A cross-sectional study on thyroid status in North Indian elderly outpatients with dementia

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Abstract

Background: Several population based studies have demonstrated an association between hypo-or hyperthyroidism and dementia in last two decades. As a consequence, thyroid stimulating hormone has become part of the screening laboratory test for dementia. Aim: The aim of the present study was to evaluate the association between thyroid function and Alzheimer’s disease (AD) and vascular dementia (VaD) and to determine the risk of AD and VaD in clinically euthyroid patients. Materials and Methods: A cross-sectional hospital based study was carried out in subjects diagnosed with AD/VaD and were assessed for thyroid status as routine screening test. Results: Free T3, free T4 and TSH were studied in 114 AD patients (mean age: 65 years), 35 VaD patients (mean age: 62 years) and 105 control subjects (mean age: 62 years). In AD group, TSH levels were significantly lower than controls \( P = 0.00 \) and for each unit increase in TSH level, the odds of having dementia decreased by 37.1%. No such relation was seen in VaD. Conclusion: The results suggest a consistent association of subclinical hyperthyroidism and AD.

Key Words

Alzheimer’s disease, Dementia, thyroid status, thyroid stimulating hormone, vascular dementia

Introduction

Alzheimer’s disease (AD) and vascular dementia (VaD) are the most common causes of dementia in elderly people affecting more than 24 million people worldwide. There is increasing evidence that Mild cognitive decline and Vascular cognitive decline (VCI) may be more common than ‘pure AD or VaD’ in the developing countries. These observations argue for a shift in thinking towards a multidimensional continuous concept rather than a dichotomous concept of the disease; and more focus on presymptomatic markers of the disease. Recent data suggests that both modifiable and non modifiable risk factors lead to preclinical disease which eventually results in cognitive impairment. Hence, the need of the hour is to address these risk factors to identify patients at early stages of cognitive impairment, to treat appropriately and prevent disease progression. In last two decades thyroid status has come to attention as a possible independent risk factor as a cause of reversible cognitive impairment. These population based studies demonstrated an association between hypo-or hyperthyroidism and AD. However, it seems that clinical thyroid disease is not related to an increased risk of dementia or AD, but subclinical thyroid disease (i.e, elevated or suppressed thyroid stimulating hormone levels with normal T3 and T4) is associated with cognitive impairment and AD. However, these studies demonstrate inconsistent findings associating both subclinical hypothyroidism and subclinical hyperthyroidism to dementia and AD. Hence, the exact nature and validity of the relationship between thyroid status and dementia is not clear. As a consequence, the serum thyroid stimulating hormone (TSH) level remains a standard screening test for the routine evaluation of patients presenting with cognitive impairment. It is further complicated by the association of thyroid disease and vascular disease as vascular risk factors increase the risk of both AD and VaD and exacerbate their symptoms.

In the present study, we demonstrated the association between thyroid function and AD and VaD as represented by the TSH level and determined the risk of AD and VaD in clinically euthyroid subjects, to address the question whether dementia and thyroid dysfunction are independent co-prevalent conditions in older people.
Materials and Methods

Study subjects
A cross-sectional hospital-based study was conducted from 2005 to 2010. It was carried out in subjects attending the Neurobehavior clinic and was diagnosed with AD/VaD and was assessed for thyroid status as routine screening test in the Institute of Human Behavior and Allied Sciences, Delhi, India. Dementia patients (149; mean age: 64 years) and cognitively normal individuals (105; mean age: 62 years) were included in the study. Of the 149 patients, 114 patients with AD (65 men, 49 women; mean age: 65 years) and 35 patients with VaD (20 men, 15 women; mean age: 62 years) were involved in the study [Table 1]. 105 subjects were recruited as control for comparison. Though controls were not matched with cases for age and gender, they were not statistically different from cases.

