Diagnosis and treatment of low T3 syndrome in neurocritical patients

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Abstract

What is known and objective: Low levels of serum triiodothyronine (T3) are a strong predictor of mortality and poor prognosis in critical care patients. Few reports, however, have focused on neurocritical patients. The application of hormone replacement therapy (HRT) in the treatment of neurocritical patients with low T3 syndrome remains controversial. We studied the role of low T3 state as a predictor of outcomes in neurocritical patients and examined the effect of HRT on prognosis.

Methods: A retrospective analysis was performed on the data of 32 neurocritical patients with low T3 syndrome who were admitted to the neuro-intensive care unit of Peking Union Medical College Hospital between January 2012 and October 2018. While 18/32 (56.25%) patients received HRT (HRT group; n = 18), 14/32 (43.75%) patients did not receive HRT (non-HRT group; n = 14). Patients were followed up for periods ranging from 3 months to 72 months. Baseline clinical and laboratory data were compared between the two groups using Mann-Whitney U tests or the t tests. Overall survival was assessed by Kaplan-Meier curve and compared by log-rank tests. Univariate and multivariate regression analyses were performed to identify the factors associated with prognosis and estimate the effect of HRT. We also assessed the influence of HRT on final neurological function, using the Glasgow Coma Scale (GCS) and the Glasgow Outcome Scale (GOS) scores.

Results and discussion: The neurocritical events in our cohort included post-operative complications (n = 18), traumatic brain injury (n = 8) and spontaneous intracerebral haemorrhage (n = 6). Mean GCS score in the cohort was 6.41 (6.44 ± 3.14 in HRT group vs 6.36 ± 2.06 in non-HRT group). A total of 15/32 (46.87%) deaths were recorded (7 in the HRT group, 8 in the non-HRT group). In the HRT group, 15 patients underwent repeat thyroid function tests after completion of HRT; the low T3 situation was corrected in only 5/15 (33.3%) patients. Overall survival was significantly shorter in the non-HRT group than in the HRT group (16.45 months vs 47.47 months; P = .034). In univariate regression analysis, the HRT group has the lower mortality risk than the non-HRT group (HR = 0.301, 95% CI: 0.094-0.964; P = .043). However, multivariate regression analysis showed no significant difference in mortality risk between the two groups (HR = 0.340 95% CI: 0.099-1.172; P = .087). There was
1 | WHAT IS KNOWN AND OBJECTIVE

Low T3 syndrome has been described in critically ill patients without prior history of thyroid disease. Typically, it manifests with low serum triiodothyronine (T3), average or low thyroid-stimulating hormone (TSH) and increased reverse triiodothyronine (rT3). Several studies have shown that low serum T3 is an independent predictor of poor prognosis in critical ill patients. Serum T3 level is associated with various physiological systems; for example, serum T3 and thyroxine (T4) levels fall sharply within 15-30 minutes of initiation of cardiac bypass, and remain low for days. Low serum T3 has also been shown to be associated with poor prognosis in patients with end-stage renal disease and in patients in intensive care units.

Patients with severe neurological diseases often experience more complications and exhibit higher mortality rates, and many studies have provided evidence for a low T3 state being an important prognostic indicator in such cases; Lieberman et al found that 87% of individuals with severe traumatic brain injury have thyroid function below the mid-normal range. Other researchers showed that low T3 syndrome is a predictor of poor prognosis in cerebral infarction patients; their findings indicated the central hypothyroidism and disturbance of thyroid hormone metabolism were involved. Low T3 syndrome is common in patients with brain tumors and has been shown to be associated with shorter survival in glioma patients. Despite these observations, however, whether the thyroid hormone abnormalities in the critically ill are a physiological adaptation or a pathological change, and whether hormone replacement therapy (HRT) can benefit such patients, remain to be established. The aim of this retrospective study was to summarize the clinical features of neurocritical patients with low T3 level and to assess the effect of HRT on survival and neurological outcomes.

