

A study of cognitive dysfunctions in patients with thyroid disorders

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Abstract

Background: Many primary endocrine disorders have notable effects on cognition. Patients with a wide range of thyroid gland abnormalities often present with combined emotional and cognitive symptoms. **Aims and Objectives:** To evaluate the cognitive dysfunctions in patients suffering with thyroid disorders. To compare the cognitive dysfunctions in patients with thyroid disorders such as hypothyroidism, hyperthyroidism and subclinical thyroid states. **Materials and Methods:** A Purposive sampling was undertaken from the outpatient department of Endocrinology, Narayana Medical College & Hospital, Nellore, Andhra Pradesh. The study included the patients with thyroid disorders and Normal healthy controls. The sample of the study comprised of 60 participants. Out of this 60 participants 30 were diagnosed with thyroid disorders and 30 volunteers who accompanied with patients without evidence of any thyroid disorders who were willing to participate in the study were selected as controls. **Results:** The mean SMMSE scores among the cases was 19.4 (\pm 4.65) and among the controls was 28.1 (\pm 1.67). The DSST scoring of the cases and controls had shown that the mean 68.1 (\pm 19.4) and controls was 95.3 (\pm 3.94). The mean (\pm SD) TMT - A scores of the cases was 25.8 (\pm 6.23) and controls was 20.5 (\pm 2.58). The mean TMT – B scores of the cases was 114.8 (\pm 51.03) and controls was 68.9 (\pm 19.2). **Summary & Conclusions:** The means of SMMSE, DSST, TMT – A, TMT – B scores have shown statistically significant difference between the patients with thyroid disorders and normal healthy controls.

Key words: Hypothyroidism, Cognition, Hyper thyroidism, Attention / concentration, Executive functions.

Introduction

Thyroid disorders are the commonest among the endocrine disorders worldwide [1]. It has been estimated that about 42 million people in India are suffering from thyroid diseases. Among them hypothyroidism is most common, and at least one in every 10 persons in India is suffering from it [2]. Thyroid function disorders are common, with a female: male ratio of 4:1[3].

Patients with a wide range of thyroid gland abnormalities often present with combined emotional and cognitive symptoms [4]. Occurrence of psychological and cognitive changes in patients

with altered thyroid function has been known for many years. There are many reports first described hypothyroid and hyperthyroid patients with wide range of mental disturbances [5,6]. Hypothyroidism together with iodine deficiency have been considered to a principal determinant of cognitive development.

Cross-sectional studies report decrements in general intelligence, as well as attention/ concentration, memory, perceptual function, language, psychomotor function, and executive function. Memory is the most consistently affected domain. Recent studies using sensitive, specific tests documented a specific deficit in verbal memory [7,8].

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Functional imaging studies (fmri) provide objective evidence that brain function is altered in hypothyroid patients, with decreased cerebral blood flow, function globally and in regions that mediate attention, visuospatial processing, working memory, and motor speed [9,10].

The onset of primary clinical hypothyroidism in adults has a variety of adverse effects on adaptive neurocognitive functioning [11,12]. Hypothyroidism can affect a wide range of cognitive domains, which includes sustained and selective visual attention, speed of visual information processing, abstract concept of formation and complex problem solving abilities, academic achievement skills, tactile perception and praxis/motor functions in patients with thyroid gland hypofunction [13,14,15]. But there is paucity of extent of research, most of the published reports on neuropsychological functioning in adults with hypothyroidism are based on the assessment of only limited aspects of cognitive domains [11,12].

Hyperthyroid patients commonly present a variety of cognitive function deficits, although of a lesser degree than in hypothyroid patients [16]. The most common cognitive deficits observed in hyperthyroid patients include poorer performance on tests of attention, memory, mental alertness and visuomotor speed.

In a study done by Asmus Vogel et al reported that acute phase of Grave's thyrotoxicosis patients often have subjective cognitive complaints. After reaching euthyroidism the level of affective symptoms including reports of cognitive deficits had decreased significantly [17].

