Original Article

Cognitive function in subclinical hypothyroidism in elderly

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ABSTRACT

Aim: To study the association of cognitive function with subclinical hypothyroidism in elderly. **Materials and Methods:** It's a cross-sectional, case-control study of 103 patients (≥65 years) who met the criteria for subclinical hypothyroidism. Similarly 103 age, sex and education-matched healthy controls were taken. Serum TSH, free T3 and free T4 were measured. Cognitive functions were assessed by using Folstein Mini Mental Examination (MMSE) and clock drawing test. **Results:** Out of the 103 diagnosed subclinical hypothyroidism cases, cognitive impairment (by MMSE) was found in 33 (30.9%) while it was present in only 15 (14.54%) out of 103 controls ($P = 0.003$), cognitive impairment (by CDT) was present in 32 patients (31.06%) out of 103 cases while it was present in 26 patients (25.24%) out of 103 controls ($P > 0.05$, insignificant). Mean TSH of subclinical hypothyroidism with cognitive impairment was 7.67 ± 1.22 mIU/liter and without cognitive impairment was 6.47 ± 0.98 mIU/liter (P value = 0.0001, significant) **Conclusions:** Prevalence of cognitive impairment was significantly higher in subclinical hypothyroidism as compared to controls. Presence of cognitive impairment correlated with the level of TSH; as TSH increased cognitive function declined.

Key words: Cognitive impairment, elderly, subclinical hypothyroidism

Introduction

Subclinical hypothyroidism is defined as an elevated TSH levels in the presence of normal circulating T4 and T3 concentrations.[1] Subclinical hypothyroidism is common with estimates ranging from 5% to 17% in the general population, with an age-related increase to as many as 20% of women and 9.5% of men over the age of 60 years.[2] The prevalence of subclinical hypothyroidism in men over the age of 74 years was 16% which approaches the 21% prevalence seen in women of same age. Clinical features of hypothyroidism may range from asymptomatic period to features like weight gain, depression, hair loss, fatigue, infertility, menstrual irregularities and many others but clinical presentation of hypothyroidism in the elderly is quite different than in younger individuals. 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. This unresolved issue is a problem in clinical practice because subclinical hypothyroidism is prevalent in older patients, many of whom already have some cognitive decline.

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Materials and Methods

This single point cross-sectional case control study was conducted at a tertiary care hospital from August 2011 to July 2013. One hundred and three educated subjects aged 65 years and over with subclinical hypothyroidism and an equal number of educated controls were studied. Thyroid stimulating hormone (TSH) in serum was assayed with the Immulite- 1000 TSH, a fully automated third-generation immunoassay analyzer, which is based on chemiluminescent detection system. The intra-assay CV ranged from 3.8%

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to 6.0% for TSH mean concentrations from 0.025 to 30.00 mIU/L. Subclinical hypothyroidism was defined by elevated serum TSH concentration i.e. >5.5 mIU/liter with serum-free T4 and T3 concentration being within the reference range. Cognitive function was assessed by Mini Mental State Examination (MMSE)[3] and clock drawing test.[4] MMSE as well as CDT were administered by single observer. MMSE test includes simple question and problem in a number of areas, the time and place of test, repeating lists of words, arithmetic such as serial sevens, language use and comprehension and basic motor skills. Maximum score is 30 and scores ≤24 are associated with cognitive impairment. It was initially developed as a screening test to distinguish 'organic' from 'non-organic' (e.g. schizophrenia) cognitive disorders. More recently, it has become a common method of screening for, and monitoring the progression of, dementia and delirium. Generally the MMSE correlates well with other cognitive screening test scores. It takes 8 minutes to perform in hospitalized elderly patients (range 4-21 min). The Clock Drawing Test (CDT) is a screen for visuospatial, constructional praxis and frontal/executive impairment. We used Shulman scoring system.[5] A score of ≥3 represents a cognitive deficit, while a score of 1 or 2 is considered normal.

All the subjects in the study were educated with minimal of primary education or higher. Age less than 65 years, subject on thyroxine therapy or taking antithyroid medication, who received treatment for hyperthyroidism, any known major illness (uncontrolled diabetes mellitus or its complications, uncontrolled hypertension, CVA, CKD, sepsis) which is known to impair cognitive performance and those unable to provide informed consent were excluded from this study.

