Original Article

Autoimmune Antibody in Encephalopathic Patients: A Pilot Study

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Objective: To investigate the specificity of the antibodies related to autoimmune encephalitis and to identify possible associated factors with the false-positive result.

Materials and Methods: The present study was a prospective observational study, conducted at the Ramathibodi Hospital between June and December 2019. All patients, who had acute to subacute encephalopathy from any causes, were recruited to the study. Their serum or cerebrospinal fluid (CSF) were taken to analyze for autoimmune encephalitis assays and anti-thyroid antibodies. The authors did not interfere with the primary physicians on any management of the patients. Clinical and laboratory data were systematically reviewed and collected from medical records. The clinical outcome was evaluated one month after the onset.

Results: Fifty-one patients were recruited. Only one patient had autoimmune encephalitis related to anti-CV2/CRMP5 antibody. Seventeen out of the remaining fifty patients had positive tests for anti-thyroid antibodies of which five had Hashimoto's thyroiditis and one of them did not have the document of thyroid status. Eleven remaining patients appeared to have false-positive test since their medical conditions were all clearly explained by other causes. Comparison of clinical and laboratory data between patients with false-positive test and patients with true negative test did not show any significant difference except the duration of the symptoms, which was significantly shorter in the false-positive group.

Conclusion: False-positive anti-thyroid antibodies appear to be common in patients with acute encephalopathy. The occurrence of serum/CSF antibody in acute encephalopathy may be a true association, but it may not be the cause of encephalopathy. Therefore, the diagnosis of autoimmune encephalopathy based on anti-thyroid antibodies should be carefully made and excluded from all other possible causes.

Keywords: Autoimmune encephalitis; Metabolic encephalopathy; Hashimoto's encephalopathy; False positive

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During the past ten years, many novel antibodies associated with autoimmune encephalitis were described leading to an increase in awareness of the condition[1]. To date, diagnosis and treatment remained challenging. Delay in the treatment often results in an unfavorable outcome, thus early diagnosis based on clinical presentations and simple laboratory data without known antibodies status becomes crucial. Serum or cerebrospinal fluid (CSF) antibodies are usually used as a confirmatory diagnostic test, however, their sensitivities maybe not be great, sometimes being less than 50%[2,3].

The initial clinical features of different types of autoimmune encephalitis may be overlapped including seizures, movement disorders, psychiatric, and cognitive alterations[4]. Combinations of headache, fever, and CSF pleocytosis may also mislead the primary physicians to start antiviral or antibiotic treatment. Psychiatric symptoms can also resemble psychiatric illness leading to the delay in treatment[5,6]. Due to non-specific symptoms of the condition, other differential diagnosis of encephalopathies including metabolic or endocrine encephalopathies, psychiatric disorders, or rheumatic diseases are required to be excluded before giving a definite diagnosis[7]. Positive results of the serum or CSF antibodies will later confirm the diagnosis of autoimmune encephalitis.

Regarding the authors' clinical experience, a few patients who suffered from non-autoimmune encephalopathy occasionally had a positive test of autoimmune encephalitis antibodies, paraneoplastic antibodies, anti-thyroid antibodies, and antinuclear

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antibody (ANA). Moreover, positive antibodies may occur as a cause of encephalopathy or a response to a specific antigen from damaged tissue caused by the primary disease. Recently, a few studies described the presence of autoimmune encephalitis antibodies in various neurological disorders other than autoimmune encephalitis and healthy individuals[8,9]. Therefore, using the positive results of serum or CSF antibodies as the gold standard for diagnosis of autoimmune encephalitis may not be wised. A prior study showed the false positive for antibody-related to autoimmune neurological disorders might be as high as 71% if testing unintentionally[10]. Anti-thyroid antibodies are also detected in various condition including encephalopathy, which is known as Hashimoto's encephalopathy. The unclear correlation between the presence of antibodies and clinical may mislead physician to inappropriate treatment. Therefore, this study aimed to identify the occurrence of antibodies commonly related to autoimmune encephalitis, which are autoimmune and paraneoplastic antibodies, anti-thyroglobulin (TG), anti-thyroid peroxidase (TPO), and ANA in encephalopathic patients. Factors associated with the false-positive test were also be investigated.

