Neuroendocrinology Letters Volume 43 No. 3 2022
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Association of thyroid hormones and white matter hyperintensity in patients without intracranial arterial stenosis

Can Xing[1], Wei Chen[1], Dan Li[1], Yan Li[1], Xiangyang Zhu[1]

1 Department of Neurology, The Second Affiliated Hospital of Nantong University, Nantong, China

Correspondence to: Xiangyang Zhu
Department of Neurology, Second Affiliated Hospital of Nantong University,
6 Haier-xiang North Road, 226000, Nantong, Jiangsu, China
e-mail: zhuxxyy2092@163.com

Submitted: 2022-04-05 Accepted: 2022-08-03 Published online: 2022-08-03

Key words: **White matter hyperintensity; cerebral microbleeds; cerebral small vessel disease; thyroid hormone; FT4; FT3**

Neuroendocrinol Lett 2022; **43**(3):167–172 **PMID:** 36179728 NEL430222A08

Abstract

OBJECTIVE: Thyroid hormones play important roles in most organs, including the brain. This study aimed to explore the association between thyroid hormones and the severity of white matter hyperintensities (WMH) in patients without intracranial arterial stenosis, which is a common manifestation in the brain.

METHODS: This retrospective study included 304 patients at the Department of Neurology in Nantong First People's Hospital between June 2018 and June 2020. Thyroid hormone levels and other laboratory data were collected on the day after admission. The patients were divided into two WMH burden groups based on Fazekas scores as follows: "mild-moderate group" and "severe group."

RESULTS: The severe WMH group had higher ages (P=0.000), higher serum concentration of fibrinogen (P=0.040), higher concentration of creatinine (P=0.040), lower concentration of low-density lipoprotein (P=0.013), and higher concentration of free thyroxine (FT4) (P=0.003). The prevalence of cerebral microbleeds (CMBs) increased with increasing quartiles (P=0.023). Multivariable logistic regression and ordinal regression analysis showed that higher concentrations of FT4, age, and CMBs were also independent risk factors for severe WMH. The concentrations of FT4 were grouped according quartiles. The results showed that the prevalence of severe WMH increased with higher quartiles. This correlation persisted after adjusting for risk factors such as sex, age, history of hypertension, diabetes, drinking history, and smoking history.

CONCLUSION: Our results support the hypothesis that FT4 is associated with the severity of WMH in patients without intracranial arterial stenosis. In addition, age and CMBs are independently related to the severity of WMH.

INTRODUCTION

Cerebral small vessel disease is a group of clinical, imaging, and pathological syndromes caused by damage to cerebral arterioles, capillaries, and venules (Wardlaw *et al.* 2019). White matter hyperintensities (WMHs) are a component of cerebral small vessel disease and are related to increased risks of vascular cognitive impairment, Alzheimer's disease, cerebral microbleeds (CMBs), and lacunar stroke (Wardlaw *et al.* 2019; Lee *et al.* 2018). The pathogenesis of WMHs has

not been established; however, possible mechanisms include endothelial dysfunction, inflammation, blood-brain barrier leakage, hyperperfusion injury, genetic factors, chronic cerebral ischemia, and subsequent β-amyloid deposition (Joutel & Chabriat 2017; Osborn *et al.* 2018).

The thyroid gland releases thyroid hormones, primarily tetra-iodothyronine (FT4 or thyroxine) and tri-iodothyronine (FT3). Thyroid hormone receptors are widely distributed in the brain, where they are present in vascular endothelial tissues and participate in lipid metabolism and the release of inflammatory cytokines (Razvi *et al.* 2018). Previous studies found an increased risk of coronary heart disease in both hypo- and hyperthyroidism (Biondi 2021; Biondi & Cooper 2018). A large prospective cohort study involving 43,598 participants concluded that higher concentrations of thyroid-stimulating hormone (TSH) are related to a decreased risk of stroke (Collet *et al.* 2012). This prospective cohort study also found that FT4 concentrations were associated with stroke (Collet *et al.* 2012). At present, few studies have explored the relationship between thyroid hormones and cerebral small vessel disease. The purpose of this study was to explore the association between thyroid hormones and WMHs.

