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Neurology

IS THYROID ASSOCIATED WITH DEMENTIA? A CASE CONTROL STUDY

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ABSTRACT **Objectives:** The present study was undertaken with an objective to explore if thyroid is related to dementia among participants aged 45 years and above.

Design: Participants aged more than 45 years of age, giving written informed consent and meeting the selection criteria were enrolled in the study. The participants were administered with a series of paper pencil tests. The data was further analyzed for any association using the Statistical Package for Social Sciences, version 22 (SPSS 22).

Setting: Participants attending the Outpatient Department (OPD) at Institute of Human Behaviour and Allied sciences (IHBAS), a tertiary care neuropsychiatric hospital and normal elderly controls from local community.

Participants: A sample size of at least 40 cases of Dementia of Alzheimer type and at least 40 cases of vascular/ mixed dementia and 60 normal controls were recruited.

Measurements: Semi-structured Performa for demographic and clinical variables; Hindi mental status examination (HMSE) for cognitive functions was applied as screening tools for both case and control groups;Tools for patients with dementia: NINCDS-ADRDA criteria for Probable Alzheimer's disease (McKhann et al), NINDS /AIREN criteria for diagnosis of probable vascular dementia (VaD), NINDS-AIREN diagnostic criteria for "Alzheimer's disease with Cerebro-Vascular Disease" (mixed dementia), Clinical Dementia Rating Scale (Morris et al 1997), and 5 ml blood sample collection and analysis through vein puncture.

Results: The results of the study indicate that subclinical hypothyroidism is associated with dementia of Alzheimer type.

Conclusion: When considered in light with varied findings of prior studies, it may be implied that subclinical thyroid dysfunction not especially hypo or hyperthyroidism is a risk for DAT.

KEYWORDS : thyroid, hypothyroidism, hyperthyroidism, dementia, Dementia of Alzheimer type (DAT), Vascular dementia (VaD), Mixed dementia, subclinical thyroid dysfunction

INTRODUCTION

Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Dementia of Alzheimer type (DAT) is the most common form of dementia and possibly contributes to 60-70% of cases. Other types of dementias include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to frontotemporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist.

Endocrine abnormalities like the role of hypo and hyperthyroidism among others are established in cases of reversible dementia. Thyroid hormone (TH) has an important role to play in neural activity and cellular metabolism in the central nervous system (CNS). TH along with Acetylcholine (Ach) and neural growth factors are important for hippocampal functioning (Liu et al, 2000). Animal studies have shown T4 treatment, administered both sub-chronically and chronically, significantly enhanced the ability of rats to learn a spatial memory task, compared with controls (Smith et al, 2002). Moreover, both short-term and long-term T4 treatment reduced the cognitive-impairing effects of scopolamine, indicating the augmenting effects of TH on Ach functions. Some cross-sectionalepidemiological studies have shown association both hypothyroidism and hyperthyroidism in cases of irreversible dementia, others have failed to show any association between them.

A prospective study of the data collected from Framingham study over a 12 year period showed that both low and high levels of Thyroid-stimulating hormone (TSH) were a risk factor for Dementia of Alzheimer type (DAT) only in elderly women but not men (Tan et al., 2008).

The results remained ambivalent with no replication of any of the aforementioned results. In this study, a cross-sectional examination of thyroid profile was done in the patients attending the neuropsychiatric and compared with normal elderly controls.

METHODS:

We started with a Null Hypothesis thatthyroid abnormalities will not be associated with dementia for the participants aged 45 years and above.The study was conducted in patients with dementia attending the Outpatient Department (OPD) at any tertiary care neuropsychiatric hospitaland normal elderly controls were recruited from the local community. It was a case-control study design with a sample size of at least 40 cases of Dementia of Alzheimer type and at least 40 cases of vascular/ mixed dementia and 60 normal controls were recruited.

Patients aged 45 and above meeting the diagnostic criteria of dementia according to the DSM-IV TR, National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders Criteria (NINCDS-ADRDA) (McKhann et al., 1984) for Probable Alzheimer's disease and National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherché et l'Enseignementen Neurosciences (NINDS-AIREN) (Roman, 1993) diagnostic criteria for vascular/ mixed dementia were enrolled in this study.

Patientswith Parkinson's disease dementia and other subcortical dementias were excluded from the study.

