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Low triiodothyronine: A new facet of inflammation in acute ischemic stroke

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ABSTRACT

Background: Patients with acute ischemic stroke (AIS) frequently experience low free triiodothyronine (fT3) concentrations. Inflammation is recognized as a key contributor to the pathophysiology of stroke. Previous studies, however, did not simultaneously evaluate fT3 and inflammation biomarkers in AIS patients.
Methods: Markers of inflammation, including serum concentrations of C-reactive protein (CRP) and albumin, and fT3 were assessed retrospectively in 117 patients. Stroke severity was measured on the National Institutes of Health Stroke Scale (NIHSS). Regression analyses were performed to adjust for confounders.
Results: Serum fT3 concentrations were significantly lower in moderate AIS patients than those in mild AIS patients ($P < 0.001$). fT3 concentration also positively correlated with serum albumin concentration ($r = 0.358$, $P < 0.001$) and negatively correlated with $\log_{10}$CRP concentration ($r = -0.341$, $P < 0.001$), NIHSS score ($r = -0.384$, $P < 0.001$). Multiple regression analysis showed that CRP, albumin concentrations and NIHSS score were independently correlated with fT3 concentration. Binary logistic regression analysis showed that fT3 concentration was an independent factor correlated with NIHSS score, the area under the receiver operating characteristic curve was 0.712 (95% CI, 0.618–0.805).
Conclusions: Low fT3 concentrations may be involved in the pathogenic pathway linking inflammation to stroke severity in AIS patients.

1. Introduction

Acute ischemic stroke (AIS) is a complex pathophysiological process. Previous studies have suggested that neuroendocrine profiles are significantly altered in AIS patients [1,2]. Low free triiodothyronine (fT3) syndrome, characterized by alterations in thyroid hormones in the absence of an underlying intrinsic thyroid disorder, may represent some form of central hypothyroidism [3,4]. It is an adaptive compensatory and therefore beneficial response aimed at maintaining energy balance and minimizing protein wasting in diseased states [5]. However, altered thyroid hormone metabolism, characterized by low circulating T3 levels, has been described in patients with cardiovascular disease, pulmonary disorders, chronic kidney disease and brain tumor [6,7,8,9], suggested that this alteration is less benign than previously thought [10]. And recent studies showed that low-T3 during the acute phase of AIS may be a predictor of poor clinical and functional outcomes [11,12].

Inflammatory processes play fundamental roles in the etiology and in the pathophysiology of ischemic cerebrovascular disease [13]. C-reactive protein (CRP), fibrinogen (FIB), erythrocyte sedimentation rate (ESR), and leukocyte count are markers of acute inflammation and associated with increased morbidity and mortality rates in AIS patients [14–16]. Serum albumin is a negative acute-phase protein in inflammation [17], as well as a highly sensitive indicator of malnutrition and strongly associated with clinical outcomes of stroke patients [18]. In this study, we tested serum concentrations of CRP, FIB, albumin, ESR and white blood cell (WBC) counts as markers of inflammation.

Although many studies have assessed the impact of inflammation dysfunction on stroke outcome in AIS patients, the correlations between low fT3 and markers of inflammation in AIS patients have not been analyzed.

2. Methods

2.1. Study design and source of data

The medical records of 674 ischemic stroke patients from June 2011 to May 2013 at the Department of Neurology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, were retrospectively reviewed. Patients were aged between 22 and 83 y and diagnosed with AIS according to World Health Organization criteria [19], with symptom onset within 72 h. All patients involved in this study were diagnosed with AIS for the first time.

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To avoid any confounding effects, patients with overt hyper- or hypothyroidism and those treated with drugs known to interact with the thyroid gland (e.g. amiodarone, dopamine, β-blockers, corticosteroids, lithium, or phenytoin) were excluded. These patients were also clinically free from cancer, infection, hematological diseases, severe renal, liver or heart failure. They also had not been treated by thrombolysis or in the intensive care unit. After exclusion, a total of 117 first-ever AIS patients were included in the definitive analysis, and the National Institutes of Health Stroke Scale (NIHSS) score in those AIS patients was ≤15. The study protocol was approved by the ethics committee of The Third Affiliated Hospital of Sun Yat-sen University.

2.2. Clinical and laboratory variables

Clinical characteristics of the patients included: 1) Demographic findings (age, gender). 2) Vascular risk factors (hypertension, atrial fibrillation, drinking, cigarette smoking, hyperlipidemia, diabetes). 3) Stroke severity, assessed by the NIHSS [20]. 4) Laboratory data within 24 h of admission (fT3, free thyroxine, thyrotropin, total cholesterol, triglycerides [TG], high-density lipoproteins, low-density lipoproteins, homocysteine, WBC, platelets, CRP, ESR, FIB, albumin, uric acid, fast glucose); and 5) other factors (heart rate, time interval, ischemic heart disease). Blood samples for evaluation of thyroid function and biochemical profiles were obtained from each fasting patient the morning after admission (07:00–08:00 h).

2.3. Statistical analyses

To test the independent association between fT3 concentration and inflammation, patients were divided into those with mild (NIHSS score ≤ 5) and moderate (NIHSS score between 6 and 15) [21].

Normally distributed data are presented as mean ± SD, non-normally distributed data as median (inter-quartile range), and categorical data as percentages. Normally and non-normally distributed continuous data were compared by using independent sample *t*-tests and Mann–Whitney U tests, respectively, and categorical data were compared using χ^2 or Fisher's exact tests.

