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Neurobiology of Aging 30 (2009) 600–606

NEUROBIOLOGY OF AGING

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Thyroid function, the risk of dementia and neuropathologic changes: The Honolulu–Asia Aging Study

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Received 5 December 2006; received in revised form 26 June 2007; accepted 28 July 2007
Available online 17 September 2007

Abstract

Thyroid dysfunction is associated with cognitive impairment and dementia, including Alzheimer's disease (AD). It remains unclear whether thyroid dysfunction results from, or contributes to, Alzheimer pathology. We determined whether thyroid function is associated with dementia, specifically AD, and Alzheimer-type neuropathology in a prospective population-based cohort of Japanese-American men. Thyrotropin, total and free thyroxine were available in 665 men aged 71–93 years and dementia-free at baseline (1991), including 143 men who participated in an autopsy sub-study. During a mean follow-up of 4.7 (S.D.: 1.8) years, 106 men developed dementia of whom 74 had AD. Higher total and free thyroxine levels were associated with an increased risk of dementia and AD (age and sex adjusted hazard ratio (95% confidence interval) per S.D. increase in free thyroxine: 1.21 (1.04; 1.40) and 1.31 (1.14; 1.51), respectively). In the autopsied sub-sample, higher total thyroxine was associated with higher number of neocortical neuritic plaques and neurofibrillary tangles. No associations were found for thyrotropin. Our findings suggest that higher thyroxine levels are present with Alzheimer clinical disease and neuropathology.

Keywords: Epidemiology; Thyroid hormones; Thyrotropin; Total thyroxine; Free thyroxine; Dementia; Alzheimer's disease; Neuropathology; Neuritic plaques; Neurofibrillary tangles

1. Introduction

Clinical thyroid disorders are associated with cognitive impairment and dementia (Dugbartey, 1998). Experimental studies report thyroid hormones to induce changes in amyloid precursor processing or deposition of amyloid-β (Belandia et al., 1998; Latasa et al., 1998), the major component of the amyloid deposits found in the brain of cases of Alzheimer's disease. This suggests there may be a role for thyroid hormones in the etiology of AD, the most frequent form of dementia.

In the past, several small case–control studies have been published, showing either no association (Small et al., 1985; Yoshimasu et al., 1991) or an association of hypothyroidism with AD (Breteler et al., 1991; Ganguli et al., 1996). Conversely, a more recent case–control study showed that sub-clinical hyper- rather than hypo-thyroidism was associated with a higher risk for AD (van Osch et al., 2004).

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doi:10.1016/j.neurobiolaging.2007.07.019

These mixed findings may result from the methodological limitations of a cross-sectional study design, including bias in subject selection and retrospective assessment of thyroid function. To date, there are few prospective studies that have examined the association between thyroid function and AD. In the Rotterdam Study, sub-clinical hyperthyroidism was associated with a higher risk for dementia and AD after a 2-year follow-up period (Kalmijn et al., 2000). In the Rotterdam Scan Study, no association was found with AD during a 5 year follow-up period, although higher thyroid hormone levels were associated with markers of brain atrophy on MRI scans of non-demented elderly (de Jong et al., 2006).

Findings of sub-clinical levels of thyroid dysregulation, in particular sub-clinical hyperthyroidism, with an increased risk of AD are of interest but need replication. In addition, it remains unclear how thyroid function is related to AD. Although thyroid dysregulation could be contributing to Alzheimer pathology it is also possible that it is merely a consequence of the disease process, reflecting sub-clinical disease. Studies with a longer follow-up for dementia with supporting data on neuropathological features of AD may give additional insight into the role of thyroid hormones in the Alzheimer process. With data from the Honolulu–Asia Aging Study (HAAS), a longitudinal study that includes assessment of clinical dementia, as well as an autopsy sub-study of the cohort, we tested the hypothesis that higher levels of thyroid measures are associated with an increased risk of AD and neuropathological markers thereof.

2. Methods

2.1. Design

The baseline sample consisted of participants of the Honolulu Heart Program, a prospective cohort study carried out among Japanese-American men living on the Island of Oahu, Hawaii from 1965 onwards (Syme et al., 1975). Participants were examined on three occasions between 1965 and 1971. Of the 4676 survivors, 3734 (80%) participated in a fourth examination between 1991 and 1993 as part of the HAAS. Between 1994–1996 and 1997–1999, two additional examinations were carried out (participation rates 84 and 75%, respectively). Prevalent dementia was ascertained at examination 4 and incident dementia at examinations 5 and 6. In 1991, an autopsy program was instituted to study risk factors for, and disease correlates, of neuropathologic markers of brain disease. All participants gave written, informed consent at each examination. Family members gave permission for cases of dementia. The study protocol was approved by the Kuakini Medical Center institutional review board.

