

Original article

Evaluation of cognitive function in subclinical hypothyroidism

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Abstract

Background and Aim : Thyroid hormones are necessary for normal cognitive function. Overt Hypothyroidism is a common cause for reversible dementia. There is evidence to suggest that even subclinical hypothyroidism (normal T3 & T4 and high TSH) is associated with cognitive impairment. The purpose of our study is to assess the cognitive function in subclinical hypothyroid patients by Mini-Mental State Examination and P300 wave recording.

Method: Thirty newly diagnosed subclinical hypothyroid females of age group 25 to 40 years were selected from the patients attending Endocrinology OPD, Government General Hospital, Chennai – 3. Age matched euthyroid females were taken as controls. Mini-Mental State Examination (MMSE) was done for both groups. The P300 wave was recorded at Cz and Pz using a computerized evoked potential recorder. The latency of P300 wave and P300 amplitude were analyzed using independent-t-test. p-value <0.05 was considered significant

Results: There was no statistically significant difference in the MMSE scores between cases and controls. There was no statistically significant change in P300 amplitude at Cz and Pz. But there was a very significant prolongation of P300 wave latency at Cz and Pz in subclinical hypothyroid group when compared to the control group.

Conclusion: The P300 wave latency in the ERP study, a measure of cognitive efficiency was significantly prolonged, showing impaired cognitive processing in subclinical hypothyroidism.

Keywords: cognition, subclinical hypothyroidism, P300, Cognitive evoked Potential, MMSE

INTRODUCTION

Thyroid hormones play a crucial role in the metabolic activity of adult human brain. Subclinical hypothyroidism refers to the condition with isolated elevated serum thyrotropin (TSH) level but normal serum thyroid hormone levels, in the presence or absence of symptoms.

Cognition includes the functions involved in synthesizing information – perception, attention, memory and reasoning. It is the higher intellectual function of the brain. Cognitive impairment in overt hypothyroidism is well documented. But there is a controversy as to if subclinical hypothyroidism is associated with impaired cognition.

Event related potential study(P300) is recommended for detecting and quantifying early cognitive impairment which is not usually detected by other traditional methods of assessment of cognition¹.

Aim & objectives

To evaluate the cognitive function in subclinical hypothyroid patients using Mini-Mental State Examination and P300 wave recording.

MATERIALS & METHODS

Type of study - Cross Sectional comparative Study

Place of study - Institute of Physiology and Experimental Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3. The study population consisted of 60

women in the age group of 25 to 40 years with comparable body mass index, education and occupation. They were allocated into two groups of 30 persons in each, on the basis of serum thyroid hormones and TSH assay.

1. *Control group* - Healthy with normal T3, T4 and TSH .
2. *Subclinical hypothyroid group* - Newly diagnosed subclinical hypothyroid patients with normal T3 and T4 and TSH value > 5.5 mIU/L who were not on thyroxine treatment.

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.

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

Persons with associated Diabetes Mellitus, Hypertension, Vascular disorders, Neurodegenerative disease, Hepatic disease, Kidney disease, ear disease, Vitamin deficiency, Persons on psychotropic drug medications, Persons with history of drug abuse, Persons with

overt dementia (MMSE < 24) or Any major medical illness at present or within three months were all 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 Institutional Ethical Committee clearance was obtained.

Mini Mental State Examination (MMSE) was done to assess cognition of all the persons involved in this study. It is a brief, quick, reliable and validated method commonly used to screen for cognitive impairment. It assesses various domains of cognition like orientation, registration, attention, calculation, recall and language function. The score obtained out of 30 was calculated and recorded. Score greater than or equal to 25 points - normal .MMSE. **P300 wave** is recorded when the subject is required to distinguish one stimulus (the target) from the other (non- target). Since P300 is related to cognitive processing associated with the distinction of target from non-target stimuli it is also called Cognitive evoked potential. P300 reflects the mnemonic and cognitive function in humans ^{2,3}, information processing ⁴, and seems to be strongly associated with short term memory⁵.

