Original Paper

NeuroImmunoModulation

Neuroimmunomodulation
DOI: 10.1159/000492179

Received: May 24, 2018
Accepted after revision: July 16, 2018
Published online: August 29, 2018

Thyroid Function and Autoimmune Indications in Patients with Anti-N-Methyl-D-Aspartate Receptor Encephalitis

Xiaoyu Ma Qingqing Yin Ziling Zeng Chunjuan Wang Yang Yang Shougang Guo

Department of Neurology, Shandong Provincial Hospital affiliated to Shandong University, Shandong, China

Keywords
Anti-N-methyl-D-aspartate receptor encephalitis · Autoimmune diseases · Thyroid function · Thyroid antibodies · Low T3 syndrome

Abstract
Objective: Previous studies have shown that functional abnormalities of the thyroid are associated with the pathogenesis of several neurological diseases. However, their relationship in patients with anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis remains to be defined. ***Methods:*** Forty-three patients with anti-NMDAR encephalitis were examined for thyroid function and autoimmune indications, in comparison with 225 healthy controls (CTL). Patients were further classified into 2 subgroups based on their free triiodothyronine (fT3) levels. Moreover, fT3 levels were also investigated after at least three months of follow-up. The clinical characteristics of the patients and CTL were described in detail. ***Results:*** Serum levels of fT3 and thyroid-stimulating hormone (TSH) were found to be relatively lower in patients with anti-NMDAR encephalitis than in CTL (both $p < 0.001$). Low T3 syndrome also occurred more frequently in anti-NMDAR encephalitis (25.6 vs. 0.4%, $p < 0.001$). However, no statistical differences were detected between patients and CTL in terms of the positive rate of thyroid antibodies and other types of thyroid dysfunction. Patients with low T3 levels tended to have a longer hospital stay ($p = 0.006$), a higher rate of abnormal brain magnetic resonance imaging (MRI) findings ($p = 0.033$), a higher frequency of consciousness declination ($p = 0.029$), and a higher modified Rankin scale (mRS) score during hospitalization. Low fT3 levels were also associated with abnormal MRI findings, a decline in consciousness, and the mRS score on admission. In addition, fT3 seemed to gradually return to normal levels upon improvement of the mRS score ($r = –0.649$, $p = 0.002$). ***Conclusions:*** Low T3 syndrome often copresents in anti-NMDAR encephalitis and indicates a longer hospitalization, abnormal MRI findings, consciousness declination, and a higher clinical severity. However, fT3 levels do not seem to influence the prognosis of anti-NMDAR encephalitis.

Introduction

For slightly more than 10 years, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has been recognized as the most common cause of nonviral encephalitis, which is characterized by the subacute devel-

Mr. Shougang Guo
Department of Neurology
Shandong Provincial Hospital affiliated to Shandong University
Jing Wu Road, Huaiyin District, Jinan, Shandong 250021 (China)
E-Mail guoshougang1124@163.com

opment of memory deficits, seizures, speech disorder, neuropsychiatric symptoms, autonomic dysfunction, and even a decline in consciousness [1]. Other systemic immune disorders that concomitantly present with neurological symptoms, such as Hashimoto's encephalopathy (HE) and Sjogren's syndrome, make the diagnosis more complex.

Several reports have revealed the intertwining relationships between systemic immune abnormalities, particularly autoimmune thyroid diseases, and immune-mediated neurological disorders, such as multiple sclerosis, and neuromyelitis optica spectrum disorder (NMOSD) [2, 3]. Autoantibodies that are indicative of systemic immune disorders, such as antinuclear antibodies, have also been detected in patients with autoimmune encephalitis, but the literature in this regard is limited [4, 5]. Thyroid dysfunction was known as an unfavorable factor for cerebrovascular diseases [6]. Recent studies suggest that free tri-iodothyronine (fT3), an indicator of thyroid function, can serve as a prognostic factor in critical illness (e.g., sepsis, heart disease, respiratory failure, and stroke) [7–10] and also some autoimmune diseases (e.g., systemic lupus erythematosus and NMOSD) [11, 12]. Thyroid hormones are also closely involved in regulating neutrosphere biology and immune system function (e.g., cell-mediated immunity) [13, 14]. However, the association between thyroid function/autoimmunity and anti-NMDAR encephalitis has not been discussed.

Therefore, this clinical study was performed to investigate whether thyroid dysfunction and autoimmunity are associated with clinical manifestation and prognosis in patients with anti-NMDAR encephalitis.