The control group comprised age, sex and education-matched normal healthy volunteers. The cases and controls were also matched for their systolic and diastolic blood pressures as well as their FBS, PPBS, and HbA1C values. The exclusion criteria were the same as those for cases. The control subjects were from the same socioeconomic background, to minimize possibility of any bias. A complete physical and mental examination was done and they were assessed on the aforementioned parameters in the same way as was done for the patient group.

Cases and controls were investigated, MMSE and CDT done in every subject. Then the data was analysed with the appropriate statistical methods. Chi-square test and Two Sample Proportion Tests were used to calculate the *P* value. Tests were considered significant if *P* values were less than 0.05.

Results

Mean age of cases was 75.74 ± 9.37 years as compared to 75.12 ± 9.40 years of controls ($P = 0.63$). In cases 60.19% were females and 39.80% were males while in control females were 55.33% and males were 44.60%. Most of cases as well as controls were married. 56.31% cases belonged to rural area compared to 53.39% of controls. Similarly 43.68% cases belonged to urban area compared to 46.60% of controls [Table 1]. Both cases and controls were comparable regarding their age, gender, socioeconomic status, marital status, education and residence. Thus there was no confounding factor as far as demographic characteristics are concerned.

Out of the 103 diagnosed cases of subclinical hypothyroidism, cognitive impairment (by MMSE) was found in 33 (32.03%) while it was present in only 15 (14.56%) out of 103 controls (*P* value = 0.003) which was significant suggesting that there was definite association between cognitive impairment and subclinical hypothyroidism in elderly [Table 2].

Out of 103 diagnosed cases of subclinical hypothyroidism, cognitive impairment (by CDT) was present in 32 patients (31.06%) while it was present in 26 patients (25.24%) out of 103 controls ($P > 0.05$) which was insignificant.

Mean TSH of females was 7.16 ± 1.23 mIU/liter while that of males was 6.40 ± 1.00 mIU/liter in subclinical

Table 1: Baseline characteristics

Characteristics	Cases	Controls	*P* value
Mean age (in years)	75.74±9.37	75.72±9.40	
Males	39.80%	44.60%	0.6351
Females	60.20%	55.40%	0.1816
Socioeconomic status			
Upper High	9.09%	12.72%	0.844
High	10.9%	14.54%	
Upper Middle	25.45%	27.27%	
Lower Middle	23.63%	25.45%	
Poor	18.18%	12.72%	
Very poor	12.72%	7.27%	
Married	101 (98.05%)	99 (96.0%)	0.401
Unmarried	2 (1.94%)	4 (4.0%)	
Rural	58 (56.31%)	55 (53.39%)	0.702
Urban	45 (43.68%)	48 (46.60%)	

Table 2: Status of cognitive impairment in cases and controls by MMSE

	Cases (*n*=103)	Controls (*n*=103)	*P* value
Cognitive impairment present	33	15	0.003
Cognitive impairment absent	70	88	

MMSE: Mini mental examination

hypothyroid group (*P* value = 0.001, significant). This showed that subclinical hypothyroidism was more common in females. Mean TSH of subclinical hypothyroidism with cognitive impairment was 7.67 ± 1.22 mIU/liter and without cognitive impairment was 6.47 ± 0.98 mIU/liter (*P* value = 0.0001, significant). It showed that there was significant association between cognitive impairment and TSH levels [Table 3]. As the TSH levels increased cognitive impairment in subclinical hypothyroidism increased [Figure 1 and Tables 4-7].

Discussion

Numerous studies[6-18] have addressed the association of cognitive impairment with subclinical hypothyroidism. In this study mean TSH in subclinical hypothyroidism group was 6.86 mIU/liter and compared well with most other studies.[9,12] In the present study the prevalence of cognitive impairment in subclinical hypothyroidism was higher in cases as compared to controls and is correlated with TSH levels such that as serum TSH levels increased the prevalence of cognitive function also increased and MMSE scores declined [Figure 1]. This study compared well with study of 1047 United Kingdom subjects aged ≥64 years which showed correlation between TSH values and cognitive performance.[6] Baldini *et al.*[7] reported significant association between cognitive impairment and subclinical hypothyroidism. Cook *et al.*[8] found that elderly patients with subclinical hypothyroidism performed more poorly than euthyroid individuals. Jorde *et al.*[9] performed an extensive battery of cognitive function tests and found no differences with thyroid status, although after secondary analyses, they did report that serum TSH was negatively correlated with the cognitive impairment. Samuels *et al.*[10] performed an RCT of subclinical hypothyroidism in 19 females and reported significant reduction in working memory at the end of the subclinical hypothyroidism phase compared with that measured at the end of the euthyroid phase. In a smaller study, Correia *et al.*[11] reported that subjects with subclinical hypothyroidism had impaired spatial and verbal memory on detailed cognitive testing. Some interventional studies like Nystrom *et al.*,[12] Jaeschke *et al.*[13] reported improvement in cognitive function in subclinical hypothyroidism who completed a double-blind randomized crossover trial.