Cognitive impairments associated with thyroid gland dysfunction are often overlooked by clinicians when patients do not overtly complain of changes in their neurocognitive status. The early recognition of conditions such as depression, dementia, and other neuropsychiatric abnormalities known to be associated with hypothyroidism are almost exclusively dependent on the routine and systematic assessment of cognition [18].

Materials and Methods

A. Type of Study- A case control study was undertaken in order to achieve the aim and objectives.

B. Source of the data: The participants of this study were recruited from the outpatient department of Endocrinology, Narayana Medical College & Hospital, Nellore, Andhra Pradesh.

The study included the patients with thyroid disorders and Normal healthy controls.

A. Duration of the study- The data for this study has been collected from January, 2017 to June, 2017 for a period of half year.

B. Sample of the study- The sample of the study comprised of 60 participants attending the outpatient department of Endocrinology, Narayana Medical College & Hospital, Nellore. Out of these 60 participants 30 were diagnosed with thyroid disorders by endocrinologist were recruited into the study. About 30 volunteers who accompanied with patients without evidence of any thyroid disorders who were willing to participate in the study were selected as controls. The clearance from Institutional Ethics committee was obtained before the study was started. All the cases and controls were obtained an informed, bilingual and written consent before they were included in to the study.

A. Type of sampling- Purposive sampling

B. Inclusion Criteria for Cases

1. Age 18-60 years
2. Both male and female.
3. Patients diagnosed to have thyroid disorders by endocrinologist.
4. Patients who are willing to give consent to participate in the study.

Inclusion Criteria for Controls

1. Age 18-60years,
2. Both male and female.
3. Participants who are healthy, with no history of thyroid abnormalities.
4. Patients who are willing to give consent to participate in the study.

Exclusion Criteria for Cases

1. Age less than 18 years
2. Age greater than 60 years.
3. Patients with any history of neurocognitive or neurological or
4. Neuro developmental disorders or head injuries.

5. Patients diagnosed with any other psychiatric disorders, mental retardation and any substance use disorders.
6. Patients with other medical co morbidities.
7. Patients with family history of cognitive dysfunction in 1st degree relatives.
8. Patients with poor communicative skills.
9. Patients who are not willing to give consent for participating in the study.

Exclusion Criteria for Controls

1. Age less than 18 years
2. Age greater than 60 years.
3. Participants with any history of neurocognitive or neurological or neurodevelopmental disorders or head injuries.
4. Patients diagnosed with any psychiatric disorder, mental retardation and any substance use disorders.
5. Participants with medical co morbidities.
6. Patients with family history of cognitive dysfunction in 1st degree relatives.
7. Participants with poor communicative skills.
8. Participants who are not willing to give consent to participate in the study.

Instruments used

1. Standardized MMSE (SMMSE)[19].
2. Trial making test- A& B[20].
3. Digit symbol substitution test (DSST)[21].

Method for data collection: The cases who were diagnosed to have thyroid disorders by the endocrinologist attending the Outpatient department of Endocrinology were included as cases. About 30 volunteers who are accompanying with patients without evidence of any thyroid disorders who were willing to participate in the study were selected as controls. The cognitive functions of both cases and controls were assessed by using Standardized Mini Mental Status Examination (SMMSE), Digit Symbol Substitution Test (DSST) and Trial Making Test – A & B

Description of the Instruments

Standardized mini mental status examination (SMMSE) [19]: Dr. Marshall Folste in first published the Mini-Mental State Examination (MMSE) in 1975. The Mini-Mental State Examination (MMSE) is a widely used screening test for cognitive impairment in older adults.

Because the guidelines for its application are brief, the administration and scoring of the test can vary between different individuals. The goal of the Standardized Mini-Mental State Examination (SMMSE) was to impose strict guidelines for administration and scoring to improve the reliability of the instrument. It is almost like a MMSE with time restrictions. It consists of 12 questions. It provides a global score of cognitive ability that correlates with function in activities of daily living.

The Standardized Mini-Mental State Examination (SMMSE) measures various domains of cognitive function including orientation to time and place; registration; concentration; short-term recall; naming familiar items; repeating a common expression; and the ability to read and follow written instructions, write a sentence, construct a diagram, and follow a three step verbal command. A total score = 30 indicates no impairment, 26-30 = normal in the general population, 20-25 = mild cognitive impairment, 10-20 = moderate, 0-9 = severe cognitive impairment.

