimuli were presented at the frequency of 1 per second, each lasting for 100 milli seconds. The responses were filtered with a band pass filter of 0.3 – 30 Hz; the responses were amplified 10,000 times and averaged for 40 responses. The individuals were asked to fix their eyes on a particular point on the wall during recording to avoid electro oculographic artefacts. The waves were then computed separately for rare and frequent stimuli, The latency and amplitude of the p300 wave of the rare stimuli were noted down.

Results

The results were expressed as mean+/-standard deviation. Statistical package for Social Sciences (SPSS) version 19.0 was used for statistical analysis. The data of the control, subclinical and overt hypothyroid groups were analysed using the one way Analysis of Variance (ANOVA) and Tukey post hoc analysis. The mean difference was considered significant when p < 0.05 level.

TABLE 1: COMPARISON OF THE CHARACTERISTICS OF THE THREE GROUPS

<i>Group</i>	<i>Control</i>	<i>Subclinical</i>	<i>Overt</i>	<i>F value</i>
<i>Age (years)</i>	33.23+/-4.55	32.43+/-4.59	34.50+/-4.42	NS
<i>BMI (kg/m²)</i>	26.59+/-1.64	26.33+/-1.55	27.10+/-0.43	NS
<i>Education(years)</i>	5.33+/-3.36	4.77+/-2.74	4.97+/-2.98	NS
<i>Occupation(level)</i>	2.13+/-0.35	2.10+/-0.31	2.10+/-0.31	NS
<i>Serum TSH(mIU/L)</i>	2.59+/-1.05	11.22+/-2.42	35.11+/-23.10	S(47.21)

The three study groups are comparable with regard to age, education, occupation and body mass index. A statistically significant increase in the serum TSH level was observed in the subclinical ($p=0.039$) and overt hypothyroid ($p<0.001$) groups on comparing

with the control group. ($df = 2; F = 47.21$). The serum TSH level in the overt hypothyroid group was significantly higher when compared to the subclinical hypothyroid group ($p<0.001$).

TABLE 2: COMPARISON OF MMSE SCORE(FOR 30) IN THE THREE GROUPS

<i>Group</i>	<i>Mean</i>	<i>SD</i>
<i>Control</i>	29.933	0.254
<i>Subclinical</i>	29.80	0.484
<i>Overt</i>	28.90	0.403

A very highly significant decrease was observed in the MMSE score of the overt hypothyroid group when compared with the control group and the

subclinical group. ($df = 2; F = 61.688 ; p<0.001$). There was no significant difference in the MMSE score of the subclinical group when compared with the control group.

TABLE 3: COMPARISON OF P300 WAVE LATENCY (MSEC) IN THE THREE GROUPS

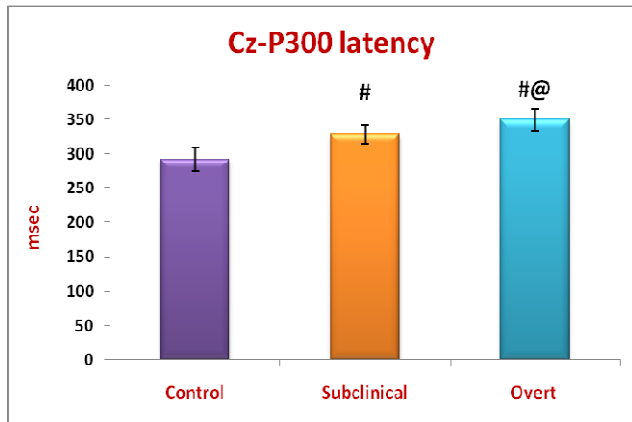
<i>Group</i>	<i>At Cz</i>		<i>At Pz</i>	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
<i>Control</i>	291.635	17.254	301.802	16.469
<i>Subclinical</i>	328.510	13.749	336.891	11.282
<i>Overt</i>	349.599	15.840	358.970	15.872

An increase in the P 300 wave latency at Cz and Pz was observed in the subclinical and overt hypothyroid groups on comparing to the control group and the difference was statistically very highly significant ($p < 0.001$). ($df = 2$; $F = 105.016$ at Cz, $F =$

