Low Free Triiodothyronine Predicts 3-Month Poor Outcome After Acute Stroke

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Background and Purpose: The association between thyroid hormone levels and long-term clinical outcome in patients with acute stroke has not yet been thoroughly studied. The purpose of the present study was to test the hypothesis that thyroid hormone levels are associated with 3-month functional outcome and mortality after acute stroke. *Methods:* We retrospectively analyzed 702 consecutive patients with acute stroke (251 women; median age, 73 years) who were admitted to our department. General blood tests, including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4), were performed on admission. Neurological severity was evaluated using National Institutes of Health Stroke Scale (NIHSS) scores on admission and modified Rankin Scale (mRS) scores at 3 months after stroke onset. Poor outcome was defined as an mRS score of 3-5 or death. The impact of thyroid function on 3-month outcome was evaluated using multiple logistic regression analysis. *Results:* Poor functional outcome was observed in 295 patients (42.0%). Age ($P < .0001$), female sex ($P < .0001$), admission NIHSS score ($P < .0001$), smoking ($P = .0026$), arterial fibrillation ($P = .0002$), preadmission mRS ($P < .0001$), estimated glomerular filtration rate ($P = .0307$), and ischemic heart disease ($P = .0285$) were significantly associated with poor functional outcome, but no relationship between FT4, TSH, and poor functional outcome was found. A multivariate logistic regression analysis showed that low FT3 values (<2.00 pg/mL) were independently associated with poor functional outcome (odds ratio [OR], 3.16; 95% confidence interval [CI], 1.60-6.24) and mortality (OR, 2.55; 95% CI, 1.33-4.91) at 3 months after stroke onset. *Conclusions:* Our data suggest that a low FT3 value upon admission is associated with a poor 3-month functional outcome and mortality in patients with acute stroke.

Key Words: Thyroid hormone—free triiodothyronine—stroke outcome—mortality.

Introduction

Stroke is a leading cause of mortality worldwide. Moreover, stroke has a higher tendency to result in sequelae than do cardiac events, and requires long-term rehabilitation and care, such that it poses a significant socioeconomic burden. Therefore, the early and accurate prediction of prognosis in patients with stroke is important for optimizing the use of health care resources and improving long-term outcomes.[1,2] Several factors, such as stroke severity, age, sex, vascular risk factors, and comorbidities, have been consistently reported to be related to stroke outcome, but some modifiable factors in current

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prognostic studies, such as endocrine hormones and inflammatory cytokines, have not yet been thoroughly investigated.[3-5]

Thyroid disorders are known risk factors for cerebrovascular disease. Accordingly, thyroid hormone screening has shown utility in patients with acute stroke.[6-8] In recent years, change or decrease in T3 concentration, particularly low T3 syndrome, also called "euthyroid sick syndrome," which reflects dysfunction of the hypothalamus/pituitary/thyroid axis,[9] and inhibited conversion of T4 to T3 in the acute stress state have been found in critical illness such as sepsis, myocardial infarction, and heart failure[10,11] and have been associated with poor disease prognosis. However, the association between thyroid hormone levels and long-term outcome, including mortality, has not been fully elucidated.[12-16]

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 with 3-month outcomes in patients after acute stroke.

Patients and Methods

Subjects and Evaluation

This study retrospectively enrolled 908 consecutive patients with acute stroke (ischemic stroke, n = 555; hemorrhagic stroke, n = 147), which were admitted to the stroke center at Nippon Medical School Hospital between October 2014 and December 2016. Informed consent was obtained from all patients or relatives of patients. All patient records and information were anonymized and deidentified prior to analysis. 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 3 months after stroke onset. A favorable outcome was defined as an mRS score of 0-2, and a poor outcome was defined as a score of 3-5 or death (mRS score of 6).

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), as previously reported.[17] The normal reference ranges for TSH, FT3, and FT4 were .1-5.00 mIU/L, 2.00-3.80 pg/mL, and .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 stroke or by antihypertensive medication use prior to admission. Diabetes was defined by the use of antidiabetic medication or as a fasting blood glucose level ≥126 mg/dL, random glucose level ≥200 mg/dL, or glycosylated hemoglobin ≥6.5% upon 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. Current smoking habit and alcohol consumption were also assessed. Prior stroke was defined as a previous diagnosis of and treatment for stroke. Prior ischemic heart disease was defined as a previous diagnosis of and treatment for myocardial infarction and/or angina. Body mass index upon admission was calculated, and body mass index <18.5 was considered underweight according to the World Health Organization classification.

Statistical Analysis

We initially compared the clinical characteristics of patients with good and poor outcomes and with mortality and nonmortality. Intergroup differences were assessed using the chi-squared test or the Wilcoxon rank-sum test. Potential variables with $P < .05$ in a univariable analysis, age, and sex were entered into a multivariable logistic regression model to identify whether they were independently associated with poor outcome and with mortality. Data are represented as odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using the JMP 13 statistical software (SAS Institute Inc., Cary, NC). A P value < .05 was considered to be statistically significant.

Results

Baseline Characteristics

Table 1 summarizes patient baseline characteristics. Patients in the poor outcome group were older ($P < .0001$), had lower body mass index ($P < .0001$), lower frequency of male sex ($P < .0001$), lower frequency of smoking ($P = .0064$), lower eGFR, higher NIHSS score on admission ($P < .0001$), and higher preadmission mRS score ($P < .0001$) than those in the good outcome group. The proportion of patients with atrial fibrillation ($P = .0002$), ischemic heart disease ($P < .0001$), and prior stroke ($P = .0298$) was also significantly higher in the poor outcome group compared to the good outcome group. Patients in the poor outcome group had lower FT3 values ($P < .0001$) compared to those in the good outcome group, but there were no significant intergroup differences in FT4 ($P = .5311$) and TSH values ($P = .1059$). Patients in the mortality group were older