2 | METHODS

2.1 | Patient population and setting

We retrospectively reviewed the medical records of patients who had attended the Neurosurgery Department of Peking Union Medical College Hospital between January 2012 and October 2018 and undergone complete thyroid function testing. Out of the 16830 patients, 1201 (7.13%) had lower-than-normal free T3 (fT3) levels. From this cohort, we excluded 343/1201 (28.56%) patients who were treated as outpatients and another 826/1201 (68.77%) patients without neurocritical events during hospitalization. Finally, 32 neurocritical patients with low T3 syndrome were included in this retrospective analysis, without history of primary thyroid disease or of use of medication that could affect thyroid hormone levels. Among these patients, 18 received HRT and 14 did not receive HRT. The HRT group patients received a daily dose of 100 μg of oral levothyroxine sodium tablet, starting immediately after the diagnosis of the low T3 state. Patients were followed up in the outpatient department or over the telephone for periods ranging from 3 months to 6 years. The neurocritical events in this cohort included post-operative complications (n = 18), severe traumatic brain injury (n = 8) and spontaneous intracerebral hemorrhage (n = 6). Complications and comorbidities in the cohort during hospitalization included infection of the central nervous system (n = 14), pulmonary infection (n = 22) and heart failure (n = 8). Table 1 lists the diagnoses and comorbidities.

2.2 | Data collection

The following data were extracted from the medical records: (a) demographic information (name, sex, age); (b) primary or secondary neurocritical events and complications; past disease history (eg cardiovascular diseases and infectious disease); (c) results of laboratory tests during the patient’s critical stage (total serum cortisol, liver function test, renal function test, complete blood cell analysis, coagulation function test, myocardial enzyme test); and (d) Glasgow Coma Scale (GCS) score at different stages. The Glasgow Outcome Scale (GOS) score and last GCS score during follow-up were also recorded.

2.3 | Laboratory tests

All tests were conducted in the same laboratory using standard methods. The laboratory at the Peking Union Medical College
Hospital has established its reference ranges for thyroid function parameters: fT3, 1.80-4.10 pg/mL; T3, 0.66-1.92 ng/mL; free thyroxine (fT4), 0.81-1.89 ng/dL; T4, 4.30-12.50 μg/dL; and TSH, 0.38-4.34 µlU/mL. Enzyme-linked immunosorbent assay (ELISA) was performed on fasting blood samples.

2.4 | Statistical analysis

Data analysis was performed using SPSS 24.0 (IBM Corp.). The Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Non-normally distributed data were summarized as the medians (and interquartile range [IQR]) and compared between groups using the Mann-Whitney U test; normally distributed data were summarized as the means (± standard deviation) and compared between groups using the Student’s t-test. The Kaplan-Meier method was used for survival analysis, and differences in survival were compared using the log-rank test. Univariate Cox regression analysis was performed to identify the factors associated with mortality. Covariates tested in the univariate Cox model were sex, age, body mass index (BMI), fT3, GCS and HRT. Variables that were significantly associated with mortality at \( P \leq .05 \) in univariate analysis, and other factors regarded as clinically important confounders, were entered into the multivariate Cox regression model to identify the independent predictors of mortality. Hazard ratios (HR) and the 95% confidence intervals (CI) were calculated. Two-tailed \( P \leq .05 \) was considered statistically significant.

3 | RESULTS

3.1 | Patients and management

A total of 32 patients (16 men and 16 women; median age, 53 years; IQR, 41.25-64 years) were included in this study. All patients had a GCS ≤ 11 during neurocritical events. Table 1 presents the details of the primary diagnoses and the comorbid conditions; Figure 1 shows representative computed tomography images of three patients who died.