Digit symbol substitution test (DSST)[20]: Digit symbol substitution test is a neuropsychological test sensitive to brain damage. This is a subtest from the corpus of intelligence tests authored by David Wechsler. The DSST contained in the Wechsler Adult Intelligence Scale is called 'Digit Symbol' (WAIS-R), 'Digit-Symbol-Coding' (WAIS-III), or most recently, 'Coding' (WAIS-IV). Since Wechsler's publication of the Bellevue Intelligence Scale (BIS; Wechsler, 1939), the basic format and concept of this test has changed very little. The test is timed. Various versions from the Wechsler corpus allow 90 or 120 s. The test requires the examinee to transcribe a unique geometric symbol with its corresponding Arabic number. The examinee is initially shown a key containing the numbers from 1 to 9. Under each number there is a corresponding geometric symbol. The examinee is then shown a series of boxes containing numbers in the top boxes, and blank boxes below them. After a short practice trial, they are then asked to copy the corresponding geometric symbol under each number. The raw score is the number of correct items completed within the prescribed time limit. The most obvious application of digit symbol substitution is to measure memory. The test requires memory to remember where each

symbol matches a digit. There is also a speed of processing component, since very small amount of time is given to enter the correct symbol.

Trail making tests [21]: Introduced by Partington & Leiter in 1949. It consists of two parts in which the subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. It can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It consists of two parts- A & B. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); and the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). Part A is used primarily to examine cognitive processing speed and part B, is used to examine executive functioning. The time taken to complete the test is used as the primary performance metric.

Statistical Analysis: The data was entered in to an excel sheet, then transferred and analysed using IBM SPSS Version 20.0. The values were

represented as frequencies and proportions for the categorical variables. Chi square test and Fischer's exact test were used as test of association. For the Quantitative variables, the values were represented by measures of central tendency and dispersion. Student t test was used as test of significance. A Pearson correlation test was used between the scores. A p value of less than 0.05 is considered as statistically significant.

Ethical considerations

- A informed, written and bilingual consent was obtained from the participants in the study.
- Participation in the study was voluntary and they had given the right to withdraw from the study at any point of time.
- Confidentiality and anonymity of the participants was assured and maintained.
- There was no direct benefit to the patients for participation in the study.
- Participants who were identified to have significant distress were offered appropriate help.
- The study has been approved by the ethical committee of Narayana Medical College and Hospital.

Results

Table-1: Distribution of the study groups according to the age group.

Age group	Cases n (%)	Controls n (%)
21 – 30 years	0	1 (3.3)
31 – 40 years	19 (63.3)	11 (36.7)
41 – 50 years	9 (30.0)	12 (40.0)
51 – 60 years	2 (6.7)	6 (20.0)
Total	30 (100)	30 (100)

χ^2 Value= 5.562 df=3 p value> 0.05, Not significant

Table 1 shows the distribution of the study group according to the age group. About 63.3% of the cases belonged to 31 – 40 years of age group, 30% belonged to 41 – 50 years age group and 6.7% belonged to 51 – 60 years of age group. Among the controls, 3.3% belonged to 21 – 30 of age group, 36.7% belonged to 31 – 40 years of age group, 40% belonged to 41 – 50 years of age group and 20% belonged to 51 – 60 years of age group.

Table-2: Distribution of the study groups according to the sex

Sex	Cases n (%)	Controls n (%)
Male	9 (30.0)	10 (33.3)
Female	21 (70.0)	20 (66.7)
Total	30 (100)	30 (100)

χ^2 Value= 0.077 df=1 p value> 0.05, Not significant

In table 2 details of the cases and controls are described among the sample of cases about 30% of the cases were males and 70% were females. Among the controls 33.3% were males and 66.7% were females. There was no statistically significant difference between the sex of cases and controls.

Table-3: Distribution of the study groups according to the SMMSE scores.

