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Original Article

Cognitive Status in Hypothyroid Patients Before & After Attainment of Euthyroid State

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Abstract

Thyroid hormones play a significant role in adult brain function. Cognition affects everyday activities and has substantial importance to the population. In this case control study we evaluated cognition in hypothyroid patients compared to euthyroid controls and their response after treatment. Various neuropsychological tests: Mini Mental State Examination, Digit Symbol Substitution Test, Letter Cancellation Task and Trail Making Test, were used to assess cognitive status of 30 newly diagnosed hypothyroid patients and compared with euthyroid controls. Tests were repeated in hypothyroid patients after the attainment of euthyroid state and in euthyroid controls at an interval of three months. We also measured the correlation between cognitive status and serum TSH levels of hypothyroid patients. Cognitive measures for attention/concentration, information processing and executive function were impaired in hypothyroid patients in pretreatment state and significant improvement was found after the attainment of euthyroid state suggesting that thyroxine therapy restores cognition.

Introduction

Cognition is the mental activities involved in the acquisition, storage, retrieval and use of information (1). 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 etc (2). 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 attention (3). Inability to focus attention on the task at hand results in inability to cope with the environment.

Amongst the other important biological processes, thyroid hormone is an important neuroregulator in fetal development of the central nervous system, and

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plays an important role after development as well. Hypothyroidism is a well-known reversible factor causing cognitive impairment, including dementia (4). Some theories suggest that the neuropsychiatric symptoms are related to changes in the brain secondary to multiple factors, including the direct effects of thyroid disease, as well as hormone deprivation in brain tissue. Hypothyroidism impacts aspects of cognitive functioning and mood. The degree by which hypothyroidism does correlates to the symptoms remains controversial (4). There remains a debate about which parameters will be predictive of cognitive decline. There have been conflicting reports about the correlation of cognition with TSH (5, 6). Improvement or complete resolution of associated neuropsychological symptoms by adequate treatment of the thyroid disorder has been reported (7-9).

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 (10, 11). 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.

Materials and Methods

Thirty newly diagnosed hypothyroid cases in the age group of 18-50 years were taken from thyroid clinic, GTB Hospital, Delhi and thirty euthyroid controls were recruited for the study after taking written informed consent. 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, or who were illiterate or had less than 5 years of schooling were excluded from the study.

The estimation of serum levels of free T_3 (fT3), free T_4 (fT_4) and Thyroid stimulating hormone (TSH) of the patients and controls were done in the Endocrine and Metabolic laboratory of Guru Teg Bahadur Hospital, Delhi by using Radioimmunoassay (RIA) kit from Immunotech Bechmancoulter. Ethical clearance was taken from the Institutional Ethical committee for the study. The patients were then started on treatment and were asked for a follow up when they had attained euthyroid status after three months of treatment as evident by changes in the levels of hormones (Table I).

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

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 analyzed (12).

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 noted (13).

Letter cancellation task:

Letter Cancellation Task is measure of sustained attention, concentration, visual scanning, and rapid response activation and inhibition (14). 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.

Trail making test parts A & B:

Trail Making is a timed test that measures complex visual scanning, motor speed, and cognitive flexibility (15). 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 Abut 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 20.0. Results were analyzed by Two way repeated measure ANOVA followed by Tukey's test. p value <0.05 was considered significant.

Results

The mean age of the cases (31.67±8.40 years) and controls (31.00±8.004 years) had no statistical difference. We found significant difference in the serum fT3, fT4 and TSH levels of the patients at diagnosis when compared to the levels post treatment after 3 months ($p<0.01$) (Table I). All patients were found to be euthyroid after 3 months of treatment with thyroxine.

As expected, the MMSE (Table II) showed significant impairment in scores of cases ($P<0.001$) in

TABLE I: Thyroid profile of cases before and after treatment.

	Before (Mean±SD)	*After (Mean±SD)*	*p value (F test)*	*Significance (Tukey's test)*
TSH levels (µIu/mL)	26.43±10.244	3.4863±0.1963	<0.001	Significant
fT_3 (pg/ml)	0.2980±.09408	1.93±0.5690	<0.001	Significant
fT_4(ng/dl)	0.2736±0.0973	1.8986±0.2853	<0.001	Significant

(p value <0.05 is significant)

TABLE II: MMSE score of cases and controls.