Tools:

1. NINCDS-ADRDA criteria for Probable Alzheimer's disease (McKhann et al)&NINDS /AIREN criteria for the diagnosis of probable vascular dementia (VaD)/ mixed dementia.
2. Clinical Dementia Rating Scale (Morris et al 1997):The Clinical Dementia Rating or CDR is used for staging the severity of dementia using six domains: Memory, Orientation, Judgment and Problem solving, Community Affairs, Home and Hobbies, and Personal Care (Morris, 1997). CDR-1 = mild, CDR-2 = moderate, CDR-3 = severe

Blood Sample Collection And Analysis

After screening the patientsand controls, blood sample by vein

puncture was collected taking all the aseptic precautions. Five millilitres of the blood sample was taken in a plain vial for serum TSH, T3 and T4 levels. Samples were transported in cold conditions. After sample collection, the serum was separated within 2 hours and rapidly stored at -200 C for biochemical analysis. All these tests were performed on Electrochemiluminescence immunoassay Analyzer, Elecsys 2010 (M/s Roche Diagnostics Asia Pacific Pte. Ltd, Singapore).

Ethics Statement

Permission was sought from the ethical committee for conducting thesis and the current result was obtained from addition result analysis of the same data set. The rights of the participants were explained and queries were answered. The written informed consent was sought from all participants.

Analysis Of Data

A master-chart was prepared using the Statistical Package for Social Sciences, version 22 (SPSS 22) and data recorded in the SSP was coded as appropriate variables on the master-chart. For the analysis of two categorical variables,the Chi-square test and Fisher's exact test were used. Where distribution was found to be normal (Kolmogorov-Smirnov test), Independent t-test and ANOVA were used for the analysis of two and three continuous variables respectively. Where distribution was not found to be normal (Kolmogorov-Smirnov test), Kruskal Wallis were used for the analysis of two and three continuous variables respectively.

RESULTS:

Around 83 cases of dementia were recruited for the study and 60 controls were taken from the community. Among the cases, 43 were of Alzheimer dementia and the rest 40 were a combination of vascular and mixed dementia. The mean TSH levels were significantly higher in dementia as compared to the controls. The difference was also significant when the cases of DAT were compared to the controls but the results did not attain statistical significant when cases of vascular and mixed dementias were compared with the healthy individuals (Table 1 & Figure 1). Among the dementia groups, the cases with DAT had a significantly higher TSH level as compared to the vascular/ mixe dementia groups (Table 1&2).

In a univariate model, the TSH levels were compared with the severity of dementia across all the groups. TSH levels increased with increasing severity of dementia. The highest mean TSH was found in the cases of severe dementia (CDR=3) (Table=3).

Table 1

Variables	Cases (N=83) Mean(±SD)	Controls (N=60) Mean(±SD)	p value
Serum TSH levels (uIU/ml)	3.23 (1.16)	2.82 (1.24)	0.04*
Serum TSH levels (uIU/ml)	DAT (N=43) Mean(±SD)	CONTROLS (N=60) Mean(±SD)	0.005*
	3.51 (1.21)	2.82 (1.24)	
Serum TSH levels (uIU/ml)	VaD &mixed dementia (N=40) Mean(±SD)	Controls (N=60) Mean(±SD)	0.613
	2.94 (1.03)	2.82 (1.24)	
Serum TSH levels (uIU/ml)	DAT (N=43) Mean(±SD)	VaD &mixed dementia (N=40) Mean(±SD)	0.023*
	3.51 (1.21)	2.94 (1.03)	

Independent t-test ***p≤0.05**

TSH: thyrotropin stimulating hormone

Table 1 shows the comparison of TSH levels between different groups. The mean TSH levels in cases (3.23 uIU/ ml) were significantly higher than the control group (2.82 uIU/ ml) using the independent t-test. In case DAT the mean TSH levels were 3.51uIU/ ml, which was significantly higher than the control group (p= 0.005).

Similarly, TSH was also significantly higher in cases of DAT as compared to VaD and mixed dementia (mean TSH=2.94 uIU/ ml) (p=0.023).

No significant difference was found between the serum TSH levels of VaD and mixed dementia and controls (p=0.613).

Table 2

Variables	DAT (N=43) Mean(±SD)	VaD & mixed dementia (N=40) Mean(±SD)	Controls (N=60) Mean(±SD)	p value
Serum TSH levels (uIU/ml)	3.51 (1.21)	2.94 (1.03)	2.82 (1.24)	0.011*

ANOVA ***p≤0.05**

Table 2 shows the comparison of mean TSH levels among all 3 groups using ANOVA. The mean TSH was 3.51uIU/ml, 2.94uIU/ml and 2.82uIU/ml among DAT, VaD and mixed dementia and control group respectively. The difference between the 3 groups was found to be significant using ANOVA (p=0.011).

