

A Study of Cognitive Function in Untreated Sub Clinical Hypothyroidism in Elderly

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Abstract: Introduction: Subclinical hypothyroidism is prevalent in elderly reaching up to 30% of total population. Various studies yielded discrepant findings regarding cognitive alteration in subclinical hypothyroidism. The present study aimed to look for cognitive dysfunction in elderly subjects with untreated subclinical hypothyroidism and compare it with cognitive function of elderly euthyroid subjects as it has therapeutic implication. Methods: This case control study included 51 cases with subclinical hypothyroidism and 51 controls with euthyroid status and was subjected to history, biochemical tests and cognitive function assessment. Mini Mental State Examination (MMSE), Digital Clock Drawing Test (DCDT), Frontal assessment battery (FAB) and Time taken to complete trail making test (TMT) were used for assessment of cognitive function. Software SPSS version 22 has been used for the statistical analysis. Results: Significantly higher number of subjects in subclinical hypothyroid patients showed lower MMSE and FAB score, poor performance in TMT, and poorly drawn DCDT in comparison to euthyroid subjects. TSH and MMSE, as well as TSH and FAB showed significant negative correlation. Conclusion: Prevalence of cognitive impairment was significantly higher in subclinical hypothyroidism in comparison to euthyroid subjects in our study along with negative correlation of TSH with cognitive function.

Keywords: Subclinical hypothyroidism, neurological involvement, cognitive dysfunction

1. Introduction

Subclinical hypothyroidism is characterized by normal thyroxine level with elevated TSH, usually paucisymptomatic, and not always requiring treatment. The incidence of subclinical hypothyroidism is estimated to be 4 to 15% depending on the population studied. [1,2] Thyroid hormones have significant effect on brain function. It is well established that overt hypothyroidism causes cognitive dysfunction. However, relation of cognitive function with subclinical hypothyroidism is less defined and needs further research. Hypothyroidism may lead to cognitive changes by a reduction of cerebral blood flow and glucose metabolism, increased risk of stroke due to atherogenic lipid profile and hypertension, hypercoagulable state and altered gene expression.[3] Subclinical hypothyroidism is prevalent in elderly population reaching up to 30% of total population.[4] Several reports suggested subclinical hypothyroidism is associated with neuropsychiatric diseases, particularly with higher TSH and age more than 75 years. [5,6] However, many other studies did not find any association of subclinical hypothyroidism with depression and cognitive decline. [7,8,9] Establishment of subclinical hypothyroidism as a definite contributory factor in neurocognitive changes may have immense impact in indication of levothyroxine replacement therapy in elderly as it is a potentially modifiable risk factor. In the present global scenario of escalating elderly population and huge proportion of them suffering from dementia, very few studies in our country actually looked for cognitive function in subclinical hypothyroidism. The aim of present study was to assess the cognitive function in elderly patients with untreated subclinical hypothyroidism and compare it with cognitive function of elderly euthyroid patients.

2. Materials and Methods

This case control study was conducted in the Department of Medicine, Endocrine unit at a tertiary care centre, over 18th month period from January, 2021 to June, 2022.

Inclusion criteria: 51 consecutive cases were selected with biochemical features of subclinical hypothyroidism above 65 years and 51 consecutive controls were selected from patients with normal thyroid function test

Exclusion Criteria:

- 1) Subjects on Thyroxine Therapy or Anti- Thyroid medication
- 2) Subjects with known major illness (uncontrolled diabetes mellitus, uncontrolled hypertension, CNS disorder, renal or liver dysfunction, infections like HIV or neurosyphilis) which is known to impair cognitive performance.
- 3) Subjects with known Alzheimer's disease, vascular cognitive impairment and dementia
- 4) Subjects with nutrient deficiency (vitamin B12, niacin) causing dementia
- 5) Subjects with known psychiatric illness

3. Methodology

A detailed history taking and thorough clinical examination was done, supplemented by relevant investigations required for the study.

Patient underwent following investigations:

Serum FT3, FT4, TSH and anti TPO antibody were measured in all subjects. Reference range of FT3, FT4, TSH and anti TPO antibody were as follows:

FT3- 2.00-4.40 pg/ml, FT4- 0.93-1.70 ng/dl, TSH -0.270-4.200 mU/L, Anti TPO-antibody- 0.00-34.00 IU/ml

Mini Mental State Examination (MMSE), [10] Digital Clock Drawing (DCD), [11] Frontal assessment battery (FAB), [12] and Time taken to complete trail making test (TMT) [13] were used for assessment of patient's cognitive function.