Dementia case-finding
The patients attending the neurobehavioral clinic were assessed in by neurologist. Dementia screening and diagnosis was done in two phases. In first phase, detailed history was taken from the care givers regarding the cognitive deficits, behaviour abnormality and activities of daily living and history of previous neurological deficits to rule out Cerebrovascular accident. MMSE was used for screening the dementia patients. In second phase, screen positive subjects (MMSE < 26) underwent detailed higher mental functions examination. The lobar functions were assessed. Few selected patients in whom the cognitive deficits were not obvious or mild were subjected to the detailed neuropsychometric analysis by clinical psychologist. Neuroimaging. Magnetic resonance imaging was done in all these patients.

The patients were categorised in subtypes Alzheimer’s disease and vascular dementia considering the clinical history, neurological examination, higher mental status examination and neuropsychometric analysis in selected patients.

Diagnosis of probable AD was made according to the criteria of the National Institute of Neurological and Communicative Disorders Association-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). The diagnosis of VaD was established according to the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherché et l’Enseignement en Neurosciences (NIINDS-AIREN) criteria for probable VaD.

Elderly individuals (105; 54 men, 51 women; mean age: 62 years) attending the hospital with ailments other than cognitive impairment and coming to clinics routinely for other neurologic diseases were taken as the control group in the study. All the patients with recent history of heart or respiratory failure, chronic liver or renal failure, malignant tumors, and recent history of alcohol abuse were excluded from the test and control group. Also subjects taking vitamin supplements were excluded from the study. All the subjects underwent clinical examination along with routine biochemical, hormonal, and radiologic examinations, including glucose, cholesterol, albumin, creatinine, thyroid hormonal assay, and MRI.

Assessment of thyroid status
At baseline non fasting serum samples were obtained from patients taking all the standard precautions. The specimen was centrifuged within 30 min of sample collection to separate the serum and examined for routine biochemistry. Specimen for evaluation of Thyroid function-free T3 (fT3), free T4 (fT4) and TSH was stored at -20°C until analysis. Serum fT3, fT4 and TSH were measured by using sandwich immunoassay technique. All these tests were performed on Electrochemiluminescence immunoassay Analyzer, Elecsys 2010 (M/s Roche Diagnostics Asia Pacific Pte. Ltd, Singapore). The Coefficient of Variation (CV %) for fT3, fT4 and TSH were 3, 4 and 6.44 (normal values) and 2.5, 6 and 7.06 (higher values), respectively. All eligible subjects with available thyroid status report (fT3, fT4and TSH) were included in the study and those subjects were excluded from all the groups having overt hypo- or hyperthyroidism (with TSH levels less than 0.1 or greater than 10 mU/L).

Statistical analysis
Descriptive statistics (Mean ± SD) was calculated for the four variables studied i.e age, fT3, fT4 and TSH in three groups AD, VaD and control. As all four variables studied were continuous, the one way analysis of variance (ANOVA) method was applied to explore the statistically significant difference among mean value in three groups (AD, VaD and Control). In the case of the ANOVA analysis was also done by Tukey-test, to examine those two groups which were significantly different from each other. The χ2-test was applied to verify the hypothesis whether gender (male/female) distribution is similar in three groups or not. The multinomial logistic regression method was applied to analyze relationship between disease status (AD, VaD and Control) considering them as dependent variable (non-metric) and age (metric), sex (non-metric), fT3 (metric), fT4 (metric) and TSH (metric) as independent variable. The utility of present analysis (Multinomial logistic regression) was assessed by classification accuracy, which compares the predicted disease group based on logistic model to the actual disease group (which is the value for dependent variable).

Results

Characteristics of the study subjects
The demographic and thyroid status of AD, VaD and control at baseline are presented in Table 1. The mean age of AD and VaD patients at baseline were 64.90 years (SD 10.11) and 62.17 years (SD 8.96), 57% of the subjects were males. Two demographic variables i.e, age and gender were not significantly associated with the dementia status in both AD and VaD.

