Journal of the Neurological Sciences 368 (2016) 89–93

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Low free triiodothyronine predicts poor functional outcome after acute ischemic stroke

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ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 16 June 2016
Accepted 27 June 2016
Available online 30 June 2016

Keywords:
Acute ischemic stroke
Thyroid hormone
Free triiodothyronine
Stroke outcome

ABSTRACT

Background and purpose: The aim of this study was to investigate the association of admission serum thyroid hormone concentration with clinical characteristics and functional outcomes in patients after acute ischemic stroke.
Methods: We retrospectively enrolled 398 consecutive patients admitted to our stroke center between July 2010 and April 2012. Serum thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were evaluated upon admission. Neurological severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) upon admission and the modified Rankin Scale (mRS) upon discharge. Poor outcome was defined as a mRS score of 3–5 or death (mRS score 6). Separate analyses were conducted according to outcome and quartile serum FT3 concentration.
Results: In total, 164 patients (41.2%) demonstrated a poor outcome. Age, male gender, blood glucose level, arterial fibrillation, dyslipidemia, smoking, NIHSS score, cardioembolic stroke type, and periventricular hyperintensities, but not FT4 or TSH, were significantly associated with poor functional outcome. Furthermore, poor functional outcome was independently associated with low FT3 (<2.29 pg/mL). In comparisons between FT3 quartiles (Q1 [≤2.11 pg/mL], Q2 [2.12–2.45 pg/mL], Q3 [2.46–2.77 pg/mL], Q4 [≥2.78 pg/mL]), patients with poor outcomes were more frequent in Q1 than in Q4 after multivariate adjustment. Death was more frequent in Q1 than in Q4 after adjustment for risk factors and comorbidities, but this difference was non-significant after additional adjustment for age and NIHSS score.
Conclusions: Our data suggest that a lower FT3 value upon admission may predict a poor functional outcome in patients with acute ischemic stroke. Further large-scale prospective studies are required to clarify the role of thyroid hormone in the acute phase of ischemic stroke.

1. Introduction

Stroke is a leading cause of mortality worldwide. Moreover, stroke has a higher tendency to result in sequelae than cardiac events and requires long-term rehabilitation and care, such that it poses a significant socioeconomic burden. The early and accurate prediction of outcomes in stroke patients is important for determining discharge destinations, optimizing the use of healthcare resources, and improving long-term outcomes [1,2].

Thyroid disorders are known risk factors for cerebrovascular disease. Accordingly, thyroid hormone screening has demonstrated utility in patients with acute ischemic stroke [3–5]. Recent studies have suggested that thyroid hormone levels can predict clinical outcomes in critical illnesses such as sepsis, myocardial infarction, and heart failure. Thyroid hormones are able to cross the blood–brain barrier and affect neurogenesis, cell differentiation, and myelination [6,7]. Experimental studies have suggested that serum thyroid hormone concentrations are inversely correlated with the clinical severity of stroke, and furthermore the administration of thyroid hormones has been demonstrated to confer neuroprotection in stroke [8,9]. However, the association between thyroid hormone and stroke outcome has not been fully elucidated [10,11].

The present study aimed to examine whether the serum concentrations of thyroid hormones including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) on admission are associated clinical characteristics and functional outcomes in patients after acute ischemic stroke.

2. Methods

2.1. Subjects and evaluation

This study retrospectively enrolled 398 consecutive patients with ischemic stroke that were admitted to the stroke center at Nippon

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http://dx.doi.org/10.1016/j.jns.2016.06.063
0022-510X/

Medical School Hospital between July 2010 and April 2012. Informed consent was obtained from all patients or relatives of patients and the study design was approved by the institutional ethics committee. All patient records and information were anonymized and de-identified prior to analysis.

Brain computed tomography scans were conducted in all subjects to rule out the possibility of cerebral or subarachnoid hemorrhage. Fresh infarcts were confirmed using diffusion-weighted magnetic resonance imaging (MRI). Examination of the cranial arteries was primarily performed using MR angiography. Stroke subtype was determined according to the Trail of Org 10172 in Acute Stroke Treatment (TOAST) subtype classification system; ischemic stroke was classified as either cardioembolic or non-cardioembolic (e.g., lacunar, atherothrombotic). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) upon hospital admission. Functional outcome was assessed using the modified Rankin Scale (mRS) at the time of discharge. A favorable outcome was defined as a mRS score of 0–2 and a poor outcome was defined as a score of 3–5 or death (mRS score of 6).

2.2. Clinical information and thyroid function measurements

Blood samples were collected upon admission and, in addition to standard blood tests, serum levels of TSH, FT3, and FT4 were determined using electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Normal values for TSH, FT3, and FT4 were 0.1–5.00 mIU/L, 2.00–3.80 pg/mL, and 0.83–1.64 ng/dL, respectively. All measurements were performed by laboratory staff who were blinded to patient clinical information.