METHODS

Patients and Evaluation

We consecutively recruited 304 patients at the Department of Neurology in Nantong First People's Hospital between June 2018 and June 2020. The inclusion criteria were as follows: (1) age ≥18 years; (2) participants having acute cerebral infarction, with the TOAST classification of small-artery occlusion lacunar; (3) participants who were simultaneously free of acute cerebral infarction and intracranial arterial stenosis. The exclusion criteria included having (1) a disease of the heart (such as recent myocardial infarction, dilated cardiomyopathy, atrial fibrillation), liver, thyroid, kidney, or hematopoietic system; (2) malignant tumors or autoimmune diseases; (3) intracranial artery or ipsilateral extracranial carotid artery stenosis; (4) communication difficulties; (5) missing laboratory examination or brain MRI data.

Baseline Data Collection and Categorization

The baseline demographic data collected on admission included age, sex, and stroke risk factors (hypertension, diabetes mellitus, current smoking, alcohol intake). Meanwhile, all patients were administered laboratory tests, including serum measurements of fibrinogen, creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, TSH, FT3, and FT4.

MRI Protocol and Assessment

During hospitalization, the participants underwent brain MRI, including axial diffusion-weighted imaging, T2-weighted fluid-attenuated inversion recovery, susceptibility-weighted imaging, and MR angiography. Brain MRI was performed with a 1.5T scanner (Siemens, GE, Germany) or a 3.0 T MR scanner (Siemens, GE, Germany).

White matter lesions were lesions around the lateral ventricle. WMH was assessed using Fazekas scale (Fazekas *et al.* 1987) independent of the clinical data.

Tab. 1. Characteristics of participants according to severity of WMH

Variable	All (n =304)	Mild-moderate WMH (n=233)	Severe WMH(n =71)	*p* value
Female, n (%)	130(42.8)	103(44.2)	27(38)	0.357
Age,mean ± SD	67.59(±11.84)	65.78(±11.94)	73.54(±9.36)	0.000
Hypertension, n (%)	215(70.7)	159(68.2)	56(78.9)	0.085
Diabetes mellitus, n (%)	79(26.0)	56(24.0)	23(32.4)	0.160
Current drinker, n (%)	50(16.4)	41(17.6)	9(12.7)	0.328
Current smoker, n (%)	57(18.8)	41(17.6)	16(22.5)	0.351
FG(g/L),mean±SD	2.61(±1.02)	2.54(±0.88)	6.63(±1.90)	0.040
CR(μmol/L),mean±SD	67.85(±25.64)	65.59(±)20.64	75.08(±36.68)	0.040
HDL(mmol/L),mean±SD	1.17(±0.27)	1.18(±0.28)	1.13(±0.25)	0.168
LDL(mmol/L),mean±SD	2.60(±0.81)	2.66(±0.78)	2.38(±0.83)	0.013
FT3(pmol/L),mean±SD	4.43(±0.60)	4.47(±0.61)	4.33(±0.54)	0.097
FT4(pmol/L),mean±SD	10.51(±1.88)	10.33(±1.88)	11.11(±1.80)	0.003
Acute lacunar infarction, n (%)	79(26.0)	56(24.0)	23(32.4)	0.160
CMBs, n (%)	126(41.4)	72(30.9)	54(76.1)	0.000

SD: standard deviation; WMH: white matter hyperintensity; CMBs: cerebral microbleeds; FG: fibrinogen; CR: creatinine; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FT3: Free Triiodothyronine; FT4: free thyroxine.

Tab. 2. Logistic regression analysis for presence of severity of WMH

Variable	OR	95%CI	*p* value
Age	1.066	1.028-1.105	0.001
FG	1.184	0.859-1.632	0.302
CR	1.000	0.985-1.014	0.946
LDL	0.830	0.517-1.332	0.440
FT4	1.260	1.025-1.549	0.028
CMBs, n (%)	8.000	3.787-16.896	0.000

OR: odd ratio; CI: Confidence interval; FG: fibrinogen; CR: creatinine; LDL: low-density lipoprotein cholesterol; FT4: free thyroxine; CMBs: cerebral microbleeds.

Two investigators assessed the MRI and MR angiography images and the severity of WMHs. The patients were divided into two WMH burden groups based on the Fazekas scores as follows: mild-moderate group, WMH Fazekas scores of 0–2; severe group, WMH Fazekas score of 3.