2.2. Dementia case finding procedures

Dementia and its subtypes were identified in a multi-step case-finding procedure, described in detail elsewhere (Havlik et al., 2000; White et al., 1996). In brief, all participants underwent neuropsychological screening with the 100-point Cognitive Abilities Screening Instrument (CASI), a measure of global function that has been validated in English and Japanese (Teng et al., 1994). Diagnosis was based on neuropsychologic testing using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery, a neurologic exam and an informant interview. Those with dementia received a work-up with neuroimaging (in 86%) and blood tests. All recognized subtypes of dementia were considered in the diagnostic consensus conference that included a neurologist and at least two other study investigators. Dementia was diagnosed according to DSM-III-R criteria (APA, 1987), probable and possible AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and related Disorders Association criteria (McKhann et al., 1984), and vascular dementia according to California Alzheimer's Disease and Treatment Centers criteria (Chui et al., 1992). The remaining subtypes included subdural hematoma, Parkinson disease, cortical Lewy body disease, Pick disease, and cause not determined. Among participants who received autopsy evaluation, approximately two-thirds of the clinical Alzheimer cases met CERAD neuropathologic criteria (Mirra et al., 1991) for AD (Petrovitch et al., 2001).

2.3. Autopsy sub-study

Procedures for autopsy and neuropathological examination have been described elsewhere (Petrovitch et al., 2001). At death, brains were fixed in formalin for a minimum of 10 days. After fixation, brains were weighed, the cerebellum and brainstem were removed from the cerebral hemispheres, and all were cut serially in the coronal plane at 1-cm thickness. Slices were examined for grossly apparent neuropathologic lesions, and the whole brain and slices were photographed. Tissue from four areas of neocortex (middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, and occipital cortex) and two areas of hippocampus (CA1 and subiculum) was used to prepare Bielschowsky silver-stained sections. Samples were evaluated by one of three neuropathologists who were blinded to clinical information. Senile plaques (SP) (diffuse and neuritic plaques), neuritic plaques (NP) and neurofibrillary tangles (NFT) were counted in five fields from the CA1 and subiculum of the hippocampus and five fields each from the four areas of neocortex. Counts were standardized to 1-mm^2 field areas (Petrovitch et al., 1997). Fields were selected for counting from areas with the highest numbers of lesions, and the field with the highest count was taken to represent the cortical or hippocampal area. A neuropathological diagnosis of AD was based on CERAD criteria (Mirra et al., 1991). These criteria included a maximum NP count of at least 4 per mm^2 for probable AD and at least 17 per mm^2 for definite AD.

2.4. Thyroid status

At time of examination 4, fasting blood samples were collected and put on ice immediately. Within 30 min, serum was separated by centrifugation and stored at −70 °C. Thyroid hormones were assessed in a random sub-sample of 1001 men who participated in examination 4. Several biochemical markers of thyroid function were assayed, including thyrotropin, free thyroxine (fT_4) and total thyroxine (T_4). Thyrotropin, fT4 and T4 were all measured by chemiluminescence assays on a DPC2000 analyzer (Diagnostic Product Co., Los Angeles, CA). The thyrotropin assay had an analytical sensitivity of 0.004 μU/dL and an inter-assay precision of 3.8% at 1.3 μU/dL. The fT4 assay had an analytical sensitivity of 0.30 ng/dL and an intra-assay precision of 4.8% at 2.10 ng/dL. The T4 assay had an analytical sensitivity of 0.30 μg/dL and an intra-assay precision of 4.6% at 8.23 μg/dL.

Thyrotropin and fT_4 serum levels were assessed to define thyroid status. Serum thyrotropin concentrations above the reference range (0.4–4.3 μU/dL) may indicate hypothyroidism and concentrations below the reference range may indicate hyperthyroidism. However, in these instances fT_4 concentrations are usually within the reference range (0.85–1.94 ng/dL). Whereas an isolated high thyrotropin level indicates sub-clinical hypothyroidism, isolated low thyrotropin levels may indicate sub-clinical hyperthyroidism but may be also due to non-thyroidal illness or drug effects (Surks et al., 2004). Clinical hypothyroidism was defined as a concentration of serum thyrotropin above the upper limit of the reference range and fT_4 concentrations below the lower limit of the reference range (Ross, 2001). Clinical hyperthyroidism was defined as a concentration of serum thyrotropin below the reference range and fT_4 concentrations above the reference range (Ross, 2001).

