Depressed TSH level as a predictor of poststroke fatigue in patients with acute ischemic stroke

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Abstract

Objective
To investigate whether thyroid function profiles can predict poststroke fatigue (PSF) in patients with acute ischemic stroke.

Methods
Patients with stroke were consecutively recruited within 3 days of onset in Jinling Hospital. Serum levels of thyroid hormones, thyroid antibodies, hematologic indexes, and biochemical indexes were measured on admission. Fatigue was scored using the Fatigue Severity Scale. Associations were analyzed with multivariate regression and restricted cubic splines.

Results
Of the 704 patients with stroke, 292 (41.5%) were diagnosed with fatigue in the acute stage and 224 (35.3%) 6 months after the index stroke. The serum levels of thyroid-stimulating hormone (TSH) were inversely associated with the risk of PSF in both the acute phase and at follow-up evaluations after adjusting for potential confounders (odds ratio 0.30, 95% confidence interval 0.24–0.37 in the acute phase, and odds ratio 0.70, 95% confidence interval 0.58–0.84 at follow-up). The subgroup analysis indicated that in the acute phase of ischemic stroke, TSH was associated with severity of PSF in the groups with euthyroidism (β = −0.70, p < 0.001), subclinical hypothyroidism (β = −0.44, p < 0.001), and low-T₃ syndrome (β = −0.34, p = 0.008). Higher TSH was associated with better Fatigue Severity Scale scores in patients with low-T₃ syndrome 6 months after the index stroke (β = −0.35, p = 0.01). Furthermore, in the group with low-T₃ syndrome, FT₃ serum level could also indicate a higher risk of PSF (β = −2.54, p < 0.001 in the acute phase, and β = −2.67, p < 0.001 at follow-up).

Conclusion
Thyroid function profiles may predict fatigue after acute ischemic stroke, suggesting that neuroendocrine responses could have a role in PSF.

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Poststroke fatigue (PSF) is a kind of pathologic fatigue, a debilitating symptom experienced by 23% to 85% of patients with stroke.\cite{1,2,3} It may negatively affect the rehabilitation and long-term outcomes of stroke survivors.\cite{4} However, PSF is often neglected or underrecognized by patients, families, and even health care professionals.\cite{5} There is considerable evidence for associations between PSF and increasing age and mental or physical disorders, such as depression, anxiety, and sleep disturbances. However, not all PSF can be fully explained by these factors.\cite{6,7} Therefore, it is essential to search new pathogenic factors for PSF in a large sample size of patients to fulfill our understanding of PSF and, furthermore, to explore treatment programs.

The thyroid gland is one of the biggest endocrine glands, which can synthesize, store, and secrete thyroid hormones. Several studies performed in recent years have demonstrated that thyroid dysfunction (either clinical or subclinical) has an influence on stroke outcomes\cite{8,9} and fatigue\cite{10} in healthy euthyroid individuals but has not been assessed in relation to PSF. These results raise the question of whether the thyroid function profile is associated with fatigue in patients with acute ischemic stroke (AIS).

There are few studies that have focused on the relationship between the thyroid function profile and PSF in both the acute phase and at the follow-up period of ischemic stroke. Thus, our primary purpose was to investigate whether the serum levels of thyroid function profile could predict PSF in our prospective stroke cohort.

Methods

Patients
The cohort is part of a longitudinal, observational study conducted in Jinling Hospital, a large-scale general hospital in China. Patients older than 18 years with AIS according to the TOAST criteria\cite{15} were recruited for the study upon hospital admission from October 2015 to February 2017. Patients with unconsciousness, aphasia, severe comprehension deficits, presence of cancer or other preexisting neuropsychiatric disorders, preexisting thyroid disease except for benign nodules, or on any medication that could cause change in emotional status or thyroid functions (including antidepressants, estrogen, androgen, amiodarone, lithium, and glucocorticoid) were excluded. All patients were assessed with the Mini-Mental State Examination (MMSE) and those with MMSE score ≤10 or MMSE score 11 to 23 but found cognitively incompetent by a physician or nurse were excluded.\cite{12}

Standard protocol approvals, registrations, and patient consents
We received approval from the local Ethical Committee on Human Experimentation. Informed consents were obtained from all participants.