Thyroid status
One way analysis of variance (ANOVA) method was applied to explore the statistical significant difference among mean value in three groups (AD, VaD and Control). Out of three biochemical studied variables, the mean of only two (FT3 and TSH) variables were significantly different (P < 0.001) in three groups which suggested that at least one average, out of the three was statistically different than rest two [Table 2]. To explore such group, the multiple comparison analysis was done by Tukey -test as shown in Table 3. In AD group, mean TSH values (2.00 ± 1.26 mU/L) were significantly lower (P = 0.00) than control (3.17 ± 1.97 mU/L), whereas there was no difference of fT3 and fT4 levels in both the groups. In VaD group, though TSH values were also found low as compared to the control
but it was not significant (P = 0.27). However, fT3 levels were significantly lower than control (P = 0.00).

**TSH and the risk of AD**

Table 4 shows the relationship of disease state (AD, VaD) with age, gender, fT3, fT4 and TSH. The presence of relationship between them was checked based on the statistical significance of the final model Chi-square and existence of relationship was established. Out of five considered independent variables only TSH had significant (P < 0.001) contribution towards AD group. The regression coefficient (B) for TSH level was 0.464 indicating that increase in TSH decreased the likelihood of dementia in AD group. The exponential (B) value for TSH level in AD group was 0.629 (95% CI: 0.511-0.744). It implies that for each unit increase in TSH level the odds of having dementia decreased by 37.1%.

In present analysis, the classification accuracy rate of logistic model was 57.1% which was greater than the proportional by chance accuracy and the criteria for classification accuracy was satisfied.

**Discussion**

India’s population is undergoing a rapid demographic transition. India was home to more than 75 million people older than sixty years in 2001. This age group, which was 7.5% of the population, is expected to grow dramatically in the coming decades. It is estimated that over 3.7 million people are affected by dementia in our country in 2010. This is expected to double by 2030.[18] Worldwide more than 24 million people have dementia.[9] Dementia and thyroid dysfunction are both prevalent conditions in elderly population. Recent studies have related thyroid dysfunction, even within the clinically ‘normal’ range to an increased risk of irreversible dementia. The results of this cross sectional study indicate that there is a consistent association among older adults with subclinical hyperthyroidism and Alzheimer’s disease but not with vascular dementia. The TSH levels were associated with an increased risk of AD but there was no association of fT3 and fT4 with AD. We found that with each unit increase in TSH level the odds of having AD decreased by 37.1%. The observed association appeared to be independent of age and gender. Our findings are consistent with Kalmijn et al. (2000),[9] who also reported association of subclinical hyperthyroidism with increased risk of dementia and AD in a prospective population-based cohort study conducted in Rotterdam which could not be explained by differences in age, sex, atrial fibrillation or potential other confounders, whereas Annerbo et al. (2009)[17] found no association of TSH with the development of AD. Bensenor et al. (2010)[18] also showed positive association between subclinical hyperthyroidism and any type of dementia and vascular dementia but not with Alzheimer’s disease in cross-sectional one-phase population based study carried out in Brazil, whereas von Osch et al. (2004)[19] indicated that even individuals whose TSH levels were only marginally reduced within normal range had an increased risk of AD. On analyzing the presence of dementia according to gender, after age and BMI adjustment, they found that subclinical hyperthyroidism was positively associated with any type of dementia and Alzheimer’s disease in men but not in women. In contrast to present study, Cardenas-Ibarra et al. (2008)[20] showed high frequency of hypothyroidism in patients with dementia and three-quarter of those with elevated TSH belonged to the subclinical variety of hypothyroidism. Lopponen et al. (2004)[21] from Finland also reported 20% and 10% of hypothyroidism in individuals with and without dementia respectively. Tan et al. (2008)[22] in the Framingham Study, a longitudinal community-based observational study followed up over a period of 12.7 years (range 1 to 25 years) observed that women