Statistical Methods

Continuous variables are expressed as Mean, Median and Standard Deviation and compared across the groups using Mann-Whitney U test. Categorical variables are expressed as

Number of patients and percentage of patients and compared across the groups using Pearson's Chi-Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. Association between continuous variables is captured by Spearman's Rank Correlation Coefficient. The statistical software SPSS version 22 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

4. Results

A total of 102 subjects were enrolled in the study out of which 51 subjects (50%) were cases (subclinical hypothyroid) and 51 subjects were controls (euthyroid). The two groups were age and gender matched (Table 1). Mean age in years in subclinical hypothyroid and euthyroid group were 77.31 ± 5.59 and 76.10 ± 5.31 respectively. Distribution of different levels of TSH in two groups are shown in Table 2. Mean TSH level in mIU/L in subclinical hypothyroid and euthyroid group were 8.40 ± 1.71 and 2.30 ± 0.94 respectively. Mean FT4 level in ng/ dl in subclinical hypothyroid and euthyroid groups were 1.17 ± 0.21 and 1.23 ± 0.21 respectively. Hypertension, type 2 diabetes and other comorbidities (osteoarthritis, cervical and lumbar spondylosis, obstructive airway disease etc.) were more or less equally distributed in both the groups (Table 3).

Higher MMSE (24-30) was significantly higher in subjects of euthyroid group (48 vs 6) whereas lower MMSE (10-18) was significantly higher in subjects of subclinical hypothyroid group (10 vs 0) (Table 4). FAB > 12 was significantly higher in subjects of euthyroid group (48 vs 2) whereas FAB (≤ 12) was significantly higher in subjects of subclinical hypothyroid group (49 vs 3) (Table 4). Similarly, TMT was well performed by significant higher number of subjects in euthyroid group (48 vs 26) whereas significantly more subjects in subclinical hypothyroid group performed it with difficulty (11 vs 2), ill performed (11 vs 1) and not performed (3 vs 0) (Table 4). Perfectly drawn DCDT was significantly higher among euthyroid group (47 vs 26), whereas significantly higher number of subjects in subclinical hypothyroid group had moderate visuospatial disorientation (5 vs 1), minor visuospatial error (9 vs 1), inaccurate representation (10 vs 2) and no reasonable representation (1 vs 0) (Table 4). Scatter plot showed significant negative correlation between TSH and MMSE (Figure 1) and TSH and FAB (Figure 2).

5. Discussion

The association between subclinical hypothyroidism and cognitive impairment or risk of dementia is not well-defined, especially in the elderly, where the assessment of the central nervous system function is challenging. Various studies yielded discrepant findings regarding cognitive alteration, some showing significant cognitive dysfunction whereas others not.

Adequate thyroid function is essential not only for brain development in-utero, but it is equally important for retention of cognitive function throughout life. Thyroid hormones are integral for brain development including neurogenesis, neurotransmitter regulation and synaptic plasticity. Hypo

functioning thyroid gland at any age deteriorates cognition as it prevents the brain from adequately sustaining energy consuming process including memory and various other brain function.^[14] The term 'cognition' means mental activities related to acquisition, storage, retrieval and use of information. Thyroid function can affect various aspects of cognitive domain including general intelligence, attention and concentration, memory, visuospatial organization, language, executive function, global cognition and cognitive or psychomotor speed.

Overt hypothyroidism undoubtedly is a known risk factor of cognitive decline in elderly, but cognitive dysfunction related to subclinical hypothyroidism is more subtle, so often need more extensive queries to reveal the disease. This is one of the probable causes of varied inferences in different studies. A study in 1047 patients with 2 years follow up indicated high TSH levels were associated with lower MMSE performance independent of FT4, age, sex, education and mood.^[15] Importantly half of the cases were unaware of the diagnosis and were untreated. Some studies show that even higher TSH levels within reference range may have a negative impact on cognitive function.^[16] In a small study with 15 subclinical hypothyroid and 82 euthyroid subjects showed significantly worse performance in immediate and delayed verbal recall and MMSE.^[17] Another study with 103 subjects above 64 years of age showed prevalence of poor cognitive function significantly higher in subclinical hypothyroid group than control.^[18]