CMBs were defined as homogeneous and round focal areas on susceptibility-weighted imaging with a very low signal intensity and a diameter of less than 10 mm. Acute lacunar infarction was defined as a round or ovoid lesion of a small penetrating artery (including pons) with increased signal on axial diffusion-weighted imaging and coronal fluid-attenuated inversion recovery imaging and a diameter between 0.3 and 1.5 cm.

Statistical Analysis

All statistical analyses were performed using SPSS version 21.0. $P<0.05$ was considered statistically significant. Continuous variables were compared using independent samples t-test and reported as mean with standard deviation. The chi-squared test was used to compare the significance of differences between the categorical variables. Multivariable logistic regression and ordinal regression were used to determine independent predictors for the severity of WMH. The FT4 concentrations were classified into quartiles: Quartile1: FT4 ≤ 9.42 pmol/L; Quartile2: 9.42 pmol/L < FT4 ≤ 10.46 pmol/L; Quartile3: 10.46 pmol/L < FT4 ≤ 11.46 pmol/L; and Quartile4: FT4 > 11.46 pmol/L.

RESULTS

During the study period, 304 patients with cerebral small vessel disease were identified. Of these, 130 (42.8%) were women, and the average age was 67.59±11.84 years. Two hundred and fifteen (70.7%) patients had a history of hypertension, and 79 patients (26%) had a history of diabetes mellitus. The risk factors included cigarette smoking for 57 (18.8%) and current drinking for 50 (16.4%). Patients with severe WMH were older than patients with mild-moderate WMH ($P<0.001$). The mean serum fibrinogen level ($P=0.040$), creatinine level ($P=0.040$) and FT4 level ($P=0.003$) were significantly higher in the severe WMH group than in the mild-moderate WMH group. The mean serum low-density lipoprotein level was lower in the severe WMH group than in the mild-moderate WMH group ($P=0.013$). The proportion of CMBs was higher in severe WMH than mild-moderate WMH ($P<0.001$). There were no significant differences in other variables between the two groups (Table 1).

Multivariable logistic regression analyses showed that higher concentrations of FT4 were independently associated with severe WMHs. Age and CMBs were also independent risk factors for severe WMHs (Table 2). Ordinal regression analysis verified the above conclusions that age (OR, 1.065; 95% CI, 1.042–1.088; $P=0.005$), concentration of FT4 (OR, 1.151; 95% CI, 1.006-1.318; $P=0.040$), and CMBs (OR, 3.108; 95% CI, 1.89-5.104; $P=0.000$) were independently associated

Tab. 3. Ordinal regression analysis of White matter lesion grade

Variable	OR	95%CI	*p* value
Age	1.065	1.042-1.088	0.000
FG	1.108	0.882-1.392	0.377
CR	1.002	0.991-1.013	0.770
LDL	0.970	0.717-1.314	0.858
FT4	1.151	1.006-1.318	0.040
CMBs, n (%)	3.108	1.89-5.104	0.000

OR: odd ratio; CI: Confidence interval; FG: fibrinogen; CR: creatinine; LDL: low-density lipoprotein cholesterol; FT4: free thyroxine; CMBs: cerebral microbleeds.

Tab. 4. Distribution of demographic and clinical characteristics across different quarter levels