3.2 | Laboratory test findings and outcomes

Table 2 presents the baseline characteristics of patients in the two groups. Age, sex composition and BMI were comparable in the two groups. The mean fT3, fT4, T3, T4 and TSH levels were 1.46 pg/mL, 1.04 ng/mL, 0.40 ng/mL, 4.72 µg/dL and 1.12 µlU/mL, respectively. While 14/32 (43.75%) patients had lower-than-normal fT4 levels, 10/32 (31.25%) patients had normal TSH levels. The decline in T3 was observed at a median of 10 days (IQR, 4.5-17.25) after the neurocritical events. Median total cortisol level was higher in the non-HRT group than in the HRT group but the difference was not statistically significant (9.75 µg/dL vs 4.66 µg/dL; \( P = .253 \)). Median GCS score at admission in the full cohort was 6 (IQR, 5-8.75); (5.5 (IQR, 3.75-10.25) in the HRT group vs 6 (IQR, 5-8) in the non-HRT group; \( P = .722 \)). The mean GCS score at discharge was 8.50 ± 0.73 in the full cohort (8.17 ± 1.07 in the HRT group vs 8.93 ± 0.98 in the non-HRT group; \( P = .587 \)). The mean GCS in the full cohort during follow-up was 8.56 ± 0.97 (9.33 ± 1.28 in HRT patients vs 7.57 ± 1.49 in non-HRT patients; \( P = .419 \)). Central nervous system infections occurred in 14/32 (43.8%) patients: 10/18 (55.55%) patients in the HRT group vs 4/14 (28.57%) patients in the non-HRT group. A total of 15/32 (46.9%) patients died: 7/18 (38.88%) in the HRT group vs 8/14 (57.14%) in the non-HRT group.

| TABLE 1 | Clinical diagnoses and comorbidities in the 32 patients |
|-------------|--------------------------------------------------|
| Clinical diagnoses | n |
| Primary diagnosis |  |
| Operation-related complications$^a$ | 18 |
| Traumatic brain injury | 8 |
| Spontaneous intracerebral haemorrhage | 6 |
| Comorbidities/complications |  |
| Cerebral |  |
| Central nervous system infection | 14 |
| Subarachnoid haemorrhage | 3 |
| Ischaemic stroke | 1 |
| Hydrocephalus | 4 |
| Hyponatraemia | 1 |
| Central diabetes insipidus | 4 |
| Central pontine myelinolysis | 1 |
| Respiratory |  |
| Pulmonary infection | 22 |
| Pulmonary embolism | 1 |
| Respiratory failure | 4 |
| Cardiovascular |  |
| Heart failure | 8 |
| Malignant arrhythmia | 5 |
| High blood pressure | 11 |
| Intestinal |  |
| Gastrointestinal bleeding | 1 |
| Urinary |  |
| Urinary tract infection | 4 |
| Acute kidney injury | 5 |
| Endocrine |  |
| Type 2 diabetes | 7 |
| Blood system |  |
| Bacteraemia | 1 |
| Chronic myeloid leukaemia | 1 |

Note: It is possible for one patient to have more than one diagnosis, so the sum exceeds the absolute number of patients.

$^a$Operation-related complications included intracranial haemorrhage (n = 3), subarachnoid haemorrhage (n = 2), cerebral infarction (n = 4), acute hydrocephalus (n = 3), central nervous system infection (n = 4) and severe cerebral oedema (n = 5). Many of the patients that died had multiorgan failure towards the end.
3.3 | Thyroid function after oral levothyroxine sodium

Patients in the HRT group received 100 µg oral levothyroxine sodium daily for a median period of 18 days (IQR, 5.75-30 days). Fifteen of the 18 patients in the HRT group were re-tested for thyroid function after treatment. The median interval from start of HRT to the second thyroid function test was 9 days (IQR, 8-15 days). While 5/15 (33.3%) patients had normal fT3 level (2.29 ± 0.12 pg/mL) in the second test, 10/15 (66.7%) continued to have low fT3 (1.39 ± 0.08 pg/mL). The paired-sample t test showed no significant difference between post-treatment and pre-treatment fT3 (1.69 ± 0.51 pg/mL vs 1.41 ± 0.08 pg/mL; P = .146), fT4 (1.00 ± 0.29 ng/mL vs 1.15 ± 0.34 ng/mL; P = .671) and TSH (1.14 ± 2.96 μIU/mL vs 1.13 ± 0.62 μIU/mL; P = .978).

3.4 | Effects of hormone replacement therapy

3.4.1 | Prognostic relevance of low T3 for survival

Follow-up ranged from 3 months to 72 months. Median survival was significantly longer in the HRT group than in the non-HRT group (47.47 months vs 16.45 months; P = .034). Figure 2 shows the Kaplan-Meier curves. In univariate regression analysis, HRT still made statistical differences, where the HRT group had the lower mortality risk than the non-HRT group (HR = 0.301, 95% CI 0.094-0.964; P = .043; Figure 3; Table 3). However, in multivariate analysis, with age and GCS entered as covariates, HRT was no longer a significant predictor of better survival (HR = 0.340, 95% CI 0.099-1.172; P = .087). The P-values for age and GCS scores were 0.781 and 0.076, respectively. (Figure 4 and Table 3).

