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Anti-thyroid antibodies and thyroid function in anti-N-methyl-D-aspartate receptor encephalitis

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1. Introduction

There has been an expanding knowledge of autoimmune encephalitis (AIE) in recent years. It is a group of inflammatory encephalopathies in association with antibodies against synaptic proteins or receptors on the surface of neurons (Leypoldt, 2013; Huang et al., 2015; Lancaster, 2016; Hao et al., 2017). Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is one of the most common types of AIE. It predominantly affects young women with or without ovarian teratomas (Guan et al., 2015).

Increased prevalence of anti-thyroid antibodies (ATAbs) were found in many autoimmune diseases such as multiple sclerosis (Munteis et al., 2007; Long et al., 2014) and neuromyelitis optica (Wang et al., 2016). Although elevated anti-thyroid peroxidase (anti-TPO) antibodies have been reported in patients with anti-NMDAR encephalitis (Guan et al., 2015; Xu et al., 2011; Tuzun et al., 2011), few studies have focused on the clinical associations of ATAbs and anti-NMDAR encephalitis.

This study aims to evaluate the thyroid function of patients with anti-NMDAR encephalitis and find whether there are differences of clinical, laboratory and imaging features between ATAbs-seropositive and ATAbs-seronegative anti-NMDAR encephalitis patients. We also compare thyroid parameters in anti-NMDAR positive patients with and without teratomas.

2. Methods

2.1. Study population

Our database comprised 42 patients with anti-NMDAR encephalitis who were admitted from March 2014 to December 2016 in the department of neurology of the Third Affiliated Hospital of Sun Yat-sen University. Anti-NMDAR encephalitis was diagnosed in the presence of a core syndrome of limbic encephalitis (seizures, behavioural and psychiatric disturbances, conscious disturbance, short-term memory deficits) and detection of IgG antibodies against NMDAR (Leypoldt, 2013) after careful exclusion of relevant differential diagnoses. Gender, age, modified Rankin Scale (mRS) and clinical manifestations were recorded. All patients underwent routine abdominal and pelvic ultrasound. And a pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI) scan was performed when an ovarian teratoma was suspected. Treatments included first-line immunotherapy, second-line immunotherapy and tumour removal. First-line immunotherapy was used steroids, intravenous immunoglobulins or plasma exchange alone or combined. Second-line immunotherapy included rituximab, azathioprine or cyclophosphamide treatment alone or combined. The control group included 121 subjects who visited the hospital for health examination.

2.2. ATAbs analysis in serum

Serum samples were analyzed for the levels of anti-thyroglobulin antibodies (TGAb), anti-thyroid peroxidase antibodies (TPOAb), free thyroxine (FT4), free triiodothyronine (FT3) and thyrotropin (TSH) by highly sensitive MAIA (magnetic antibody enzyme linking immunoassay) following the procedure of the manufacturer's instructions in all patients. The normal range of TPOAb and TGAb is 0–60 U/ml. The normal range of the assays is 11.5–22.7 pmol/L and 3.5–6.5 pmol/L for FT4 and FT3, respectively.

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The normal range of TSH is 0.55–4.78 u IU/ml. Thyroid parameters outside the normal range were defined as abnormalities. All of the patients weren't treated with corticosteroids and immunosuppressives in the last 3 months before blood testing. Thyroid diseases were diagnosed by endocrinologists according to the relevant criteria.

2.3. Detection of autoantibodies

After obtaining informed consent, cerebrospinal fluid (CSF) was collected from patients prior to treatment with methylprednisolone and other immunotherapies. The CSF sample was used for routine analysis and autoantibodies. Antibodies against NMDAR were tested by indirect immunofluorescence assay using commercial sampling kits (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany).

2.4. Magnetic resonance imaging (MRI) analysis

Brain MRI scans were performed at 3.0 T (Discovery MR750, GE Healthcare, Milwaukee, WI, USA). The slice thickness of the axial scans was 5 mm. Conventional MRI protocols were applied to all patients: T2-weighted (4392–5658/88.8–106 ms, TR/TE), T1-fluid-attenuated inversion recovery (FLAIR) (1782.6–1925.4/19.6–24.6 ms, TR/TE) and T2 FLAIR (8400–8800/139.4–151.4 ms, TR/TE) for brain MRI. All of the patients underwent their MRI scans before corticosteroids and immunosuppressive treatments.