Materials and Methods

Ethical approval

The present study was approved by the Research Ethics Committee of the Ramathibodi Hospital, Mahidol University (COA No. MURA2019/407). All patients were informed with verbal and written consent.

Study design and population

The present study was a prospective observational study. The study enrolled patients admitted at the Ramathibodi Hospital either in the internal medicine department or were consulted from other departments between June and December 2019. The inclusion criteria were patients age more than 18 years old and had clinical encephalopathy. The encephalopathy was defined by clinical criteria for diagnosis of autoimmune encephalitis, which is subacute onset or rapid progression of fewer than three months of either working memory deficits, short-term memory loss, altered mental status, personality change, or psychiatric symptoms[2]. Criteria for diagnosis of definite autoimmune encephalitis and Hashimoto's encephalopathy from the recent systematic review were applied to patients[1]. Patients who had a duration of symptoms greater than three months and those who denied informed consent were excluded from the study[1].

Antibodies testing

All available blood or CSF samples were collected. All samples were tested for a panel of the autoimmune encephalitis including antibodies to NMDAR, LGI1, CASPR2, AMPA, DPPX, GABAB, ANNA1, ANNA2, ANNA3, PCA1, PCA2, PCA3, PCATr, GAD, CV2/CRMP5, Amphiphysin, and IgLON5. All the assays were carried out at the Prasart Neurological Institute by Apiwattanakul M who was unaware of all clinical data. Each sample was tested by both immunohistochemistry assay (IHA) and cell-based assay (CBA). IHA was done in all samples as the first step test and detected fluorescence-conjugated antibodies to human IgG. The specific staining patterns noticed at hippocampus, forebrain, or cerebellum were considered positive. Positive samples were further tested in the second step by CBA, which was done with human embryonic kidney 293 that transfected with NR1 subunit of NMDAR, AMPAR1/2 subunit, DPPX, GABAB receptor, LGI1 or CASPR2 receptor, and IgLON5 subunit. Positive staining for at least five fields microscope were considered positive. Antibodies to GAD, CV2/CRMP5, Amphiphysin, ANNA, and PCA were tested by Western blot as the second step. All samples that yielded positive results by IHA but subsequently got negative results by CBA, would be reported as an unclassified neuronal specific antibody (UNCA). UNCA might imply other antibodies that could not be confirmed by currently available commercial kits such as anti-GABAA or anti-Glycine. Autoimmune encephalitis assays were sometimes tested in Ramathibodi Hospital based on the primary physician. These assays were carried out with the Autoimmune Encephalitis Mosaic kit and the EUROLINE Paraneoplastic neurologic syndrome 12 Ag from EUROIMMUN (Luebeck). Results from the Ramathibodi Hospital were also used for analysis in the present study. Anti-TPO, anti-TG, ANA, and erythrocyte sedimentation rate (ESR) were routinely tested. Other systemic autoimmune antibodies would not be tested in the present study due to less clinically relevance to encephalopathic condition.

Data collection

Demographic, clinical, laboratory characteristic, details of treatment, final diagnosis, and cause of encephalopathy were carefully obtained from the medical records by the authors (Charoensri

A). Electroencephalogram results were reported by epileptologist. Magnetic resonance imaging (MRI) finding reported from radiologist were defined as abnormalities when it was compatible with autoimmune encephalitis criteria[1]. Etiologies of encephalopathy were categorized into four categories as a) autoimmune encephalitis in patients who were compatible with criteria of definite autoimmune encephalitis or antibody-negative possible autoimmune encephalitis, b) infection of central nervous system (CNS), c) metabolic encephalopathy that included patients with uremic and hepatic encephalopathy, severe hypo-hyper-natremia, hypercalcemia, endocrine disorders, hypertensive encephalopathy, hypoxic ischemic encephalopathy, or toxic and drug induced encephalopathy, and d) other causes. Outcome of treatment were reviewed from the medical records up to one months after admission.