Baseline assessments
Fasting blood samples were collected at 6 AM the second day after admission. Samples were drawn into standardized tubes containing an anticoagulant (EDTA) at admission and stored at −80°C. We used a standardized radioimmunoassay kit to measure serum free triiodothyronine (FT$_3$), free thyroxine (FT$_4$), and thyroid-stimulating hormone (TSH) levels. Thyroid peroxidase antibody and antithyroglobulin antibody titers were also measured and defined as being positive or negative consistent with the manufacturer’s reference. The reference intervals of thyroid indicators in our laboratory are as follows: TSH 0.49–4.5 mIU/L, FT$_3$ 3.8–6.5 pmol/L, and FT$_4$ 7.9–17.2 pmol/L. Patients were categorized according to the measurements of thyroid function: (1) euthyroidism: TSH, FT$_3$, and FT$_4$ within normal ranges; (2) subclinical hypothyroidism: TSH >4.5 mIU/L and normal FT$_3$/FT$_4$; (3) subclinical hyperthyroidism: TSH <0.49 mIU/L and normal FT$_3$/FT$_4$; and (4) low-T$_3$ syndrome: FT$_3$ <3.8 pmol/L and TSH and FT$_4$ within normal ranges.\cite{13}

Details of basic information were collected from all patients according to our interview process. All clinical data and neurologic function scale scores were collected within 24 hours of admission. Related medical history was obtained by questionnaire. In addition, the body mass index (BMI) of each patient was calculated based on their height and weight. BMI was defined as the weight in kilograms divided by the square of the height in meters.\cite{14} The stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.\cite{15}

Measurements of fatigue and related parameters
The 9-item Fatigue Severity Scale (FSS) is the most commonly used instrument to assess PSF.\cite{16} The Chinese version of the FSS used in our study included 9 statements about stroke, which was a 7-point Likert scale ranging from strongly disagree to strongly agree.\cite{17} A higher score indicates a greater degree of fatigue. It has been confirmed and validated in the Asian population.\cite{18} We chose 4 points as cutoff point of the
FSS score. Patients with a mean FSS score of 4 points or more were considered to have fatigue, as previously reported.6,19

The symptoms of depression, anxiety, and interpersonal communication were evaluated on the 24-item Hamilton Depression Scale (HAMD-24),20 14-item Hamilton Anxiety Scale (HAMA-14),21 and the Lubben Social Network Scale,22 respectively. The HAMD-24 is a clinician-rated scale that assesses depressive symptoms. It consists of 24 symptoms, each of which is rated from 0 to 2 or 0 to 4. The total score is calculated as the sum of the 24 individual symptom scores. Higher scores indicate more severe depression.23 The HAMA is a widely used rating scale that measures the severity of anxiety symptoms, which ranged from 0 to 4. The higher total scores, the more severe the anxiety symptoms.20 The social communication network is defined as the level of social support from friends and relatives. The Chinese version of the Lubben Social Network Scale, consisting of 10 questions, used in Chinese populations in 1995, was administered to the patients with stroke.24 The score for each question ranged from 0 to 5. Higher scores indicate better social networks. All of the scales were validated elsewhere.24–26

Follow-up measurements
The same protocol was administered 6 months after the index stroke. The patients were evaluated once again for FSS.

Statistical analysis
Participants were dichotomized according to the FSS score. Continuous variables are presented as mean (SD) or median (interquartile range). Differences in continuous variables between groups were compared by Student t test or Mann-Whitney U test. Categorical variables are expressed as proportions and were analyzed with the χ2 test or Fisher exact test. Associations among thyroid hormones, antibodies, and clinical parameters were first tested by univariate analysis. Significant predictors for PSF were entered into a multivariate regression model. We selected all covariates a priori based on clinical implications and previous research suggesting they might confound the association between thyroid function profiles and PSF. In addition, we performed post hoc analyses. We explored the relationship between the serum TSH levels and PSF with restricted cubic splines. These analyses are described in the supplemental data in Dryad (doi.org/10.5061/dryad.b5pj61f). Data were analyzed using SPSS Statistics 23.0 software (IBM Corp., Armonk, NY) and Stata/SE 14.0 (@StataCorp LP, College Station, TX).