Multivariate regression analysis was performed to evaluate factors independently associated with stroke severity and plasma fT3 concentration. Factors evaluated included those differed between patients with mild and moderate stroke, as well as all correlates of plasma fT3.Correlations were assessed by Spearman/Pearson correlation analysis, as appropriate. Continuous variables with skewed distribution were log transformed ($\log_{10}$) before correlation analysis. The results of regression analysis are presented as correlation coefficients (r) or regression coefficients (β), *P* values, and 95% confidence intervals (CI). The receiver operating characteristics (ROC) curve analysis was utilized to determine which serum fT3 level was the most powerful predictive of stroke severity. Area under the curve (AUC) was calculated as measurements of the accuracy of the test. All statistical analyses were performed using the Statistical Package for Social Sciences v.13.0 for Windows (SPSS), with statistical significance defined as 2-tailed $P < 0.05$.

3. Results

The 117 AIS patients consisted of 71 (60.7%) males and 46 (39.3%) females, of mean age 58.8 ± 13.7 y. The demographic, clinical, and biochemical characteristics of the patients included in the study are summarized in Table 1.

3.1. Relationship of fT3 with inflammation markers and stroke severity

AIS patients were divided into mild stroke group and moderate stroke group according to NIHSS scores. There were no differences in age, sex distribution, or any of the risk factors recorded in this study between two groups. fT3 concentrations were significantly higher in mild than in moderate group (4.62 ± 0.69 pmol/l vs 4.03 ± 0.74 pmol/l, $P < 0.001$), but fT4 and TSH concentrations did not differ significantly (Table 1). The association between NIHSS and fT3 was existed when NIHSS was treated as continuous variable. Indeed, fT3 concentration negatively correlated with NIHSS score ($r = -0.384$, $P < 0.001$), $\log_{10}$CRP ($r = -0.341$, $P < 0.001$), $\log_{10}$ESR($r = -0.304$, $P = 0.003$), fibrinogen($r = -0.226$, $P = 0.024$), and positively correlated with albumin concentration ($r = 0.358$, $P < 0.001$) (Fig. 1). The ROC curve analysis (Fig. 2) revealed that serum level of fT3 ≤ 4.40 pmol/l in AIS was the most powerful predictor of stroke severity with a sensitivity of 68.8% and a specificity of 65.2%, the area under the curve was 0.712(95% CI, 0.618–0.805). Importantly, the associations between fT3 and CRP, albumin and NIHSS score remained significant in multiple regression analyses ($P \le 0.007$, Table 2).

3.2. Relationship between stroke severity and biochemical profiles

Binary logistic regression analysis was performed to eliminate the confounding effects of other factors on stroke severity. The stroke severity of patients on admission after stroke was coded as 0 for mild and 1 for moderate severity, and set as the outcome variable. Predictive variables included $\log_{10}$TG, fT3 and log10CRP, which were significantly different between groups of patients with mild and moderate stroke severity (Table 1). fT3 was an independent factor correlated with stroke severity ($P = 0.002$), whereas $\log_{10}$TG showed a weak correlation ($P = 0.044$) and log10CRP showed no correlations ($P = 0.430$) (Table 3). Importantly, there were no correlations between albumin and $\log_{10}$CRP, albumin and $\log_{10}$TG, or between $\log_{10}$CRP and $\log_{10}$TG (Table 4).

4. Discussion

This study showed that thyroid function, especially the level of the active form of thyroid hormone (fT3), was associated with CRP and albumin concentrations, as well as NIHSS score in AIS patients. The optimal cut-off value of fT3 levels as an indicator for diagnosis of the stroke severity was projected to be 4.40 pmol/l, which yielded a sensitivity of 68.8% and a specificity of 65.2%, the area under the curve was 0.712(95% CI, 0.618–0.805). These results suggested that fT3 levels in the acute stage of AIS can be useful in distinguishing stroke severity. However, NIHSS score was not correlated with CRP concentration, and there were no correlations among albumin, CRP, and TG concentrations, while these markers correlated with fT3/NIHSS in regression analysis. These results showed a pathogenic pathway linking inflammation to stroke severity in AIS patients.

Inflammation is increasingly recognized as a key contributor to the pathophysiology of cerebrovascular diseases, especially stroke caused by arterial occlusion or ischemia [22]. CRP may reflect systemic inflammation related to the pathobiology of ischemic stroke [23,24]. High CRP concentrations may reflect the activity of circulating proinflammatory cytokines [25]. The inflammatory processes may start within 2 h of stroke onset and be sustained for several days [26], and may contribute to ischemic brain damage even during early stages [27]. And CRP may also constitute a marker of AIS by promoting the activation of inflammatory biomarkers. Despite the essential role of CRP in promoting inflammation during stroke, there were no correlations between CRP concentration and NIHSS score, which is consistent with another study that also excluded patients with infection or inflammation [28]. These results suggested that CRP levels did not change significantly after stroke [28].

A lower serum albumin concentration, which indicates malnutrition, and a higher TG level occurred in moderate AIS patients than those in mild AIS patients. This finding is consistent with previous reports, showing that the frequency of undernutrition after stroke varied from 18% to 57% [29,30]. Stroke patients are at particularly high risk for malnutrition because cognitive deficits and hemiparesis