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Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease

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ABSTRACT

Background: In epidemiological studies, thyroid hormones (THs) have been associated with the risk of dementia. However, little is known of the relation between THs and risk of Alzheimer's disease (AD) or vascular dementia (VaD) in a memory clinic population.

Methods: In a mono-center study, serum concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were assessed in 302 patients. All patients had subjective or objective mild cognitive impairment and none received treatment with THs. Cox proportional hazards regression analyses was used to determine whether THs at baseline were associated with the risk of conversion to all-cause dementia, AD or VaD.

Results: During the follow-up (mean 2.8 years), 82 (28%) of the patients progressed to dementia [AD, n = 55 (18%) and VaD, n = 17 (6%)]. Serum concentrations of TSH, FT4, and FT3 did not associate with all-cause dementia or VaD. Higher serum FT3 was associated with lower risk of conversion to AD [hazard ratio (HR) = 054; 95% confidence interval (CI): 0.32–0.92 per 1 pmol/L increase]. Furthermore, patients in the lowest serum FT3 quartile had a twofold increased risk of AD compared to those in the highest quartile (HR = 2.63; 95% CI: 1.06–6.47). These associations remained after adjustment for multiple covariates.

Conclusions: In a memory clinic population, there was an inverse, linear association between serum FT3 and risk of AD whereas THs did not associate with all-cause dementia or VaD. Further studies are needed to determine the underlying mechanisms as well as the clinical significance of these findings.

1. Introduction

Thyroid hormone (TH) receptors are widely expressed in the brain (Wallis et al., 2010). THs are essential for the development of the central nervous system (CNS) during perinatal growth, and also influence the adult CNS by promoting neurogenesis, myelination and cellular repair (Lin et al., 2011; Remaud et al., 2014). Late in life, serum levels of thyroid-stimulating hormone (TSH) and unbound levels of the bioactive triiodothyronine (T3) decline, while free levels of thyroxine (T4), often viewed as a prohormone to T3, are maintained (Boelaert, 2013). This may be of importance as not only excess and deficiency of THs, but also variations within the normal range, have been associated with increased risk of age-associated phenotypes and mortality (Cappola et al., 2015, 2006; Gussekloo et al., 2004; Taylor et al., 2013). Moreover, the pathogenesis of Alzheimer's disease (AD) may be affected by THs as *in vitro* and *in vivo* studies suggest that THs could affect the transcription of the amyloidprecursor protein (APP) gene as well as the phosphorylation of tau (Belakavadi et al., 2011; Belandia et al., 1998; Contreras-Jurado and Pascual, 2012; Luo et al., 2002; O'Barr et al., 2006; Oyanagi et al., 2015).

Several population-based studies have identified that excess of THs poses a greater risk for dementia (Kalmijn et al., 2000; Vadiveloo et al., 2011). However, even within the reference range, low-normal TSH and high-normal total T4 (TT4) and free T4 (FT4) are risk factors for all-cause dementia and AD (Annerbo et al., 2006; Chaker et al., 2016; Moon et al., 2014; Yeap et al., 2012). Furthermore, TH deficiency could also be of importance as overt hypothyroidism is accompanied by cognitive impairment (Baldini et al., 2009; Kramer et al., 2009). A population-based, cross-sectional study observed an association between elevated TSH and all-cause dementia (Ganguli et al., 1996). In a re-analysis of eight case-control studies, history of hypothyroidism was more frequent in AD patients compared to controls (Breteler et al., 1991). In manifest AD, serum TSH was higher and cerebrospinal fluid (CSF) TT4 was lower compared to that in healthy controls (Johansson

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et al., 2013).

Few studies have examined the relation between serum levels of T3, especially the bioactive free T3 (FT3), and the risk of dementia. In very old individuals included in the Leiden 85-Plus Study, low serum FT3 was associated with faster cognitive decline whereas the risk of dementia was not investigated (Gussekloo et al., 2004). Two population-based studies did not find any association between circulating levels of total T3 (TT3) and the risk of all-cause dementia or AD (Cappola et al., 2015; de Jong et al., 2006). In addition, two cross-sectional studies in manifest AD found unchanged serum levels of FT3 in AD patients whereas TT3 concentrations in CSF were unchanged or reduced compared to controls (Accorroni et al., 2017; Sampaolo et al., 2005). Similarly, a post-mortem study displayed lower brain levels of TT3 in AD patients (Davis et al., 2008).

In summary, several epidemiological studies have observed that higher TH levels are associated with increased risk of dementia. In manifest dementia, however, the results are less clear and studies in AD patients suggest that TH concentrations in serum and CNS may even be reduced. Little is known of the predictive role of THs in the early disease stages, in which the patients show signs of cognitive dysfunction without clinically detectable dementia. In this mono-center study of patients with subjective cognitive impairment (SCI) or objective mild cognitive impairment (MCI), we determined whether serum TH concentrations including FT3 were associated with the risk of conversion to AD or vascular dementia (VaD).

