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Review Article

# Thyroid Function and Alzheimer's Disease

Zaldy S. Tan[a,*] and Ramachandran S. Vasan[b]
[a]*Division of Aging, Brigham and Women's Hospital; GRECC, VA Boston Healthcare System; Harvard Medical School* (*ZST*), *Boston, MA, USA*
[b]*Department of Medicine* (*RSV*), *Boston University School of Medicine, Boston, MA, USA*

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**Abstract**. Thyroid dysfunction has been implicated as a cause of reversible cognitive impairment and as such, the thyroid stimulating hormone has long been part of the screening laboratory test for dementia. Recently, several population-based studies demonstrated an association between hypo- or hyperthyroidism and Alzheimer's disease. This review discusses the role of thyroid hormone in the normal development and regulation of central nervous system functions and summarizes the studies that have linked thyroid function and dementia risk. Finally, it explores possible biological mechanisms to explain this association, including the direct effects of thyroid hormone on cerebral amyloid processing, neurodegeneration and thyrotropin-mediated mechanisms and vascular mediated enhancement of Alzheimer's disease risk.

Keywords: Alzheimer's disease, dementia, hyperthyroidism, hypothyroidism, thyroid

## INTRODUCTION

Alterations in the endocrine system have increasingly been linked to the pathogenesis of Alzheimer's disease (AD) and other dementias. Insulin resistance [1], elevated cortisol [2] and low estrogen and testosterone [3] levels have all been implicated in the development and/or progression of AD. But arguably the most widely recognized association between endocrine and cognitive functions involves the thyroid hormone. Clinical thyroid dysfunction has been linked to cognitive abnormalities since Asher described "myxoedematous madness" in 1949 [4]. Since then, hypo- and hyperthyroidism have been considered potentially reversible causes of cognitive impairment. 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 [5].

*Corresponding author: Zaldy S. Tan, M.D. Division of Aging, Brigham and Women's Hospital, 1620 Tremont Street, 3rd Flr, Boston, MA 02160, USA. Tel.: +1 617 525 7631; Fax: +1 617 525 7739; E-mail: ztan@hms.harvard.edu.

The association of TSH levels with cognition spans the normal range of the hormone, as well as with values reflecting subclinical dysfunction or overt thyroid dysfunction. Thus, several studies have reported that both higher [6] and lower [7] TSH levels within the 'normal' (euthyroid) range are associated with poor cognitive performance in the absence of clinical thyroid disease. Yet, some other studies [8,9] failed to demonstrate such an association. More recently, thyroid dysfunction has come to attention as a possible independent risk factor for the development of irreversible dementia, with a number of epidemiological studies suggesting a relationship between both hypothyroidism [10] and subclinical hyperthyroidism [11,12] and the risk for dementia. This review explores the possible link between thyroid function and the risk of developing AD.

## THYROID HORMONE AND THE CENTRAL NERVOUS SYSTEM

Thyroid hormones are powerful neuroregulators and neuromodulators of the functions of the central nervous system (CNS). The effects of thyroid hormones

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on neuronal cells begin early during CNS development, with thyroid hormone receptors demonstrated in human neuronal cells as early as the tenth week of gestation [13]. Thyroid hormones have been shown to have profound effects on the maturation of specific neuronal populations [14,15], metabolic effects on mitochondrial respiratory enzyme activity [16], and expression of astrocyte structural proteins [17]. Further, thyroid hormones have a close association with CNS cholinergic function [18], most notably on the basal forebrain and hippocampus [19]. The effects of thyroid hormones on the CNS extend from neuronal development to adult life. Indeed, adult-onset thyroid dysfunction has been associated with a wide range of behavioral and neurological abnormalities, from memory impairment, cerebellar ataxia and tremulousness to depression, irritability and psychosis [20]. Considering the importance of thyroid hormones on CNS function, it is not surprising that cerebral levels of T4 and the more active T3 are tightly regulated and maintained within a narrow range even in the face of fluctuations in serum T4 levels [21]. Such regulation suggests that even slight deviations from this narrow range of normal cerebral thyroid hormone levels may result in cognitive dysfunction [22]. In fact it has been shown that even subclinical hypothyroidism, wherein TSH is elevated but the serum T4 level remains normal, can affect performance on cognitive tests [23]. However, the Leiden-85 plus study showed that in the oldest old, plasma thyrotropin and free thyroxine levels were not associated with cognitive impairment at baseline and after 3.7 years of follow-up [24]. Graves' thyrotoxicosis has been associated with cognitive dysfunction in several studies [25–27], but other studies [28,29] contradict this. A case-control study found that while the majority of patients in the acute phase of Graves' disease reported memory and concentration problems, there were no significant differences in neuropsychological performance in these patients compared to controls [30].

## DEMENTIA AND THYROID FUNCTION

Dementia and thyroid dysfunction are conditions that become more prevalent with advancing age. Previously published data from the original Framingham cohort have demonstrated that the prevalence of overt hypothyroidism (defined as TSH greater than 10 mU/L) is 4.4% in participants over age 60 years [31]. When thyroid deficiency is more liberally defined as TSH levels $>5$ mU/L, the prevalence rises to 10.3%. On the other hand, 'suppressed' TSH levels ($<0.5$ mU/L) have been reported to be present in 3.9% of the original Framingham cohort participants over the age of 60 years. In the Framingham cohort, it was estimated that the cumulative incidence between age 65 and 100 years for AD was 25.5% in men and 28.1% in women [32]. The cumulative incidence in this age group for all-cause dementia was even higher: 32.8% in men and 45% in women. The question remains whether dementia and thyroid dysfunction are independent co-prevalent conditions in older people, or whether a pathophysiological link exists.