Methods

Patients and Controls

This retrospective study enrolled 43 patients with anti-NMDAR encephalitis who were admitted to the Shandong Provincial Hospital affiliated to Shandong University from January 2014 to January 2018. Patients were included if they met the diagnostic criteria for possible autoimmune encephalitis and were further confirmed as definite anti-NMDAR encephalitis based on the presence of NMDAR antibodies [15]. Patients with other neurological disorders (metastases, infections, stroke, etc.) or without thyroid function tests on admission were excluded. Another 225 ordinary people from the health examination center at our hospital were selected as the contrast group randomly. Patients had at least 3 months of follow-up to observe long-term outcomes. NMDAR antibodies were detected by indirect immunofluorescence assay using transfected human embryonic kidney cells (HEK293) expressing NR1 subunits of the NMDA receptor by third-party medical testing agencies.

Clinical Data Collection

Examinations including brain magnetic resonance imaging (MRI), CT scan of the thorax, ultrasound of the abdomen and pelvic region, and lumbar puncture were done in all of the patients. Neuronal cell surface antibodies including the α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid (AMPA) receptor antibody, the leucine-rich glioma inactivated protein 1 (LGI1) antibody, the contactin-associated protein 2 (CASPR2) antibody and the γ-aminobutyric acid-B receptor ($GABA_BR$) antibody, and paraneoplastic antibodies covering anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ri (ANNA-2), anti-CV2/CRMP5, and amphiphysin antibodies were checked in all of the patients. Most of them were checked using immunological related antibodies containing anti-nuclear antibody, anti-double-stranded DNA (anti-dsDNA), anti-Ro/SSA or anti-La/SSB (SS-A/SS-B) antibodies, anti-neutrophil cytoplasmic antibody (ANCA), and anti-cardiolipin antibody. We also evaluated the severity of illness through modified Rankin scale (mRS) scores on blood samples at admission, at discharge, and 3 months after discharge. Additional data comprised age, sex, time from symptom onset to treatment initiation, and treatments received.

Thyroid Function Tests

The test for serum thyroid hormone levels included serum fT3, serum free thyroxin (fT4), thyroid-stimulating hormone (TSH), anti-thyroglobulin (anti-Tg), and anti-thyroid peroxidase (anti-TPO) antibodies. Normal values were: 3.5–6.5 pmol/L, 11.5–22.7 pmol/L, 0.55–4.78 μIU/ml, 0–60 IU/mL, and 0–60 IU/mL, respectively. Values were measured using a Siemens ADVIA Centaur XP automatic chemiluminescence immunoassay system. Low T3 syndrome was diagnosed based on serum fT3 values below the normal level and low or normal levels of serum fT4 and TSH.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney *U* test. Fisher's exact test or the χ^2 test was used for categorical variables. mRS scores and fT3 levels were compared before and after treatment using the Wilcoxon signed-rank test. Spearman's correlation and partial correlation coefficients were used to examine the correlation between fT3 levels and clinical indexes. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics and Clinical Features

A total of 43 patients (11 males [25.6%] and 32 females [74.4%], mean age 29.65 ± 12.18 years, range 14–65) met the diagnostic criteria for anti-NMDAR encephalitis. Cerebrospinal fluid (CSF) DNA tests for the herpes simplex virus, cytomegalovirus, and the Epstein-Barr virus were all negative. Six patients (14%) had ovarian teratoma. Other tumors were not detected. The average interval from onset to sampling was 21.77 ± 19.20 days. The average length of hospital stay was 25.19 ± 17.92 days. On admission, the median mRS score which used to evaluate

Table 1. Demographic features and thyroid function/antibodies of patients with anti-NMDAR encephalitis and CTL