Variable	All (n = 304)	FT4 Q1 (n =76)	FT4 Q2 (n =78)	FT4 Q3(n = 74)	FT4 Q4 (n =76)	*p* value
Female, n (%)	130 (42.8)	39 (51.3)	30 (38.5)	32 (43.2)	29 (38.2)	0.317
Age, mean ± SD	67.59 (±11.84)	65.63 (±11.40)	66.99 (±11.76)	67.93 (±12.56)	69.84 (±11.48)	0.165
Hypertension, n (%)	215 (70.7)	51 (67.1)	52 (66.7)	54 (73)	58 (76.3)	0.488
Diabetes mellitus, n (%)	79 (26.0)	19 (25)	19 (24.4)	21 (28.4)	20 (26.3)	0.946
Current drinker, n (%)	50 (16.4)	9 (11.8)	11 (14.1)	13 (17.6)	17 (22.4)	0.589
Current smoker, n (%)	57 (18.8)	13 (17.1)	17 (21.8)	16 (21.6)	11 (14.5)	0.322
FG(g/L),mean±SD	2.61 (±1.02)	2.51 (±1.34)	2.51 (±0.88)	2.54 (±0.66)	2.87 (±1.07)	0.085
CR(μmol/L),mean±SD	67.85 (±25.64)	62.35 (±16.58)	68.47 (±25.05)	72.17 (±35.67)	68.60 (±21.60)	0.134
HDL(mmol/L), mean±SD	1.17 (±0.27)	1.18 (±0.54)	1.20 (±0.28)	1.13 (±0.27)	1.16 (±0.29)	0.545
LDL(mmol/L), mean±SD	2.60 (±0.81)	2.84 (±0.82)	2.62 (±0.75)	2.49 (±0.83)	2.46 (±0.77)	0.028
TSH(mIU/L),mean±SD	2.83 (±7.67)	4.40 (±14.60)	2.51 (±2.27)	2.30 (±1.15)	1.99 (±1.39)	0.212
FT3(pmol/L),mean±SD	4.43 (±0.60)	4.39 (±0.63)	4.40 (±0.60)	4.44 (±0.57)	4.51 (±0.60)	0.561
Acute lacunar infarction	79 (26.0)	17 (22.4)	16 (20.5)	24 (32.4)	22 (28.9)	0.298
CMBs, n (%)	126 (41.4)	27 (35.5)	29 (37.2)	34 (45.9)	36 (47.4)	0.334
Severe WMH, n (%)	71 (23.4)	11 (14.5)	17 (21.8)	18 (24.3)	25 (32.9)	0.061

Q1: Quarter 1; Q2: Quarter 2; Q3: Quarter 3; Q4: Quarter 4; WMH: white matter hyperintensity; CMBs: cerebral microbleeds; FG: fibrinogen; CR: creatinine; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; FT3: Free Triiodothyronine; FT4: free thyroxine.

with WMH severity when the WMH score increased by one level (Table 3).

Patients in the FT4 group of Quartile4 had a higher incidence of severe WMH (Table 4). The low-density lipoprotein index decreased significantly in the group of Quartile4 (P=0.028). After adjusting for sex and age, the Quartile2, Quartile3, and Quartile4 of FT4 were significantly associated with the prevalence of severe WMH. These associations persisted after adjusting for sex, age, history of hypertension, history of diabetes, drinking history, and smoking history (model 1). After adjusting for sex, age, hypertension history, diabetes history, drinking history, smoking history, and CMBs (model 2), an association between the FT4 of Quartile4 and severe WMH was observed (Table 5).

DISCUSSION

Our results indicate that FT4, age, and CMBs are independently associated with severe WMH in patients without intracranial arterial stenosis. However, there was no significant association between FT3 and white matter hyperintensity. To our knowledge, this is a novel study, given its focus on the associations between thyroid hormones and the severity of WMH.

TH receptors are widely present in the brain, and they play important roles in the development of the central nervous system, including perinatal growth, promoting neurogenesis, and cellular repair (Remaud *et al.* 2014). Ming Chu *et al.* demonstrated that subclinical hypothyroidism was related to EPVS and overall CSVD load in the stroke-free population. Recent research has shown that TSH value predicts functional outcome in patients with acute ischemic stroke after endovascular thrombectomy (Chen *et al.* 2020). At present, the study's finding on the association between FT4 and WMH is novel. Studies have shown that high to normal T4 (FT4) and total T4 (TT4) are associated with all-cause dementia and Alzheimer disease (Chaker *et al.* 2016b). Layal *et al.* reported that higher concentrations of FT4 within the reference range have a bearing on adverse clinical outcomes, such as stroke (Chaker *et al.* 2016a). As we all know, WMH, as a kind of small vessel disease, plays an important role in cognitive impairment and cerebrovascular disease (Lee *et al.* 2018). Therefore, our group reasonably hypothesized that FT4 is involved in the development of WMH. De Jong found that higher FT4 concentrations were related to amygdalar and hippocampal atrophy on cranial magnetic resonance imaging scans of the brain (de Jong *et al.* 2006). WMH is probably due to the breakdown of the blood-brain barrier, destruction of cerebral small blood vessels, glial activation, small infarcts in the white matter, demyelination, and loss of oligodendrocytes caused by hypoxia/hypoperfusion (Wardlaw *et al.* 2019; Tanabe *et al.* 2015). However, the pathogenesis remains uncertain. At present, studies have verified the relationship between insulin resistance and WMH accompanied

