Free triiodothyronine is associated with poor outcome after acute ischemic stroke

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Abstract

Aims It is unclear whether thyroid hormones are associated with functional outcome after ischemic stroke. We aimed to investigate the impact of thyroid hormones at admission on functional outcome at 3 months after acute ischemic stroke. Methods A total of 480 consecutive patients for ischemic stroke within 48 hours of onset were enrolled in this study. Thyroid hormones including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured at admission and functional outcomes were assessed at 3 months with the modified Rankin Scale (mRS) ranging from 0 to 6. Poor outcome was defined as mRS[?]3. Results FT3 levels at admission were considerably lower in poor outcome patients than those with good outcome at 3 months (3.53±0.70pmol/L vs 4.04±0.68pmol/L, respectively; P¡0.001). Lower levels of FT3 were observed with higher mRS scores. Multivariable logistic regression analysis revealed that FT3 levels were significantly associated with risk of poor outcome at 3 months independent of conventional risk factors such as age, NIHSS score and recanalized therapy. In addition, patients in the bottom quartile of FT3 levels had a 2.56-fold higher risk of developing poor outcome compared with patients in the top quartile (OR=2.56; 95%CI 1.15-5.69, p =0.021). The sensitivity and specificity of FT3 ([?]3.69pmol/L) predicting poor outcome were 62.70% and 72.03% respectively. Conclusion Our study suggests that FT3 levels at admission are significantly and independently associated with risk of poor outcome after ischemic stroke and lower FT3 levels can be regarded as a prognostic biomarker for poor outcome at 3 months.

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A total of 480 consecutive patients for ischemic stroke within 48 hours of onset were retrospectively enrolled in this study. Thyroid hormones including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured at admission and functional outcomes were assessed at 3 months with the modified Rankin Scale (mRS) ranging from 0 to 6. Poor outcome was defined as mRS[?]3.

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associated with risk of poor outcome at 3 months independent of conventional risk factors such as age, NIHSS score and recanalized therapy. In addition, patients in the bottom quartile of FT3 levels had a 2.56-fold higher risk of developing poor outcome compared with patients in the top quartile (OR=2.56; 95%CI 1.15-5.69, p =0.021). The sensitivity and specificity of FT3 ([?]3.69pmol/L) predicting poor outcome were 62.70% and 72.03% respectively.

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Keywords: Acute ischemic stroke, Thyroid hormones, Free triiodothyronine, Functional outcome

What is known?

Ischemic stroke severity and prediction of functional outcome are assessed with standardized clinical criteria. However, the prognostic value of these clinical parameters in ischemic stroke is quite subjective and insufficient. Thyroid hormones play a neuroprotective role in the recovery of post-ischemic stroke.

What is new?

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Introduction

The burden of stroke in china is very serious and the annual stroke mortality rate is approximately 1.6 million, which has exceeded heart disease to become the leading cause of death and adult disability (1). Of all stroke types, ischemic stroke is the most prevalent accounting for 69.6% (2). Currently, ischemic stroke severity and prediction of functional outcome are assessed with standardized clinical criteria (3, 4). However, the prognostic value of these clinical parameters in ischemic stroke is quite subjective and insufficient, such that identification of new biomarkers may potentially improve the accuracy of the current prognostic scales for functional outcome.

Recent studies suggest that serum concentrations of thyroid hormones are altered in the acute phase of ischemic stroke and may have a potential influence on functional outcome (5, 6). There are some evidences that thyroid hormones play a neuroprotective role in the recovery of post-ischemic stroke (7) and display a protective association between subclinical hypothyroidism and better outcomes(8, 9) However, other studies suggest that lower serum concentrations of T3 are associated with poor outcome after ischemic stroke (6, 10).In addition, it is not well recognized whether there are any associations between FT3, the bioactive form of T3, and functional outcome of ischemic stroke. Studies on the relationship between FT3 levels and functional outcomes after ischemic stroke are controversial(10-16) .Thus, our study aimed to investigate whether the serum concentrations of thyroid hormones on admission, including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were associated with 3-month functional outcome in acute ischemic stroke.

Material and Methods

Study population

We performed a single-center, retrospective, observational study. Patients with acute ischemic stroke who were hospitalized in West China Hospital, Sichuan University from May 1, 2018 to October 1, 2019 were enrolled. The inclusion criteria were as follows: (1) age[?]18 years, (2) ischemic stroke confirmed by clinical symptoms and computed tomography (CT) or magnetic resonance imaging (MRI) on admission, (3)ischemic stroke onset within 48 hours before admission. The exclusion criteria were as follows: (1) history of thyroid diseases such as hyperthyroidism or hypothyroidism, (2) acute hemorrhagic stroke and transient ischemic

stroke. The diagnosis and treatment of all patients with acute ischemic stroke were based on Chinese guidelines (17).

