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Thyroid function in patients with Alzheimer's disease treated with cholinesterase inhibitors

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Short communication

Abstract. The aim of the present study was to explore a possible interplay between cholinesterase inhibitors (ChEIs) and thyroid function tests (TFTs) in patients with Alzheimer's disease (AD). We reviewed thyroid function tests in 19 patients with AD before and after treatment (Rx) with ChEIs. Immunoradiometric assays were used for measuring serum thyrotropin, free thyroxin (FT_4) and free triiodothyronine (FT_3). Significant differences were observed among FT_3 levels according to the duration of therapy. Subtle variations in thyroid function tests – before and after therapy – could be possibly related to ChEIs-induced altered thyroid function.

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Endocrine changes have long been studied in Alzheimer's disease (AD) (Davidson et al. 1988). Among them, thyroid function has received particular attention. Epidemiologic studies have yielded conflicting results in the evaluation of previous thyroid disease as a possible risk factor for AD (Kalmijn et al. 2000, Lopez et al. 1989, Yoshimasu et al. 1991). An abnormal thyrotropin (TSH) response to thyrotropin-releasing hormone (Molchan et al. 1991, Sunderland et al. 1985) and low levels of free triiodothyronine (FT_3) (Thomas et al. 1987) have been found in some AD patients. A significant percentage of patients with Down's syndrome – a population that develops AD at very young age – show increased levels of antithyroid antibodies (Genovesi et al. 1996). Autoimmune thyroid disorders like Hashimoto's thyroiditis and the euthyroid sick syndrome share with AD the involvement of some common inflammatory mediators, such as increased interleukin-6 release (Martinez et al. 2000).

Cholinesterase inhibitors (ChEIs) are currently the treatment (Rx) of choice for patients with AD (Emilien et al. 2000). Acetylcholinesterase presents structural and immunological similarities with thyroglobulin, which plays a pivotal role as a matrix for thyroid hormone production (Mappouras et al. 1995). In experimental studies, acetylcholine (ACh) has been shown to favor iodine organification and to alter the TSH-induced thyroxin (T_4) release from the thyroid (Maayan et al. 1983); consequently, in patients with AD receiving ChEIs Rx, a tentative interplay between ChEIs Rx and thyroid function tests (TFTs) could exist. The present study has been undertaken in order to investigate this hypothesis.

We reviewed the cases of 19 AD patients (9 men and 10 women; mean age ± SD: 69.4 ± 7.8 years), suffering from AD in the proceeding 5-6 years, based on personal history and information provided by caregivers and diagnosed with probable AD according to the NINCDS-ADRDA criteria (MacKhann et al. 1984). The patients received ChEIs Rx with either donepezil *(n* = 10) or rivastigmine (*n* = 9), both titrated at therapeutic doses (5-10 mg/day or 6-12 mg/day, respectively; median duration of Rx: 5 months, maximum: 22 months, minimum: 3 months). There was no history of thyroid disease or of any other major ailment in any of the patients. Immunoradiometric assays were used for measuring serum TSH (Clinical Assays Gammacoat hTSH, DiaSorin, MN, USA; normal range: 0.4-4.0 mIU/ml), free T_4 (FT_4; FT_4 Myria, Technogenetics, MI, Italy; normal range: 7.0-18.0 pg/ml;) and FT_3 (FT_3 Myria, Technogenetics, MI, Italy; normal range: 2.3-4.0