SMMSE	Cases	Controls	T value	P value, Sig
Mean \pm SD	19.4 \pm 4.65	28.1 \pm 1.67	9.645	<0.001, HS

In table 3, The mean SMMSE scores among the cases was 19.4 (\pm 4.65) and among the controls was 28.1 (\pm 1.67). There was a statistically significant difference between the SMMSE scores of the cases and controls.

Table-4: Distribution of the study groups according to the DSST scores.

DSST	Cases	Controls	T value	P value, Sig
Mean \pm SD	68.1 \pm 19.4	95.3 \pm 3.94	7.524	<0.001, HS

The DSST scoring of the cases and controls had shown that the mean 68.1 (\pm 19.4) and controls was 95.3 (\pm 3.94). There was a statistically significant difference between the DSST scores of the cases and controls.

Table-5: Distribution of the study groups according to the TMT – A scores

TMT – A	Cases	Controls	T value	P value, Sig
Mean \pm SD	25.8 \pm 6.23	20.5 \pm 2.58	4.327	<0.001, HS

The mean (\pm SD) TMT - A scores of the cases was 25.8 (\pm 6.23) and controls was 20.5 (\pm 2.58). There was a statistically significant difference between the TMT – A scores of the cases and controls. The mean (\pm SD) TMT – A errors of the cases was 0.87 (\pm 0.73) and mean (\pm SD) score of controls was 0.9 (\pm 0.556). This difference in mean TMT – A scores was not statistically significant between the cases and controls.

Table-6: Distribution of the study groups according to the TMT – B scores.

TMT – B	Cases	Controls	T value	P value, Sig
Mean \pm SD	114.8 \pm 51.03	68.9 \pm 19.2	4.608	<0.001, HS

The mean TMT – B scores of the cases was 114.8 (\pm 51.03) and controls was 68.9 (\pm 19.2). There was a statistically significant difference in TMT – B scores of the cases and controls. The mean (\pm SD) TMT – B errors among the cases was 4.77 (\pm 2.49) and controls was 3.57 (\pm 1.22) among the controls. There was a statistically significant difference between the TMT – B scores of the cases and controls.

Table-7: Comparison of thyroid disorders with cognition scores among the study groups.

Test	SMMSE Mean \pm SD	DSST Mean \pm SD	TMT - A Mean \pm SD	TMT – B Mean \pm SD
Hyperthyroidism	19.2 \pm 5.03	69.5 \pm 19.51	25.1 \pm 6.19	127.1 \pm 56.32
Hypothyroidism	18.9 \pm 4.47	62.5 \pm 21.97	27.07 \pm 6.94	106.3 \pm 45.76
Subclinical hypothyroidism	18.3 \pm 5.77	77.67 \pm 3.78	25.67 \pm 5.69	119.3 \pm 61.85
Subclinical hyperthyroidism	23.67 \pm 2.3	80.0 \pm 4.0	22.7 \pm 4.16	109.0 \pm 68.56
F value	31.343	22.367	6.867	7.604
P value, Sig	0.000, Sig	0.000, Sig	0.001, Sig	0.000, Sig

Among the normal scoring, 66.7% had hyperthyroidism and 33.3% had hypothyroidism. Among the very mild scoring, all had hypothyroidism. Among the mild scoring, 30.8% had hyperthyroidism, 30.8% had hypothyroidism, 15.4% had subclinical hypothyroidism and 23.1% had subclinical hyperthyroidism. Among the moderate scoring, 36.4% had hyperthyroidism, 54.5% had hypothyroidism and 9.1% had subclinical hypothyroidism.

The mean SMMSE scores among the hyperthyroidism cases was 19.2, hypothyroidism cases were 18.9, sub clinical hypothyroidism was 18.3 and subclinical hyperthyroidism was 23.67. This difference in mean SMMSE scores was statistically significant. The mean DSST scores among the hyperthyroidism cases was 69.5, hypothyroidism cases were 62.5, sub clinical hypothyroidism was 77.67 and subclinical hyperthyroidism was 80. This difference in DSST was statistically significant between the different cases. The mean TMT – A scores among the hyperthyroidism was 25.1, hyperthyroidism was 27.07, subclinical hypothyroidism was 25.67 and subclinical hyperthyroidism was 22.7. There was a statistically significant difference between the TMT – A scores of the patients with thyroid disorders. The mean TMT – B scores among the patients with hyperthyroidism was 127.1, the mean hyperthyroidism was 106.3, subclinical hypothyroidism was 119.3 and subclinical hyperthyroidism was 109.0. This difference in TMT – B scores was statistically significant between the patients with thyroid disorders.