3.4.2 | Prognostic relevance of low T3 for neurological outcome

The mean GCS scores at discharge were not significantly different between the HRT group and the non-HRT group (8.93 ± 0.98; P = .615). The mean GCS and GOS scores at the last follow-up were also not significantly different between the two groups (GCS: 9.33 ± 1.28 vs 7.57 ± 1.49; P = .419; and GOS: 3.00 ± 0.41 vs 2.43 ± 0.47; P = .419; Table 4). Thus, short-term and long-term neurological outcomes were not significantly different between the two groups.

4 | DISCUSSION

In the 1970s, Reichlin and Protnay et al had found that thyroid hormone levels dropped in some critically ill patients and, in 1982, Wartofsky and Bunnan from Washington Hospital proposed the concept of low T3 syndrome.12 The low T3 syndrome is a disorder of thyroid hormone metabolism under various stress states, most commonly presenting with reduction in T3 as early as 24 hours after onset of the precipitating event.13 The primary mechanism is inhibition of 5’-deiodinase. In such cases, free T4 level is within the normal range, but it could sometimes be slightly high. In our cohort the decline in T3 was observed at a median of 10 days (IQR, 4.5-17.25) after the neurocritical events, and half of the patients had normal T4 levels. Activation of 5’-deiodinase induces the conversion of T4 into rT3; rT3 levels are typically elevated in non-thyroid disease states. However, high rT3 alone cannot reliably distinguish non-thyroid disease from a hypothyroid state.14 A low serum T3 state has been regarded an independent predictor of mortality in critically ill patients, especially for critical events involving heart failure.15 Past studies have identified relationships
between low T3 levels, cardiac risk factors and mortality. Abnormal thyroid hormone levels were consistently observed in patients with organ failure. In a study on hormone levels in patients with end-stage renal disease undergoing haemodialysis, 74/167 (44.3%) patients had low T3 levels, which was found to be significantly associated with mortality at 6 months and 12 months (P = .007). The liver is involved in the conversion of T4 into T3, and so patients with liver cirrhosis often show thyroid hormone abnormalities. In one study, nearly 67% of liver cirrhosis patients in intensive care units (ICU) had low T3 syndrome, and the authors showed that fT3 and fT4 levels were predictors of mortality in these patients. Wehmann et al found low T3 syndrome in 54% of patients with haematological malignancies. Wawrzyński et al tested thyroid hormone levels in ICU patients with severe respiratory failure and found that low T3 level was related to decrease of PO2 (partial pressure of oxygen) levels; they reported that dying patients have the lowest total T3 levels, and that increase of T3 serum level closely correlated with clinical improvement. Low fT3 levels have been interpreted as a physiological response aimed at reducing energy expenditure and minimizing protein catabolism. Therefore, low T3 syndrome is common in patients with malnutrition and individuals who are fasting or restricting energy intake. A survival analysis of 669 haemodialysis patients with low T3 syndrome showed that nutritional status might serve as a ‘bridge’ linking low T3 levels and mortality. The authors of that study found that age, serum cholesterol, and serum albumin were related to the extent of T3 decline in some patients and speculated that low fT3 levels might also be an indicator of disease progression.