**Table 1: Characteristics of study population**

| Characteristics | AD (N=114) | VaD (N=35) | Control (N=105) |
|-----------------|------------|------------|-----------------|
| Age, years (Mean±SD) | 64.9±10.11 | 62.17±8.96 | 61.93±10.23 |
| Gender | | | |
| Male | 65 | 20 | 54 |
| Female | 49 | 15 | 51 |
| MMSE Score (Mean±SD) | 18.5±0.88 | 21.25±0.95 | 28.59±1.90 |
| fT3, mU/L (Mean±SD) | 3.17±0.92 | 2.64±0.58 | 3.24±0.55 |
| fT4, mU/L (Mean±SD) | 1.30±0.39 | 1.22±0.20 | 1.21±0.22 |
| TSH, mU/L (Mean±SD) | 2.00±1.26 | 2.67±1.65 | 3.17±1.97 |

AD: Alzheimer’s disease, VaD: Vascular dementia, fT3: Free T3, fT4: Free T4, TSH: Thyroxine stimulating hormone

**Table 2: Comparison of mean value of age, gender, various parameters of thyroid function in AD, VaD and controls**

| Variables | AD (N=114) | VaD (N=35) | Control (N=105) | F value | DF | P value |
|-----------|------------|------------|-----------------|--------|----|---------|
| Age, years (Mean±SD) | 64.9±10.11 | 62.17±8.96 | 61.93±10.23 | 2.66 | 2, 251 | 0.07 |
| Gender | | | | | | |
| Male (%) | 65 (57.00%) | 20 (57.10%) | 54 (51.40%) | 0.79 | 2 | 0.68 |
| Female (%) | 49 (43.00%) | 15 (42.90%) | 51 (48.60%) | | | |
| fT3, mU/L (Mean±SD) | 3.17±0.92 | 2.64±0.58 | 3.24±0.55 | 0.71 | 2, 251 | 0.00* |
| fT4, mU/L (Mean±SD) | 1.30±0.39 | 1.22±0.20 | 1.21±0.22 | 2.09 | 2, 251 | 0.08 |
| TSH, mU/L (Mean±SD) | 2.00±1.26 | 2.67±1.65 | 3.17±1.97 | 5.26 | 2, 251 | 0.00* |

*Highly Significant, AD: Alzheimer’s disease, VaD: Vascular dementia, fT3: Free T3, fT4: Free T4, TSH: Thyroxine stimulating hormone
with serum TSH concentrations in the lowest (TSH < 1.0 mU/L) and highest (TSH > 2.10 mU/L) tertiles had a >2-fold higher risk of developing AD but no such risk was found in men.

Such conflicting results found in different studies showing different outcomes in terms of hypo- or hyperthyroidism as risk factor for AD and VaD raises the question whether altered TSH levels occur before or after the onset of AD pathology. What could be the mechanism behind the association between hyperthyroidism and AD? One theory proposes that accumulation of amyloid plaques and neurofibrillary tangles secondary to neurodegenerative changes occurring during AD may lead to a reduction in secretion of Thyrotrophin Releasing Hormone (TRH) by the hypothalamus or decreased pituitary responsiveness to TRH, manifesting as reduced TSH and thyroxine levels. Thus low TSH and TRH levels may be a consequence of AD rather than it's cause. On the other hand, altered TSH levels could precede dementia and contribute to the development of AD. As per this theory, TSH and TRH depletion has direct effect on processing of cerebral amyloid-β proteins and/or the local synthesis and release of acetylcholine from neurons. Several in vitro and in vivo studies have demonstrated that thyroid hormone regulates the gene expression of amyloid β protein precursor (APP). In hyperthyroid state it represses the APP promoter activity and in hypothyroid state enhances the expression of APP gene product. On a parallel note, another group shows that TRH and TRH analogues increase acetylcholine release in rats, indicating that decreased TRH may cause acetylcholine depletion. Also, TRH depletion has been associated with enhanced phosphorylation of tau proteins. Furthermore, increased oxidative stress and decreased antioxidant metabolites have been detected in clinical hyperthyroidism and exposure to thyroid hormone has been shown to enhance neuronal death.