2. Material and methods

2.1. Study participants

The Gothenburg MCI study is a longitudinal, single-center study including consecutive patients at a memory clinic (Wallin et al., 2016b). All patients undergo a thorough baseline investigation including medical history, physical, radiological, neurological and psychiatric examinations and are then followed biannually. n the Gothenburg MCI study, inclusion criteria comprise age > 40 and < 79 years, Mini Mental State Examination (MMSE) score > 19, and self- or informant-reported cognitive decline with a duration ⩾6 months. The exclusion criteria were designed to prevent the enrollment of patients with acute, systemic or other somatic and psychiatric disorders that could cause cognitive impairment (Wallin et al., 2016b). Thus, patients with subdural hemorrhage, malignant disease including brain tumor, thyroid disease except for treated hypothyroidism, encephalitis, and unstable heart disease were excluded as well as patients with major affective disorder, bipolar disorder, schizophrenia, substance abuse, and confusion.

At the time of the present analyses, 751 patients were enrolled in the study. In this study, participants were excluded due to lack of adequate blood sample (n = 121), manifest dementia (n = 206), lack of follow-up visit (n = 95), and levothyroxine treatment (n = 27). None of the remaining 302 patients received treatment with amiodarone, lithium, or thyreostatics (methimazole or propylthiouracil) at any time point of the study.

2.2. Ethical considerations

The study was approved by the ethical committee at University of Gothenburg. Oral and written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki.

2.3. Diagnostic procedure

Cognitive decline was classified using the global deterioration scale (GDS), in which GDS stage 1 equals no cognitive deficit and stage 4 indicates possible mild dementia. Stage 2 equals subjective cognitive impairment (SCI) and stage 3 equals objective mild cognitive impairment (MCI) (Reisberg et al., 1982). The classification was based on the medical history (self-reported and medical record review) and assessment of cognitive symptoms including the cognitive variables 13–20 of the Stepwise Comparative Status Analysis (STEP) covering memory disturbance, disorientation, impaired abstract thinking, impaired spatial functioning, poverty of language, agnosia and apraxia (Wallin et al., 1996); I-Flex, a short form of the Executive Interview (EXIT) (Royall et al., 1992); MMSE (Folstein et al., 1975); and the Clinical Dementia Rating Scale (CDR) (Morris, 1997). The CDR rating was based on information provided by the participant and an informant. The algorithm for GDS 2–3 was: STEP ≤ 1; IFLEX ≤ 3; CDR ≤ 0.5; MMSE ≥ 26.

The follow-up time was calculated from the inclusion to the date of conversion to dementia (generally at one of the follow-up visits) or, for those who remained stable, to the last follow-up examination. The mean follow-up was 2.8 (SD 1.3) years. The maximum follow-up time was 6 years. During the follow-up, 82 patients converted to dementia. The diagnostic process has been described previously in detail (Wallin et al., 2016b). For the diagnosis of dementia subtypes, the clinicians had access to magnetic resonance imaging (MRI) data but were blinded to CSF biomarkers and neuropsychological test results.

For the diagnosis of AD, the 1984 criteria of The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were used (McKhann et al., 1984). AD patients with concomitant MRI findings of cerebral white matter changes (n = 21) were classified as AD since a vascular contribution is common in AD (Lo and Jagust, 2012). Thus, a total of 55 patients were classified as suffering from AD. Vascular dementia (n = 17) was diagnosed as either the subcortical small vessel type of dementia (SSVD) according to the Erkinjuntti criteria (Erkinjuntti et al., 2000) or cortical vascular dementia (cVaD) according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (Roman et al., 1993).

Ten patients converted to dementias other than AD or VAD. Lewy body dementia (n = 2) and primary progressive dementia (n = 1) were diagnosed as described previously (Wallin et al., 2016a, b). Seven patients converted to unspecified dementia.

2.4. Assessment of covariates

Body weight was recorded to the nearest 0.5 kg, and body height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as kilograms per meter squared (kg/m^2). Medication, smoking habits as well as the presence of diabetes mellitus and hypertension was evaluated at each visit by a specialist physician.

2.5. Biochemical methods

At each visit, blood was drawn in the fasted state between 8 A.M. and 10 A.M. and then stored at −80 °C pending biochemical analyses. Low-density lipoprotein (LDL)-cholesterol was calculated according to Friedewald's formula (Friedewald et al., 1972) based on routine clinical measurements of total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides. *APOE* (gene map locus 19q13.2) genotyping was performed by minisequencing as described previously (Blennow et al., 2000).

Serum concentrations of TSH, FT4, and FT3 were measured by Elecsys electrochemiluminescent immunoassays on a Cobas 8000 instrument (Roche Diagnostics Scandinavia AB, Stockholm, Sweden). The analyses of TSH, FT4, and FT3 in serum were performed at one occasion in 2015 at the central laboratory of Sahlgrenska University Hospital. The reference ranges were: TSH: 0.3–4.2 mlU/l, FT4: 12–22 pmol/L, and FT3: 3,1–6,8 pmol/L.