Low Free Triiodothyronine at Admission Predicts Poststroke Infection

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Background: Poststroke infection (PSI) is common and is usually associated with a severe prognosis. We investigated the association between PSI and thyroid hormones, which are critical to immune regulation, in patients with acute stroke. *Methods:* We retrospectively enrolled 520 consecutive patients with acute ischemic stroke (326 men; age, 71.9 ± 13.2 years) admitted to our department between September 2014 and June 2016. The impact of serum thyroid hormone levels measured at admission (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], and free thyroxine [FT4]) on the PSI was evaluated using multivariate logistic regression analysis. *Results:* We diagnosed 107 patients (20.6%; pneumonia, 65; urinary tract infection, 19; others, 23) with PSIs. While age ($P < .001$), body mass index ($P = .0012$), preadmission modified Rankin scale score ($P = .0001$), National Institutes of Health Stroke Scale score on admission ($P < .001$), admission FT3 level ($P < .001$), atrial fibrillation ($P < .001$), and ischemic heart disease ($P = .0451$) were significantly associated with PSI, we found no relationship among TSH levels, FT4 levels, and PSI occurrence. After multivariate adjustment, patients with PSIs were more frequently in the Q1 quartile (≤2.25 pg/mL) than in the Q2 (2.26-2.55 pg/mL; $P = .0251$), Q3 (2.56-2.89 pg/mL; $P = .0007$), or Q4 (≥2.90 pg/mL; $P = .0010$) quartiles of FT3 levels. Moreover, low FT3 levels (<2.29 pg/mL) were independently associated with PSI occurrence ($P = .0013$). *Conclusions:* Low FT3 levels at admission are independently associated with PSI occurrence. **Key Words:** Free triiodothyronine—poststroke infection—thyroid hormone—pneumonia.

Introduction

Infection is a common complication observed during the acute phase following stroke. A recent meta-analysis involving 87 studies comprising 137,817 patients found an overall pooled poststroke-associated infection rate of 30%, with pneumonia and urinary tract infections (UTIs) being the most commonly observed infections.[1] Poststroke infections (PSIs) are associated with poor clinical outcomes and increased mortality after stroke.[2] The risk of infection increases with the severity of stroke, age, and level of dysphagia. Moreover, poststroke immune suppression, likely mediated by sympathetic nervous system activation, increases the risk of infection.[3,4] However, prophylactic antibiotics have not been successful in reducing the frequency of pneumonia with dysphagia following stroke in patients managed in stroke units.[5] Moreover, recent clinical studies have shown that beta-blocker therapy does not reduce the risk of PSI.[6] Thus, given the

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Received June 8, 2017; revision received August 11, 2017; accepted September 11, 2017.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.09.012

multifaceted etiology of PSI, new predictors of stroke outcome need to be identified.

Thyroid disorders are known risk factors for cerebrovascular disease.[7] Recent studies have suggested that thyroid hormone levels are predictors of clinical outcome in critical illnesses such as sepsis, myocardial infarction, heart failure, and stroke.[8-10] Furthermore, thyroid hormones play a crucial role in cellular metabolism and immune system function, including the modulation of cell-mediated immunity.[11,12] However, the association between thyroid hormone levels and PSI occurrence has not been investigated.

We investigated whether thyroid hormone (thyroid-stimulating hormone [TSH], free triiodothyronine [FT3], and free thyroxine [FT4]) levels at admission are associated with the development of PSIs in patients with acute ischemic stroke.

Methods

Subjects and Evaluation

This study was approved by the ethics committee of Nippon Medical School; all the participants or their family members provided written informed consent prior to their participation in the study. From September 2014 through June 2016, 520 consecutive patients with acute ischemic stroke who were admitted to our stroke unit within 7 days of symptom onset were retrospectively recruited from a prospective registry. The stroke subtype was determined based on the Trial of Org 10172 in Acute Stroke Treatment subtype classification system.[13] The stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score measured at admission.

A PSI was defined as any infection diagnosed during the hospitalization period. The infections were diagnosed based on modified Centers for Disease Control and Prevention criteria by trained and experienced clinicians,[14] and were divided into 3 groups: pneumonia, UTI, and other infections.[15,16] The definitions of pneumonia and UTI that we used were similar to those used in previously published studies.[15,17,18] Briefly, pneumonia was defined based on the presence of relevant clinical symptoms and/or signs (e.g., purulent cough, unilateral inspiratory crackles, bronchial breath sounds) with at least one of the following: leukocytosis, fever, or a positive chest radiograph. UTI was defined based on the presence of relevant clinical symptoms and/or signs (e.g. dysuria, urinary frequency changes) with positive microbiological cultures, or negative cultures with leukocytosis, fever (temperature ≥ 38.0°C), or both. Fever (>38.0°C), in combination with leukocytosis that did not fulfill the diagnostic criteria for pneumonia or UTI, was classified into the "other infections" group.

Thyroid Function Measurements and Clinical Information

Blood samples were obtained from the patients at admission; in addition to routine blood tests, the serum TSH (normal range: .1-5.00 mIU/L), FT3 (normal range: 2.00-3.80 pg/mL), and FT4 (normal range: .83-1.64 ng/dL) levels were determined using the electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). All the measurements were performed by the laboratory staff, who were blinded to the clinical diagnosis.

We assessed risk factors including age, sex, hypertension, blood glucose levels, dyslipidemia, history of smoking, history of alcohol consumption, and history of stroke or ischemic heart disease. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher persisting after the acute stage following ischemic stroke, or on the basis of the use of antihypertensive medication prior to admission. Dyslipidemia was defined as a fasting plasma cholesterol level of 220 mg/dL or higher, a fasting plasma triglyceride level of 150 mg/dL or higher, or on the basis of the use of lipid-lowering medication prior to admission. Smoking habits, history of smoking, and alcohol consumption were also assessed. Prior ischemic heart disease was defined as previous diagnosis of and administration of treatment for myocardial infarction and/or angina.

Statistical Analysis

The clinical characteristics of patients with and without PSIs were compared using the chi-square test or the Wilcoxon rank-sum test, as appropriate. The differences between the modified Rankin Scale (mRS) scores at admission and discharge (ΔmRS) were compared between the groups using the Wilcoxon rank-sum test. Variables showing P values lower than .05 in the univariable analysis were entered into a multivariable logistic regression model to identify whether these variables were independently associated with PSI occurrence. The optimal cutoff values for distinguishing the PSI group from the non-PSI group were determined for each continuous variable using receiver operating characteristic curves. The odds ratios (ORs) were presented with the corresponding 95% confidence intervals (CIs). Patients were also classified into quartiles based on their serum FT3 levels at admission. The baseline demographic and clinical characteristics were compared among quartiles using the chi-square test or the Wilcoxon rank-sum test, as appropriate. Associations between FT3 quartiles and PSI (and poststroke pneumonia) occurrence were assessed using multivariate logistic regression models. All the analyses were performed using the JMP version 13 statistical software (SAS Institute Inc., Cary, NC). Results with P values lower than .05 were considered statistically significant.