2.5. Covariates

The association between thyroid hormones and dementia or neuropathological markers may potentially be confounded by a number of variables affecting health status; further, vascular risk factors may play an important role in the etiology of AD (Launer, 2002), and are also related to thyroid function (Boelaert and Franklyn, 2005). Therefore, we adjusted for the following variables: age at death (for the autopsy sub-study), educational level and depressive symptoms, albumin levels, body mass index (kg/m^2) (BMI), total and HDL cholesterol, diabetes mellitus, smoking status (never, former, and current) systolic and diastolic blood pressure. Use of thyroid medication and other drugs potentially changing thyroid hormone levels including beta-blocking agents and use of anti-arrhythmics at time of blood draw was also entered in the statistical models. *APOE* genotyping was performed at the Joseph and Kathleen Bryan Alzheimer's Disease Research Center with restriction isotyping using a polymerase chain reaction protocol (Hixson and Vernier, 1990).

2.6. Statistical analysis

2.6.1. Incident dementia

After exclusion of one participant with an unusually high level of fT_4 (4.35 ng/dL) and otherwise normal levels of measured thyroid hormones, the analytical sample consisted of 1000 participants. Of 1000 participants with thyroid hormone assessments, 131 were demented at exam 4, and 204 participants died or refused further participation, leaving 665 participants at risk for dementia. After a duration of 3204 person years of follow-up (mean: 4.7 years, S.D.: 1.8 years), 106 participants developed dementia, of whom 74 had AD (including AD cases with contributing cerebrovascular disease). Of those 106 dementia cases, 71 were diagnosed at exam 5, and 34 at exam 6. Analysis of covariance adjusted for age was used to compare characteristics of participants according to tertiles of fT_4 and to compare participants with and without thyroid hormone assessments at examination 4. No statistically significant differences in socio-demographic variables or cardiovascular risk factors were observed between participants in the sub-sample with thyroid hormone assessments and those without (data not shown).

To test the hypothesis that higher thyroid function is associated with an increased risk of dementia and AD, we analyzed thyroid function in two ways. First, thyroid status was classified as high, normal, or low levels of thyrotropin. The normal thyroid group was the reference and consisted of subjects with thyrotropin levels within the reference range. Second, we expressed the continuous measures as unit of a standard deviation increase if the observed association was not obviously non-linear.

A Cox proportional hazards regression delayed entry model with age as the time scale was used to calculate hazard ratios (HR) with 95% confidence intervals (95% CI) for total dementia and AD (with and without cerebrovascular disease). Age of onset was assigned as the midpoint of the interval between the last examination without dementia and the first follow-up examination with dementia. Subjects who died or did not participate in subsequent follow-up examinations were censored as of the time of their last evaluation. Cox models are typically used when the time-to-event is measured continuously across participants. Because it is difficult to surveil and dementia onset is usually gradual, the mid-way point between two visits is typically used as a measure of time of onset. However, in essence, the time of onset and diagnosis are bounded by discrete study exams. We therefore reran the clinical dementia analyses with a discrete time analysis model. This approach did not change the results. We tested the Cox proportional hazards assumption by adding the interaction term between hormone level and age to the model. For AD, all the interaction terms for the different hormones were not significant (p-value for interaction ≥ 0.11).

2.6.2. Autopsy sub-sample

The analytical sample for the autopsy study is 143, only five of whom had high and four of whom had low thyrotropin

levels. Therefore we did not examine differences in pathology among these sub-groups. Analysis of covariance adjusted for age was used to compare characteristics of the autopsy cases with participants who dropped out after exam 4 within the thyroid sample. Baseline characteristics of the included autopsy cases did not differ from those in the thyroid sample who dropped out after exam 4 (data not shown).

The distributions of NP and NFT counts are skewed. Using goodness to fit statistics we determined the distributions of the NFT and NP were best fit by a negative binomial distribution. This model assumes an outcome that is measured in discrete counts, and a coefficient is interpreted as a count ratio giving the relative ratio of (i.e., NP) counts in the cases versus control group. As an example, a coefficient of 0.10 means the case has 10% higher count than the controls.

2.6.3. Adjusted analyses

In addition to adjusting for age we also adjusted for the socio-demographic, medical history and biochemical markers described above. All analyses were repeated after exclusion of participants with clinical hypo- ($n = 5$) or hyperthyroidism ($n = 1$) and thyroid medication ($n = 5$).