Table 3

Severity of Dementia (CDR SCORE)	Mild	Moderate	Severe	p-value
	Mean (±SD)	Mean (±SD)	Mean (±SD)	
Serum TSH levels (uIU/ml)	2.88 (1.10)	3.45 (0.79)	4.57 (1.06)	0.000*

ANOVA ***p≤0.05**

Table 3 shows the TSH levels in cases of dementia divided into 3 groups of mild, moderate and severe according to the CDR scores. The mean TSH level in mild dementia was 2.88uIU/ml, 3.45uIU/ml in moderate dementia and 4.57uIU/ml in severe dementia, with a significant difference, was found among all 3 groups using ANOVA (p=0.000).

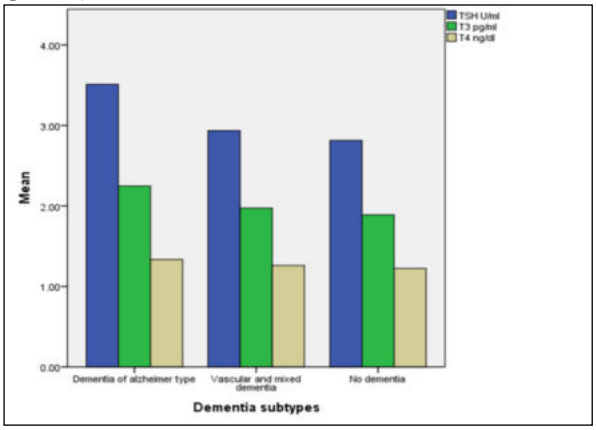

Figure 1: Thyroid profile among the 3 dementia subtypes and controls. The highest abnormalities were in the DAT group and all the cases of dementia had a higher mean TSH level as compared to the controls.

DISCUSSION

Normal thyroid function is responsible for the development and sustenance of cognitions throughout the lives. Deficiency from early childhood leads to cretinism and later life has been shown to be linked to impaired cognition. Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose. It has been postulated that impairment in the functioning of thyroid leads to inefficient glucose uptake in the brain leading to a plethora of dysfunction which cognitive symptoms are a part of (Gussekloo et al., 2004). Functional imaging studies have shown impaired glucose uptake in the brain in cases of dementia, however, no causality has yet been reached. Studies have been conducted in cases of clinical hypothyroidism and various effects on cognitions. Capet et al, Mennemeier et al, Haggerty et al found impairment in general intelligence, memory, attention, visuospatial functions, language and executive functions, most of which improved some after levothyroxinereplacement(Capet et al., 2000; Mennemeier et al., 1993; Haggerty et al., 1990).Attention and visual memory impairment persisted even after participants attaining euthyroid status after 3 and 6 months. These results indicatethat significant memory deficit in middle-aged adults withhypothyroidism can persist even after "adequate" thyroidreplacement. In the elderly age group, Capet et

al and Osterweil et al showed worse performance on cognitive tests as compared to the younger group, which lead to the conclusion of age increasing vulnerability in cognitive functions in hypothyroidism (Capet et al., 2000).

Several studies have been done examining the relationship between TSH and dementia predominantly DAT. Ganguli et al. in 1996 studied 194 patients of dementia in a community-based cross-sectional studyfound the odds ratio of elevated TSH and definite dementia was 3.8 (Ganguli et al., 1996). It was the first community study to show an association between elevated TSH and dementia.In contrast,van Osch al in 2004 showed in a cross-sectional study of 178 DAT patients that lowered TSH was associated with a more than twofold increased risk of AD (odds ratio = 2.36) independent of other risk factors (Hogervorst et al., 2008). Kalmijnet al in 2000 did a population-based prospective study of 1843 participants and found 3 fold risk of dementia and DAT in patients of subclinical hypothyroidism (RR 3.5) (Kalmijn et al., 2000). Finally,ZS Tan et al 2008 studied data from Framingham study in 1864 euthyroid participants found 209 developed DAT in 12 year follow up. The result of this study was aU shaped relationship between TSH levels and risk of DAT only in women. Both high and low TSH levels were associated with an increased risk of dementia in elderly women (Tan, 2008).

