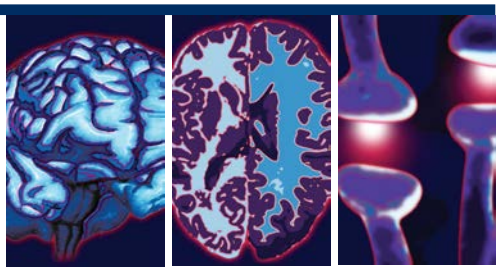

The Relationship Between Thyroid Status, Cortisol Level, Cognition And Neuropsychiatric Symptoms In Patients With Alzheimer Disease

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ABSTRACT

Objective: Growing evidence suggests an association between alterations in thyroid function and cortisol level and the pathogenesis and progression of Alzheimer disease (AD). The aim of this study was to investigate whether these hormones are related to the cognitive and neuropsychiatric manifestations in the patients with AD.

Methods: This was a cross-sectional, case control study. Cortisol level and thyroid status were evaluated in 40 outpatients with mild to moderate AD and 20 normal controls, and cognitive and neuropsychiatric assessments were performed using the Cognitive Ability Screening Instrument (CASI), Neuropsychiatric Inventory, and Geriatric Depression Scale.

Results: The patients had worse cognitive function and lower free triiodothyronine (FT3) level than the controls. Those with aberrant motor behavior had a lower FT3 level, and those with dysphoria had a higher cortisol level than those without these symptoms. The patients with a higher level of FT3 also had higher concentration and abstract thinking/judgment scores on the CASI, and those with a higher level of cortisol were associated with a decline in global cognition.

Conclusion: Our results indicate a possible association between thyroid hormones and neuropsychiatric manifestations as well as cognitive function in euthyroid patients with AD, and suggest the potential efficacy of adjunctive T3 treatment in these patients. We hypothesize that patients with dysphoria subjectively experience more stress. Further studies are needed to elucidate whether this would increase the risk of depression or exacerbate cognitive function, and to investigate whether a non-pharmacological approach can relieve dysphoria symptoms according to the psychological attachment theory.

Keywords

Alzheimer disease, Cognition, Cortisol, Mood, Neuropsychiatric symptom, Thyroid

Introduction

The relationship between thyroid function and cortisol level and the risk of cognitive decline and dementia, and in particular Alzheimer disease (AD), has been extensively investigated. Over-activation of the hypothalamic-pituitary-adrenal (HPA) axis has been reported to potentially lead to neuronal damage, hippocampal atrophy, and cognitive impairment [1], and an increased cortisol plasma level has been associated with more rapid disease progression in patients with AD [2]. However, the association between thyroid function and dementia and cognitive

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impairment is controversial. For example, a low thyrotropin level has been associated with prevalent dementia in older adults [3] and poorer performance on an executive function test in middle-aged adults without overt thyroid dysfunction [4]. In addition,a high thyrotropin level has been reported to able to predict incident dementia in older adults [5], whereas [6] found no association between thyrotropin level and incident dementia. Nevertheless, all of these conflicting results suggest that dysregulation of the hypothalamic- pituitary-thyroid (HPT) axis is present in patients with AD.

Although progressive cognitive decline is a critical clinical feature of AD, mood disturbance and behavioral symptoms are very common, and thyroid status has been associated with mood symptoms such as agitation, irritability, depression, fear and fatigue [7-8]. However, none of these studies performed complete surveys of thyroid hormones (THs) or their free fractions, yet they all suggested that the free fractions may be more closely related to cognitive dysfunction and neuropsychiatric symptoms in AD. In addition, dysregulation of the HPA axis is the most prevalent and well documented neuroendocrine abnormality in stress-related disorders, and particularly in depression and anxiety [9-11].

Although thyroid function and cortisol level have been shown to play a role in the cognitive and neuropsychiatric manifestations of patients with AD, few studies have investigated the relationship between thyroid function, cortisol level and the cognitive and neuropsychiatric manifestations in patients with AD. Therefore, the aim of this study was to investigate whether thyroid function and cortisol level are related to cognitive and neuropsychiatric manifestations in patients with mild to moderate AD.