Finally, for dementia we repeated the analyses in strata of *APOE* genotype; we classified participants into those with and without an ε4 allele. Due to small numbers in the autopsy sub-study, these analyses were not stratified according to *APOE* status. All statistical analyses were performed using SPSS statistical software version 11 (SPSS Inc., Chicago, IL) (SPSS Inc., 2000) and SAS version 8 (SAS, Cary, NC) (SAS Institute Inc., 1999).

3. Results

The sample included 615 (92.5%) participants with normal thyrotropin levels. Of these, 596 also had normal fT_4 levels, 14 had low and 5 had high fT_4 levels. In those with low or high fT_4, the levels deviated only slightly from the reference range; therefore, all 615 participants were considered euthyroid. Twenty-six participants had a high thyrotropin level: 23 of these had a sub-clinical and three a clinical hypothyroidism according to biochemical criteria. Twenty-four participants had a low thyrotropin level: all of these had a sub-clinical and none had clinical hyperthyroidism according to biochemical criteria. Plasma levels of thyrotropin were inversely correlated with both T_4 ($r = -0.20$, $p < 0.01$) and fT_4 ($r = -0.22$, $p < 0.01$).

No differences were observed in thyroid hormone levels between the prevalent dementia cases and the non-demented participants at exam 4 (data not shown). Characteristics of the remaining 665 participants at risk for dementia are presented in Table 1, stratified according to tertiles of fT_4. Higher age, higher serum total and lower HDL cholesterol, were all related to a lower fT_4. No significant associations were found with the other characteristics, including *APOE* genotype.

3.1. Thyroid hormones and incident dementia

Thyrotropin was not associated with the risk of dementia or AD. However, with each standard deviation increase in fT_4, the risk of dementia increased over 20% and the risk of AD increased over 30% (Table 2). Per standard deviation increase in T_4, the risk of dementia increased 19% and the risk of AD increased 22%; however, this was not statistically significant. Results did not markedly change after additional adjustment for potential confounders, stratification by Apo E ε4 status or exclusion of participants with hyper- or hypo-thyroidism or on thyroid medication.

In addition, the risk of dementia did not differ between participants with normal thyrotropin levels and those with a high or low thyrotropin level, but these analyses were limited by low numbers: three of the 26 participants with a high thyrotropin level at baseline developed dementia, whereas six of the 24 participants with a low thyrotropin level developed dementia.

3.2. Thyroid hormones and neuropathology

Thyrotropin and fT_4 were not associated with neuropathologic markers of AD. For instance, per S.D. increase in

Table 1
Baseline characteristics of the study sample at risk for dementia ($n = 665$) stratified according to tertiles of free thyroxine, The Honolulu–Asia Aging Study

Characteristics	Sample at risk for dementia, stratified by tertiles of free thyroxine[a]			
	T1	T2	T3	*p* for trend
Age at baseline (years)	78.6 (5.2)	78.4 (7.2)	77.3 (4.1)	<0.0001
Education (years)	10.3 (3.2)	10.2 (3.2)	10.4 (3.1)	0.63
Late-life total cholesterol (mg/dL)	188.1 (33.7)	183.6 (34.8)	191.6 (30.5)	0.008
Late-life HDL-C (mg/dL)	48.5 (12.4)	49.8 (12.8)	53.0 (13.3)	<0.0001
Late-life body mass index (kg/m^2)	23.5 (3.2)	23.3 (3.2)	23.4 (3.2)	0.65
Diabetes mellitus (%)	32	36	37	0.29
Late-life smoking (current) (%)	43	36	37	0.16
Late-life diastolic blood pressure (mmHg)	80.1 (11.6)	78.6 (11.3)	79.8 (10.8)	0.19
Late-life systolic blood pressure (mmHg)	147.6 (25.1)	146.6 (22.9)	146.6 (23.1)	0.80
Late-life beta-blocker use (%)	8	7	10	0.16
ApoE ε4, %carrier	18	18	22	0.27

[a] Values are age-adjusted means (S.D.) or percentages.

