

Cognitive status in hypothyroid patients before and after attainment of euthyroid state: A prospective study at tertiary care centre

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Abstract

Background: Thyroid hormones have profound effects on the central nervous system and the consequences of overt hypothyroidism are well known. In contrast, there is less evidence regarding cognitive effects of subclinical hypothyroidism. **Objectives:** To study the association of cognitive function with subclinical hypothyroidism. **Methodology:** Total 56 participants who met the criteria for subclinical hypothyroidism included. Serum TSH, free T3 and free T4 were measured. Cognitive functions were assessed by using Folstein Mini Mental Examination MMSE (Mini Mental State Examination), DSST (Digit Symbol Substitution Test), LCT (Letter Cancellation Task), TMT tests (Trail making test). **Results:** Difference between serum FT3, FT4 and TSH levels of the patients at diagnosis and after treatment was found to be significant. The MMSE score, error hits of DSST and LCT were found significantly higher ($P < 0.001$) and negative correlation with TSH level and MMSE score. **Conclusions:** Prevalence of cognitive impairment was significantly higher in subclinical hypothyroidism as compared to controls.

Key Words: Hypothyroidism, MMSE, DSST.

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INTRODUCTION

Adequate thyroid function is essential for normal development and retention of cognitive function throughout life. The association between thyroid hormones and cognition has been recognized since the demonstration that cretinism stems from iodine and thyroid deficiencies. Low thyroid function at any age causes cognition to deteriorate because hypothyroidism prevents the brain from adequately sustaining the energy (glucose)-consuming processes needed for neurotransmission, memory, and other higher brain functions. Low brain uptake of glucose is commonly associated with deteriorating cognition^{1,2}.

Hypothyroidism is a common medical condition associated with low thyroid hormone levels and has a large number of physical and neurocognitive symptoms that may manifest across life based on when the disorder sets in.³ The important point is that many of these neurocognitive deficits may, in fact, be reversible with the correction of thyroid abnormalities.⁴ Clinical (or overt) hypothyroidism is characterized by high levels of TSH and low levels of T4 and T3. Hypothyroid patients demonstrate deficits in cognitive abilities such as attention, visual perception, memory, language, executive functions as well as depression^{5,6}. Severe hypothyroidism can cause symptoms similar to Alzheimer's disease (AD) such as memory loss, confusion, slowness, paranoid depression and, in extreme stages, hallucinations⁷. Even mild, or subclinical hypothyroidism (defined as elevated levels of TSH and normal levels of free T4) has been associated with cognitive and mood disturbances^{8,9}. Cognition is the mental activities involved in the acquisition, storage, retrieval and use of information¹⁰. Integration of a variety of processes and activities such as perception, imagery, memory, reasoning, problem solving, decision-making and language plays an important role in cognition. Cognition affects everyday

activities and has substantial importance to the population. Changes in cognition do impact efficiency of multiple operations such as working memory, attention, information processing etc¹¹. Attention is a basic cognitive mechanism by which a person can focus on relevant objects and ignore the irrelevant ones. It is of various types like selective attention, vigilance or divided attention¹². Various tests are used to measure the speed of information processing and specific cognitive domains like attention/concentration, executive functions, spatial working memory, visual attention, task switching etc. Among the psycho-physiological assessment of vigilance, paper pencil tests like the Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Letter Cancellation Task (LCT) and Trail making test (TMT) are well established (13,14). As they are paper-pencil based the advantage of these tests is that they can be administered bedside and persons with minimal literacy level can be tested easily with these tests. As most of our subjects were of lower literacy status we preferred to use these tests. Most of the earlier studies are done in western population with fewer numbers of subjects. In the present study, we evaluated the effect of hypothyroidism on cognitive functions in Indian population. Various neuropsychological tests are used and results compared after attainment of euthyroid state. Serum TSH levels were correlated with the performance of these tests.¹⁵

MATERIAL AND METHODS

28 newly diagnosed hypothyroid cases in the age group of 18-50 years were taken from MIMS Hospital, Nellimarla, Vizianagaram and 28 euthyroid controls were recruited for the study after taking written informed consent. Institute ethical committee approval was obtained. The cases and controls were age and sex matched. The subjects who were suffering from neuropsychiatric illness like depression using DSM IV criteria, or were on medications, especially anti-allergic etc., with a history of alcoholism or any other drug addiction, had a history of myocardial infarction, hypertension or diabetes mellitus were excluded. Thyroid function has been measured as serum concentrations of thyroid-stimulating hormone (TSH) or thyroid hormones (total or free thyroxine [T4], total or free tri-iodothyronine [T3], or T3 resin uptake). Most studies reported TSH, since it is very reproducible and is commonly believed to be the best marker of thyroid status, in combination with one or two thyroid hormones measurements¹⁶. Samples were sent to the central laboratory, MIMS hospital and patients were put on treatment according to reports. Patients followed up to their euthyroid state, which was again determined by thyroid tests. The patients and controls were made to abstain from nicotine and caffeine for at least 12 hours

before testing. Testing was done following a restful overnight sleep.