Data collection

Data of demographic features (age, gender, weight, and height), risk factors (diabetes mellitus, hypertension, atrial fibrillation, excessive alcohol consumption, smoking), history of concomitant cardiovascular diseases (coronary heart disease and heart failure), blood pressure and stroke severity were collected at admission. Stroke severity on admission was assessed with the National Institutes of Health Stroke Scale (NIHSS) (3). Immediately after admission, white blood cell, hemoglobin, platelet, glucose, albumin, estimated Glomerular Filtration Rate, uric acid, triglyceride, total cholesterol, high density lipoprotein cholesterol were measured and serum levels of TSH, FT3, and FT4 in the following morning were collected. In addition, head computed tomography or magnetic resonance imaging was performed at admission. All the measurements were performed by the laboratory and radiological staffs in our hospital. The stroke subtype was determined by the Trial of Org 10172 in Acute Stroke Treatment subtype classification system (18). We classified ischemic stroke as large-artery atherosclerosis, cardio-embolism, small-artery occlusion and unclassified (other determined or undetermined etiology) subtypes.

End points

Functional outcome of all patients was assessed with the modified Rankin Scale (mRS) at 3 months after ischemic stroke, with scores ranging from 0 (no symptoms) to 6 (death) (19). Information of functional outcome was collected via direct or telephone interviews with patients or family members by trained neurologists. The mRS score was dichotomized into good outcome (mRS score 0–2) and poor outcome (mRS score 3–6) (20).

Statistical analysis

All the data were analysed using IBM SPSS Statistics Version 21 (IBM Corp., Armonk, NY, USA). Normally distributed continuous data were presented as the mean +- standard deviation. Data with a skewed distribution were expressed as the median (quartile). Categorical variables were expressed as percentage. The baseline characteristics between the two groups were compared using Student's t-tests, Mann–Whitney U tests or Chi-Square tests, depending on the appropriate value properties. Logistic regression analysis was used for correlation analysis. The results of poor outcome at 3 months were present as odds ratios (ORs) and 95% confidence intervals (CIs). The AUC of the receiver operator characteristic (ROC) curve was computed using the predicted probability of poor outcome. The results were considered significant when $P < 0.05$.

Results

Of the 539, we excluded 25 patients without data of thyroid indices, 10 patients diagnosed with hyperthyroidism or hypothyroidism and 24 patients lost follow-up. Eventually, we included 480 ischemic stroke patients. During 90 days follow-up, 244(50.8%) patients have poor outcome. The baseline characteristics (demographic, clinical, and laboratory data) according to the functional outcome assessed by the mRS score were presented in Table 1. Compared to the patients with good outcome, those with poor outcome were older, lower hemoglobin, albumin, eGFR and higher White Blood Cell, NIHSS score. The proportions of female (p=0.001) , atrial fibrillation(p¡0.001), coronary heart disease/heart failure(P=0.001) and recanalized therapy(P=0.005)were also significantly higher in the poor outcome group compared to the good outcome group. In addition, patients with poor outcome had lower level of TSH, FT3,but higher FT4 levels.

To explore the independent risk factors for 3-month poor outcome, we selected variables $P < 0.1$ in univariate analysis to perform multivariable logistic regression analysis. It revealed that lower FT3 level was an independent risk factor of poor outcome at 3 months (OR= 0.561; 95%CI 0.375-0.841, P=0.005). In addition, older age (OR = 1.023, 95% CI 1.001-1.047, P=0.044), higher NIHSS score (OR=1.286, 95%CI 1.213-1.363, P¡0.001) and no recanalized therapy (OR = 3.527, 95% CI 1.808-6.880, P¡0.001) were also independent risk factors of poor outcome. However, TSH and FT4 levels were not statistical after adjusting for other variables (See Table 2).