Risk factors for ischemic stroke included age, hypertension, atrial fibrillation, dyslipidemia, smoking, and a history of ischemic stroke or ischemic heart disease. Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic pressure ≥90 mmHg persisting after the acute stage of ischemic stroke, or by antihypertensive medication use prior to admission. Atrial fibrillation was diagnosed using electrocardiography upon admission and or by the occurrence of paroxysmal atrial fibrillation during hospitalization. Dyslipidemia was defined as a fasting plasma cholesterol level ≥220 mg/dl, a fasting plasma triglyceride level ≥150 mg/dl, or by the use of lipid-lowering medications prior to admission. Smoking habits and history were also assessed. Prior ischemic stroke was defined as a previous diagnosis of and treatment for ischemic stroke. Prior ischemic heart disease was defined as a previous diagnosis of and treatment for myocardial infarction and/or angina.

2.3. Cerebral white matter lesions

Patients were examined for cerebral white matter lesions upon admission using brain MRI. All lesions related and unrelated to acute ischemic stroke were evaluated. Lesions were defined as having a high signal intensity on T2-weighted and fluid-attenuated inversion recovery images, and as being isointense on T1-weighted images. Lesions were investigated in the periventricular white matter and the deep or subcortical white matter. Neurologists who were blinded to patient clinical information performed the classification of periventricular hyperintensities according to Fazekas et al. [12].

2.4. Statistical analysis

We initially compared the clinical characteristics of patients with good outcomes (the good outcome group) and poor outcomes (the poor outcome group). Intergroup differences were assessed using either the chi-square test or the Wilcoxon rank-sum test. The optimal cutoff points for distinguishing the good outcome group from the poor outcome group for each continuous variable were determined using receiver operating characteristics (ROC) curves. Potential variables with $P < 0.10$ in a univariable analysis were entered into a multivariable logistic regression model to identify whether variables were independently associated with poor outcome. Data are represented as odds ratios (ORs) with 95% confidence intervals (CIs).

Patients were also classified into quartiles based upon admission serum FT3 value. Baseline demographics and clinical characteristics were compared across quartiles by serum FT3 value using the chi-square test or the Kruskal–Wallis rank-sum test. Associations between each FT3 quartile and the distribution of mRS scores were assessed using multivariate regression models. All analyses were performed using JMP 10 statistical software (SAS Institute Inc.). A P value <0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Table 1 summarizes patient baseline characteristics. Patients in the poor outcome group were older ($P < 0.001$) and had a lower frequency of male gender ($P = 0.03$), smoking ($P = 0.0077$), and dyslipidemia ($P = 0.025$) but a higher frequency of atrial fibrillation ($P < 0.001$) and cardioembolic stroke subtype ($P < 0.001$) than those in the good

Table 1
Factors related to discharge outcome in acute ischemic stroke patients.

	Total (n = 398)	Good outcome (n = 234)	Poor outcome (n = 164)	*P* value
Age, years	73.3 ± 11.9	9.8 ± 11.4	78.3 ± 11.0	<0.001
Male gender	253 (63.6)	159 (68.0)	94 (57.3)	0.030
FT3 (pg/mL)	2.45 ± 0.57	2.64 ± 0.45	2.19 ± 0.62	<0.001
FT4 (ng/dL)	1.20 ± 0.21	1.20 ± 0.19	1.20 ± 0.23	0.69
TSH (mIU/L)	2.41 ± 4.23	2.14 ± 1.74	2.81 ± 6.25	0.42
Hypertension	301 (75.6)	181 (77.4)	120 (73.2)	0.34
Dyslipidemia	172 (43.2)	112 (47.9)	60 (36.6)	0.025
Atrial fibrillation	136 (34.2)	56 (23.9)	80 (48.8)	<0.001
Glucose level (mg/dL)	133.6 ± 52.1	125.5 ± 42.1	145.0 ± 62.0	<0.001
Ischemic heart disease	51 (12.8)	29 (12.4)	22 (13.4)	0.76
Smoking	111 (27.9)	77 (32.9)	34 (20.7)	0.0077
Prior stroke	104 (26.1)	54 (23.1)	50 (30.5)	0.0978
Cardioembolic stroke	117 (29.4)	49 (20.9)	68 (41.5)	<0.001
NIHSS score on admission	4 (2–9)	3 (1–4)	10 (5–20)	<0.001
Intravenous r-tPA	22 (5.5)	9 (3.9)	13 (7.9)	0.08
PVH grading	1 (0–2)	1 (0–2)	1 (1–3)	<0.001

Values are expressed as median with interquartile range for NIHSS score and PVH or as number with percentage or mean ± SD for other items. FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue plasminogen activator; PVH, periventricular hyper-intensity.