The following tests were done:

1. **Mini Mental State Examination (MMSE):** It is an eleven-question measure that tests cognitive functions: orientation, registration, attention, calculation, recall and language. Subjects with a score of <24 were not recruited for the study. The mean scores of the controls and cases were recorded and analyzed¹⁷.
2. **Digit symbol substitution test:** This is a test of visuomotor coordination, motor persistence, sustained attention and response speed. The task requires rapid information processing in order to substitute the symbols accurately and quickly. The test consists of numbers (1 to 9) arranged randomly in 4 rows of 25 squares each. The subjects were asked to substitute each number with a symbol using a number-symbol key given on each page. The time taken to complete the test along with the errors was noted¹⁸.
3. **Letter cancellation task:** Letter Cancellation Task is measure of sustained attention, concentration, visual scanning, and rapid response activation and inhibition¹⁹. One and Three Letter Cancellation Tasks were used to assess the effect of increasing complexity of task. In the One Letter Cancellation Task the subjects were asked to cancel out letter 'A'. The time taken to complete the task along with the error score was noted. In the Three Letter Cancellation Task, the subjects were asked to cancel out letter 'A', 'Q' and 'T'. The time for completion with the number of errors was noted.
4. **Trail making test parts A and B:** Trail Making is a timed test that measures complex visual scanning, motor speed, and cognitive flexibility²⁰. Trail Making Test consists of two parts each having 25 circles distributed over a sheet of paper. In part A the circles are numbered 1-25, and the patient was asked to draw lines to connect numbers in ascending order. In part B, the circles include both numbers (1-13) and letters (A-L); the patient draw lines to connect the circles in ascending pattern as in part A but with the added task of alternating between the numbers and letters. Time taken to complete the task including the time for correction of errors was noted. Testing of the patients was done before initiating treatment and after attainment of euthyroid state. The controls were tested twice at an interval of three months. Cognitive status of cases and controls were compared in both states. Serum TSH levels of hypothyroid patients were correlated with cognitive status.

Statistical Analysis: The data obtained was analyzed by SPSS version 25.0. Results were analyzed by Two way repeated measure ANOVA followed by Tukey's test. p value <0.05 was considered significant.

RESULTS

In this study the mean age of the cases was (32.67±9.40 years) and controls was (32.00±9.004 years) which had no statistical difference.

Table 1: Comparison of thyroid profile of cases before and after treatment

Thyroid Hormones	Before (Mean±SD)	After (Mean±SD)	p value
TSH levels (μIU/mL)	27.4±10.233	4.4±0.1952	<0.001
fT3 (pg/ml)	0.28±0.08	0.93±0.4	<0.001
fT4 (ng/dl)	0.26±0.10	1.08±0.39	<0.001

Difference between serum fT3, fT4 and TSH levels of the patients at diagnosis and after treatment was found to be significant.

Table 2: Comparison of MMSE score of cases and controls

Variables	Before (Mean±SD)	After (Mean±SD)	p value
Cases	30.52±0.681	30.73±0.44	0.012
Controls	30.95±0.185	30.95±0.185	
Significance (Tukey's test)	Significant	Significant	

Euthyroid state was achieved after 3 months of treatment with thyroxine. The MMSE (Table II) scores were found to be significantly impaired in cases in comparison to controls at the start of treatment.