	Anti-NMDAR encephalitis patients (n = 43)	CTL (n = 225)	p value
Age, years	29.65±12.18	29.67±11.58	0.952
Females	32 (74.4)	168 (74.7)	0.973
mRS score	4 (2–5)	–	–
Abnormal MRI findings	19 (44.2)	–	–
Tumor presence	6 (14.0)	–	–
CSF routine			
Median CSF WBC, $n \times 10^6$/L	23 (2–286)	–	–
Median CSF protein, g/L	0.28 (0.12–1.05)	–	–
Thyroid function			
fT3, pmol/L	4.17±0.99	5.25±2.01	**<0.001**
fT4, pmol/L	16.94±3.09	16.39±4.90	0.142
TSH, μIU/mL	1.53±1.25	2.18±1.14	**<0.001**
Thyroid autoantibodies			
Anti-Tg antibody positivity	10 (23.3)	42 (18.7)	0.486
Anti-TPO antibody positivity	9 (20.9)	35 (15.6)	0.383
Thyroid function dysfunction	16 (37.2)	19 (8.4)	**<0.001**
Low T3 syndrome	11 (25.6)	1 (0.4)	**<0.001**
Clinical hypothyroidism	0 (0.00)	1 (0.4)	1
Subclinical hypothyroidism	1 (2.3)	6 (2.7)	1
Clinical hyperthyroidism	1 (2.3)	4 (1.8)	0.586
Subclinical hyperthyroidism	3 (7.1)	7 (3.1)	0.196

Values are presented as means ± SD, numbers (%), or medians (range). $p < 0.05$ was considered statistically significant.

the severity of anti-NMDAR encephalitis was 4 (range 2–5). Nineteen patients had abnormal MRI findings, which were primarily located in the temporal lobe, the hippocampus, the occipital lobe, the frontal lobe, and the basal ganglia. Moreover, no abnormal hypothalamic/pituitary MRI findings were observed. The median CSF white blood cell and protein counts were 23 × 10^6/L (range 2–286) and 0.28 g/L (range 0.12–1.05), respectively. Before admission, 13 patients were treated with glucocorticoids and 13 patients were given with intravenous immunoglobulin (none with immunosuppressive agents).

Comparison of Thyroid Dysfunction/Autoimmunity in Patients with anti-NMDAR Encephalitis and Controls

The results of the comparison are summarized in Table 1. Of the 43 patients with anti-NMDAR encephalitis,16 showed abnormal thyroid function, which is significantly higher than the frequency in the controls (CTL) (37.2 vs. 8.4%, $p < 0.001$). The mean fT3 and TSH values for anti-NMDAR encephalitis patients were on the low side compared to CTL values (both $p < 0.001$), while the difference in mean TSH values and percentages of thyroid autoantibodies was not statistically significant. Eleven (25.6 vs. 0.4%, $p < 0.001$) patients exhibited low T3 syndrome, which might be the most prevalent thyroid dysfunction in anti-NMDAR encephalitis; 3 patients had subclinical hyperthyroidism, 1 patient had subclinical hypothyroidism, and another had hyperthyroidism.

Comparison of Subgroups of Anti-NMDAR Encephalitis according to fT3 Levels

Table 2 presents data on anti-NMDAR encephalitis patients divided on the basis of fT3 levels after excluding 1 patient with clinical hyperthyroidism. Of those patients, 11 patients had low fT3 levels; the remaining 31 patients had normal fT3. This study did not identify differences in treatment methods at the time of sampling (e.g., glucocorticoids and immunoglobulin; $p = 0.713$ and $p = 0.270$, respectively). Importantly, patients with low T3 syndrome had a significantly longer hospital stay and higher mRS scores both at admission and at dis-

Table 2. Comparison of demographic, serologic, and clinical features among patients divided by fT3 levels

	Anti-NMDAR encephalitis patients[1]		*p* value
	with low T3 syndrome	without low T3 syndrome	
Demographic characteristics			
Age, years	31.45±13.00	28.90±12.21	0.538
Females	9 (81.8)	23 (74.2)	1
Interval until sampling, days	21.46±14.71	21.61±21.02	0.456
Length of hospital stay, days	36.64±27.34	20.48±10.80	0.006
Abnormal MRI findings	9 (81.8)	10 (32.3)	0.033
Tumor presence	3 (27.3)	3 (9.7)	0.314
mRS score			
At admission	5 (3–5)	3 (2–5)	0.002
At discharge	3 (1–5)	2 (0–6)	0.022
At 3 months after discharge[2]	0.5 (0–5)	0 (0–6)	0.896
Treatment at sampling			
Glucocorticoid use	4 (36.4)	9 (29.0)	0.713
Intravenous dexamethasone use	1 (9.1)	4 (12.9)	1
Intravenous methylprednisolone use	3 (27.3)	5 (19.0)	0.412
Intravenous immunoglobulin use	5 (45.5)	8 (25.8)	0.270
Symptoms			
Prodrome	8 (72.7)	17 (54.8)	0.477
Memory disorder	7 (63.6)	15 (48.4)	0.384
Abnormal behavior and cognition	11 (100)	25 (80.6)	0.172
Speech disorder	6 (54.5)	16 (51.6)	0.867
Seizures	8 (72.7)	23 (74.2)	1
Movement disorder	6 (54.5)	13 (41.9)	0.504
Declination of consciousness	8 (72.7)	9 (29.0)	0.029
Autonomic dysfunction	7 (63.6)	16 (51.6)	0.726
Central hypoventilation	4 (36.4)	6 (19.4)	0.412
CSF tests			
CSF WBC, $n \times 10^6$/L	23 (2–286)	24 (2–286)	0.606
CSF protein, g/L	0.28 (0.17–1.051)	0.27 (0.12–0.94)	0.587
Thyroid autoimmunity			
Anti-Tg antibody positivity	3 (27.3)	6 (19.4)	0.676
Anti-TPO antibody positivity	3 (27.3)	5 (16.1)	0.412
Associated autoantibodies			
FANA	4/9 (44.4)	8/28 (28.6)	0.432
SSA or SSB	2/28 (22.2)	0/28 (0.0)	0.054