Few studies on subclinical hypothyroidism did not find any significant neurocognitive dysfunction unlike the above studies. In a study with total 89 subclinical hypothyroid and 154 euthyroid subjects, no significant neuropsychological dysfunction was noted when TSH level in subclinical hypothyroid patients was up to 10 μ IU/ ml.^[19] A meta-analysis included six studies which analysed the risk of dementia (n=7401) and seven studies which analysed MMSE decline in subclinical hypothyroidism could not find significant difference between subclinical hypothyroid and euthyroid subjects.^[20] A systematic review and meta-analysis of fifteen studies assessing global cognition using MMSE, executive function and memory also provided no supportive evidence regarding cognitive impairment in people over 60 years with subclinical hypothyroidism.^[21] In a recent individual participant data analysis with large number of patients also did not find any cognitive decline in subclinical hypothyroidism.^[22] 100 cases of elderly Indians more than 60 years when compared with 100 controls in euthyroid status also could not reveal any significant cognitive decline.

Amidst so many studies with diversities and variable results, our study consistently showed significant cognitive impairment in subclinical hypothyroidism group compared to euthyroid groups irrespective of the method of assessing cognitive function. Significant negative correlation between TSH and MMSE as well as TSH and FAB also supported cognitive decline with rising TSH.

Varying results in different studies can be attributed to several factors that affects the relation between thyroid function and cognition. The main factor contributing to these mixed results is study design and methodology. Various health condition

including neurological and systemic diseases may influence cognition in various ways. These compounding factors may have large impact in interpretation of the results. Duration of the disease is very important determining factor; longer the duration, more is the chance of cognitive impairment. Treatment status is also a major contributory factor as levothyroxine therapy can alter underlying pathology and may mask the neurocognitive disturbances. Tests for assessing cognitive function also may largely influence study results. Many studies were based on MMSE only which provides inaccurate and incomplete results. Cognitive dysfunction associated with subclinical hypothyroidism is so subtle that it is not easily picked up by standard neuropsychological tests. Cut off age for elderly as well as cut off level of TSH may also influence the study results to a great extent. In many studies the cut off level of TSH was as low as 3.5 to 4 μ IU/ml which rarely affects cognitive function. Similarly, in many studies upper level of TSH was up to 10 μ IU/ml whereas more liberal inclusion might have shown positive result.

The strength of our study was that it had very extensive exclusion criteria so that no associated comorbidities could affect result. In this study cognitive function assessed clinically using more than one standard cognitive function assessment tools. Population selected for the study was treatment-naïve. All the biochemical parameters were measured by modern and latest lab techniques so the accuracy of the measurement was unremarkable. The study was conducted in a Tertiary care referral hospital so the data reflects a widespread population of the country rather than only localized population in a particular city. Definitely, small sample size is a limitation of the study. Another lacuna was variable duration of subclinical hypothyroid state which may influence cognitive function. Prospective studies including the effect of levothyroxine on elderly subclinical hypothyroid patients are further scope for research.

6. Conclusion

Subclinical hypothyroidism is a common disorder of elderly population which may be associated with cognitive deficit. Prevalence of cognitive impairment was significantly higher in subclinical hypothyroid as compared to euthyroid subjects in our study when several cognitive assessment tools were used along with negative correlation of cognitive function with TSH level.

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Table 1: Age and gender distribution in 2 groups

		Group		Total	p Value	Significance
		Sub-clinical hypothyroidism	Euthyroid			
Age (in years)	60-74	10 (19.61)	14(27.45)	24(23.53)	0.35	Not Significant
	>=75	41 (80.39)	37(72.55)	78(76.47)		
	Total	51 (100)	51(100)	102(100)		
Gender	Female	25 (49.02)	24(47.06)	49(48.04)	0.843	Not Significant
	Male	26 (50.98)	27(52.94)	53(51.96)		
	Total	51 (100)	51(100)	102(100)		

Table 2: TSH level in 2 groups

		Group		Total	p Value	Significance
		Sub-clinical hypothyroidism	Euthyroid			
TSH	<5	0 (0)	51 (100)	51 (50)	<0.001	Significant
	5-7.4	18 (35.29)	0 (0)	18 (17.65)		
	7.5- 9.9	22 (43.14)	0 (0)	22 (21.57)		
	>=10	11 (21.57)	0 (0)	11 (10.78)		
	Total	51 (100)	51 (100)	102 (100)		

