SUMMARY

Background: Clinical hypothyroidism & hyperthyroidism are recognized causes of reversible dementia, but previous studies relating TSH levels to cognitive performance in clinically euthyroid persons have yielded inconsistent results.

Methods: The authors related serum TSH concentrations measured at baseline (1977-1979) to the risk of Alzheimer disease (AD) in 1,864 cognitively intact, clinically euthyroid Framingham original cohort participants (mean age 71 years; 59% women). Sex-specific Cox proportional hazards models were constructed using tertiles of TSH concentration (tertile 2 was considered the reference range) and adjusting for age, apolipoprotein E epsilon4 allele status, educational level, plasma homocysteine level, current smoking, body mass index, prevalent stroke, and atrial fibrillation.

Results: During a mean follow-up of 12.7 years (range: 1-25 years), 209 participants (142 women) developed AD. Women in the lowest (<1.0 mU/L) and highest (>2.1 mU/L) tertiles of serum TSH were at increased risk for AD (multivariate-adjusted hazard ratio: 2.39 [95% C.I.: 1.47-3.87; P<0.001] and 2.15 [95% C.I.: 1.31-3.52; P=0.003], respectively) compared with those in the middle tertile. TSH levels were not related to AD risk in men. Analyses excluding individuals receiving thyroid supplementation did not significantly alter these relationships. In analyses limited to participants with serum TSH levels between 0.1-10 mU/L, the U-shaped relationship between TSH and AD risk was maintained in women but not when analyses were limited to those with TSH between 0.5-5 mU/L.

Conclusions: Low & high TSH levels were associated with an increased risk of incident AD in women, but not in men.

COMMENT

Hypo- & hyperthyroidism are known causes of potential cognitive impairment, but they are classically considered to be reversible upon restoration of euthyroidism. In the last decade, thyroid dysfunction has emerged as a possible risk factor for irreversible dementia, based on a few epidemiologic studies implicating hypothyroidism (from Pittsburgh, USA, 1996 & Oxford, UK, 2004) and hyperthyroidism (Rotterdam study 2000). The strength of present study included its prospective design, a long follow-up period of over 12 years, and the large number of subjects (close to 2,000) followed within the frame of the Framingham cohort studies. Its limitations were the availability of only a single TSH determination (without thyroid hormone measurements) and the lack of information concerning possible confounders, such as depression or non-thyroidal illnesses.

In this study sample, 13% of women and 9% of men developed Alzheimer disease after a follow-up period of ~13 years. Also, 4.2% of participants had a serum TSH >10 µU/ml and 5% less than 0.1 µU/ml.
The main results were to show that both low (0.1 → 1.0 µU/ml) and high (2.1 → 50 µU/ml) serum TSH levels were associated - in women but not in men - with a significantly increased risk for incident Alzheimer disease yielding an adjusted hazard ratio greater than 2.

Since serum TSH was measured only once at the onset of the follow-up period, it is unclear whether the alterations in serum TSH occurred before or after the onset of dementia.

Concerning the mechanisms that might explain this association, the authors speculate on direct adverse effects of thyroid hormone depletion on cholinergic neurons, possible vascular-mediated mechanisms, and the known implication of thyroid hormones in the regulation of gene expression for APP (the amyloid precursor protein).

This work, despite its inherent weaknesses, has the interest of being a ‘hypothesis generating’ study (to keep an open mind), to be validated further in more complete population studies before one can draw clinical conclusions.

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See Figure below

(Female population in study: the lowest curve shows the incidence of Alzheimer disease in women with serum TSH in the middle tertile, i.e. between 1.0 and 2.1 mU/L (black squares). The upper curve shows women with a low serum TSH (black circles) and the middle curve women with a high serum TSH (above 2.1 mU/L).