Values are presented as means ± SD, numbers (%), or medians (range). FANA, fluorescent antinuclear antibody; SSA or SSB, anti-Ro/SSA or anti-La/SSB antibody. [1] One patient with clinical hyperthyroidism was excluded. [2] Twenty-eight patients were followed up, including 10 patients with low T3 syndrome and 18 patients without low T3 syndrome on admission.

charge compared to patients without low T3 syndrome ($p = 0.006$, $p = 0.002$, and $p = 0.022$, respectively). However, no significant difference in mRS scores 3 months after discharge was observed between the subgroups ($p = 0.896$). The percentages of disturbance of consciousness and abnormal MRI were significantly higher in patients with low T3 syndrome than in those without low T3 syndrome ($p = 0.029$ and $p = 0.033$, respectively). There were no significant differences in terms of other symptoms or clinical characteristics including sex, age of onset, thyroid autoimmunity, and associated autoantibody levels. None of the patients in our study copresented with ds-RNA, ANCA, paraneoplastic antibodies, or anti-cardiolipin antibody.

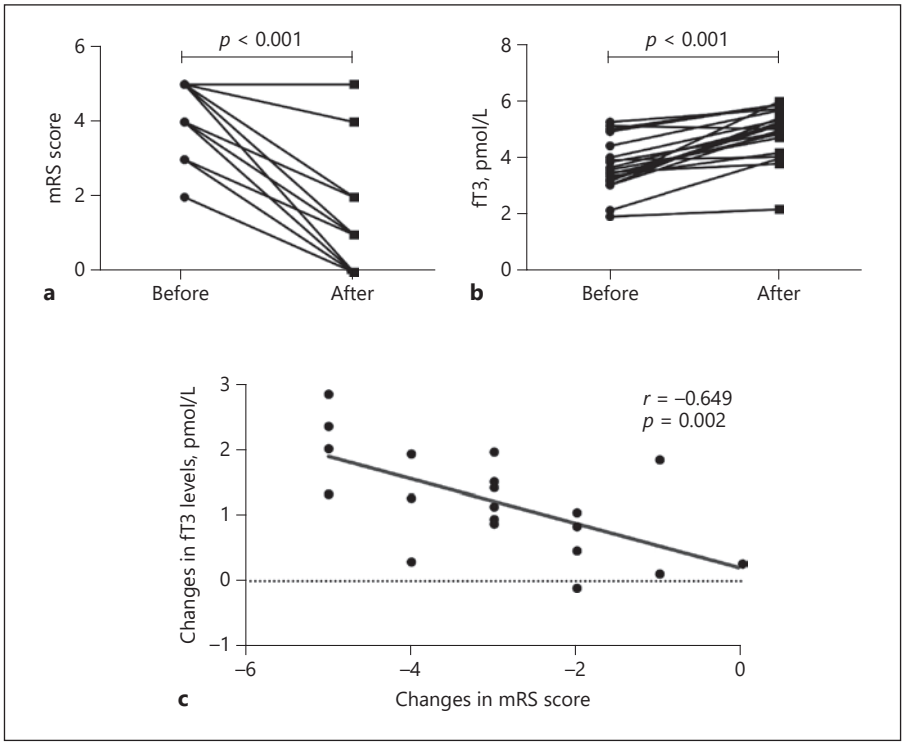

Fig. 1. a, **b** Changes in mRS scores and fT3 levels in patients with anti-NMDAR encephalitis during treatment. **c** Correlation between changes in mRS scores and fT3 levels after treatment (r = –0.0649, p = 0.002). n = 20.