Patients were divided into quartile groups according to FT3 levels. The distribution of mRS scores at 3 months differed according to FT3 quartile (Q1, Q2, Q3, Q4) (Fig1) since higher mRS scores were observed with lowering FT3 levels. Further analyses were performed by constructing two models to explore the relationship between FT3 and poor outcome. In model 1 adjusted for gender, AF, CHD/HF, Hemoglobin, WBC, ALB, eGFR, TSH, TG, TC, FT4 and TOAST Classification, lower FT3 levels were associated with a worse functional outcome at 3 months (OR=4.63; 95% CI 2.33-9.02, $p < 0.001$ for tertile1 vs. tertile4; OR=2.42; 95% CI 1.35-4.35, $p = 0.003$ for tertile2 vs. tertile4). In model 2, after further adjusting variables of age, NIHSS score and recanalized therapy on the basis of model 1, compared with those in the 1st quartile, FT3 levels in the 4th quartile were still significantly associated with poor outcome (OR=2.56; 95% CI 1.15-5.69, $p = 0.021$) (See Table 3). Additionally, the ROC curve analysis (Fig2) revealed that serum level of FT3<3.69pmol/L in AIS patients was a powerful predictor of poor outcome (sensitivity 62.70%; specificity 72.03%; AUC 0.713).

Discussion

Our study showed that lower FT3 levels were associated with poor outcome at 3 months after acute ischemic stroke, and this association remained significant after adjusting for the effect of risk factors and comorbidities. There were two previous studies consistent with our findings. Ambrosius et al (16) found that in acute ischemic stroke patients lower free T3 levels were an important factor related to unfavorable outcome. Zhang et al (14)found that FT3 was significantly decreased in AIS patients with poor outcome and served as an independent predictor for neurological outcomes for which the cut-off value of FT3 was 4.38pmol/L. However, O'Keefe et al (11) enrolled 129 ischemic stroke patients and found that low FT3 value was not associated with poor outcome at 3 months in the multivariate analysis when other known predictors of outcome such as stroke severity (NIHSS) were controlled. The contradictory findings could be due to the relatively small sample size of the study. In addition, our study also showed that the detrimental effect of FT3 level on functional outcome increased as FT3 level decreased and neither TSH nor FT4 were associated with poor outcome at 3 months after ischemic stroke. There was one previous study to confirm and strengthen our findings. Satoshi et al (21)retrospectively enrolled 398 consecutive ischemic stroke patients to investigate the association of admission serum thyroid hormone concentration with functional outcomes and a dose-effect relationship between FT3 levels upon admission and poor outcome was noticed. In addition, critical illness could result in decreased peripheral conversion of FT4 to FT3 in the absence of a primary thyroid disorder indicating that FT3 might be more sensitive to the influence of critical illness than FT4, TSH(22), which indirectly supported our findings as well.

The potential pathophysiological mechanism linking low levels of FT3 to poor outcome is not well established. Previous study indicates that low T3 syndrome is independently associated with the risk of hemorrhagic transformation in acute ischemic stroke (23). Low FT3 levels at admission are independently associated with Post-stroke infection occurrence and may contribute to poor outcome(24).Although it is unknown whether administration of exogenous thyroid hormone in ischemic stroke patients improves outcomes, in animal experiment demonstrate that administration of T3 could modulate neuronal plasticity mechanisms to enhance functional outcome after stroke(25). Therefore, further well-designed studies and randomized controlled trials are needed to demonstrate the underlying mechanism between FT3 and functional outcome and whether supplementation of T3 could reduce disability after acute ischemic stroke.

Several limitations should be considered in the interpretation of our study. First, it was based on single center data, thus inevitably leading to selection bias. Second, we only measured the thyroid hormone levels once and not dynamically as a function of time. Another limitation was that we did not have the opportunity to measure total T3 and T4 levels, which might have given slightly different results.

Conclusion

Our data suggests that low FT3 levels at admission are independently associated with poor outcome in acute ischemic stroke after 3 months. Further investigations are needed to explore the mechanisms underlying the association and their potential exploitation in terms of therapeutic strategies to reduce disability after acute

ischemic stroke.

Figure legend

Fig1. Distribution of modified Rankin Scale scores at 3 months according to FT3 quartile

Fig2. Receiver operating characteristic analysis of FT3 for the prediction of 3-month poor outcome after ischemic stroke.

Table1. Baseline characteristics (demographic, clinical and laboratory data) according to functional status at 3 months