	Before (Mean±SD)		*After (Mean±SD)*	*p value (F test)*	*Significance (Tukey's test)*
Cases	29.53±0.681		29.73±0.450	0.012	Significant
Controls	29.97±0.183		29.97±0.183		Not Significant
p value (F test)		0.012			
Significance (Tukey's test)	Significant		Significant		

(p value <0.05 is significant)

comparison to controls at the start of treatment. But there was significant improvement (P<0.001) after treatment on attainment of euthyroid state. Though the difference in reaction time of cases and controls for Digit Symbol Substitution Test (Table III) was not statistically significant (P=0.249). However, the attainment of euthyroid state led to a significant improvement (P=0.015) in comparison to the pre-treatment state. 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).

The cases showed a significant improvement in reaction time (P<0.001) and error hits (P<0.001) on One Letter Cancellation Task (Table III) after treatment in comparison to pretreatment state. But the difference for reaction time between cases and controls was not significant (P=0.234) and for error hits (Table IV) was significant (P<0.001) in both states. The reaction time on Three Letter Cancellation Task (Table III) was also more in cases in comparison to controls but the difference was not significant (P=0.597). The cases showed a significant improvement (P<0.001) after treatment. The error hits (Table IV) were higher in cases (before and after treatment) in comparison to controls (P<0.001). Significant improvement was found in error hits of cases (P<0.001) after treatment.

Cases showed a significant improvement in response time of Trail Making Test A (P<0.001) and Trail Making Test B (P<0.001) after treatment in comparison to pretreatment state.

MMSE score showed a negative correlation (correlation coefficient = –0.755) with serum TSH levels. 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 V).

TABLE III: Reaction time in cases and controls (in seconds).

		Before (Mean±SD)	*After (Mean±SD)*	*P value (F test)*	*Significance (Tukey's test)*
DSST	Cases	239.07±63.425	218.70±62.625	0.015	Significant
	Controls	223.43±36.938	222.13±34.483		Not Significant
One Letter Cancellation Task	Cases	261.17±29.813	242.93±30.908	<0.001	Significant
	Controls	250.33±34.004	251.47±36.630		Not Significant
Three Letter Cancellation Task	Cases	291.1±29.463	279.30±29.573	<0.001	Significant
	Controls	275.70±53.607	277.87±52.433		Not Significant
Trail Making Test part A	Cases	86.5±13.985	81.20±12.380	<0.001	Significant
	Controls	83.13±14.897	82.43±12.353		Not Significant
Trail Making Test part B	Cases	102.53±23.948	95.67±17.373	<0.001	Significant
	Controls	97.57±10.150	97.60±12.025		Not Significant

No significant difference in the reaction time of DSST, LCT, TMT A & TMT B between cases and controls was found.

TABLE IV: Error hits in cases and controls.

		Before (Mean±SD)	*After (Mean±SD)*	*P value (F test)*	*Significance (Tukey's test)*
DSST	Cases	1.73±1.048	0.90±.803	<0.001	Significant
	Controls	0.30±.535	0.30±.484		Not Significant
One Letter Cancellation Task	Cases	1.77±.935	0.90±.803	<0.001	Significant
	Controls	0.20±.484	0.20±.407		Not Significant
Three Letter Cancellation Task	Cases	1.77±1.073	0.73±.640	<0.001	Significant
	Controls	0.23±.504	0.20±.407		Not Significant

The error hits of DSST & LCT were significantly higher (P<0.001) in cases in comparison to controls in both states (before & after).

TABLE V : Correlation between Cognitive measures and serum TSH levels of patients.

Cognitive measures	*TSH*	
	Coefficient	*P value*
Mini Mental State Examination	–0.755*	0.000
Digit Symbol Substitution Test	0.559*	0.001
One letter cancellation Task	0.699*	0.000
Three letter cancellation Task	0.697*	0.000
Trail Making Test A	0.794*	0.000
Trail Making Test B	0.923*	0.000

Pearson correlation is significant at the 0.01 level.

Discussion

In the present Case Control study we compared cognitive status of hypothyroid patients with age and sex matched controls and also assessed cognitive status of hypothyroid patients before and after treatment. 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.

We found statistically significant impaired MMSE score in overt hypothyroid patients. Studies by Baldini et al (16) and Bono et al (17) on subjects with subclinical hypothyroidism also found neuropsychological changes in global cognitive functioning by using MMSE score while de Jongh et al (18) & Formiga et al (19) did not found impaired MMSE score in subclinical hypothyroidism.