Table 3. Correlation analysis of possible factors that may affect fT3 levels in patients with anti-NMDAR encephalitis

	r	*p*
Sex	–0.116	0.459
Age at sampling	–0.281	0.068
Length of hospital stay	–0.273	0.077
Degree of antibody titers[1]	–0.252	0.103
mRS at sampling	–0.556	**<0.001**
Decreased consciousness	–0.533	**<0.001**
Abnormal MRI findings	–0.453	**0.002**
CSF WBC	–0.042	0.789
CSF protein	–0.185	0.234
Glucocorticoid use	–0.184	0.238
Immunoglobulin use	–0.145	0.354

The total number of patients was 43. [1] Classified as weakly positive (CSF 1:1, serum 1:10), positive (CSF1:10 or 1:32, serum 1:32), or strongly positive (CSF 1:100 or 1:320, serum 1:100). $p < 0.05$ was considered statistically significant.

Association between fT3 Levels and Clinical Features in Patients with anti-NMDAR Encephalitis

As can be seen in Table 3, mRS score at sampling, consciousness declination, and abnormal MRI findings were significantly and reversely associated with fT3 levels ($p < 0.001$, $p < 0.001$, and $p = 0.002$, respectively). However, no significant correlations were detected between fT3 levels and parameters including sex, age, length of hospital stay, CSF tests, and treatments at sampling. Differences were still present when a partial correlation was done and treatments were selected as the control variables.

Follow-Up Evaluation of fT3 Levels in Patients with Anti-NMDAR Encephalitis after Treatment

Twenty patients were followed up to discern a potential relationship between the variations of mRS scores and changes in fT3 levels after treatment. mRS scores decreased significantly while concomitantly fT3 levels increased significantly (Fig. 1a, b). Moreover, there was clearly a reverse correlation between changes in mRS scores and changes in fT3 levels (r = –0.649, p = 0.002; Fig. 1c).

Discussion

In this study, we compared 5 categories of thyroid dysfunction in patients versus CTL. Approximately 25.6% of the patients showed low T3 syndrome during the acute process. Previous studies have demonstrated that thyroid

hormones play a critical role in the proliferation and differentiation of neuronal and glial progenitors during normal brain development [16] and in regulation of adult hippocampal neurogenesis [17]. This constitutes the bases for investigation of the potential relationship between thyroid function/antibody and anti-NMDAR encephalitis. Based on the results of this study, we concluded that thyroid dysfunction, especially low T3 syndrome, is a common manifestation in patients with anti-NMDAR encephalitis. Although previous reports have shown that drugs such as glucocorticoids may have an influence on thyroid function [18], we did not observe differences in thyroid function among different treatments including glucocorticoids, immunoglobulin, and other immune inhibitors.

Anti-NMDAR encephalitis may also develop with autoimmune disorders, such as autoimmune thyroid diseases, systemic lupus erythematosus, acute disseminated encephalomyelitis, and NMOSD [5, 19, 20]. HE is an autoimmune encephalopathy which is characterized by high titers of anti-thyroid antibodies [21]. We observed similar levels of positive anti-thyroid antibodies between patients and CTL in the present study. Moreover, no literature has proven that these antibodies themselves are mediators of encephalopathy. None of our patients produced ds-RNA, ANCA, paraneoplastic antibodies, or anti-cardiolipin antibody. The presence of FANA and SSA/SSB in the subgroups according to fT3 was also very similar. We presume that the coexistence of other antibodies in anti-NMDAR encephalitis is probably only a tendency toward a disturbed autoimmune function.

As patients with low T3 syndrome also correlate with a higher rate of decreased consciousness, higher mRS scores before and after hospitalization, and a longer in hospital stay, we propose the possibility that fT3 could be considered as a measurement of disease severity. Low T3 syndrome has been found in several critical disorders. Moreover, accumulating evidence suggests that fT3 could be a valuable parameter in evaluating the prognosis of patients with illness requiring admission to the ICU, acute cerebrovascular disorders, NMOSD, and even noncritical illness [12, 22–24]. The detection of several thyroid hormones simultaneously or individually can predict a poor outcome in children with central nervous system infections [25]. However, our study did not show a distinction in terms of mRS scores between patients with fT3 and low fT3 levels in the normal range in the follow-up evaluation for at least 3 months. Thus, we speculate that fT3 levels may not be sufficient to predict the eventual outcome of anti-NMDAR encephalitis. Low fT3 levels might only be clinically significant during acute processes. However, we still wish to advocate that sufficient attention should be paid to patients with higher mRS scores and decreased consciousness as they might simultaneously present with other serious complication which might lead to a poor prognosis and the need for prolonged hospital care.