Methods

■ Participants

This was a cross-sectional, case control study. Forty outpatients (14 men and 26 women; mean age: 79.4 ± 5.9 years; mean years of education: 4.5 ± 4.6 years) with mild to moderate AD according to the Clinical Dementia Rating scale [12] and a Mini-Mental State Examination (MMSE) [13] score of 10 to 24 [14] were enrolled. The diagnostic criteria were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) [15] and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [16] for probable AD. All of the patients underwent a neurological examination, neuroimaging and laboratory workup to rule out other treatable.

Twenty normal controls (9 males and 11 females; mean age: 77.5 ± 4.4 years; mean years of education: 6.6 ± 4.4 years) were recruited from our hospital and the general community. None of the participants had a history of stroke, epilepsy, thyroid disease, pathological levels of urea or creatinine, or other significant psychiatric diseases. In addition, none of the patients were either using or had used glucosteroid supplements or were currently receiving any antipsychotic, antidepressant, anxiolytic or central nervous system (CNS)-active drug treatment.

Procedures

Clinical assessments of cognitive and neuropsychiatric symptoms, depression, cortisol level and thyroid status were conducted within 7 days of recruitment in each subject. All of the patients had a liable caregiver who could participate in the interviews. Written informed consent was obtained from all subjects before participation in the study, which was conducted with the approval of the Ethics Committee of Kaohsiung Municipal Kai-Syuan Psychiatric Hospital (KSPH-2015-24).

■ Serum cortisol and thyroid status measurements

Fasting blood samples (5 ml) were collected by venipuncture between 8:00 and 9:00 a.m. to determine levels of thyrotropin, T3, T4, free fractions (FT3 and FT4), and cortisol. Serum was separated immediately after blood collection, and the samples were stored at –20°C until analysis. Quantitative determination of cortisol and thyroid status in the serum was performed using paramagnetic particles in a chemiluminescent immunometric assay using a Beckman Access system (Beckman Coulter Inc., Fullerton, CA, USA) for cortisol level and an Abbott I2000 system (Abbott Ireland Diagnostics Division, Longford, Ireland) for thyroid status. The lower limits of detection were 0.0025 mIU/L (thyrotropin), 25.0 ng/dl (T3), <1.0 µg/dl (T4),<1.0 pg/ml (FT3), 0.4 ng/dl (FT4), and 0.4 µg/dl (cortisol), respectively. The intra-assay coefficient of variation averaged 5% for each item.

■ Neuropsychological assessments

Cognitive function was assessed using the Cognitive Ability Screening Instrument (CASI) [17-18], which was conducted by a clinical psychologist who was blinded to the thyroid status and cortisol level. The CASI consists of nine component scores including remote memory, recent memory, attention, concentration, language, abstract thinking/judgment, orientation, visual instruction, and verbal fluency. The sum of the nine component scores yields one global score of cognitive function (maximum, 100), with higher scores representing better cognitive function. Some of the CASI items are comparable with those used in the MMSE. Thus, CASI-estimated MMSE scores (MMSE-CE) [19] were also obtained.

■ Neuropsychiatric symptoms and depression assessments

Neuropsychiatric symptoms and depression were assessed using the Neuropsychiatric Inventory (NPI) [20-21] and the 30-item Geriatric Depression Scale (GDS) [22-23], respectively, by a psychiatrist who was blinded to the subjects' thyroid status, cortisol level and psychometric test score, following interviews with both the subjects and caregivers. The reference was the 2-week period prior to the interview. The NPI includes measures of delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. Total frequency and severity scores for 12 items served as primary outcome variables in data analyses. An item score of >1 was regarded as the existence of this particular symptom.

Statistical analysis

The distribution of a categorical variable (sex) between groups was compared using the χ^2 test. Group differences in age, years of education, neuropsychological, depression, thyroid status and cortisol level assessments were evaluated using the Student's t-test. Bonferroni correction was applied to adjust for multiple comparisons and differences were considered statistically significant at $p < 0.004$.

Multivariate logistic regression was used to evaluate independent associations between the neuropsychiatric symptoms according to the NPI and age, gender, years of education, MMSE-CE scores, thyroid status and cortisol level. Multivariate linear regression analysis was also performed to identify the significant hormone factors from between group comparisons including age, years of education, MMSE-CE scores, previous significant NPI items and the CASI subscores as predictor variables. Results were considered significant at the $p < 0.05$ level.

All analyses were conducted using SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY).