In the current study, the TSH levels were compared between dementia and controls. The mean TSH levels were significantly higher in dementia cases as compared to controls however the levels were in the clinically normal range. When the subtypes of the dementia were studied separately then it was found that the serum levels of TSH in cases of DAT were raised as compared to normal elderly group and cases of vascular and mixed dementia. But no significant difference was observed between TSH levels of vascular and mixed dementia and normal elderly controls. In all cases, the levels were within the normal clinical range. These findings are consistent with the above findings of an association between raised TSH and DAT. No difference in the levels of fT3 and fT4 were observed in any of the groups in the current study.

Serum TSH levels were studied among the cases of DAT divided according to the severity using CDR rating. Results show a progressively increasing TSH level from mild to severe, with the highest TSH levels in cases of severe DAT (CDR=3), again the results were within the normal clinical range. The currently accepted range of serum TSH is 0.5 to 5.0 mIU/L. The National Association of Clinical Biochemistry argues that the upper limit of the serum thyrotropin euthyroid range should be reduced to 2.5 mIU/L to better detect mild thyroid disease, citing data that more than 95% of rigorously screened healthy euthyroid volunteers have TSHlevels of 0.4 to 2.5 mIU/L (Garber et al., 2012). Tan in 2008 argues that TSHlevels of 0.1 to 0.4 mIU/L represents thyroid hormone excesses that are associated with increased risk of atrial fibrillation and cardiovascular mortality in elderly individuals according to some studies (Tan, 2008). The present findings of association of DAT in individuals with TSH levels greater than 2.1 mIU/L but less than 5.0mIU/L corroborates with similar findings in other studies, support these recommendations to narrow the target TSH range.

The effect of elevated TSH levels in DAT pathology could be summarized in the following proposed mechanisms. Interaction of thyroid hormone and nerve growth factor and choline acetyltransferase activity was studied in embryonic rat brain and recently it was corroborated by the findings of levothyroxine protecting hippocampal cholinergic neurons in aged mice (Hayashi and Patel, 1987). Findings of these above studies indicate towards development and maintenance of cholinergic neurons in hippocampus and forebrain by thyroid hormones.The second proposed mechanism is thyroid hormone affects gene expression of amyloid precursor protein (APP). Studies by C Contreras-Jurado et al 2012 shows thyroid hormones repressing APP in neuroblastoma cells which lead to a finding of APP messenger RNA and protein levels were found to be significantly higher in the brain of hypothyroid rats and mice, and also in Alzheimer-related brain regions dissected from KO mice (Contreras-Jurado and Pascual, 2012).These findings suggest that subclinical hypothyroidism and resulting low central nervous system thyroid hormone levels may contribute to the development of DAT by directly increasing APP expression and circulating β-amyloid peptide levels. The third proposed mechanism is the cardiovascular changes caused by thyroid hormone. The cardiovascular system responds to minimal but persistent changes in circulating thyroid hormone levels producing changes in vascular reactivity and endothelial function. And changes in the endothelium have been increasingly linked with neurodegenerative diseases including Alzheimer's disease (Klein and Ojamaa, 2001). Finally, the neuroprotective action of thyroid hormone protects against brain injury. Thyroid hormonereduces intracellular H^+ accumulation by stimulation of the Na^+/H^+ exchanger and can support desirably low intracellular $Ca^{2+}$by activation of plasma membrane Ca^{2+}–ATPase. Thyroid hormone also stimulates astrocyte glutamate uptake, an action that protects both glial cells and neurons (Davis et al., 2011). The exact mechanism is still unclear and the above mechanisms may be acting in a multifactorial manner to prevent the pathogenesis of DAT. The above mechanism doesn't also provide clear answers to whether the higher or lower level of thyroid hormones provides protection against Alzheimer's disease, which could indicate a state of thyroid dysfunction either elevated or lower levels may be important for the pathogenesis of Alzheimer's disease.

The study had several limitations. This was a cross-sectional study design with no data about the pre-existing thyroid condition. There was also no follow-up done to study the progress of the thyroid abnormalities with dementia. No post hoc/ regression analysis was performed to identify any confounders in the data.

CONCLUSION

The study concludes that subclinical hypothyroidism is associated with dementia of Alzheimer type. When compared with varied findings of prior studies it can be implied that subclinical thyroid dysfunction not especially hypo or hyperthyroidism is a risk for DAT.