In a follow up study by Gussekloo et al (20), an association was found between low fT_3 levels and decreased global functioning by using MMSE score in an unselected general population of 558 individuals aged 85 years. However there was no correlation of MMSE found with serum levels of TSH or fT4 in their study**.** Our study as well found a negative correlation of MMSE score with serum TSH levels in hypothyroid patients.

Studies that used MMSE as a general-purpose cognitive screening test have reported clinically significant impairments that were refractory to treatment in patients with hypothyroidism (21, 22) Correia et al (23) studied the cognitive functions in normal, hypothyroid and subclinical hypothyroid patients and reported specific cognitive deficits rather than a general decrease in cognitive performance. They found deficits in visuospatial, verbal, and associative memory before levothyroxine treatment. After 6 months of therapy, patients with overt hypothyroidism showed improvement unlike subclinical hypothyroid patients. Our findings are also consistent with their findings.

Jorde et al (24) used a battery of tests in a population study to assess attention, visual and verbal memory, intelligence and executive functions. Our findings of no significant difference in reaction time in DSST between cases and controls are in line with findings of Jorde et al (24).

The case group in their study was subclinical hypothyroid patients, defined as patients with elevated serum TSH level with serum fT_4 and fT_3 levels within the normal range and no overt symptoms of hypothyroidism, in contrast to overt hypothyroid patients in our study.

We found statistically significant post treatment improvement in reaction time & error hits of DSST in comparison to pretreatment state.

In hypothyroid patients we found increased reaction time in Three Letter Cancellation Tasks in comparison to that in One Letter Cancellation Tasks suggesting that processing of attention load was hampered during hypothyroidism. Restoration of euthyroid state led to functional normalcy as revealed by significant decrease in reaction time and error hits in One and Three Letter Cancellation Tasks. In a recent study by Samuel et al on women receiving TSH suppressive or replacement LT-4 doses did not show affect on memory & executive functions (Letter Cancellation Task & Trail Making Test) compared to healthy controls (25).

We found positive correlation in TMT A & TMT B with serum TSH levels in our study. Baldini et al (16) and Bono et al (17) also reported an association between subclinical hypothyroidism and neuropsychological changes with regard to logical

memory, attention, global cognitive functioning and some executive functions by using MMSE and TMT A & TMT B.

For cognitive flexibility/executive function, Jorde et al (24) also used the Trail Making Test part A and part B but they did not found any difference between patient with subclinical hypothyroidism and euthyroid individuals.

Our study shows that time taken to complete Trail Making test- B was more than in Trail Making Test-A, suggests that processing of additional information is affected more in hypothyroidism since Trail Making Test-B involves an additional attention load.

Our finding of post treatment significant improvement in performance of Trail Making Test in hypothyroid patients are in line with Osterweil et al (21) who reported an improvement using TMT part A and Symbol Digit Modalities Test (SDMT) after therapy for eight months in hypothyroid patients. Similar improvement in attention using TMT parts A have been also reported by Capet et al (26).

Contrary to our finding, Miller et al (27) and Schraml et al (28) found no improvement in attention and executive function in overt hypothyroid patients even after treatment by using TMT part A and TMT part B as a cognitive test. Similarly Whybrow et al (6) found no change in attention by using TMT part A and part B after 10.5 months of treatment in hypothyroid patients. Their results demonstrated that when the hypothyroidism was long standing, organic brain impairment persisted after thyroid replacement therapy. In a recent study by Parsaik et al (29) they found no significant association between MCI & clinical or subclinical hypothyroidism using TMT B & DSST in elderly persons.

Former studies (6, 24, 27) reveal that severity and duration of hypothyroidism are also determining factors in cognitive assessment in hypothyroid patients.

In the present study, we assessed the cognitive status in newly diagnosed overt hypothyroid patients and euthyroid controls. We found an overall improved performance in hypothyroid patients after treatment. The improvement was in various domains of cognition including global cognition, attention, concentration, visuospatial organization, executive function and psychomotor speed. Our findings are consistent with previous reports (21, 23, 26) that thyroxine therapy appears to restore cognitive functions in hypothyroid patients.

Conflicting findings in different studies potentially reflect differences in the age of the populations studied, differing degrees of severity of subclinical hypothyroidism, differing degree of response to therapy with irreversible changes in cognitive functions in chronic versus newly diagnosed cases of hypothyroidism and a lack of uniformity in administered cognitive tests.

The current study concludes that there is a significant reduction in cognitive skills with hypothyroidism but treatment does have significant effect on restoration of cognitive functions. This reduction in cognition is best correlated with TSH values in comparison to T3 and T4.

Conflict of Interest

None

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