Data availability
Anonymized data will be shared by request from any qualified investigators. See data available from Dryad (additional methods, tables e1–e6, and figures e1–e3, doi.org/10.5061/dryad.b5pj61f).

Results
After application of the aforementioned eligibility criteria, 704 of 1,028 screened patients with AIS met the inclusion criteria and were enrolled in the development cohort (data available from Dryad, figure e-1, doi.org/10.5061/dryad.b5pj61f). During the 6-month follow-up period, 7 patients died, 33 withdrew from the study, 10 could not respond because of deterioration of physical function, and 20 were lost to follow-up. As a result, the remaining 634 samples completed the follow-up data. There were no differences in baseline characteristics between those included in and excluded from the final analysis (data available from Dryad, table e-4). The baseline demographic data of the study population are presented in table and data available from Dryad (table e-1).

For the patients in the final analysis, the mean age was 60.5 ± 13.1 years; 458 (65.1%) were men. Patients were stratified into 4 groups (euthyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, and low-T3 syndrome) according to the criteria described above. The proportions of the 4 groups of patients were 71.9%, 9.6%, 6.0%, and 12.5%, respectively (table). In univariate analysis, age, sex, smoking history, history of stroke or TIA, NIH Stroke Scale score, BMI, hemoglobin, C-reactive protein, total cholesterol, and TOAST classification in different thyroid states indicate significant difference.

The prevalence of PSF was 41.5% in the acute phase following stroke and 35.3% at the 6-month follow-up. The univariate analysis indicated that the predictors of sex (p = 0.024), diabetes mellitus (p = 0.017), BMI (p = 0.045), serum glucose (p = 0.04), C-reactive protein (p = 0.002), total cholesterol (p = 0.015), FT4 (p = 0.021), TSH (p < 0.001), TOAST classification (p = 0.003), HAMD score (p < 0.001), and HAMA score (p < 0.001) were significantly different in the acute phase fatigue, whereas only TOAST classification (p = 0.006), HAMD score (p < 0.001), and HAMA score (p < 0.001) showed a significant difference with the nonfatigue group at follow-up (data available from Dryad, table e-1, doi.org/10.5061/dryad.b5pj61f).

For the fatigue assessment in the acute phase, higher levels of TSH (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.33–0.46) were related to a lower risk of PSF. At the same time, there was a significant difference in TSH levels with the euthyroidism subgroup (OR 0.58, 95% CI 0.48–0.69). Multivariable adjustment showed that the level of TSH was a protective biomarker for PSF not only in all patients (OR 0.30, 95% CI 0.24–0.37) but also in the euthyroidism subgroup (OR 0.49, 95% CI 0.39–0.61). For the fatigue assessment at the 6-month follow-up, the level of TSH was also associated with PSF (OR 0.70, 95% CI 0.58–0.84). However, in the euthyroidism subgroup, there were no significant associations between the TSH level and PSF (OR 0.84, 95% CI 0.64–1.04).

According to the level of thyroid indicators, patients were divided into 4 groups. When comparing patients with a higher level of TSH to those with a lower level, the risk of PSF gradually reduced. Multivariate adjustments did not significantly alter the results (data available from Dryad, figure e-2, doi.org/10.5061/dryad.b5pj61f).

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In addition, we assessed the potential nonlinear association between the level of TSH and PSF by using restricted cubic splines with 3 knots. The result further indicated that high TSH levels were related to a lower risk of PSF, not only in the acute phase but also at follow-up (figures 1 and 2).