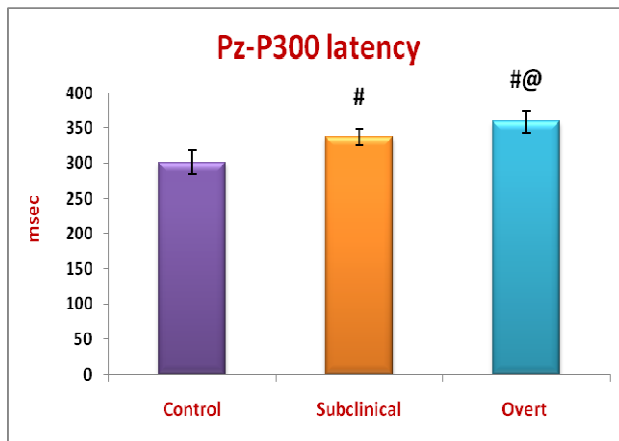
115.008 at Pz). A very highly significant increase in P300 wave latency ($p < 0.001$) was observed in the overt hypothyroid group when compared to the subclinical hypothyroid group.

Comparison of P300 wave latency (msec) in the three groups

a. At Cz



b. At Pz



- significance when compared to control group

@ - significance when compared to subclinical group

Mean difference is significant when $p < 0.05$



TABLE 4 : COMPARISON OF P300 AMPLITUDE (μV) IN THE THREE GROUPS

Group	At Cz		At Pz	
	Mean	SD	Mean	SD
Control	8.316	2.304	9.779	2.356
Subclinical	7.532	2.395	8.934	2.489
Overt	6.348	2.023	7.805	2.032

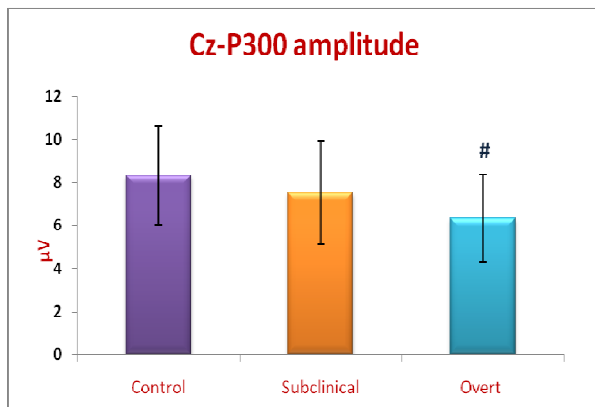
A highly significant decrease in the P300 wave amplitude at Cz and Pz was observed in the overt hypothyroid group on comparing with the control group. (df = 2; F = 5.834; p=0.003 at Cz, F = 5.558; p=0.004 at Pz). The mean P300 wave amplitude of the overt hypothyroid group was less when

compared to the subclinical group but it was not statistically significant.

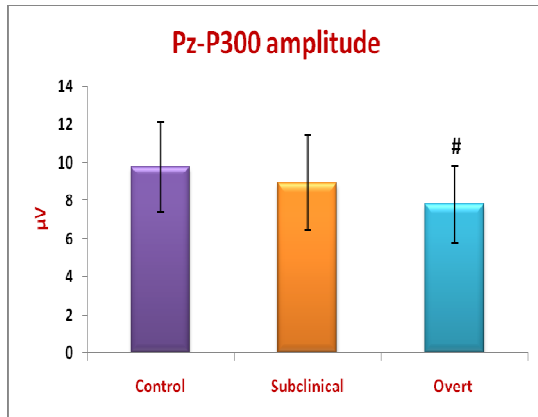
A decrease in the P300 amplitude at Cz and Pz was observed in the subclinical hypothyroid group when compared to the control group, but it was not statistically significant.