Results

There were no significant differences in sex, age, and years of education between the patients with AD and the controls. However, there were significant differences in FT3 level, CASI and MMSE-CE scores after Bonferroni correction **(Table 1)**. Compared to the controls, the patients with AD had a higher cortisol level, lower FT3 level, and lower CASI and MMSE-CE scores. With regards to neuropsychiatric symptoms, multivariate logistic regression analysis showed that the patients with AD with dysphoria had a higher cortisol level (OR: 1.98, 95% CI: 1.13 - 3.49, p = 0.018), the patients with AD with anxiety had lower T3 and T4 levels (OR: 0.85, 95% CI: 0.74 - 0.99, p = 0.033; OR: 0.05, 95% CI: 0.01- 0.43, p = 0.007), and that the patients with AD with aberrant motor behavior had a lower FT3 level (OR: 0.01, 95% CI:0.00 - 0.66, p = 0.034) compared to the patients with AD without these symptoms.

Because aberrant motor behavior is related to frontal behavior symptoms [24-25], and the four subfactors of the CASI (abstract thinking/judgment, verbal fluency, attention, and concentration) are classified into a frontal cortex cluster [26], we included these cognitive subfactors as predictors when FT3 was used as a dependent variable. Because a link between depression, anxiety, and HPA axis overdrive [11] has been reported to be related to prefrontal cortex regulation [27], we also included the GDS scores, anxiety scores of the NPI, and the four frontal related subfactors of the CASI as predictors when cortisol level was used as a dependent variable.

There were no significant correlations between age, education, and FT3 and cortisol level, respectively. Cortisol level was significantly associated with dysphoria and MMSE-CE scores ($\beta = 0.469$, $p = 0.013$; $\beta = -0.852$, $p = 0.010$, respectively). FT3 level was significantly

Table 1: Demographic and clinical characteristics between in patients with Alzheimer disease (AD) and controls.

Variables (mean ± SD)	Controls	AD patients	*t* (df=58) or χ^2 (df=1) values	*p* value
n (M/F)	20 (9/11)	40 (14/26)	0.56	0.575
Age (y)	77.5 ± 4.4	79.4 ± 5.9	-1.42	0.163
Years of education	6.6 ± 4.4	4.5 ± 4.6	1.69	0.099
GDS scores	8.6 ± 7.3	10.9 ± 7.8	-1.15	0.257
CASI scores	85.6 ± 6.4	44.5 ± 14.4	15.31	< 0.001
MMSE-CE scores	27.5 ± 1.9	14.4 ± 3.8	17.64	< 0.001
Cortisol (μg/dl)	7.8 ± 3.7	10.2 ± 4.6	-2.23	0.031
Thyrotropin (mIU/L)	1.4 ± 0.7	1.4 ± 0.7	0.15	0.884
Total T_3 (ng/dL)	94.8 ± 10.2	89.7 ± 11.0	1.77	0.084
Free T_3 (pg/ml)	2.5 ± 0.4	2.2 ± 0.2	3.73	0.001
Total T_4 (μg/dl)	6.3 ± 1.1	6.3 ± 1.0	-0.04	0.968
Free T_4 (ng/dL)	1.0 ± 0.1	1.0 ± 0.1	0.54	0.591

Adjust p value < 0.004 after Bonferroni correction

Abbreviations: GDS Geriatric depression scale, CASI Cognitive Ability Screening Instrument, MMSE-CE CASI-estimated Mini-mental state examination

Table 2: Multivariate linear regression analysis of free triiodothyronine and cortisol concentrations, demographics, cognition, and neuropsychiatric symptoms variables.

Variables	Free triiodothyronine		Cortisol	
	β value	*p* value	β value	*p* value
Age	0.001	0.894	0.154	0.281
Education	-0.005	0.503	0.082	0.608
MMSE-CE scores	-0.018	0.207	-0.852	0.010
GDS scores			0.086	0.411
Dysphoria scores			0.469	0.013
Anxiety scores			0.127	0.429
Verbal fluency scores	0.014	0.415	0.499	0.199
Abstract thinking/judgment scores	0.050	0.017	0.110	0.806
Attention	0.012	0.556	0.475	0.270
Concentration	0.051	0.004	0.372	0.339
Aberrant motor behavior scores	-0.019	0.012		

Abbreviations: MMSE-CE Cognitive Ability Screening Instrument-estimated Mini-mental state examination, GDS Geriatric depression scale

associated with abstract thinking/judgment, concentration, and aberrant motor behavior scores (β = 0.050, p = 0.017; β = 0.051, p = 0.004; β = -0.019, p = 0.012, respectively) **(Table 2)**.