2.5. Statistics analyses

All statistical analyses were conducted by using the SPSS 13.0 package for Windows (SPSS Inc, Chicago, IL, USA). Continuous data were presented as the mean ± standard deviation or median (range). Continuous data were compared by Student's t-test or the Mann Whitney *U* test. Nominal variables were analyzed using the chi-square test or Fisher's exact test.

3. Result

3.1. Comparison of serum thyroid parameters between patients with anti-NMDAR encephalitis and controls

Baseline characteristics of anti-NMDAR patients with encephalitis and healthy controls were presented in Table 1. A total of 42 patients with anti-NMDAR encephalitis (mean age 27.38, female/male: 22:20) were evaluated. Amongst them, 8 patients (19.0%) had ovarian teratoma and 34 patients (81.0%) were non-tumor associated. As for the clinical presentation at onset, 22 patients (52.4%) had epileptic seizures, 32 patients (76.2%) had behavioral and psychiatric disturbances, 21 patients (50.0%) had conscious disturbance, 10 patients (23.8%) had short-term memory deficits. All patients with anti-NMDAR encephalitis didn't have past medical history of hashimoto thyroiditis. Serum thyroid parameters of anti-NMDAR patients with encephalitis and healthy controls were shown in Table 2. Compared to controls, patients with anti-NMDAR encephalitis presented higher abnormal TPOAb, TGAb and serum FT3 levels (all $P < 0.001$). While there were no significant differences in serum levels of FT4 and TSH between these two groups.

3.2. Clinical correlation between ATAbs (+) and ATAbs (−) anti-NMDAR encephalitis patients

As shown in Table 3, patients with anti-NMDAR encephalitis were divided into two groups based on the status of serum TPO/TG antibody. There was no difference in gender ratio, age, CSF abnormalities and number of patients with an mRS decline of 3 or more after immunotherapy between ATAbs (+) and ATAbs (−) patients. As for the clinical presentation at onset, the TPOAb (+) and TGAb (+) groups had higher percentages of patients with epileptic seizures ($p = 0.006$ and $p = 0.021$, respectively) and conscious disturbance ($p = 0.013$ and $p = 0.011$, respectively). And no significant difference was found for behavioral and psychiatric disturbances and short-term memory deficits. The modified Rankin Scale (mRS) scores of TPOAb (+) and TGAb (+) groups were significantly higher when compared with TPOAb (−) and TGAb (−) groups both at day one ($p = 0.002$ and $p = 0.025$, respectively) and at discharge (both $p < 0.001$).

3.3. MRI findings between ATAbs (+) and ATAbs (−) patients with anti-NMDAR encephalitis

In the current study, 24 of the 42 patients with anti-NMDAR encephalitis presented brain lesions on MRI scans while the other

Table 2
Thyroid parameters in patients with anti-NMDAR encephalitis and healthy controls.

	Anti-NMDAR encephalitis (N = 42)	HC (N = 121)	P
ATAbs (+), n (%)	22 (52.4)	9 (7.4)	<0.001
TPOAb (+), (n%)	22 (52.4)	6 (5.0)	<0.001
TGAb (+), n (%)	16 (38.1)	7 (5.8)	<0.001
FT3 (pmol/l)	4.98 ± 1.19	4.27 ± 1.12	<0.001
FT4 (pmol/l)	17.92 ± 3.30	17.99 ± 3.51	0.904
TSH (uIU/ml)	1.73 ± 1.86	1.53 ± 0.92	0.73

NMDAR, N-methyl-d-aspartate receptor; HC, healthy control; ATAbs, anti-thyroid antibodies; TPOAb, anti-thyroid peroxidase antibodies; TGAb, anti-thyroglobulin antibodies; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyrotropin.

Table 1
Baseline characteristics of anti-NMDAR encephalitis patients and healthy controls.

Characteristics	Anti-NMDAR encephalitis	HC	P
	N = 42	N = 121	
F/M	22/20	59/62	0.686
Age (mean ± SD, years)	27.38 ± 12.46	30.51 ± 13.82	0.235
Patients with ovarian teratoma, n (%)	8 (19.0)	–	–
Patients without ovarian teratoma, n (%)	34 (81.0)	–	–
Clinical presentation at onset			–
Epileptic seizures, n (%)	22 (52.4)	–	–
Behavioral and psychiatric disturbances, n (%)	32 (76.2)	–	–
Conscious disturbance, n (%)	21 (50.0)	–	–
Short-term memory deficits, n (%)	10 (23.8)	–	–
Hashimoto thyroiditis	0	0	–
Patients with brain lesions on MRI, n (%)	24 (57.1)	–	–

NMDAR, N-methyl-d-aspartate receptor; HC, healthy control; F, female; M, male; SD, Standard Deviation; MRI, magnetic resonance imaging.