Table 3: Distribution of hypertension, diabetes and other comorbidities in 2 groups

		Subclinical hypothyroid	Euthyroid	Total	p value	Significance
Hypertension	No	39(76.47)	41(80.39)	80(78.43)	0.630	Not significant
	Yes	12(23.53)	10(19.61)	22(21.57)		
Diabetes	No	38(74.51)	40(78.43)	78(76.47)	1.641	Not significant
	Yes	13(25.49)	11(21.57)	24(23.53)		
Other comorbidities	No	43(84.31)	44(86.27)	87(85.29)	0.780	Not significant

Table 4: Status of MMSE, FAB, DCD and TMT in two groups

		Subclinical hypothyroidism	Euthyroid	Total	P value	Significance
MMSE	10-18	10(19.61)	0(0)	10 (9.8)	<0.001	Significant
	19-23	35(68.63)	3 (5.88)	38 (37.25)		
	24-30	6(11.76)	48 (94.12)	54 (52.94)		
FAB	>12	2(3.92)	48 (94.12)	50 (49.02)	<0.001	Significant
	≤12	49(96.08)	3 (5.88)	52 (50.98)		
TMT	Not performed	3(5.88)	0 (0)	3 (2.94)	<0.001	Significant
	Ill Performed	11(21.57)	1 (1.96)	12 (11.76)		
	Performed with Difficulty	11(21.57)	2 (3.92)	13 (12.75)		
	Well Performed	26(50.98)	48 (94.12)	74 (72.55)		
DCDT	No reasonable representation	1(1.96)	0 (0)	1 (0.98)	<0.001	Significant
	Inaccurate Representation	10(19.61)	2 (3.92)	12 (11.76)		
	Minor Visuo- spatial Error	9(17.65)	1 (1.96)	10 (9.8)		
	Moderate Visuo-spatial Disorganization	5(9.8)	1 (1.96)	6 (5.88)		
	Perfectly Drawn	26(50.98)	47 (92.16)	73 (71.57)		

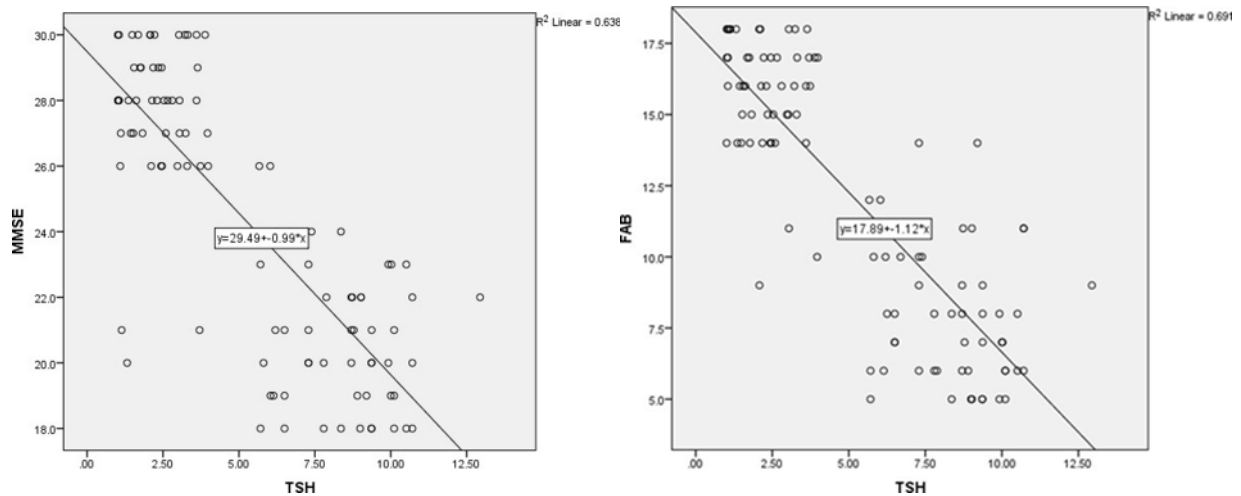

Fig 1a (above): Scatter plot showing significant negative correlation between TSH and MMSE.

Fig 1b (below): Scatter plot showing significant negative correlation between TSH and FAB