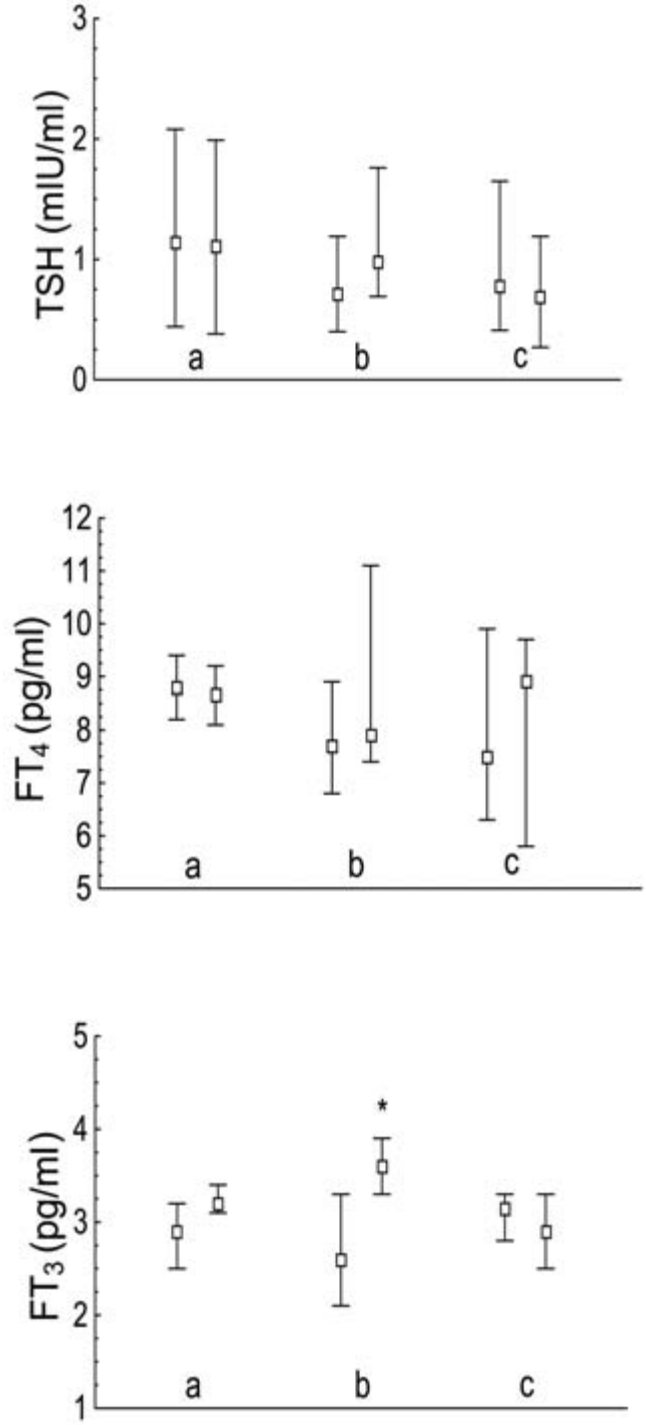

Fig. 1. Median, minimum and maximum thyroid function tests values at baseline (left) and according to cholinesterase inhibitor therapy duration (right); (a) duration of treatment for up to 6 months; (b) duration of treatment between 6 and 12 months; (c) duration of treatment for more than 12 months; (TSH) thyrotropin; (FT_4) free thyroxine; (FT_3) free triiodothyronine; an asterisk denotes significant differences (P<0.05; Wilcoxon matched-pairs test).

pg/ml). Each patient was assessed twice, before and after ChEI Rx. Evaluation of TFTs – before and after ChEIs Rx – was done with the Kruskall-Wallis non-parametric analysis of variance (K-W) and the Wilcoxon matched-pairs test (W-M).

All the patients were clinically and biochemically euthyroid, although at low-normal levels (Fig. 1). No overall significant differences were observed in TFTs before and after ChEIs Rx (all $P>0.50$; K-W), however, FT_3 levels were higher in patients who received ChEIs Rx for 6-12 months ($P<0.05$; W-M) (Fig. 1).

In this small-scale review of cases a relation of yet-unknown pathophysiological significance could be suggested between FT_3 and the duration of ChEIs Rx in patients with AD. Increases in FT_3 were observed during the initial period of therapy followed by a decrease.

Experience with ChEIs Rx in patients with AD has shown that these medications are most beneficial to cognition and other neuropsychological functions of treated patients, within the first 6 months of administration followed by a gradual decline (Emilien et al. 2000); in fact, the long-term efficacy of such compounds is being questioned. One possible explanation for this decline is that elevated levels of ACh in the synapse can induce inhibition of further ACh release by activation of presynaptic muscarinic M_2 receptors (Svensson et al. 1996). In the present study the FT_3 response seem to follow an inverted U-shape that runs in parallel with the inverted U-shape time-mode of cognitive function of patients given ChEIs (Grutzendler and Morris 2001).

There is an increasing amount of evidence for an extensive inter-reliance between thyroid hormones and ACh (Smith et al. 2002). There is also evidence that thyroid hormones influence the expression of transmitter-specific enzymes by central cholinergic neurons. T_3 was found to stimulate choline acetyltransferase activity in a dose-related manner (Hefti et al. 1986). Rats treated with T_4, administered both sub-chronically and chronically, significantly enhanced the ability to learn a spatial memory task, compared with controls (Smith et al. 2002). In a recent report, total T_4 – within "normal" range of variation – was shown to be positively associated with general cognition (assessed with the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Dementia Rating Scale (DRS) and the Rivermead Behavioral Profile (PROFILE) in healthy elderly men (Prinz et al. 1999). Additionally, in patients with hypothyroidism, partial substitution of T_4 with T_3 has been shown to improve mood and neuropsychological function (Bunevicius et al. 1999). In AD patients thyroid hormone receptor c-ERB A alpha levels have been found decreased in the hippocampus (Sutherland et al. 1992).

The results of the present study support previous findings of a relationship between thyroid hormones and ACh. The beneficial effects of ChEIs in cognition may partially be mediated by up-regulation of thyroid function through increased ACh levels. This report has limitations, the major one being the small number of patients studied. Additionally, thyroid antibodies determinations were not available. Further studies are required to corroborate the relationship between TFTs and ChEIs Rx in AD patients and possibly to assess an eventual beneficial effect of small doses of T_3 or T_4 in patients with AD.

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