Discussion

A case control study was undertaken in order to achieve the aim and objectives. The participants of this study were recruited from the outpatient department of endocrinology, Narayana Medical College & Hospital, Nellore, Andhra Pradesh. The study included the patients with thyroid disorders and normal healthy controls. The sample of the study comprised of 60 participants. Out of this 60 participants, 30 participants were diagnosed with thyroid disorders by endocrinologist were recruited in to the study. 30 patient attendants without evidence of any thyroid disorders who were willing to participate in the study were selected as controls. Cases and controls were administered with Standardized Mini Mental Status Examination (SMMSE), Digit Symbol Substitution Test (DSST) and Trail Making Test A & B in order to assess the cognitive dysfunction among the cases and controls.

In the present study, the mean SMMSE scores among the cases was 19.4 (\pm 4.65) and among the controls was 28.1 (\pm 1.67). There was a statistically significant difference between the SMMSE scores of the cases and controls. In a study by Osterweil et al, the mean SMMSE among the hypothyroid cases was 26.1 and 28.7 among the euthyroid controls.

Hypothyroid patients showed significantly lower scores on the Mini-Mental Status examination (MMSE) and on five of 14 neuropsychological tests as compared to controls. The lower levels of SMMSE score in this study compared to Osterweil

study may be due to change in the settings of the study and other factors such as increased duration of thyroid diseases among the patients [22]. In a study by Mennemeir et al, the MMSE by itself was sensitive in differentiating hypothyroid patients with cognitive deficits from controls, while electrophysiological measures did not generally differentiate the hypothyroid patients from normal controls. The MMSE was not sensitive to treatment effects, but treatment was associated with significant improvements in three of the most sensitive measures of cognitive dysfunction [23].

A decrease in verbal fluency was noted in the study of Manciet et al in a population sample of 425 individuals (65–85 years old or older) comprising 89.7% euthyroid subjects, 4.2% with subclinical hypothyroidism, 1.9% with clinical hypothyroidism, and 4.2% with hyperthyroidism [24].

Bono et al also examined the improvement of cognitive functions by using TMT – A & B instrument and noted slight but significant improvement of verbal fluency in 36 women with subclinical hypothyroidism after 6 months treatment with L-thyroxine but this showed no correlation with TSH changes after treatment [25].

In a study in China among elderly persons with thyroid disorders, the mean MMSE score was 28.0 among normal controls, mild cognitive impairment was 26.1 and with Alzheimer's disease was 23.4 which was higher than this study. This China study

also had higher scores of SMMSE than present study. It can be attributed to change in the location and duration of thyroid disorder in the study group [26].

In a similar study of thyroid disorders among the elderly persons by Wijsman et al, the mean MMSE scores of the patients with subclinical hyperthyroidism was 28.04, euthyroid cases was 28.04 and subclinical hypothyroid cases was 27.87 which had also recorder higher scores of SMMSE than present study [27].

A study by del SerQuijano noted improvement in attention, memory, verbal fluency and executive function of cognitive domain after treatment in subclinical hypothyroidism cases as evidenced by MMSE compared to controls [28].

Cook et al reported that elderly patients with subclinical hypothyroidism performed more poorly than euthyroid individuals on measures of verbal recall as well as on the Mini-Mental State Examination but working memory and processing speed were unaffected [29].

In The present study DSST scoring of the cases had shown that the mean 68.1 (\pm 19.4) and controls was 95.3 (\pm 3.94). There was a statistically significant difference between the DSST scores of the cases and controls.