Comparison of P300 wave amplitude (μV) in the three groups

a. At Cz



b. Pz



- significance when compared to control group
 Mean difference is significant when $p < 0.05$

Discussion

In the present study the age, body mass index, education and occupation were comparable among the three groups. There is gender difference in the evoked potential study. The females tend to have shorter latency and higher amplitude. Since hypothyroidism is more common in females, the present study included only female individuals. MMSE score was significantly lower in the overt hypothyroid group when compared to the control group and subclinical group, implying definitive cognitive dysfunction, in the overt hypothyroid patients. This is in line with the findings of **Hala S Sweed et al**¹⁵ who found significantly lower MMSE scores in the hypothyroid females when compared to the age matched euthyroid females. MMSE score in the subclinical hypothyroid group was not significantly different from the control group. **Tombaugh et al**¹¹ in 1996 has stated that MMSE has limited ability to detect subclinical cognitive impairment.

The overt hypothyroid group had significant prolongation of P 300 wave latencies and decreased P 300 wave amplitude, when compared to the control

group. The overt hypothyroid group showed significant prolongation of P300 wave latency when compared to the subclinical group. P300 amplitude depends on the selective attention of the individual; it is greater with attentive individual, and with better motivation and task priority. The significantly decreased P 300 amplitude in the overt hypothyroid group implies impaired attention.

The P 300 wave latency reflects the information processing¹⁶, and it is strongly associated with short term memory¹⁷. The significant prolongation of P 300 latency in the overt hypothyroid individuals implies defective information processing and impaired memory. This is supported by the brain perfusion studies in overt hypothyroid patients, which show global hypo perfusion, more pronounced in parieto temporal regions¹⁸. **Ozata et al**¹⁹, **Osizik**²⁰ **et al**, **Tutuncu et al**²¹, **Khedr et al**²² and **Mahmoud et al**²³ observed significant prolongation of P 300 wave latency in hypothyroidism is in equivalence with the present study. In the present study, the subclinical hypothyroid group showed significant prolongation of P 300 wave latency when compared to the control group which is in consistent with the findings of

Samuels et al²⁴, Tutuncu et al²¹ and Jensovsky et al²⁵. This shows working memory is most affected in subclinical hypothyroidism. **Jorde et al⁷ and Kudrajavcev et al²⁶** reported normal memory function in subclinical hypothyroid patients. Both the studies differed from the present study in that they had used neuro psychological battery of tests and the TSH range was 3.5 – 10 mIU/L.

The possible mechanisms leading to impaired neuronal processing in hypothyroidism.

Decreased thyroid hormones lead to reduction in cell size, RNA and protein content, tubulin, microtubule associated protein, lipid and protein content of myelin and local production of critical growth factors and neurotrophins. Hypothyroidism leads to reduced cell energy metabolism, compromising the microcirculation and the oxygenation of involved organs. Cerebral blood flow is reduced but cerebral oxygen consumption is usually normal. In very severe cases, reduced cerebral blood flow leads to cerebral hypoxia. Hyperlipidemia in hypothyroidism may also contribute to the vascular changes.

The plasma half- life of TSH is very short. It is about 30 minutes while that of T3 is 1 day and T4 is 1 week. Hence as put forth by **McDermott et al⁴⁶**, the continuous elevation of plasma TSH levels in the setting of long lived T4 and T3 implies a state of **continuous intracellular hypothyroidism in the subclinical hypothyroid patients** stimulating TSH synthesis and release from thyrotrophs in the anterior pituitary. Though the optimal level is not yet known,

the intraneuronal T3 concentration is important for cellular activities including downregulation or transcription of genes related to neurotrophins, mitochondrial proteins, substrate for protein kinase C, myelin, actin and various other protein molecules responsible for intracellular signalling.

Conclusion

There is significant cognitive impairment in both subclinical and overt hypothyroid patients when compared to normal persons as evidenced by cognitive evoked potential study.

Hypothyroidism is generally considered a reversible cause of cognitive dysfunction in adults. But, the complete reversibility of cognitive impairment after attainment of euthyroidism is still a controversial issue. This warrants early detection of cognitive impairment in hypothyroidism so that timely interventions may help to preserve the quality of the patients' life.

Cognitive evoked potential study could be used as an investigatory tool in hypothyroidism, especially subclinical hypothyroidism to detect early cognitive impairment so that timely interventions may help to preserve the quality of the patients' life.

Scope of the study

The study can be continued to repeat cognitive evoked potential study in the hypothyroid patients after attainment of euthyroidism with levothyroxine therapy, to see if cognitive impairment is completely reversible (or) persistent.

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