Tab. 5. Logistic regression analysis for presence of Severe WMH

	adjusting for gender, age (OR,CI)	*p* value	adjusting for model 1 (OR,CI)	*p* value	adjusting for model 2 (OR,CI)	*p* value
FT4 Q1	Reference		Reference		Reference	
FT4 Q2	1.496 (0.629, 3.560)	0.362	1.472 (0.608, 3.56)	0.391	1.558 (0.592, 410)	0.369
FT4 Q3	1.65 (0.629, 3.921)	0.255	1.625 (0.672, 3.926)	0.281	1.455 (0.558, 3.795)	0.443
FT4 Q4	2.33 (1.02, 5.34)	0.046	2.57 (1.10, 6.01)	0.029	2.584 (1.023, 6.527)	0.045

Q1: Quarter 1; Q2: Quarter 2; Q3: Quarter 3; Q4: Quarter 4; OR: odd ratio; CI: Confidence interval; FT4: free thyroxine; Model 1: adjusting for gender, age, history of hypertension, history of diabetes, drinking history, smoking history; Model 2: adjusting gender, age, hypertension history, diabetes history, drinking history, smoking history and CMBs.

by type 2 diabetes (Shimomura *et al.* 2008; Anan *et al.* 2008). Katsumata *et al.* also found that insulin resistance was associated with WMH in non-diabetic patients (Anan *et al.* 2008). Roos *et al.* reported that low to normal FT4 was associated with insulin resistance (Roos *et al.* 2007). Therefore, we hypothesized that FT4 affects the occurrence and development of WMH through insulin resistance.

In this study, we conclude that CMBs were independently correlated with severe white matter hyperintensity. There are inconsistent conclusions in the current literature. A study, conducted in Taiwan, showed a relationship between CMBs and the volume of white matter independent of demographic characteristics and vascular risk factors (Wang *et al.* 2020). A recent prospective population-based cohort study showed that multiple domains of the white matter skeleton were related to strictly lobar CMBs, while only a few voxels were associated with deep microbleeds (Liu *et al.* 2020). There are hypotheses on the mechanism underlying the association between white matter integrity loss and CMBs. First, CMBs may directly impair the adjoining white matter (Liu *et al.* 2020). Second, white matter integrity damage and CMBs may simultaneously occur due to a downstream interaction of vascular risk factors (Han *et al.* 2018). Third, CMBs may be associated with the impairment of the blood-brain barrier (Schreiber *et al.* 2013).

We also found that age was an independent risk factor of WMHs, which was consistent with the findings of previous studies. There is converging evidence of an association between severe WMH and old age (Prins & Scheltens 2015; Garnier-Crussard *et al.* 2020). Age-related WMH is attributed to chronic ischemic cerebrovascular disease. Recently, Wei *et al.* showed that WMH had a significant relationship with white matter hyperintensity volume (Wei *et al.* 2019). Finally, aging contributed to mild cognitive impairment or dementia.

Several limitations should also be mentioned. First, this is a single-center cross-sectional study, which prevented us from establishing causality. Second, the size of our sample is relatively small, and we need to conduct a study involving a large sample. Third, our research is lacking thyroid pathologies and antibodies against thyroid peroxidase or against the thyroid receptor. In future research, we will focus on thyroid pathologies and antibodies associated with the thyroid.

CONCLUSION

In conclusion, our results support the hypothesis that FT4 is associated with the severity of WMH in patients without intracranial arterial stenosis. Age and CMBs were independently related to the severity of WMH. In future studies, we will further explore the relationship between FT4 and WMH in a larger population.

ACKNOWLEDGMENTS

The authors wish to acknowledge patients and their families who agreed to participate in our study.

AUTHOR CONTRIBUTIONS

CX was responsible for the concept and design of the study, data collection and analysis, and writing the manuscript. WC was responsible for data collection and analysis. DL and YL were responsible for data collection. XYZ was responsible for concept and design of the study and interpretation. All authors read and approved the final manuscript for publication.

ETHICS STATEMENT

This study was approved by the Internal Review Ethics Board at the Second Affiliated Hospital of Nantong University.

DECLARATION OF INTEREST

None.

FUNDING

This study was supported by Scientific Research Project of the Health Commission of Jiangsu Province H2019057.

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