Discussion

In this study, the patients with AD had a statistically significantly higher cortisol level, lower level of FT3, and a decline in global cognition compared with the controls. However, there were no significant differences in GDS scores and levels of thyrotropin, T3, T4, and FT4 between the two groups.

Laboratory studies have suggested a relationship between THs and factors associated with the pathogenesis of AD. Circulating THs are produced in the thyroid gland, primarily in the form of T4, and are transported into the brain by transthyretin [28]. T4 is then converted to its bioactive form, T3 and the inactive isomer, rT3. T3 has been shown to negatively regulate the expression of the amyloid precursor protein gene [29], T4 has been shown to modulate choline acetyltransferase activity [30], and transthyretin has been shown to create soluble β-amyloid complexes [31]. Compared with age-matched controls [32], the level of transthyretin has been reported to be lower in the cerebrospinal fluid (CSF) of patients with AD, suggesting a possible reduction in T4 transport into the brain in patients with AD. However, most T3 within the brain is produced locally by the intracerebral conversion of T4 to T3 [33]. In addition, patients with AD have been shown to have significantly increased rT3 levels and an increased rT3 to T4 ratio in the CSF [33]. Taken together, these findings suggest abnormal intracerebral metabolism of THs and possibly brain hypothyroidism in AD [34]. Although the

circulating level of THs does not properly reflect the bioactive portion involved in the CNS, the lower level of FT3 in our results suggests a link between HPT axis abnormalities and dementia.

A high concentration of glucocorticoid receptors exists in the hippocampus, and this brain region is thought to be involved in the negative-feedback mechanism of glucocorticoid secretion [35]. The degeneration of the hippocampus is one of the most notable features of AD [36], where hippocampal cell loss induces hypercortisolemia, which in turn acts as a cofactor in further degeneration as the disease progresses. We also found higher levels of cortisol in the patients with AD than in the controls.

Both hypo- and hyperthyroidism have been associated with an increased risk of mood disorders [37]. However, the relationship between thyroid status and mood symptoms in patients with AD is controversial. Zhang et al. [7] reported that euthyroid patients with AD with agitation and irritability according to the NPI had a lower thyrotropin level than those without these symptoms, and that the core scores of the Hamilton Rating Depression Scale were significantly positively associated with thyrotropin level. Other studies have reported no significant relationships between thyroid status and depression and anxiety symptoms in euthyroid patients with AD [8]. However, these studies did not measure FT3, and all suggested that T3 and its free fraction may be more closely associated with cognitive dysfunction and neuropsychiatric symptoms in AD. In this study, we did not find any relationships between the free fractions of THs and mood symptoms, however we did find that the patients with AD with anxiety according to the NPI had a lower T3 and T4 levels than those without this symptom.

In this cross-sectional study, we found no significant relationship between FT3 and cognitive function as measured by the MMSE-CE in the patients with AD. This is consistent with the results of previous studies [7-8] that also failed to identify a significant relationship between global cognition (i.e., MMSE) and concentrations of THs in euthyroid patients with AD. However, we found significant positive associations between the concentrations of THs and subfactors of CASI scores, including a significant association between a higher level of FT3 and higher concentration and abstract thinking/judgment scores. In addition, we found a significant negative association between FT3 level and aberrant motor behavior scores on the NPI. These specific cognitive and neuropsychiatric symptoms are both related to the fontal cortex [24-26], and our results may be supported by previous pathology findings in which the prefrontal cortices of patients with AD had significantly lower levels of T3, but not T4, compared with controls [38].

In this study, the cortisol level in the patients with AD was negatively correlated with MMSE-CE scores. Many studies have proposed that patients with AD with a higher cortisol level experience an accelerated progression of the disease [1, 35, 39]. Gil-Bea et al. [40] reported that dysregulation of the HPA axis in patients with AD seemed to be a consequence rather than a cause of AD. That is, the cortisol level in patients with AD may be of prognostic relevance.