There is evidence suggesting a possible genetic link between the two conditions. In a small study of older persons with Down syndrome, a positive association was found between apolipoprotein E allele status and thyroid status, with E2 being negatively- and E4 positively-associated with hypothyroidism [33]. This association was found only in women and not in men. In the Rotterdam Study, de Jong and colleagues examined the association of polymorphisms in the type 1 and 2 deiodinase genes with circulating thyroid hormone levels and the atrophy of the medial temporal lobe [34]. They found an association between polymorphisms of the D1a-C/T and D1b-A/G genes and iodothyronine levels in the elderly but no association of these polymorphisms with early neuroimaging markers for AD.

The majority of investigations that have directly explored the purported relationship between circulating TSH levels and the risk of AD have been case-control and cross-sectional studies [10,11,35,36]. In a small case-control study, Thomas et al. found lower free T3 and blunted TSH response to thyroid releasing hormone (TRH) in patients with severe AD compared to controls [33]. Ganguli and collaborators showed that elevated TSH was significantly and positively associated with a diagnosis of prevalent dementia in an elderly cohort of 194 patients aged 65 years or over [10]. On the other hand, Van Osch and colleagues reported in a cross-sectional study that AD patients had significantly lower levels of circulating TSH compared to controls and that lower TSH was associated with an over two-fold increase in risk of AD, independent of other risk factors [11]. Similarly, in the prospective, population-based Rotterdam study, baseline subclinical hyperthyroidism (defined as TSH $<0.4$ mU/L and thyroxine levels between 65-140 nm/L) in the elderly is associated with a three-fold increased risks for dementia and AD compared to the euthyroid reference group after an average follow-up period of 2 years [12]. In a follow-up study using a population sample independent

of that used for the original study, Rotterdam investigators found no association between TSH levels and the risk of AD after a mean 5.5 years of follow-up [37]. In this study, higher fT4 and rT3 levels were associated with atrophy of the hippocampus and amygdala on MRI, suggesting that hyperthyroidism has a role in the development of AD.

## BIOLOGICAL MECHANISMS UNDERLYING ASSOCIATION OF TSH AND COGNITION

While there is evidence to support a possible link between thyroid function and AD risk, the biological mechanism for such a relationship remains unclear. Theories that have been proposed include both thyroxine-mediated mechanisms (thyroid dysfunction as a consequence of AD neuropathology) and the direct effects of TSH on amyloid-$\beta$ (thyroid dysfunction as a contributing factor to AD neuropathology).

### *Neurodegeneration and thyrotropin-mediated mechanisms*

As a neurodegenerative condition, AD pathology leads to the progressive accumulation of amyloid plaques and neurofibrillary tangles and nerve cell loss. It has been proposed that this process may also lead to a reduction in secretion of TRH by the hypothalamus and/or alterations in pituitary responsiveness to TRH, manifesting as reduced TSH and thyroxine levels. This theory suggests that the observed low TSH is the result, rather than the cause, of AD. If such were the case, one would also expect blood T4 concentrations to be low. However, in the Rotterdam study, it was found that circulating T4 levels were higher in those who subsequently developed dementia. Consequently, the validity of the 'reverse epidemiology' theory to explain the relationship between thyroid function and AD risk may be questioned.

### *Direct effects of thyroid hormones*

Altered TSH or TRH levels may precede and contribute to the development of AD through direct effects on the processing of cerebral amyloid-$\beta$ proteins and/or the local synthesis and release of acetylcholine from neurons. This theory relies on studies that show elevated thyroid hormone levels are associated with increased oxidative stress [38] and neuronal death [39]. Thyroid hormone has been shown to regulate the gene expression of the amyloid-$\beta$ protein precursor (A$\beta$PP); *in vitro*, triiodothyronine (T3) represses A$\beta$PP promoter activity and regulates A$\beta$PP processing and secretion in neuroblastoma cells [40,41] and *in vivo*, a hypothyroid state enhances the expression of A$\beta$PP gene product in mouse brains [42]. Thus, low CNS thyroid hormone levels may contribute to the development of AD by directly increasing A$\beta$PP expression and consequently, amyloid-$\beta$ peptide and amyloid-$\beta$ levels. On a parallel note, TRH depletion has been associated with enhanced phosphorylation of tau proteins [43]. Further, TRH analogues have been shown to increase acetylcholine synthesis and release in rodents, a process that in turn may lead to relative shortage of local acetylcholine and eventually its depletion [44]. Increased oxidative stress and decreased antioxidant metabolites have been detected in hyperthyroid patients [17] and exposure to thyroid hormone has been shown to enhance neuronal death [18].

### *Vascular factor-mediated mechanisms*

An alternative explanation for a thyroid-AD link is the mediation of risk by vascular factors. Both clinical and sub-clinical thyroid dysfunction affect cardiovascular risk [45–47] and in parallel, vascular risk factors have been correlated with an increase in the risk for AD [48,49]. Thus, through an increase in vascular risk factors such as diabetes, hypertension, heart disease and smoking, thyroid function may indirectly affect AD risk.

## CONCLUSIONS

Accumulating evidence has linked thyroid dysfunction with a heightened risk of developing AD; plausible biological mechanisms have been proposed to explain this possible association. Larger, prospective studies are needed to further elucidate whether high or low thyroid hormone levels is a modifiable AD risk factor.

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