Free thyroxine, cognitive decline and depression in Alzheimer's disease

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Abstract

The role of thyroid function in Alzheimer's disease (AD) has been subject to a number of studies during the last years. We investigated the possible relationship between plasma levels of the biologically active free form of thyroxin (fT4) and cognitive function in 227 outpatients with mild to moderate Alzheimer´s disease (AD) in a cross-sectional study design. A significant negative correlation was found between plasma fT4-levels and Mini-Mental state examination (MMSE) score (Spearman Rho = –0.14, p=0.04). When the lowest quartile of fT4-levels (<15.1 pmol/l) was compared to the highest quartile (>19.0 pmol/l), statistically significant lower mean MMSE-scores were seen in the group with the highest fT4-levels ($p<0.05$, ANOVA). The mean difference between the 1st and the 4th quartile of fT4 was 2.6 MMSE-score points. No correlations were found between plasma total T4-levels, plasma total T3-levels, plasma TSH-levels and the MMSE score ($p>0.05$). When fT4 quartile groups were compared for depression measured in the Geriatric Depression Score (GDS 15), a slightly higher score was seen in the 1s and 2nd compared to the 3rd and 4th quartile groups without reaching statistical significance (1st quartile of fT4: GDS 5.2 ± 3.8; 2nd :5.3 ± 4.0; 3rd: 4.4 ± 3.4; 4th : 4.5 ± 3.8) pointing to a reverse correlation of fT4 levels and depressive mood. This study leads to the conclusion that high levels of plasma fT4 might result in a worsening of cognitive impairment and a positive effect on depressive mood in AD.

Introduction

Altered thyroid function may lead to impaired cognition and neuropsychiatric symptoms in non-demented individuals [1]. While in earlier studies no association between thyroid dysfunction and AD was seen [2–4], the Rotterdam study, a large prospective study on AD risk factors, found a 2.9-fold increased AD risk in individuals with subclinical increased thyroxin (T4) levels and low plasma thyroid stimulating hormone (TSH) [5]. Dobert et al. found decreased levels of TSH indicative of a subclinical hyperthyreodism in patients with AD and vascular dementia compared to

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controls [6], and lowered TSH within the normal range was identified as an independent risk factor for AD [7]. In a study with 28 AD patients an inverse correlation between T4 levels and self reported fear and fatique was seen in euthyreotic individuals, but no relationship between thyroid function and cognition [8]. Taken together these studies suggest, that subclinical hyperthyreodism before clinical onset of AD, seen either as reduced TSH or increased thyroxin, might increase the risk of developing AD, and that thyroxin and TSH levels are altered in a sense of subclinical hyperthyreodism in patients who clinically suffer from AD. In this study we aimed to investigate the relationship between fT3, fT4, TSH, total T4, total T3 and cognition and depression in patients with mild to moderate AD.

Materials, Methods and Patients

We included 227 consecutive outpatients (133 female, 94 male) of the Memory Clinic of the Department of Psychiatry, University Hospital Hamburg-Eppendorf with mild to moderate probable AD in this study. Clinical evaluation included detailed medical history, psychiatric, somatic and neurological status, neuropsychological tests, routine blood tests, specific blood tests, an electroencephalogram, a computed tomographic scan or magnetic resonance imaging. Mini-Mental-Status Examination (MMSE) was used for staging severity of cognitive impairment [9], Geriatric Depression Score (GDS 15) was performed to quantify depressive symptoms. The examination took place prior to the start of any treatment affecting the central nervous system (eg. acetylcholineesterase inhibitors, antidepressants or antipsychotic drugs). AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [10,11,12,13,14]. Blood samples for the determination of plasma hormone levels were taken after overnight fasting and analysis were performed routinely in our central laboratory within 24 hours of sample preservation. The apo E genotype was determined using the restriction isotyping method as described elsewhere [15]. The study was performed in the framework of the Alzheimerforschergruppe Hamburg and was approved by the Ethical Committee, Hamburg. Informed consent according to the declaration of Helsinki was obtained from each patient.

Results

The mean age of the 227 included AD patients was 71.6 ± 8.4 (SD), ranging from 49 to 91 years, the mean MMSE score in the study population was 18.6 ± 6.2 (SD), reflecting mild to moderate AD. The levels of fT4 were predominantly within the normal range (mean 17.3 ± 3.2 pmol/l). A significant negative correlation was found between plasma free-T4-levels and Mini-Mental state examination (MMSE) score (Spearman Rank Correlation, Spearman Rho = –0.14, p=0.04).

No correlations were found between plasma total T4-levels, plasma total T3-levels, plasma TSH-levels and the Mini-Mental state examination scores or GDS 15.

When the study population was divided into quartiles of fT4, the lowest quartile group (<15.1 mmol/l fT4) had significantly higher MMSE scores than the highest quartile group (>19.0 mmol/l fT4, $p<0.05$, ANOVA), while the middle quartile groups showed intermediate MMSE-scores (1^{st} quartile of fT4: MMSE 20.3 ± 5.1, 2^{nd} :18.0 ± 7.1, 3^{rd} :18.3 ± 5.5, 4^{th}:17.7 ± 6.4) The mean difference between 1^{st} and 4^{th} quartile of fT4 was 2.6 MMSE points. When fT4 quartile groups were compared for depression measured in the GDS 15, a slightly higher score was seen in the 1^{s} and 2^{nd} compared to the 3^{rd} and 4^{th} quartile groups without reaching statistical significance (1^{st} quartile of fT4: GDS 5.2 ± 3.8; 2^{nd} :5.3 ± 4.0; 3^{rd}: 4.4 ± 3.4; 4^{th} : 4.5 ± 3.8) pointing to a reverse correlation of fT4 levels and depressive mood. We did not observe any statistically significant association between fT4 levels and vascular risk factors such as hypertension, smoking status, low-density lipoprotein levels, high-density lipoprotein levels or Apo E 4-allel frequency (data not shown).

Discussion

We could demostrate an inverse relationship between plasma levels of fT4 and MMSE scores, pointing to an interaction of thyroid dysfunction and cognition in patients with AD. We also found a weak association of depressive symptoms and low fT4 which might represent the widely discussed influence of thyroid function on mood [1;8]. Especially in elderly persons, subclinical changes of thyroid hormones are thought to influence the cognitive and neuropsychiatric functions [1], an effect that might be more accentuated in AD patients due to the a concomitant affection of the central nervous system. Subclinical hyperthyroidism has been identified as a risk factor for developing AD in elderly people in the Rotterdam study [5]. It has also been found in case-control studies in relatively small samples of AD [6;7]. We could observe increased fT4 levels associated with decreased mental status in a large study population. These findings show that AD might be associated with subclinical hyperthyroidism. Thus, thyroid hormones might play a causative role in AD, or subclinical hyperthyreodism is a reaction to AD pathomechanisms.

The role that thyroid hormones play in the CNS is not exactly understood, but recent studies suggest that thyroid hormones are also functioning as neurotrophic factors capable of enhancing synaptic plasticity and remyelination [16,17] and are able to influence neurotransmitter release in the CNS [18]. Thus it could be speculated that subclinical hypothyroidism might be a neurotrophic physiological reaction to synaptical

loss and presymptomatic AD. This hypothesis may be supported by our finding of increased fT4 values in the group of more severely impaired AD patients, but further validation by longitudinal studies is needed.

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