Table 3: Comparison of reaction time in cases and controls (in seconds)

Test		Before (Mean±SD)	After (Mean±SD)	p value
DSST	Cases	241.07±65.5	220.70±64.7	<0.05
	Controls	225.43±37.1	224.13±35.5	
One Letter Cancellation Task	Cases	262.17±30.8	244.93±31.9	<0.001
	Controls	252.33±34.1	253.47±36.7	
Three Letter Cancellation Task	Cases	292.1±30.4	280.30±30.5	<0.001
	Controls	276.70±54.6	278.87±53.5	
Trail Making Test part A	Cases	87.5±14.9	82.20±13.3	<0.001
	Controls	82.13±13.7	81.43±11.2	
Trail Making Test part B	Cases	103.6±22.9	96.7±16.3	<0.001
	Controls	98.57±9.1	98.57±9.1	

No significant difference in the reaction time of DSST, LCT, TMT A and TMT B between cases and controls was found. Difference in reaction time of cases and controls for Digit Symbol Substitution Test (Table III) was not found to be statistically significant (P=0.249). But, the attainment of euthyroid state led to a significant improvement when compared to the pre-treatment state.

Table 4: Comparison of error hits in cases and controls

Tests		Before (Mean±SD)	After (Mean±SD)	p value
DSST	Cases	1.63±1.05	0.80±.9	<0.001
	Controls	0.31±.535	0.31±.484	
One Letter Cancellation Task	Cases	1.80±.92	0.93±.81	<0.001
	Controls	0.21±.484	0.21±.407	
Three Letter Cancellation Task Cases	Cases	1.79±1.08	0.75±.65	<0.001
	Controls	0.24±.51	0.21±.41	

Significantly higher (P<0.001) error hits of DSST and LCT were seen in cases in comparison to controls in both states (before and after). The error hits (Table IV) on DSST were higher in cases before treatment in comparison to controls (P<0.001) and the difference was significant. Significant improvement was found in error hits after treatment (P<0.001). There was a significant improvement in reaction time and error hits of cases on One Letter Cancellation Task (Table III) after treatment in comparison to pretreatment state. The reaction time between cases and controls was not significant for error hits (Table IV) was significant (P<0.001) in both states. The reaction time on Three Letter Cancellation Task (Table III) was not significant. There was significant improvement (P<0.001) after treatment in cases. The error hits (Table IV)

were significantly higher in cases (before and after treatment). There was significant improvement in cases for response time of Trail Making Test A ($P < 0.001$) and Trail Making Test B ($P < 0.001$) after treatment when compared to pretreatment state.

Table 5: Correlation between Cognitive measures and serum TSH levels of patients

Cognitive measures	TSH	
	Coefficient	P value
Mini Mental State Examination	-0.74	0.000
Digit Symbol Substitution Test	0.54	0.001
One letter cancellation Task	0.68	0.000
Three letter cancellation Task	0.68	0.000
Trail Making Test A	0.78	0.000
Trail Making Test B	0.92	0.000

Negative correlation (correlation coefficient = -0.74) with serum TSH levels and MMSE score. Reaction time of DSST, One Letter Cancellation Task, Three Letter Cancellation Task, Trail Making Test A and Trail Making Test B showed a positive correlation with serum TSH levels (Table 5) in this study.

DISCUSSION

In this study with we compared cognitive status of 28 hypothyroid patients with age and sex matched 28 controls. also assessed cognitive status of hypothyroid patients before and after treatment. Various tests like Mini Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Letter Cancellation Task (LCT) and Trail making test (TMT) were used for assessment of cognition in cases and controls. We in our study found statistically significantly impaired MMSE score in overt hypothyroid cases. Similar results were seen in study by Wekking EM *et al*²³ clinical hypothyroidism found neuropsychological changes in global cognitive functioning by using LCT and MMSE score. Bajaj S *et al*²⁴ also found MMSE score significant in their cross sectional study on 103 elderly participants. Contrast results regarding MMSE score in subclinical hypothyroidism was seen in de Jongh *et al*²⁵ and Formiga *et al*²⁶ who did not found impaired score. While study done by Gussekloo *et al*²⁷, an association was found between low fT3 levels and decreased global functioning by using MMSE score. Bajaj S *et al*²⁴ found significance in TSH level when compared between two groups, similar was seen in our study. While at the same time they did not find any correlation of MMSE with serum levels of TSH or fT4 which was similar with our study. Few Studies which used MMSE cognitive screening test have reported clinically significant impairments which was refractory to treatment in patients with hypothyroidism.^{28,29} Roberts LM *et al*³⁰, said one of the key factors in clinical populations is the need for endocrinologists, psychiatrists and psychologists to be on the same page when examining patients with hypothyroidism and giving every patient a thorough evaluation. We can say that there is also a need for cognitive evaluation and home-based cognitive rehabilitation techniques being used in adults with hypothyroidism.

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