We also found that the patients with AD with dysphoria according to the NPI had a higher cortisol level than those without this symptom, and that those with higher dysphoria scores were also positively correlated with cortisol level; however there were no statistically significant associations between cortisol level and GDS or anxiety scores. Depressive symptoms are one of the most frequent psychiatric complications of AD, affecting as many as 50% of patients [41]. The link between AD and depression may be due to HPA axis overdrive, neuroinflammatory mechanisms induced by stress, decreased serotonin levels, and disturbances in other signaling pathways [42]. Although stress and HPA axis activity are known to participate in the onset and progression of both depressive disorder and AD, Zvěřová et al. [29] reported that an increased plasma cortisol level in patients with AD had relatively little effect on comorbid depressive symptoms. Rather, they found that the level of plasma cortisol reflected the degree of cognitive impairment in AD rather than the severity of comorbid depression. In addition, Meynen et al. [43] reported that levels of cortisol in the CSF were no higher in patients with AD with depression than in those with depression. The role of depression in AD is likely to involve genetic vulnerability, brain damage, and possibly psychological reactions to cognitive decline [41].

Dysphoria is an unpleasant mood which may accompany depression, anxiety, and agitation. Exposure to stress can result in an increase in the stress hormone cortisol through the central HPA system [44], and the patients with AD with a higher dysphoria score had a higher

cortisol level in our results, which may suggest that the patients subjectively experienced more stress. The experience of stress is known to exacerbate mental illness, thereby contributing to the risk of depression [45]. Further studies are warranted to elucidate whether patients with AD had dysphoria symptoms and associated with a higher cortisol level are at an increased risk of depression or worse cognitive function. Besides, attachment has long been known to be a fundamental psychological need in patients with dementia [46], and this may be due to insecurity and feelings of dysphoria that such patients experience as a result of their chronic advancing disease [47]. This also implied that a non-pharmacological approach may be able to treat patients with dysphoria [48].

Because dysregulation of the HPA axis impacts pathological anxiety and exposes the brain to chronic stress, many studies have proposed that anxiety is associated with an increased risk of AD in cognitively normal elderly and in those with amnestic mild cognitive impairment [8-9]. However, few studies have explored the relationship between cortisol level and anxiety in patients with AD. Although we did not find a significant association between cortisol level and anxiety in our patients with AD, whether AD and anxiety lead to HPA axis overdrive and whether this is reflected in the association between cortisol level and the severity of comorbid anxiety in patients with AD is still worthy of further study.

There are several limitations to the present study. First, the cross-sectional design and small sample size limit the interpretation of the findings. Second, measures more sensitive to anxiety and depression may have demonstrated an effect on mood. Third, circulating hormone assessments do not properly reflect the bioactive portion involved in the CNS. Fourth, we did not record body mass index or concomitant diseases such as diabetes mellitus and hypertension, all of which could have affected the levels of THs and cortisol. Fifth, the CASI is a rather brief assessment tool, and studies using more comprehensive, sensitive, and more specific cognitive assessment instruments are warranted. Sixth, blood samples were not collected in the early morning when cortisol release should be reaching a peak level which could have masked differences in cortisol production among the study groups. This was because this study was designed to investigate an association between a single serum cortisol measurement and clinical assessments and to avoid the concentration of cortisol being influenced by an acute effect. Finally, because several studies have reported conflicting results with regards to associations between subclinical hyper- [49] and hypothyroidism [50] with dementia and cognitive impairment, one might argue that our results of a decreased FT3 level could be due to subclinical thyroid dysfunction; however, none of our patients or controls presented with an abnormal thyrotropin level.

Conclusion

In summary, we found that the patients with AD had a lower FT3 level, and that this was associated with concentration and abstract thinking/judgment cognitive function and aberrant motor behavior symptoms. These results indicate a possible association between THs and neuropsychiatric manifestations as well as cognitive function in euthyroid patients with AD. Clinical investigations of the possible efficacy of adjunctive T3 treatment in patients with AD may be warranted. In addition, the patients with AD who had a higher cortisol level were associated with global cognitive decline and dysphoria symptoms, but were not significantly associated with depressive or anxiety symptoms. We hypothesize that patients with dysphoria subjectively experience more stress. Further studies are needed to elucidate whether this would increase the risk of depression or exacerbate cognitive function, and to investigate whether a non-pharmacological approach can relieve dysphoria symptoms according to the psychological attachment theory.

Disclosure Statement

The authors report no conflicts of interest.

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