Multiple linear regression analysis was performed to further explore the correlation between thyroid function and PSF. In the acute phase of stroke in the euthyroid group, TSH was inversely related to PSF (β = −0.70, p < 0.001), whereas FT4 was positively related to PSF (β = 0.10, p = 0.007). In the
### Table

<table>
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<tr>
<th>Value</th>
<th>Acute phase</th>
<th>OR (95%CI)</th>
<th>Follow-up</th>
<th>OR (95%CI)</th>
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<td>0.79 (0.68, 0.92) **</td>
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<tr>
<td>2</td>
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<td>1.16 (1.00, 1.35)</td>
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<td>0.74 (0.34, 1.64)</td>
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<td>0.97 (0.81, 1.16)</td>
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<td>0.85 (0.70, 1.04)</td>
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<tr>
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<td></td>
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<td></td>
<td>0.84 (0.64, 1.04)</td>
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<td>0.94 (0.78, 1.12)</td>
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<td>0.90 (0.73, 1.13)</td>
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<td>1.05 (0.86, 1.29)</td>
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<td>1.21 (0.98, 1.48)</td>
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<td>1.07 (0.86, 1.33)</td>
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</table>

Model 1: adjusted for age and sex. Model 2: model 1 + hypertension, diabetes mellitus, smoking, history of stroke or TIA, NIH Stroke Scale score, body mass index, serum glucose, hemoglobin, cholesterol, uric acid, C-reactive protein, and TOAST classification. Model 3: model 2 + Hamilton Depression Scale score, Hamilton Anxiety Scale score, and Lubben score. TG* and TPO* were analyzed as categorical variables; other values were analyzed as continuous variables. *p < 0.05, **p < 0.01, ***p < 0.001, CI = confidence interval; FT3 = free triiodothyronine; FT4 = free thyroxine; N-FT3 = free triiodothyronine in euthyroid patients; N-FT4 = free thyroxine in euthyroid patients; N-TSH = thyroid-stimulating hormone in euthyroid patients; OR = odds ratio; TGAb = thyroid globulin antibody; TOAST = Trial of Org 10172 in Acute Stroke Treatment; TPOAb = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone.
subclinical hypothyroidism group, the level of TSH ($\beta = -0.44, p < 0.001$) and FT4 ($\beta = 0.18, p = 0.005$) was also associated with PSF; in the low-T3 syndrome group, both TSH ($\beta = -0.34, p = 0.008$) and FT3 ($\beta = -2.54, p < 0.001$) were independently associated with PSF in the multivariate analysis. At the 6-month follow-up, the risk of PSF increased with higher levels of FT4 not only in the euthyroid group ($\beta = 0.08, p = 0.021$) but also in the low-T3 syndrome group ($\beta = -2.67, p < 0.001$; data available from Dryad, table e-2, doi.org/10.5061/dryad.b5pj61f).

We did not find any statistically significant correlation between poststroke depression and TSH ($p = 0.633$), FT3 ($p = 0.568$), and FT4 ($p = 0.601$).

Discussion

In this study, our data suggest that (1) the serum TSH levels were negatively associated with the risk of PSF in patients with AIS not only in the acute phase but also in the follow-up period; (2) TSH was a predictor in various thyroid statuses; lower FT3 values were associated with a higher risk of PSF in low-T3 syndrome; and (3) PSF changed over time, as TSH could predict the PSF in euthyroidism during the acute phase but not in the follow-up period.

The purposes of this study included determining whether the thyroid function profile can predict PSF, as well as describing the difference between early fatigue and later fatigue. The results indicated that TSH was a protective predictor for PSF in our study. The risk of PSF decreased 70% with higher-increment TSH in the full range of thyroid function, and the risk of PSF decreased 60% with higher TSH in the full range of thyroid function. For patients at 6 months after the index stroke, the risk of PSF decreased 30% with higher TSH in the full range of thyroid function, and there was no correlation between thyroid function and PSF in the normal range of thyroid function. The association between thyroid function and stroke prognosis has been addressed previously. Two studies have reported that the functional outcome of patients with stroke is inversely proportional to the level of TSH.8,9 Moreover, a large population-based survey of general individuals found that participants with low-normal TSH and high-normal FT4 levels had a greater likelihood of experiencing fatigue.10 These studies are consistent with our study. However, this is the first survey to elaborate the relationship of thyroid function with PSF, as the biological mechanism between them is not clear.