It is notable that mRS scores gradually decrease with the elevation of fT3 levels and that patients with normal fT3 levels recover faster than those with low fT3 levels. The explanation for this may be that the acute process of this illness results in a worse condition in patients with low fT3. Indicators of a good prognosis have been published before and they involve early diagnosis and treatment [1]. This brings up the possibility that early administration of second-line immunotherapy could be helpful in patients with low fT3.

Among the most striking clinical manifestations in patients diagnosed with NMDAR encephalitis, deficits in cognition, such as memory, and behavior are also associated with thyroid function [17, 26, 27]. In our findings, patients, especially those whose consciousness decreased, frequently had low T3 syndrome. As a complement, fT3 levels rose steadily during recovery. The existing literature suggests that thyroid hormones can cross the blood-brain barrier, promote myelinogenesis, and participate in the secretion of neurotrophic factors, linking thyroid physiology and neurocognitive dysfunction in humans [28]. Thus, it is plausible to take into account whether thyroid hormones play important roles in the pathogenesis of anti-NMDAR encephalitis and that the rise in fT3 levels is conducive to improvement of the condition. Thyroid drugs can improve cognition in patients with hypothyroidism [29]. However, the effects of thyroid hormones on patients with anti-NMDAR encephalitis in terms of improvement of consciousness, cognition, and behavior performance still require further studies and discussion.

Not every MRI in NMDAR encephalitis is abnormal. Our results showed that 44.2% of patients with NMDAR encephalitis had an abnormal MRI on admission, which is in general agreement with previous observations [1, 30]. Abnormal MRI findings also have no relationship with clinical presentations and do not affect clinical outcomes [31]. However, an association remains between low fT3 levels and abnormal MRI findings in anti-NMDAR encephalitis as shown in our study. Hypothyroidism and memory declination have been found to be associated with a decreased hippocampal size [32], suggesting that thyroid hormones dysfunction can cause

structural alterations. The mechanism of low T3 syndrome might be attributed to the abnormal hypothalamus-pituitary-thyroid axis or metabolic disorders of peripheral thyroid hormones. Hypothalamic/pituitary lesions can also cause insufficient TSH secretion resulting in low levels of thyroid hormones, which is called central hypothyroidism [33]. However, it was rare to see abnormal hypothalamic/pituitary MRI findings in anti-NMDAR encephalitis and no hypothalamic/pituitary lesion was observed in our study. Furthermore, low T3 syndrome could derive from cytokine deregulation. Several studies have focused on the role of cytokine/chemokine in NMDAR encephalitis. Among them, interleukin-6 (IL-6) has been found to be elevated in CSF of anti-NMDAR encephalitis [34]. IL-6 knockout mice have been shown to be resistant to experimental autoimmune encephalomyelitis [35]. IL-6 can promote low T3 syndrome by inducing oxidative stress which can reduce T4-to-T3 conversion and increase T3 inactivation [36]. Consistent with this finding, tocilizumab, an anti-IL-6 antibody, appears to improve symptoms in rituximab-refractory autoimmune encephalitis [37]. This provides further evidence that low T3 syndrome might provide valuable guidance for medication decisions.

We are aware that this study has some limitations. First, the follow-up period was relatively short, so we cannot establish a reasonable association between thyroid function and relapses. Second, the sample size was relatively small.

Conclusion

Our results showed that thyroid dysfunction, especially low T3 syndrome, is often observed in anti-NMDAR encephalitis. These patients usually show a longer duration of hospitalization, more severe conditions such as decreased consciousness in the acute process, and a higher frequency of abnormal MRI compared to those without low fT3 levels. fT3 levels could were found to increase during recovery. Nevertheless, low T3 levels do not represent a poor prognosis. Further studies on the role of thyroid function in autoimmune encephalitis are desirable.

Acknowledgement

This study was supported by the National Natural Science Foundation of China (No. 81671183).