In a study by Osterweil et al, the mean symbol Digit modality Test scores was 27.3 among the cases and 37.3 among euthyroid controls [22]. In a study by Wijsman et al, the LDCT scores, digits coded was 24.31 among the patients with subclinical hyperthyroidism, 23.63 among the euthyroid cases and 23.51 among the subclinical hypothyroidism cases [27,30].

In The present study mean (\pm SD)of TMT - A scores of the cases was 25.8 (\pm 6.23) and controls was 20.5 (\pm 2.58). There was a statistically significant difference between the TMT – A scores of the cases and controls. This shows that the patients with thyroid disorders are taking more time in performing the task when compared to healthy controls. The mean (\pm SD) TMT – A errors of the cases was 0.87 (\pm 0.73) and mean (\pm SD) score of controls was 0.9 (\pm 0.556). This difference in mean TMT – A scores was not statistically significant

between the cases and controls in this study. In The current study mean of TMT – B scores of the cases was 114.8 (\pm 51.03) and controls was 68.9 (\pm 19.2).

There was a statistically significant difference in TMT – B scores of the cases and controls. This shows that the patients with thyroid disorders are taking more time to complete the task when compared to healthy controls. The mean (\pm SD) TMT – B errors among the cases was 4.77 (\pm 2.49) and controls was 3.57 (\pm 1.22) among the controls. There was a statistically significant difference between the TMT – B scores of the cases and controls.

In a study by Miller et al, the mean Trial A score of the healthy controls at time 1 was 24.5 and hypothyroid cases was 26.21. The mean trials A score at time 2 among the healthy controls was 30.5 and among the hypothyroid cases was 29.9. The mean trials – B score at time – 1 of the controls was 52.7 and hypothyroid cases was 60.43 and at time 2, the mean trials – B score of the healthy controls was 80.9 and 65.5 among the hypothyroid cases [15]. In a study by Osterweil et al, the mean TMT A score was 79.9 sec among the hypothyroid cases and 42.8 sec among the euthyroid cases. The mean TMT – B scores among the hypothyroid cases was 127.5 sec and among the euthyroid controls was 113.5 secs [22,30].

Bono et al also examined the improvement of cognitive functions by using TMT – A & B instrument and noted slight but significant improvement of verbal fluency in 36 women with subclinical hypothyroidism after 6 months treatment with L-thyroxine but this showed no correlation with TSH changes after treatment [31].

A study by Del Ser Quijano noted improvement in attention, memory, verbal fluency and executive function of cognitive domain after treatment in subclinical hypothyroidism cases as evidenced by MMSE and TMT – A & B tests compared to controls [28].

Summary and Conclusion

- a. The mean SMMSE scores among the hyperthyroidism cases was 19.2, hypothyroidism cases was 18.9, sub clinical hypothyroidism was 18.3 and subclinical hyperthyroidism was 23.67.

The scores of abnormal thyroid status patients were statically significant when compared to control subjects on SMMSE scale.

- b. The mean DSST scores among the abnormal thyroid status patients showing clear cut difference when compared to euthyroid controls.
- c. The mean TMT – A scores among the abnormal thyroid status patients has shown higher values when compared to controls.
- d. The mean TMT – B scores among the patients with hyperthyroidism was 127.1, the mean hyperthyroidism was 106.3, subclinical hypothyroidism was 119.3 and subclinical hyperthyroidism was 109.0. The score difference in hypo/hyper thyroid patients is significant when compared to subclinical thyroid states.

Limitations of this study

- a. The sample size was small. The comparison of the results by using this small sample size reduces the effect size.
- b. The study samples were chosen from the department. Since it is general hospital setting results could not be extrapolated to community samples.
- c. Illiterates were not included in the study. So, the cognitive deficits in them were not assessed.
- d. It was not possible to correlate the duration with severity of cognitive dysfunctions.

Implications of the study

- a) Assessing the cognitive functions in thyroid disorders could help the clinicians to ensure appropriate clinical practice.
- b) This study helps the mental health professionals about the risk of development of cognitive dysfunction in thyroid disorders.
- c) The screening of cognitive dysfunctions should be incorporated in routine clinical care in thyroid disorders.
- d) Furthermore, this study would provide the basis of enhancing the clinical research in this area of psychiatry.

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