Table 2
Thyroid hormone levels and the risk of dementia and Alzheimer's disease, the Honolulu–Asia Aging Study

Thyroid hormones	Dementia ($n = 106$), Hazard ratio (95% CI)[a]	Alzheimer's disease ($n = 74$), Hazard ratio (95% CI)[a]
Model 1[b]		
Thyrotropin (per S.D.)	0.93 (0.82; 1.06)	0.92 (0.78; 1.09)
fT4 (per S.D.)	1.21 (1.04; 1.40)	1.31 (1.14; 1.51)
T4 (per S.D.)	1.19 (0.99; 1.43)	1.22 (0.98; 1.52)
Model 2[c]		
Thyrotropin (per S.D.)	0.89 (0.74; 1.07)	0.90 (0.71; 1.13)
fT4 (per S.D.)	1.20 (1.05; 1.37)	1.30 (1.14; 1.47)
T4 (per S.D.)	1.10 (0.87; 1.39)	1.14 (0.86; 1.52)

[a] Values are hazard ratios for dementia and Alzheimer's disease per S.D. increase in thyroid hormone level (95% confidence interval).
[b] Model 1: age adjusted.
[c] Model 2: also adjusted for albumin, educational level, depressive symptom score, BMI, systolic and diastolic blood pressure, anti-arrhythmic and beta-blocking agent use.

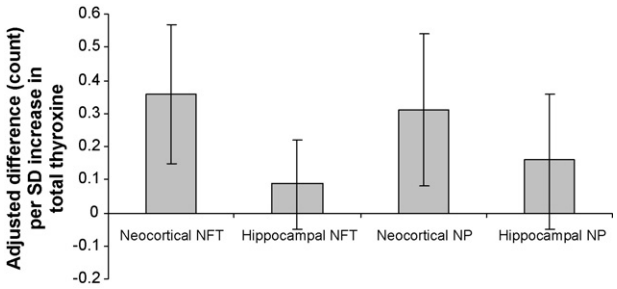

Fig. 1. Values represent adjusted differences (95% confidence intervals) in autopsy measures per S.D. increase in total thyroxine. NFT: neurofibrillary tangles; NP: neuritic plaques; CI: confidence interval. Values are adjusted for age, albumin, educational level, depressive symptom score, body mass index, systolic and diastolic blood pressure, anti-arrhythmic and beta-blocking agent use.

thyrotropin the neocortical NFT count was 0.01 (95% CI −0.04; 0.07) lower and the neocortical NP count was 0.01 (95% CI −0.05; 0.06) lower. Per S.D. increase in fT_4 the neocortical NFT count was 0.15 (95% CI −0.04; 0.34) higher and the neocortical NP count was 0.01 (95% CI −0.28; 0.29) higher. There were no significant associations between thyroid function and NFT and NP count in the hippocampus.

Higher levels of T_4 were associated with more neocortical NFT and NP. Per S.D. increase in T_4, the neocortical NFT count was 0.25 (95% CI, 0.05; 0.46) higher and the neocortical NP count was 0.22 (95% CI, −0.01; 0.44) higher, although the latter was non-significant. T_4 was not associated with hippocampal NFT and NP. These results were slightly strengthened after adjusting for potential confounders (Fig. 1). Stratifying by presence or absence of dementia did not change the results.

4. Discussion

In this population-based study of very old men, higher levels of fT_4 and T_4 were associated with an increased risk for both dementia and AD. T_4 was also associated with more neurofibrillary tangles and neuritic plaques in the cerebral cortex, whereas fT_4 was not. Adjustment for potential confounding factors did not change the results.

Strengths of this study are its prospective population-based design, the 6 years of follow-up and the extensive diagnostic work-up for dementia including neuroimaging in most cases. In addition to the diagnosis of a clinical dementia syndrome, neuropathologic markers of AD were available in an autopsy series of the cohort. It should be noted, thyroid hormones were assayed in only one third of all study participants. However, we randomly selected participants for the assessments of thyroid hormones, and did not find any differences between the subgroups with and without thyroid hormone assessments. Further, the number of participants with (subclinical) hypo- and hyper-thyroidism was quite small, thus limiting our analyses on participants with abnormal thyroid function.

Whereas in the Rotterdam Study, an association between sub-clinical hyperthyroidism and dementia was found (Kalmijn et al., 2000), in this study thyrotropin was not related to clinically diagnosed AD or Alzheimer-type neuropathology. This was the case when analyzed continuously or when analyzed in strata of normal or abnormal thyroid function, although the analyses on high and low thyrotropin were limited due to low numbers. Thyrotropin values may however be altered by as much as 30% depending on time of day of phlebotomy, and the fasting or non-fasting status of the participant (Scobbo et al., 2004). The absence of an effect of thyrotropin in our study could thus in part be due to differences in time of blood collection or in certain characteristics of the population studied. Moreover, a blunted response of thyrotropin to thyrotropin-releasing hormone has been reported in elderly with major depression or AD (Molchan et al., 1991), indicating that in these conditions thyrotropin does not always adequately reflect thyroid function (Mariotti et al., 1995). Whereas, thyrotropin was not associated with AD in our study, both T_4 and fT_4 were associated with an increased risk. This is in line with findings from the Rotterdam Study but contrasts findings from the Rotterdam Scan Study where thyroid function was not related to dementia-risk.