Statement of Ethics

This study was approved by the Committee of Clinical Investigation at Shandong Provincial Hospital affiliated to Shandong University of Science and Technology. Informed consent was obtained from all of patients or their relatives.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, Honig LS, Benseler SM, Kawachi I, Martinez-Hernandez E, Aguilar E, Gresa-Arribas N, Ryan-Florance N, Torrents A, Saiz A, Rosenfeld MR, Balice-Gordon R, Graus F, Dalmau J: Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 2013;12:157–165.

2 Niederwieser G, Buchinger W, Bonelli RM, Berghold A, Reisecker F, Koltringer P, Archelos JJ: Prevalence of autoimmune thyroiditis and non-immune thyroid disease in multiple sclerosis. J Neurol 2003;250:672–675.

3 Wang X, Yi H, Liu J, Li M, Mao ZF, Xu L, Peng FH: Anti-thyroid antibodies and thyroid function in neuromyelitis optica spectrum disorders. J Neurol Sci 2016;366:3–7.

4 Lai M, Hughes EG, Peng X, Zhou L, Gleichman AJ, Shu H, Mata S, Kremens D, Vitaliani R, Geschwind MD, Bataller L, Kalb RG, Davis R, Graus F, Lynch DR, Balice-Gordon R, Dalmau J: AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. Ann Neurol 2009;65:424–434.

5 Guan W, Fu Z, Zhang H, Jing L, Lu J, Zhang J, Lu H, Teng J, Jia Y: Non-tumor-associated anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis in Chinese girls with positive anti-thyroid antibodies. J Child Neurol 2015;30:1582–1585.

6 Squizzato A, Gerdes VE, Brandjes DP, Buller HR, Stam J: Thyroid diseases and cerebrovascular disease. Stroke 2005;36:2302–2310.

7 Meyer S, Schuetz P, Wieland M, Nusmaumer C, Mueller B, Christ-Crain M: Low triiodothyronine syndrome: a prognostic marker for outcome in sepsis? Endocrine 2011;39:167–174.

8 Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'Abbate A, Donato L: Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation 2003;107:708–713.

9 Scoscia E, Baglioni S, Eslami A, Iervasi G, Monti S, Todisco T: Low triiodothyronine (T3) state: a predictor of outcome in respiratory failure? Results of a clinical pilot study. Eur J Endocrinol 2004;151:557–560.

10 Suda S, Muraga K, Kanamaru T, Okubo S, Abe A, Aoki J, Suzuki K, Sakamoto Y, Shimoyama T, Nito C, Kimura K: Low free triiodothyronine predicts poor functional outcome after acute ischemic stroke. J Neurol Sci 2016;368:89–93.

11 Tektonidou MG, Anapliotou M, Vlachoyiannopoulos P, Moutsopoulos HM: Presence of systemic autoimmune disorders in patients with autoimmune thyroid diseases. Ann Rheum Dis 2004;63:1159–1161.