Table 3
Comparison of clinical features in patients with anti-NMDAR encephalitis based on anti-thyroid antibody status.

	TPOAb (+)	TPOAb (−)	P	TGAb (+)	TGAb (−)	P
	N = 22	N = 20		N = 16	N = 26	
F/M	14/8	8/12	0.126	11/5	11/15	0.096
Age (mean ± SD, years)	26.05 ± 11.40	28.85 ± 13.68	0.473	25.69 ± 11.38	28.42 ± 13.19	0.496
Clinical presentation at onset						
Epileptic seizures, n (%)	16 (72.7)	6 (30.0)	0.006	12 (75.0)	10 (38.5)	0.021
Behavioural and psychiatric disturbances, n (%)	16 (72.7)	16 (80.0)	0.849	13 (81.3)	19 (73.1)	0.817
Conscious disturbance, n (%)	15 (68.2)	6 (30.0)	0.013	12 (75.0)	9 (34.6)	0.011
Short-term memory deficits, n (%)	6 (27.3)	4 (20.0)	0.849	3 (18.8)	7 (26.9)	0.817
CSF abnormalities, n (%)	13 (59.1)	13 (65.0)	0.694	9 (56.3)	17 (65.4)	0.554
mRS score at day one (median, range)	4 (1,5)	3 (2,4)	0.002	4 (1,5)	3 (2,5)	0.025
mRS score at discharge (median, range)	3 (0,5)	1 (0,2)	<0.001	3 (1,5)	1 (0,4)	<0.001
Patients with an mRS decline≥3 after immunotherapy	4 (18.2)	9 (45.0)	0.06	3 (18.8)	10 (38.5)	0.318

NMDAR, N-methyl-d-aspartate receptor; TPOAb, anti-thyroid peroxidase antibodies; TGAb, anti-thyroglobulin antibodies; F, female; M, male; CSF, cerebrospinal fluid; mRS, modified Rankin Scale.

Table 4
MRI features between anti-NMDAR encephalitis with and without TPO/TG antibody positive.

	TPOAb (+)	TPOAb (−)	P	TGAb (+)	TGAb (−)	P
	N = 22	N = 20		N = 16	N = 26	
Brain lesions, n (%)	17 (77.3)	7 (35.0)	0.006	12 (75.0)	12 (46.2)	0.067
Limbic system, n (%)	8 (36.4)	1 (5.0)	0.036	4 (25.0)	5 (19.2)	0.956
Hippocampi, n (%)	2 (9.1)	1 (5.0)	1.000	1 (6.3)	2 (7.7)	1.000
Parahippocampal gyrus, n (%)	0	1 (5.0)	0.476	0	1 (3.8)	1.000
Uncinate gyrus, n (%)	0	1 (5.0)	0.476	0	1 (3.8)	1.000
Callosum, n (%)	2 (9.1)	2 (10.0)	1.000	3 (18.8)	1 (3.8)	0.291
Callosal convolution, n (%)	2 (9.1)	0	0.489	0	2 (7.7)	0.571
Thalami, n (%)	2 (9.1)	1 (5.0)	1.000	3 (18.8)	0	0.094
Insula, n (%)	4 (18.2)	2 (10.0)	0.753	3 (18.8)	3 (11.5)	0.846
Frontal orbital gyrus, n (%)	2 (9.1)	1 (5.0)	1.000	2 (12.5)	1 (3.8)	0.659
Brain lobes, n (%)	10 (45.5)	5 (25.0)	0.167	7 (43.8)	8 (30.8)	0.394
Basal ganglia, n (%)	2 (9.1)	1 (5.0)	1.000	2 (12.5)	1 (3.8)	0.659
Brainstem, n (%)	3 (13.6)	2 (10.0)	1.000	3 (18.8)	2 (7.7)	0.559
Cerebellum, n (%)	2 (9.1)	1 (5.0)	1.000	2 (12.5)	1 (3.8)	0.659

MRI, magnetic resonance imaging; NMDAR, N-methyl-d-aspartate receptor; TPOAb, anti-thyroid peroxidase antibodies; TGAb, anti-thyroglobulin antibodies.

did not. As shown in Table 4, anti-NMDAR encephalitis patients with TPO antibody positive had higher brain abnormalities than TPO antibody negative group (P = 0.006). Limbic system lesions were more frequently observed in the TPO antibody positive group than those in TPO antibody negative group (P = 0.036), but we didn't find any significant differences for the specific locations of limbic system lesions between these two groups. There was no statistical difference for other brain MRI features between TPO/TG antibody positive group and TPO/TG antibody negative group.