variable	Good outcome n=236	Poor outcome n=244	P value
Age (years)	64.53±14.22	70.11±12.02	¡0.001**
female(n,%)	69(29.2)	107(43.8)	0.001*
BMI (kg/m2)	23.5±3.2	23.1±3.2	0.213
smoking(n,%)	78(33.0)	76(31.1)	0.655
Alcohol consumption(n,%)	64(27.1)	57(23.3)	0.343
History of stroke(n,%)	23(9.7)	26(10.6)	0.742
Hypertension(n,%)	131(55.5)	144(59.0)	0.437
AF(n,%)	50(21.1)	101(41.4)	¡0.001**
DM(n,%)	60(25.4)	64(26.2)	0.840
CHD/HF(n,%)	47(19.9)	81(33.2)	0.001*
SBP at admission	140.58±25.82	142.27±22.76	0.449
DBP at admission	81.86±15.78	80.40±14.53	0.293
Hemoglobin (g/L)	139.09±17.87	134.14±20.15	0.005*
Platelet (10ˆ9/L)	181.20±60.95	173.41±66.84	0.183
White Blood Cell (10ˆ9/L)	7.63±2.75	8.48±3.16	0.002*
Glu (mmol/L)	7.97±3.31	8.27±3.30	0.316
Albumin (g/L)	42.41±4.15	40.70±4.09	¡0.001**
eGFR (ml/min/1.73m2)	85.12±19.29	79.69±21.62	0.004*
Uric Acid(μmol/L)	363.86±106.12	349.23±106.93	0.162
TG (mmol/L)	1.35(0.93, 2.05)	1.23(0.88, 1.73)	0.05
TC (mmol/L)	4.40±1.04	4.26±0.91	0.055
HDL (mmol/L)	1.24±0.35	1.27±0.37	0.334
NIHSS score	3(2, 7)	13(8, 17)	¡0.001**
TOAST classification			¡0.001**
LAA(n,%)	65(27.5)	94(38.5)	
CE(n,%)	51(21.6)	94(38.5)	
SAO(n,%)	93(39.4)	36(14.8)	
Unclassified(n,%)	27(11.4)	20(8.2)	
Recanalized therapy(n,%)	60(25.4)	91(37.2)	0.005*
TSH(mU/ L)	1.97(1.29, 3.22)	1.29(0.73, 2.51)	¡0.001**
FT3(pmol/L)	4.04±0.68	3.53±0.70	¡0.001**
FT4(pmol/L)	16.05±2.55	16.64±2.69	0.014*

Values are mean±standard deviation, n (%), or M (P25, P75). M (P25, P75): median (25th percentile, 75th percentile).BMI, body mass index; AF, atrial fibrillation; DM, diabetes mellitus; CHD, coronary heart disease; HF, heart failure; eGFR, estimated Glomerular Filtration Rate; TG, triglyceride; TC, total cholesterol; HDL-C,, high density lipoprotein cholesterol; Glu; glucose, NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10 172 in acute stroke treatment; LAA, Large artery atherosclerosis; CE, cardio-embolism; SAO, Small artery occlusion; TSH; thyroid-stimulating hormone, FT3;free triiodothyro-

nine, FT4;free thyroxine. * : P¡0.05; **: P¡0.001.

Table2. Multiple logistic regression analysis of predictors for poor outcome.

Variables
Age Female CHD/HF AF Hemoglobin WBC ALB Egfr TG TC NIHSS No recanalized therapy TSH FT3 FT4 TOAST clas

* : P¡0.05. **: P¡0.001.

Table3. Odds ratios for poor outcome according to the quartiles of FT3

FT3 quartiles	Model 1	Model 1	Model 1	Mode 2	Mode 2
	OR (95%CI)	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Q1(¡3.26pmol/L)	Q1(¡3.26pmol/L)	4.63 (2.33-9.02)	¡0.001*	2.56 (1.15-5.69)	0.021*
Q2(3.26-3.79pmol/L)	Q2(3.26-3.79pmol/L)	2.42 (1.35-4.35)	0.003*	1.88 (0.96-3.71)	0.066
Q3(3.79-4.26 pmol/L)	Q3(3.79-4.26 pmol/L)	1.24 (0.69-2.23)	0.465	0.95 (0.48-1.87)	0.885
Q4(¿4.26 pmol/L)	Q4(¿4.26 pmol/L)	1 (reference)	-	1 (reference)	-

Model 1 was adjusted for gender, AF, CHD/HF, Hemoglobin, WBC, ALB, eGFR, TSH, TG, TC, FT4 and TOAST Classification; Model 2 was further adjusted variables of age, NIHSS score and recanalized therapy on the basis of Model 1.

* : P¡0.05.

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Disclosures

We disclose any conflict of interest, including specific financial interests and relationships and affiliations relevant to the subject.

Ethical standard

Our study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of West China Hospital, Sichuan University.

Informed consent

The study is based on a retrospective analysis of examinations already performed, justified by good clinical practice. All patients have signed an informed consent for the management of their data.

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Authorship

SY, YCQ and WH conceptualized and designed the study, SY, YCQ and WH drafted the initial manuscript, and reviewed and revised the manuscript. SY collected data. YCQ performed data analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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