In addition to direct effects of thyroid hormone on cholinergic neurons, APP processing and phosphorylation of tau protein, another mechanism proposed to explain the association between thyroid dysfunction and AD risk is vascular factor mediated mechanism. Both clinical and subclinical hyperthyroidism affect cardiovascular risk and in parallel, vascular risk factors like diabetes, hypertension, heart disease and smoking have been correlated with an increased risk of AD.

The present study showed that subclinical hyperthyroidism is a risk factor for developing AD only in both men and women. But there are certain limitations in this study which are to be addressed more in details before drawing any clinical conclusion. First, there are number of medications like thyrostatic medication, antipsychotic and glucocorticoids use and hormone replacement therapy which can affect the thyroid status of the subjects as well as the measured thyroid results. Though we excluded the subjects who were on thyroid medication or had TSH <0.1 and >10.0 mU/L, but there was no control for other medication use by the subjects under study which could influence the thyroid status. Second, all the subjects underwent measurement of thyroid status in their first visit and no follow up of these patients were done in terms of repeat assessment of their thyroid status. Hence, further prospective studies with a longer follow up period and larger sample size are needed to further elucidate whether high TSH levels is a modifiable risk factor for AD.

### Table 3: Multiple Comparison Analysis (Tukey test) of various parameters of thyroid function in AD, VaD and Controls

| Variable | Mean difference | SE of Mean difference | P value |
|----------|-----------------|-----------------------|---------|
| fT3 AD vs. Control | -0.07 | 0.10 | 0.75 |
| fT3 VaD vs. Control | -0.60 | 0.14 | 0.00* |
| fT4 AD vs. Control | 0.09 | 0.04 | 0.08 |
| fT4 VaD vs. Control | 0.01 | 0.06 | 0.99 |
| TSH AD vs. Control | -1.17 | 0.22 | 0.00* |
| TSH VaD vs. Control | -0.50 | 0.32 | 0.27 |

*Highly Significant. AD: Alzheimer’s disease, VaD: Vascular dementia, fT3: Free T3, fT4: Free T4, TSH: Thyroxine stimulating hormone

### Table 4: Summary of multinomial logistic regression analysis

| Variable | Regression coefficient (B) | SE | P value | Exp (B) | 95% CI for exponential (B) |
|----------|-----------------------------|----|---------|---------|--------------------------|
| AD Age  | 0.023                       | 0.015 | 0.128 | 0.994-0.53 | |
| sex Male | 0.006                       | 0.297 | 0.984 | 1.006 | 0.562-0.799 |
| Female | --                          | -- | -- | -- | -- |
| fT3 | -0.336                      | 0.227 | 0.139 | 0.714 | 0.458-0.115 |
| fT4 | 0.988                       | 0.560 | 0.078 | 2.687 | 0.896-0.56 |
| TSH | -0.464                      | 0.106 | 0.000* | 0.629 | 0.511-0.774 |
| VaD Age | -0.016                     | 0.022 | 0.458 | 0.984 | 0.943-0.027 |
| sex Male | 0.297                      | 0.434 | 0.494 | 1.345 | 0.575-3.147 |
| Female | --                         | -- | -- | -- | -- |
| fT3 | -1.857                      | 0.407 | 0.000* | 0.156 | 0.070-0.347 |
| fT4 | 1.094                       | 0.800 | 0.172 | 2.986 | 0.622-4.330 |
| TSH | -0.137                      | 0.129 | 0.289 | 0.872 | 0.677-1.23 |

AD: Alzheimer’s disease, VaD: Vascular dementia, fT3: Free T3, fT4: Free T4, TSH: Thyroxine stimulating hormone
Conclusion

Based on above study, it can be concluded that subclinical hyperthyroidism has consistent association with dementia especially AD.

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