Conflict Of Interest Declaration: None

Description Of Author's Roles:

SS is the principal author, contributed in conception and design of the study, acquisition of data, drafting the article. OP has contributed to discussing the concept, design and written draft of the study. AS contributed in analysis, interpretation of data, and critical revision of the draft of the article.

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REFERENCES

1. Liu, D., Diorio, J., Day, J.C., Francis, D.D. and Meaney, M.J., 2000. Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature neuroscience*, *3*(8), pp.799-806.
2. Smith, J.W., Evans, A.T., Costall, B. and Smythe, J.W., 2002. Thyroid hormones, brain function and cognition: a brief review. *Neuroscience & Biobehavioral Reviews*, *26*(1), pp.45-60.
3. Tan, Z.S., Beiser, A., Vasan, R.S., Au, R., Auerbach, S., Kiel, D.P., Wolf, P.A. and Seshadri, S., 2008. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Archives of internal medicine*, *168*(14), pp.1514-1520.
4. McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS–ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), pp.939-939.
5. Román, G.C., Tatemichi, T.K., Erkinjuntti, T., Cummings, J.L., Masdeu, J.C., Garcia, J.H., Amaducci, L., Orgogozo, J.M., Brun, A., Hofman, A. and Moody, D.M., 1993. Vascular dementia: diagnostic criteria for research studies: report of the NINDS–AIREN International Workshop. *Neurology*, *43*(2), pp.250-250.
6. Morris, J.C., 1997. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International psychogeriatrics*, *9*(S1), pp.173-176.
7. Gussekloo, J., Van Exel, E., de Craen, A.J., Meinders, A.E., Frölich, M. and Westendorp, R.G., 2004. Thyroid status, disability and cognitive function, and survival in old age. *Jama*, *292*(21), pp.2591-2599.
8. Capet, C., Jego, A., Denis, P., Noel, D., Clerc, I., Cornier, A.C., Lefebvre, H., Levesque, H., Chassagne, P., Bercoff, E. and Doucet, J., 2000. Is cognitive change related to hypothyroidism reversible with replacement therapy?. *La Revue de medecine interne*, *21*(8), pp.672-678.
9. Mennemeier, M., Garner, R.D. and Heilman, K.M., 1993. Memory, mood and measurement in hypothyroidism. *Journal of clinical and experimental neuropsychology*, *15*(5), pp.822-831.
10. Haggerty Jr, J.J., Garbutt, J.C., Evans, D.L., Golden, R.N., Pedersen, C., Simon, J.S. and Nemeroff, C.B., 1990. Subclinical hypothyroidism: a review of neuropsychiatric aspects. *The International Journal of Psychiatry in Medicine*, *20*(2), pp.193-208.
11. Ganguli, M., Burmeister, L.A., Seaberg, E.C., Belle, S. and DeKosky, S.T., 1996. Association between dementia and elevated TSH: a community-based study. *Biological psychiatry*, *40*(8), pp.714-725.
12. Hogervorst, E., Huppert, F., Matthews, F.E. and Brayne, C., 2008. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology*, *33*(7), pp.1013-1022.
13. Kalmijn, S., Mehta, K.M., Pols, H.A., Hofman, A., Drexhage, H.A. and Breteler, M.M., 2000. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. *Clinical endocrinology*, *53*(6), pp.733-737.

14. Garber, J.R., 2012. Woeber for the American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on hypothyroidism in adults KA. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*, *22*, pp.1200-1235.
15. Hayashi, M. and Patel, A.J., 1987. An interaction between thyroid hormone and nerve growth factor in the regulation of choline acetyltransferase activity in neuronal cultures, derived from the septal-diagonal band region of the embryonic rat brain. *Developmental Brain Research*, *36*(1), pp.109-120.
16. Contreras-Jurado, C. and Pascual, A., 2012. Thyroid hormone regulation of APP (β-amyloid precursor protein) gene expression in brain and brain cultured cells. *Neurochemistry international*, *60*(5), pp.484-487.
17. Klein, I. and Ojamaa, K., 2001. Thyroid hormone and the cardiovascular system. *New England Journal of Medicine*, *344*(7), pp.501-509.
18. Davis, P., Lin, H.Y., Davis, F.B., Luidens, M., Mousa, S., Cao, J. and Zhou, M., 2011. Molecular basis for certain neuroprotective effects of thyroid hormone. *Frontiers in molecular neuroscience*, *4*, p.29.