3.4. Comparison of thyroid parameters in anti-NMDAR positive female patients with and without teratomas

Among the anti-NMDAR positive 22 female patients, 8 patients had ovarian teratoma and 14 patients were non-tumor associated. Comparison of thyroid parameters between these two groups was presented in Table 5. And we found anti-NMDAR positive female patients with ovarian teratomas had lower level of TSH than that without ovarian teratomas (P = 0.017).

4. Discussion

In this present study, we found higher frequencies of abnormal TPOAb, TGAb and higher levels of FT3 in patients with anti-NMDAR encephalitis than those in control group. The presence of ATAbs in anti-NMDAR encephalitis was reported in recent years (Guan et al., 2015; Xu et al., 2011; Tuzun et al., 2011). Researchers in Turkey found that 33.3% of limbic encephalitis patients had abnormal anti-

Table 5
Comparison of thyroid parameters in NMDAR-Ab positive female patients with and without teratomas.

	NMDAR-Ab (+) patients with teratomas	NMDAR-Ab (+) patients without teratomas	P
	N = 8	N = 14	
Mean age (mean ± SD, years)	25.38 ± 4.34	26.58 ± 12.08	0.615
TPOAb (+), n (%)	5 (62.5)	10 (71.4)	1.000
TGAb (+), n (%)	4 (50.0)	8 (57.1)	1.000
FT3 (pmol/l)	3.74 ± 0.67	4.31 ± 0.72	0.09
FT4 (pmol/l)	17.27 ± 3.33	17.19 ± 2.57	0.954
TSH (uIU/ml)	0.69 ± 0.48	2.23 ± 2.81	0.017

NMDAR-Ab, N-methyl-d-aspartate receptor antibody; SD, Standard Deviation; TPOAb, anti-thyroid peroxidase antibodies; TGAb, anti-thyroglobulin antibodies; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyrotropin.

thyroid antibodies as opposed to 10%–15% of the general population (Tuzun et al., 2011). While we found that 52.4% of patients with anti-NMDAR encephalitis had ATAbs as opposed to 7.4% of healthy controls. TPO and TG are two main autoantigens which are responsible for the autoimmune disease (Dawe et al., 1993). Previous studies have demonstrated that TPO and TG have several antigenic binding sites (Henry et al., 1990; Arscott et al., 1996). Epitope mapping of TG has identified seven antigenic regions. The first antigenicsite, aminoacids 84–149 of TG have a VDAEG motif, which can cross-react with an immunodominant peptide 143–168 of myelin basic protein (Sakuma et al., 1999; Ota et al., 1990). So there might be a molecular mimicry between a myelin epitope and a thyroglobulin epitope. ATAbs have immunemodulatory effects and they may form immune complexes to myelin basic protein (Sakuma et al., 1999), thus could cause cerebral injuries. Gini et al. found that anti-TG IgG, isolated from the CSF of HE patients, localised to both neurones and vascular tissue in HE patients (Gini et al., 2008). In another study conducted by Moodley et al. anti-TG IgG was demonstrated in smooth muscle cells of the tunica media in blood vessels in all brain regions examined (Moodley et al., 2011). However, the correlation of anti-thyroid antibodies and anti-NMDAR encephalitis has yet to be determined. Previous study reported a higher incidence of thyroid dysfunction in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis (Jara et al., 2017). And Moodley et al. demonstrated TSH receptors on endothelial cells of blood vessels in the cingulate gyrus (Moodley et al., 2011). Furthermore, elevated FT3 was found in patients with anti-NMDAR encephalitis, indicating that FT3 might play a role in the nosogenesis of anti-NMDAR encephalitis. But the mechanism remains to be determined.