P300 was recorded by a computerised recorder, RMS EMG EP MARK II using standard auditory odd ball paradigm⁶. The individuals were instructed to have a shampoo bath on the day of recording and were advised not to use hair spray or oil. They were taken to a silent room, and made to sit down comfortably in a chair. The electrode placement sites were cleaned with spirit and cotton. Electrode paste was used to

reduce the impedance below 5 kilo ohms. The electrodes were placed according to International 10 – 20 system.

* Two Active electrodes : one on Cz and other on Pz

* Two linked reference electrodes , one on each mastoid.

* Ground electrode over the forehead.

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 milliseconds. 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 P 300 wave amplitude and latency of the rare stimuli were noted down. The data of the control and subclinical hypothyroid groups were expressed as mean +/- standard deviation and analysed by the unpaired t test using SPSS 19.0. The mean difference was significant when $p < 0.05$ level.

RESULT

In the present study the age, body mass index, education and occupation were comparable among the two groups (Table:1)

Group	Control	Subclinical	P value
Age (years)	33.23+/-4.55	32.43+/-4.59	NS
BMI (kg/m ²)	26.59+/-1.64	26.33+/-1.55	NS
Education(years)	5.33+/-3.36	4.77+/-2.74	NS
Occupation(level)	2.13+/-0.35	2.10+/-0.31	NS
Serum TSH(mIU/L)	2.59+/-1.05	11.22+/-2.42	S(p= 0.039)

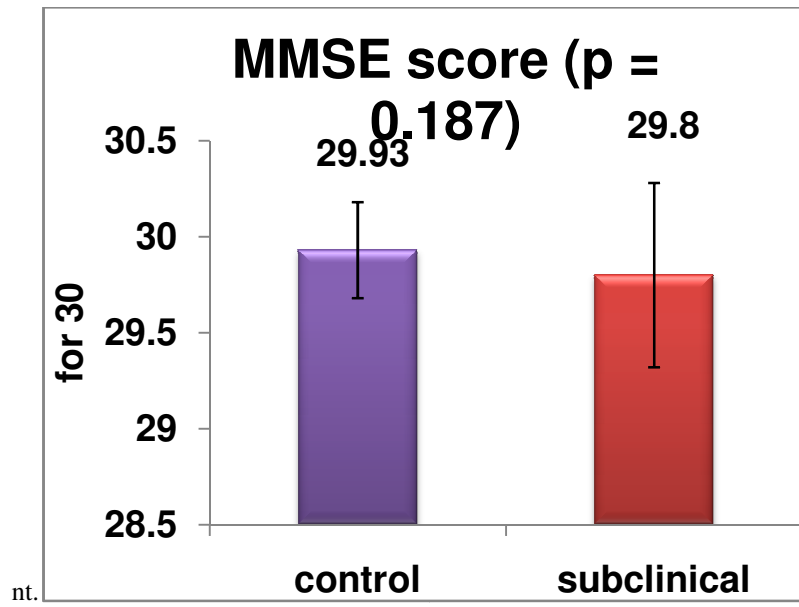
Table:1 Comparison of Age, BMI, Education and Occupation and Serum TSH

NS- Not Significant ; S- Significant

MMSE score in the subclinical hypothyroid group was not significantly different from the control group. (Fig:1)

Tombaugh et al¹¹ in 1996 has stated that MMSE has limited ability to detect subclinical cognitive impairment