One possible explanation is that depressed TSH serum levels lead to an increased basal metabolic rate. Subsequently, excess reactive oxygen species and free radicals are produced, resulting in neurotoxic cytotoxicity.27 Moreover, the ischemic tolerance might be impaired as a result of high energy and oxygen demand.29 There might exist a compensatory mechanism between TSH and increased FT4, and it had an important role in the association between thyroid function profiles and PSF. However, our results did not clearly indicate this trend between the level of TSH and FT4. We could not rule out a possibility that other mechanisms in the body weakened the compensation effects between the level of TSH and FT4.

An interesting finding in our study is that FT3 was a strong predictor of the risk of PSF in patients with low-T3 syndrome. Low-T3 syndrome, also named nonthyroidal illness syndrome, is characterized by reduced FT4 to FT3 conversion as a result of alterations in deiodinase activity in severe illness.25 Based on previous studies, the activity of deiodinase could

Figure 2 Relationships between PSF and TSH value levels in the stroke acute phase and follow-up

The figure represented the relationships between the level of TSH and relative risk of PSF (A) in the acute phase ($p$ for nonlinearity <0.001) and (B) at 6-month follow-up ($p$ for nonlinearity <0.001). Data were modeled with fixed-effects restricted cubic splines with 3 knots at percentiles 5%, 50%, and 95% of the distribution. The model was adjusted for age, sex, hypertension, diabetes mellitus, smoking, history of stroke or TIA, NIH Stroke Scale score, body mass index, serum glucose, hemoglobin, cholesterol, uric acid, C-reactive protein, TOAST classification, Hamilton Depression Scale score, Hamilton Anxiety Scale score, and Lubben score. The blue dashed lines represent the point-wise 95% confidence intervals for the fitted nonlinear (solid red line). PSF= poststroke fatigue; TOAST = Trial of Org 10172 in Acute Stroke Treatment; TSH= thyroid-stimulating hormone.
change with different types of tissues and organs. The messenger RNA of type 2 deiodinase was upregulated in astrocytic cell bodies after ischemic stroke.\(^{28,29}\) This results in a dramatic increase in activity of type 2 deiodinase, which catalyzes the deiodination of \(\text{FT}_4\) into the more active \(\text{FT}_3\). Based on the above, an alternative explanation was speculated for the relationship between PSF and thyroid function. Excessive thyroid hormones in the brain are involved in regulation of gene transcription, hippocampal neurogenesis, and having a negative role in regulation of emotions (data available from Dryad, figure e-3, doi.org/10.5061/dryad.b5pj61f).\(^{30,31}\)

Fatigue is a dynamic process in stroke recovery. In our study, the prevalence of PSF was 41.5% in the acute phase of stroke and 35.3% at the 6-month follow-up. TSH could predict PSF in euthyroidism during the acute phase but not in the follow-up period. The mechanism is identical to Chalder’s conceptual model of PSF.\(^{32}\) Neuroendocrine mechanisms might be a more important determinant of early fatigue, with psychological factors important in determining later fatigue.

In our study, TSH was not correlated with depression and thus mood is unlikely to be mediating the association between TSH and PSF.

There are several strengths and limitations that should be considered in our study. This is the first large-sample, prospective study to systematically elaborate the relationships between PSF and thyroid function, providing new insight to explain the biological mechanism of PSF. However, thyroid hormone levels were measured only once in the acute phase of stroke. It is difficult to interpret whether the changes in thyroid hormones occurred before or after stroke, despite that patients with preexisting abnormal thyroid-related conditions were excluded. Furthermore, individuals with serious cognitive and communication deficits were excluded from our study, thus the sample does not represent all patients with ischemic stroke. In addition, we did not take all the possible confounders into consideration, such as sleep disorder, medications, and especially the Barthel index, an important measure of functional status, and these should be considered in further study. Finally, fatigue is common in the general population and possibly higher in persons with stroke risk factors or premorbid depression. It is also a limitation to draw causal inferences between the level of TSH and PSF, although we have controlled for the variable of baseline depression and stroke risk factors.

In brief, thyroid hormones, especially TSH serum levels measured in the acute phase of stroke, can predict PSF. However, a cohort study of dynamic monitoring of thyroid function and PSF is still needed.

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**Disclosure**

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