12 Cho EB, Min JH, Cho HJ, Seok JM, Lee HL, Shin HY, Lee KH, Kim BJ: Low T3 syndrome in neuromyelitis optica spectrum disorder: Associations with disease activity and disability. J Neurol Sci 2016;370:214–218.
13 De Vito P, Balducci V, Leone S, Percario Z, Mangino G, Davis PJ, Davis FB, Affabris E, Luly P, Pedersen JZ, Incerpi S: Nongenomic effects of thyroid hormones on the immune system cells: new targets, old players. Steroids 2012;77:988–995.
14 van der Spek AH, Fliers E, Boelen A: Thyroid hormone metabolism in innate immune cells. J Endocrinol 2017;232:R67–R81.
15 Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, Cortese I, Dale RC, Gelfand JM, Geschwind M, Glaser CA, Honnorat J, Höftberger R, Iizuka T, Irani SR, Lancaster E, Leypoldt F, Prüss H, Rae-Grant A, Reindl M, Rosenfeld MR, Rostásy K, Saiz A, Venkatesan A, Vincent A, Wandinger KP, Waters P, Dalmau J: A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016; 15:391–404.
16 Bernal J: Thyroid hormone receptors in brain development and function. Nat Clin Pract Endocrinol Metab 2007;3:249–259.
17 Desouza LA, Ladiwala U, Daniel SM, Agashe S, Vaidya RA, Vaidya VA: Thyroid hormone regulates hippocampal neurogenesis in the adult rat brain. Mol Cell Neurosci 2005;29: 414–426.
18 Surks MI, Sievert R: Drugs and thyroid function. N Engl J Med 1995;333:1688–1694.
19 Wu YY, Feng Y, Huang Y, Zhang JW: Anti-N-methyl-D-aspartate receptor encephalitis in a patient with systemic lupus erythematosus. J Clin Neurol 2016;12:502–504.
20 Titulaer MJ, Hoftberger R, Iizuka T, Leypoldt F, McCracken L, Cellucci T, Benson LA, Shu H, Irioka T, Hirano M, Singh G, Calvo AC, Kaida K, Morales PS, Wirtz PW, Yamanoto T, Reindl M, Rosenteld MR, Graus F, Saiz A, Dalmau J: Overlapping demyelinating syndromes and anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol 2014;75: 411–428.
21 Zhou JY, Xu B, Lopes J, Blamoun J, Li L: Hashimoto encephalopathy: literature review. Acta Neurol Scand 2017;135:285–290.
22 Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Scholmerich J, Wrede CE: Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metabolism 2007;56:239–244.
23 Bunevicius A, Iervasi G, Bunevicius R: Neuroprotective actions of thyroid hormones and low-T3 syndrome as a biomarker in acute cerebrovascular disorders. Expert Rev Neurother 2015;15:315–326.
24 Pappa TA, Vagenakis AG, Alevizaki M: The nonthyroidal illness syndrome in the noncritically ill patient. Eur J Clin Invest 2011;41: 212–220.
25 Jiao F, Zhang X, Bai T, Lin J, Cui W, Liu B: Clinical evaluation of the function of hypothalamo-pituitary-thyroid axis in children with central nervous system infections. Ital J Pediatr 2011;37:11.
26 Jahagirdar V, McNay EC: Thyroid hormone's role in regulating brain glucose metabolism and potentially modulating hippocampal cognitive processes. Metab Brain Dis 2012;27: 101–111.
27 Schraml FV, Goslar PW, Baxter L, Beason-Held LL: Thyroid stimulating hormone and cognition during severe, transient hypothyroidism. Neuro Endocrinol Lett 2011;32:279–285.
28 Remaud S, Gothié JD, Morvan-Dubois G, Demeneix BA: Thyroid hormone signaling and adult neurogenesis in mammals. Front Endocrinol (Lausanne) 2014;5:62.
29 Kramer CK, von Muhlen D, Kritz-Silverstein D, Barrett-Connor E: Treated hypothyroidism, cognitive function, and depressed mood in old age: the Rancho Bernardo Study. Eur J Endocrinol 2009;161:917–921.
30 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R: Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74.
31 Wang R, Lai XH, Liu X, Li YJ, Chen C, Li C, Chi XS, Zhou D, Hong Z: Brain magnetic resonance-imaging findings of anti-N-methyl-D-aspartate receptor encephalitis: a cohort follow-up study in Chinese patients. J Neurol 2018;265:362–369.
32 Cooke GE, Mullally S, Correia N, O'Mara SM, Gibney J: Hippocampal volume is decreased in adults with hypothyroidism. Thyroid 2014; 24:433–440.
33 Persani L: Clinical review – central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. J Clin Endocrinol Metab 2012;97:3068–3078.
34 Byun JI, Lee ST, Moon J, Jung KH, Sunwoo JS, Lim JA, Kim TJ, Shin YW, Lee KJ, Jun JS, Lee HS, Lee WJ, Kim YS, Kim S, Jeon D, Park KI, Jung KY, Kim M, Chu K, Lee SK: Distinct intrathecal interleukin-17/interleukin-6 activation in anti-N-methyl-D-aspartate receptor encephalitis. J Neuroimmunol 2016;297:141–147.
35 Eugster HP, Frei K, Kopf M, Lassmann H, Fontana A: IL-6-deficient mice resist myelin oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis. Eur J Immunol 1998;28:2178–2187.
36 Wajner SM, Goemann IM, Bueno AL, Larsen PR, Maia AL: IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells. J Clin Invest 2011; 121:1834–1845.
37 Lee WJ, Lee ST, Moon J, Sunwoo JS, Byun JI, Lim JA, Kim TJ, Shin YW, Lee KJ, Jun JS, Lee HS, Kim S, Park KI, Jung KH, Jung KY, Kim M, Lee SK, Chu K: Tocilizumab in autoimmune encephalitis refractory to rituximab: an institutional cohort study. Neurotherapeutics 2016;13:824–832.