Impact of Thyroid Autoantibodies on Functional Outcome in Patients with Acute Ischemic Stroke

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Background: Recent studies have shown that thyroid autoantibodies contribute to the development of cerebrovascular diseases, including atherosclerosis, moyamoya disease, and even arterial dissection, induced by immune-mediated endothelial dysfunction on the cerebral vasculature. The aim of this study was to investigate the impact of thyroid autoantibodies on functional outcome in patients with acute ischemic stroke. *Methods:* We reviewed the patients with acute ischemic stroke who consecutively underwent thyroid autoantibody tests. We divided the patients into positive thyroid autoantibody (PAB) and negative thyroid autoantibody (NAB) groups. Demographic profiles, risk factors, stroke subtypes, laboratory results, and functional outcomes were compared between the 2 groups. We performed the multivariate analysis to determine whether thyroid autoantibodies were independently associated with functional outcome. *Results:* Of the 763 patients, 121 (15.9%) were of the PAB group. Compared with the NAB group, higher baseline National Institutes of Health Stroke Scale score ($P = .001$) and prevalence of large-artery atherosclerosis ($P = .014$) were found in the PAB group. The PAB group had significantly higher proportion of unfavorable outcome at 3 months (modified Rankin Scale score ≥ 3) than the NAB group ($P = .002$). On multiple regression analysis, lower tri-iodothyronine level (odds ratio [OR] .985, 95% confidence interval [CI] .976-.995, $P = .002$) and PABs (OR 1.661, 95% CI 1.013-2.724, $P = .044$) were significant and independent predictors of unfavorable outcome. *Conclusions:* This study showed that elevated thyroid autoantibodies were independently associated with unfavorable outcome in patients with acute ischemic stroke. We speculate that immune-mediated vascular damage may contribute to the increased risk of unfavorable outcome by providing insufficient cerebral blood flow to the ischemic area. **Key Words:** Cerebral infarction—stroke—thyroid gland—autoantibodies—prognosis.

Introduction

Several studies have provided the evidences for the relationship between thyroid autoimmunity and vascular diseases.[1-4] Apart from the histopathologic data reporting cerebral vasculitis in autoimmune thyroiditis patients,[5,6] a recent study showed higher prevalence of elevated thyroid autoantibodies in stroke patients with intracranial stenosis than those without.[4] In other studies,

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thyroid autoantibodies were associated with moyamoya disease and even arterial dissection.[7-9] Although the exact mechanism is not fully understood, these findings have been ascribed to immune-mediated inflammatory reaction and resultant endothelial dysfunction on the cerebral vasculature, based on the fact that vascular tissues share some antigenic properties with thyroid tissues.[1-3]

Given the association between thyroid autoimmunity and endothelial dysfunction, the previous studies that showed impaired cerebral perfusion in patients with autoimmune thyroiditis arouse concerns as to whether thyroid autoimmunity may contribute to the unfavorable cerebrovascular prognosis.[10,11] However, until now, there have been few considerations of the possibility that thyroid autoantibodies may affect functional outcome in acute ischemic stroke patients. Thus, we investigated the impact of thyroid autoantibodies on functional outcome in these patients.

Methods

Patient Selection

From November 2010 to April 2013, we reviewed 1035 patients with acute ischemic stroke who were admitted to the stroke center and registered in a prospectively collected stroke registry. Eligible for this study were patients who had acute cerebral infarction demonstrated by diffusion-weighted imaging within 7 days of symptom onset and underwent thyroid function tests accompanied with thyroid autoantibody tests. We excluded patients with pre-existing thyroid disease except for benign thyroid nodules, use of levothyroxine or antithyroid medication during admission, or administration of thrombolytic treatment. This study was approved by the hospital's institutional review board.

Clinical Information

We collected baseline demographics, laboratory results, and vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking. Hypertension was defined as high blood pressure (systolic $\geq$ 140 mm Hg or diastolic $\geq$ 90 mm Hg) or the taking of antihypertensive agents. Diabetes mellitus was diagnosed by a high fasting plasma glucose level ($\geq$7.0 mmol/L) or the taking of hypoglycemic agents. Hyperlipidemia was defined by a high level of fasting serum total cholesterol ($\geq$6.2 mmol/L), low-density lipoprotein cholesterol ($\geq$4.1 mmol/L), or treatment with antihyperlipidemic agents after a diagnosis of hyperlipidemia. Patients were considered as smokers if they smoked within the 3-month period before admission.

Stroke severity was assessed according to the National Institutes of Health Stroke Scale (NIHSS) score at admission and discharge. Functional outcome was evaluated using the modified Rankin Scale (mRS) and unfavorable outcome was defined as an mRS score of 3 or more at 3 months after symptom onset. Stroke subtypes were established using the Trial ORG 10172 in Acute Stroke Treatment classification system.[12] Both high and medium risk cardiac sources were considered as potential sources of cardioembolism.

Thyroid Function and Autoantibody Tests

During the study period, we performed the laboratory tests for thyroid function and autoantibodies in the consecutive patients with acute ischemic stroke presenting within 7 days of symptom onset. Blood samples were taken in the morning after admission. Thyroid function was evaluated by measuring serum levels of tri-iodothyronine (T3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). The reference ranges for T3, FT4, and TSH were 80-170 ng/dL, .75-2.0 ng/dL, and .3-5.0 mIU/mL, respectively. For the assessment of thyroid autoimmunity, serum concentrations of thyroperoxidase (TPO-Ab) and thyroglobulin (TG-Ab) autoantibodies were measured using radioimmunoassay with a commercial kit (Brahms, Hennigsdorf, Germany). The analytic sensitivities of the assays for TPO-Ab and TG-Ab were 5.5 and 5.5 U/mL, respectively, and the ranges for intra-assay coefficients of variation were 2.9%-4.5% and 2.0%-7.5%, respectively. The normal ranges for TPO-Ab and TG-Ab were of 60 U/mL or less each according to the manufacturer's reference.

Thyroid function was categorized into 3 groups based on the level of TSH, which consisted of hyperthyroidism (TSH $<$ .3 mIU/L), euthyroidism (TSH .3-5.0 mIU/L), and hypothyroidism (TSH $>$ 5.0 mIU/L). We divided the patients into 2 groups according to the levels of thyroid autoantibodies. Positive thyroid autoantibody (PAB) group was defined as either TPO-Ab or TG-Ab greater than 60 U/mL. Negative thyroid autoantibody (NAB) group was defined as TPO-Ab and TG-Ab of 60 U/mL or less concurrently. We evaluated the association of functional outcome and thyroid autoantibody levels with tertiles of TPO-Ab and TG-Ab titers.

Statistical Analysis

Categorical variables were compared using Pearson chi-square or Fisher exact test, where appropriate. Continuous variables were compared using Mann–Whitney test because the values of T3, FT4, and TSH were not normally distributed. Descriptive data were given as frequencies (percentage) or median (interquartile range [IQR]). Multiple logistic regression analysis was used to determine the independent predictors associated with unfavorable outcome, in which variables with P less than .1 on univariate analysis were included. The results were expressed as odd ratios (OR) and 95% confidence intervals (CIs). Values of P less than .05 were considered statistically significant. All statistical analyses