However, some studies have not showed any association between cognitive impairment and subclinical

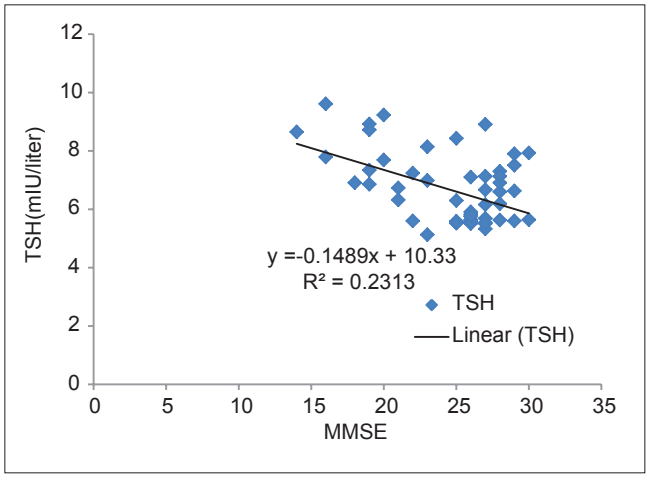

Figure 1: Scatter diagram showing relationship between TSH and MMSE scores

Table 3: TSH levels in cognitive impairment present vs. absent in subclinical hypothyroidism

TSH (mIU/liter)	Subclinical hypothyroidism		*P* value
	Cognitive impairment present (*n*=33)	Cognitive impairment absent (*n*=70)	
Mean	7.67	6.47	0.0001
SD	1.22	0.98	

SD: Standard deviation, TSH: Thyroid stimulating hormone

Table 4: Number of cases with or without cognitive impairment based on their education status

Education	Cognitive impairment present (*n*=33)	Cognitive impairment absent (*n*=70)	*P* value
5-8 years	26	41	0.12
9-12 years	5	19	(insignificant)
College or higher	2	10	

Table 5: Number of controls with or without cognitive impairment based on their education status

Education	Cognitive impairment present (*n*=15)	Cognitive impairment absent (*n*=88)	*P* value
5-8 years	9	49	0.75
9-12 years	5	27	(insignificant)
College or higher	1	12	

Table 6: Mini Mental Examination scores of cases and controls in the study

MMSE scores	Cases (*n*=103)	Controls (*n*=103)
25-30	70	88
19-24	24	11
≤18	9	4

MMSE: Mini mental examination

Table 7: Status of cognitive impairment in cases and controls as evaluated by clock drawing test

	Cases (*n*=103)	Controls (*n*=103)	*P* value
Cognitive impairment present	32	26	>0.05
Cognitive impairment absent	71	77	(insignificant)

CDT: Clock drawing test

hypothyroidism. A large cross-sectional community-based study of subjects aged ≥65 years measuring cognitive function showed no association between subclinical hypothyroidism and cognition.[14] In this study no significant difference between the cognitive status of cases and controls was found when the cognitive status was measured using the clock drawing test. No differences were found by Osterweil *et al.*[15] between the 14 patients with subclinical hypothyroidism and 30 controls. Similarly, in a group of elderly subjects aged 65-92 years, Luboshitzky *et al.*[16] reported no significant differences in cognitive impairment measured by the Mini-Mental State Examination in 39 untreated sub-clinically hypothyroid patients compared to 570 euthyroid controls. Bono *et al.*[17] provided evidence that subclinical hypothyroidism in 36 women barely affected their cognitive status but may have caused an age-related impairment of attentive function. Parle *et al.*[18] found no differences between the L-T4- and placebo-treated groups in any cognitive measure, where as a study by Aghili *et al.*[19] showed the efficacy of levothyroxine for cognitive function of subjects with subclinical hypothyroidism.

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