### Table 2 Baseline characteristics of patients in the two groups

| Characteristics | All patients (n = 32) | HRT group (n = 18) | Non-HRT group (n = 14) | P value |
|-----------------|----------------------|-------------------|------------------------|---------|
| Demographic characteristics | | | | |
| Age, years | 53 (41.25-64) | 46 (37.75-58.75) | 54 (49-75.25) | .059 |
| Male sex (%) | 50 (n = 16) | 38.8 (n = 7) | 64.28 (n = 9) | — |
| BMI (kg/m²) | 24.20 ± 0.59 | 24.72 ± 0.74 | 23.53 ± 0.76 | .319 |
| Thyroid hormone | | | | |
| fT3 (pg/mL) | 1.46 ± 0.04 | 1.44 ± 0.06 | 1.49 ± 0.05 | .722 |
| fT4 (ng/mL) | 1.04 ± 0.16 | 1.11 ± 0.28 | 0.95 ± 0.09 | .464 |
| T3 (ng/mL) | 0.40 ± 0.02 | 0.36 ± 0.03 | 0.45 ± 0.04 | .122 |
| T4 (μg/dL) | 4.72 ± 0.43 | 3.75 ± 0.40 | 5.90 ± 0.71 | .057 |
| TSH (μIU/mL) | 1.12 ± 0.37 | 0.97 ± 0.52 | 1.33 ± 0.53 | .613 |
| Laboratory findings | | | | |
| Blood cortisol (μg/dL) | 4.83 (1.54-15.86) | 4.66 (1.32-12.04) | 9.75 (2.10-22.24) | .224 |
| Blood sugar (mmol/L) | 9.95 ± 0.79 | 10.18 ± 1.11 | 9.66 ± 1.16 | .834 |
| Albumin (g/L) | 30.69 ± 0.88 | 31.39 ± 1.37 | 29.79 ± 0.97 | .633 |
| Haemoglobin (g/L) | 90.75 ± 3.27 | 92.61 ± 4.18 | 88.36 ± 5.32 | .442 |
| White blood cell count (×10⁹/L) | 15.86 (12.93-20.54) | 17.66 (13.09-21.32) | 13.71 (10.10-17.36) | .254 |
| Fibrinogen (g/L) | 3.98 ± 0.36 | 3.51 ± 0.48 | 4.59 ± 0.53 | .102 |
| Clinical findings | | | | |
| GCS | 6 (5-8.75) | 5.50 (3.75-10.25) | 6 (5-8) | .722 |
| GCS at discharge | 8.50 ± 0.73 | 8.17 ± 1.07 | 8.93 ± 0.98 | .615 |
| GCS (follow-up) | 8.56 ± 0.97 | 9.33 ± 1.28 | 7.57 ± 1.49 | .419 |
| GOS (follow-up) | 2.75 ± 0.31 | 3.00 ± 0.41 | 2.43 ± 0.47 | .419 |
| CNS infection (%) | 43.8 (n = 14) | 55.55 (n = 10) | 28.57 (n = 4) | — |
| Survival outcome (death%) | 46.9 (n = 15) | 38.88 (n = 7) | 57.14 (n = 8) | — |

Abbreviations: BMI, body mass index; CNS, central nervous system; fT3, free triiodothyronine; fT4, free thyroxine; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HRT, hormone replacement therapy; TSH, thyroid-stimulating hormone.

For data following non-normal distribution, results were expressed as median and interquartile range. For data following a normal distribution, results were expressed as mean ± standard deviation.
individuals with severe traumatic brain injury, 7,20,21 and this may be related to dysfunction of the hypothalamic-pituitary-target organ axis during acute progression. Stress is a defensive mechanism that allows the body to maintain homeostasis when challenged by various stressors. Under stress, the body's three major regulatory systems – the nervous system, the endocrine system and the immune system – are fully activated to protect the body by responding to internal and external stress. However, when stress is prolonged or the homeostatic response is inadequate, this mechanism could lead to worsening of the clinical outcomes.22

Thyroid hormones are essential role for driving development and maintaining functions of the central nervous system (CNS). 23,24 CNS functions are impaired in thyroid disorders such as myxedema coma and thyrotoxic crisis. Therefore, alterations in thyroid hormone levels are often used as an explanation for some CNS dysfunctions. 25,26 Low T3 syndrome also affects the prognosis of neurological diseases such as acute stroke 1,27 and brain tumours 9,28; however, the CNS, as a complex functional network, interacts with multiple organ systems. In neurocritical patients, multiorgan dysfunctions are common; however, there are few clinical reports on patients with multisystem and multiorgan dysfunctions compared with those exhibiting severely low T3 states.