Figure:1 MMSE Score



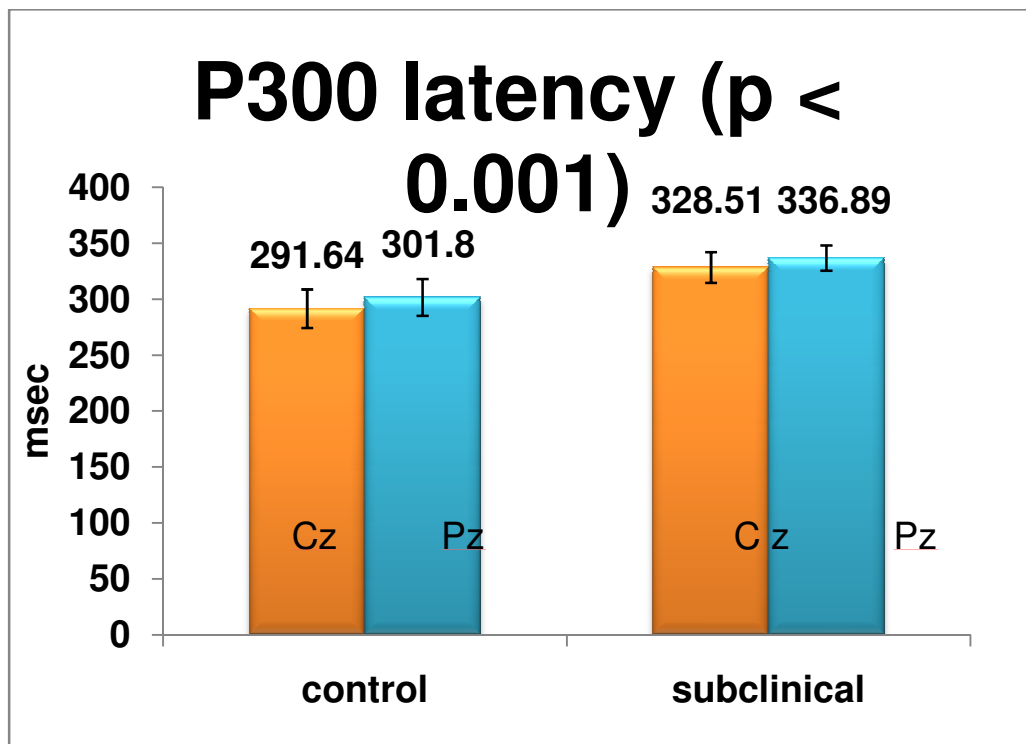
A decrease in the P300 amplitude at Cz and Pz was observed in the subclinical hypothyroid group when compared to the control group, but it was not statistically significant.(Table:2)

Table :2 Comparison of P300 wave amplitude (μ V)

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

The P 300 wave latency reflects the information processing, and it is strongly associated with short term memory⁷ In the present study, the subclinical hypothyroid group showed significant prolongation of P 300 wave latency when compared to the control group.(Fig:2)

Figure:2 P300 wave latency



DISCUSSION

The result of this study is in consistent with the findings of **Tutuncu et al⁸** and **Jensovsky et al⁹**. This shows working memory is most affected in subclinical hypothyroidism. This is similar to the findings of **Samuels et al¹⁰** who found that, the brain areas responsible for working memory are affected in experimentally induced subclinical hypothyroidism. The impairment of working memory in the subclinical hypothyroid patients is also supported by a functional MRI study done by **Zhu et al¹¹**.The impaired memory function in subclinical hypothyroidism in the present study is in line with the findings of **Del Ser Quijano¹²**, **Baldini et al¹³** and **Monzani et al¹⁴**. They all have employed various neuro psychological tests to assess the memory. **Jorde et al¹⁵** and **Kudrajavcev et al¹⁶** 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. **Baburhan et al¹⁷** has reported no changes in P 300 latency in subclinical hypothyroidism. This may be due to the low cut of value of TSH level (3.5mIU/L) to diagnose subclinical hypothyroidism. In the present study it was higher (5.5 mIU/L). The definition of subclinical hypothyroidism largely depends on the reference range of TSH. **Mahmoud et al¹⁸** observed no significant P300 wave prolongation in subclinical hypothyroidism. This may be because the study group consisted of patients already on thyroxine treatment, but in the present study, only newly diagnosed subclinical hypothyroid patients were included.

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. 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 al**¹⁹, 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.

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CONCLUSION

In the subclinical hypothyroid patients, there is definite impairment in the cognitive function, especially the short term memory as evidenced by the prolonged p300 wave latency in auditory event related 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 study can be extended to record P300 after attaining euthyroidism by supplementing L-thyroxine to subclinical hypothyroid patients and look for reversibility of P300 wave latency changes.

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