This study also focused on the characteristics of anti-NMDAR encephalitis patients with ATAbs abnormalities. Epileptic seizures and conscious disturbance are typical severe syndromes of anti-NMDAR encephalitis (Leypoldt, 2013). In our study, more than one half of anti-NMDAR encephalitis patients had epileptic seizures. And a study conducted by Dubey et al. showed that autoimmune epilepsy is not uncommon (Dubey et al., 2017), which is consistent with our result. Interestingly, the mRS score in ATAbs (+) anti-NMDAR encephalitis patients was significantly higher when compared to that in ATAbs (−) group. NMOSD is another autoimmune disease in central nervous system, the severity of which was also proved to be related with ATAbs (Wang et al., 2016; Li et al., 2015). It was speculated that the elevated levels of anti-thyroid antibodies may cause immune dysfunction in the brain by interacting with antibodies against neuronal surface antigens. And this may cause more aggressive immune responses which would have a detrimental effect on neurons. These immune dysregulations might cause more severe symptoms such as epileptic seizures and conscious disturbance which result in higher mRS score. However, the exact pathological mechanisms of anti-NMDAR encephalitis remain unknown.

We compared MRI features between anti-NMDAR encephalitis with and without TPO/TG abnormalities. We found higher brain lesions in TPO antibody positive group than those in TPO antibody negative group. Previous study reported higher frequencies of brain MRI abnormalities in TPO/TG antibody positive NMOSD patients than those in TPO/TG antibody negative NMOSD patients (Wang et al., 2016). And Garg et al. found larger T2 lesion volume in ATAbs (+) group than that in ATAbs (−) group inpatients with multiple sclerosis (Garg et al., 2007). These two studies indicated that ATAbs (+) might play an important role in cerebral injury of autoimmune diseases such as multiple sclerosis and neuromyelitis optica. Immunologic derangement could induce the synthesis of anti-thyroid antibodies. So we speculate that anti-NMDAR encephalitis patients with ATAbs abnormalities might have more hyperactive immune response, which results in more brain lesions. Naicker et al. reported expression of TG in limbic regions in the adult human brain (Naicker and Naidoo, 2017). So ATAbs could attack brain tissue in this region, though our results showed that anti-NMDAR encephalitis patients with TPO antibody positive rather than TG antibody positive had higher limbic system abnormalities, which are typical lesions of anti-NMDAR encephalitis.

Previous literature indicated that an ovarian tumor could not be found in approximately 40–80% of adult patients with anti-NMDAR encephalitis (Dalmau et al., 2008; Florance et al., 2009; Niehusmann et al., 2009), which was consistent with our finding (81.0%). Elevated anti-thyroid antibodies were found in both tumor and non-tumor associated anti-NMDA receptor encephalitis (Guan et al., 2015; Xu et al., 2011; Tuzun et al., 2011). Interestingly, we found lower level of TSH in anti-NMDAR positive female patients with teratomas when compared to those without teratomas instead of the difference of anti-thyroid antibodies. Presence of teratomas is one of immunological triggers of anti-NMDAR encephalitis. Patients with a teratoma develop more robust immune responses than those without a tumour (Dalmau et al., 2008). Previous studies reported the presence of TSH receptors in teratomas (Anastasilakis et al., 2013; Teale et al., 2006). Thus TSH receptor stimulating antibodies might exist in anti-NMDAR positive patients and then increase thyroid hormone production, which in result suppress the production of TSH in a negative feedback way.

Anti-NMDAR encephalitis is often manifested by behavioral changes, epileptic seizures and conscious disturbance which are similar to the symptoms of hashimoto encephalopathy (HE) (Zhou et al., 2017). And our study found high prevalence of ATAbs in anti-NMDAR encephalitis. So when a patient is suspect of having HE, antibodies against NMDAR should be tested to make a differential diagnosis.

5. Limitations and conclusions

There are some limitations in this study: (a) the patient sample size was small (42 patients), suggesting that our results may not accurately represent anti-NMDAR encephalitis; (b) because we only enrolled patients with anti-NMDAR encephalitis, our conclusions may not be applied to AIE patients with other antibodies or seronegative AIE; (c) bias is inevitable in retrospective studies.

In summary, this study confirmes that ATAbs abnormalities are frequent in patients with anti-NMDAR encephalitis. ATAbs seropositive anti-NMDAR encephalitis patients had a higher mRS score, higher prevalences of epileptic seizures and conscious disturbance and more brain lesions, suggesting that ATAbs may be associated with illness severity and brain abnormalities, but the mechanism remains unclear. We also found a lower level of TSH in anti-NMDAR positive patients with ovarian teratomas, though the exact relation between TSH and tumor-associated anti-NMDAR encephalitis need further study.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuint.2017.11.019.

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