As acute progression ceases, thyroid hormone levels may return to normal. 29 This may imply that thyroid hormone supplements could improve the prognosis of low T3 patients. Previous clinical studies have examined the effect of thyroid HRT on patients undergoing

| Variable | $P$  | Hazard ratio | 95% confidence interval |
|----------|------|--------------|-------------------------|
| Multivariate regression analysis  
Age          | .781 | 0.995        | 0.961-1.030             |
| GCS        | .076 | 0.778        | 0.590-1.027             |
| HRT        | .087 | 0.340        | 0.099-1.172             |
| Univariate regression analysis  
HRT          | .043 | 0.301        | 0.094-0.964             |

Abbreviations: GCS, Glasgow Coma Scale; HRT, hormone replacement therapy.

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cardiac surgery\textsuperscript{30-32}; patients with malnutrition,\textsuperscript{33,34} heart failure\textsuperscript{35,36} or acute renal failure\textsuperscript{37}; and premature infants with acute respiratory distress syndrome.\textsuperscript{38} Most of these past studies found no significant positive effects on prognosis, and no harmful effects either. Some smaller studies have demonstrated potential promise for the use of HRT; for example, one study showed that T3 supplementation in patients undergoing cardiac surgery could lead to less need for inotropic support and better haemodynamic parameters.\textsuperscript{39} There are no reports of thyroid HRT improving the prognosis of neurocritical patients with low T3 syndrome.

We evaluated the effects of oral levothyroxine sodium on survival outcomes and neurological outcomes in neurocritical patients with the low T3 syndrome. Kaplan-Meier analysis showed overall survival to be significantly better in patients receiving HRT. Univariate regression analysis showed the mortality risk in the non-HRT group to be higher than in the HRT group. However, after adjusting for the effect of age and GCS score in multivariate analysis, there was no statistically significant difference in mortality risk between the HRT and non-HRT groups. The failure to demonstrate a significant effect may have been due to the small sample size and the presence of several serious complications and comorbidities among the patients.

We also examined how oral hormone supplementation affects neurological outcomes. Although descriptive statistics showed better short- and long-term neurological outcomes in patients receiving HRT, the differences between the two groups were not statistically significant. Thyroid hormones enhance the biological response to catecholamines,\textsuperscript{40} which play a vital role in maintaining vascular volume. The velocity of cerebral arterial blood flow has been shown to be positively correlated with thyroid hormone levels.\textsuperscript{41} We believe that normal thyroid hormone level is essential for maintaining craniocebral haemodynamic stability. However, our study could not demonstrate any positive effect of HRT on neurological outcomes. We speculate that this may have been because of the overall abnormal neurological prognosis in the neurocritical patients in this study, as well as methodological limitations. It is also possible that indices such as GCS or GOS are not sensitive enough.

In our study, oral hormone supplementation did not rapidly restore fT3 levels to a normal range. Among the 15 patients in the HRT group who were re-tested for thyroid function, only 5 (33.3%) patients experienced a recovery of thyroid function, while the other ten (66.7%) did not. Despite this result, we still believe that hormone supplementation can contribute to correcting the low T3 state. A prospective study on patients with low T3 syndrome and ischaemic or non-ischaemic dilated cardiomyopathy who were treated with intravenous infusion of synthetic levothyroxine-T3 for 3 days (initial dose: 20 μg/m\textsuperscript{2}/d) reported a rapid increase in free T3 level, as well as a significant improvement in neuroendocrine profile and ventricular performance.\textsuperscript{36} Thus, proper HRT administration with an optimal dosage, combined with dynamic fT3 concentration monitoring, may be necessary for achieving correction of low serum T3 in critically ill patients.

### 5 | WHAT IS NEW AND CONCLUSION

This study demonstrated that hormone replacement therapy has a significant impact on prognosis and survival in neurocritical patients with low T3 syndrome but has no apparent influence on short or long-term neurological outcomes. Our results support calls to pursue large multicenter prospective studies to verify the effectiveness of HRT as a new approach to better treat neurocritical patients.

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### CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest.

### AUTHORS’ CONTRIBUTIONS

Yihao Chen and Jianbo Chang contributed equally to the manuscript. Yihao Chen and Jianbo Chang performed the analysis and co-wrote the manuscript. Junji Wei was study chief investigator and edited the manuscript. All authors read and approved the final text.

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