Our findings are in line with several reports from experimental studies showing thyroid hormones to induce changes

in amyloid precursor processing or deposition of amyloid-β (Belandia et al., 1998; Latasa et al., 1998). Moreover, we also found an association of T4 with neuropathological markers of AD in the non-demented subjects. The higher count of neocortical NFT and NP in participants with higher T_4 is consistent with our findings of an association between T_4 and AD. In addition, in the Rotterdam Scan Study in subjects who were not demented, higher thyroid hormone levels were associated with a smaller hippocampal and amygdalar volumes on MRI, both of which are putative MRI markers of Alzheimer's disease. Taken together, these findings suggest that higher thyroid function within the normal range could be involved in the pathophysiology of dementia and AD.

Alternative explanations should be discussed. Although the mean follow-up duration for dementia in our study population was nearly 5 years, the insidious onset and slowly progressive nature of AD may also indicate that higher thyroid function is a marker of sub-clinical disease rather than causal factor in the development of AD. Subclinical dementia might lead to higher thyroid hormone levels through several mechanisms. First, higher T_4 levels may be due to neurodegeneration The hippocampus, a structure in the medial temporal lobe of the brain, is involved early in Alzheimer pathogenesis and has been shown to be reduced in volume on brain imaging up to 6 years before clinical detection of AD (den Heijer et al., 2006). The hippocampus is involved in the setting of the basal activity of the thyroid axis through hippocampal-hypothalamic connections. By decreasing thyroid-hormone-releasing hormone gene expression in the hypothalamus, the hippocampus exerts a negative effect on this axis (Shi et al., 1993). If the affected hippocampus in AD leads to less feedback on the hypothalamo–pituitary–thyroid axis, higher levels of fT_4 could follow. The finding that higher serum fT_4 levels are associated with smaller hippocampal volumes on MRI scans of non-demented elderly (de Jong et al., 2006), may offer support for this hypothesis.

Second, higher T_4 levels may result from dementia through concomitant nonthyroidal illness. Evaluation of thyroid function in the elderly is complicated by an increased prevalence of non-thyroidal illness (Chiovato et al., 1997), in which thyroid hormone and thyrotropin concentrations are altered, without overt thyroid dysfunction being present. Several conditions including malnutrition, starvation, and inflammatory processes accompanying disease are associated with non-thyroidal illness. In these situations, T_4 is converted preferentially to reverse T_3 instead of T_3 (Chopra et al., 1983). The finding that not only fT_4 but also higher levels of reverse T_3 were found to be associated with smaller hippocampal volume on MRI of non-demented elderly (de Jong et al., 2006) indeed suggests that this may be an important mechanism. Since both T_3 and reverse T_3 were not measured in our study, we were not able to adjust for nonthyroidal illness. The fact that results remained unaltered after adjusting for potential other confounders, argues at least in part against an effect of comorbidity, although residual confounding by other measures influencing both thyroid hormone levels and our outcome measures cannot be excluded.

To conclude, in our study of elderly Japanese-American men, higher thyroid function as indicated by increased levels of fT_4 and T_4 levels within the normal range was associated with an increased risk of dementia and AD. In addition, higher levels of total T_4 were associated with Alzheimer-type neuropathology. Taken together, our findings suggest that higher fT_4 and T_4 levels may reflect early AD. Yet, future studies are needed to determine whether higher thyroid hormone levels are a causal factor in the development of AD, or whether they reflect sub-clinical disease.

Conflict of interest

All authors reported no actual or potential conflict of interest.

Acknowledgements

The Honolulu–Asia Aging Study is supported by the National Institute on Aging (contract # N01-AG-4-2149, grant # UO1-AG-0-9349-03 and RO1-AG-0-7155-06A1), the National Heart Lung and Blood Institute (contract # N01 - HC-0-5102), and by the Intramural Research Program of the National Institute on Aging. This research was also made possible in part by grants from the International Foundation of Alzheimer Research (ISAO grant 01500) and the Netherlands Organization for Health Research and Development (ZonMW, grant 904-61-155).

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