Outcome measurement

All patients who fulfilled the clinical criteria for diagnosis of autoimmune encephalitis[1] including Hashimoto's encephalopathy were excluded from the analysis. The remaining patients would be defined as non-autoimmune encephalopathy and were divided into antibody false-positive and true-negative group. Antibody-positive group was defined as patients with a positive result of one of the anti-thyroid antibodies or autoimmune encephalitis assays. False positive was defined as patients in the antibody-positive group who were identified as primary non-autoimmune cause of encephalopathy. False positive antibodies detection among encephalopathic patients were recorded as primary outcome of the study. While true negative was defined as patients whose encephalopathic causes were undoubtful. Comparison of clinical characteristic, investigation data, etiology, and outcome between false-positive group and true-negative group were analyzed as secondary outcome.

Statistical analysis

Occurrence of false positive antibodies and demographic data of all patients were analyzed using descriptive analysis. Chi-square or Fisher's exact test were used to analyze the comparison of categorical data between false-positive group and true-negative group. Age and duration of symptom were reported by mean ± standard deviation (SD) and median (interquartile range [IQR]) respectively. Comparisons of age and duration between the groups were analyzed using Student t-test and Mann-Whitney U test, respectively. All statistical analyses were performed using Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA). A p-value of less than 0.05 was considered as statistically significant.

Results

Fifty-one patients with encephalopathy were identified during the study period. Two patients had positive tests for autoimmune encephalitis assays. The first patient with anti-CV2/CRMP5 was clinically fulfilled to the diagnostic criteria of autoimmune encephalitis. The second patient was defined as UNCA, which the positive test was observed in only the first step. However, the patient suffered from hepatic encephalopathy. Clinical and laboratory data of all studied patients, after excluded the patient with definite autoimmune encephalitis, are summarized in Table 1. Mean age was 68.4 years. The most common symptom was altered mental status. Concurrent infection was found in 27 patients, which seven of them were CNS infection. Abnormal thyroid function was found in 28 patients; however, their primary disease was mostly non-thyroidal illness. Twenty-eight patients underwent lumbar puncture in which three-quarter of them had elevated CSF protein. Anti-TPO and anti-TG were identified in 15 and 11 patients, respectively. Cause of encephalopathies of all studied patients are summarized in Table 2.

Regarding patients with non-autoimmune encephalopathies, 17 out of 50 remaining had positive tests for anti-TPO or anti-TG. None of the patients had positive test for the other studied antibodies. Five patients were subsequently shown to have Hashimoto's thyroiditis and one patient had no data of thyroid function. Eleven remaining patients were classified in the false-positive group. Thus, the frequency of the false positive rate from the study was 22.0%. The clinical details of all 17 anti-thyroid antibody-positive patients are described in Table 3.

In the antibody-negative group, 31 of 33 patients were classified in the true negative. The two remaining patients were unable to determine the cause of encephalopathy although they were under carefully comprehensive investigations. Although characteristics were not compatible with the diagnostic criteria of antibody-negative autoimmune encephalitis, clinical improvements after the treatment of intravenous methylprednisolone were observed. Therefore, they were not included in comparison analysis. Study flow chart is shown in Figure 1. Comparisons of clinical characteristics between false-positive and true-negative group are shown in Table 4.

Duration from the onset to first presentation at

Table 1. Clinical characteristics and laboratory data of non-autoimmune encephalopathic patients (n=50)

Characteristics	n (%)
Female	27 (54.0)
Age (years); mean±SD	68.4±14.5
Clinical presentation	
Altered mental status	40 (80.0)
Behavioral change	8 (16.0)
Cognitive impairment	2 (4.0)
Duration (days); median (IQR)	2 (1, 14)
Clinical characteristics	
Altered mental status	38 (76.0)
Psychiatric symptom	8 (16.0)
Language impairment	7 (14.0)
Memory impairment	4 (8.0)
Seizure	12 (24.0)
Fever	24 (48.0)
Coexisting conditions	
Cancer	14 (28.0)
Chronic kidney disease	13 (26.0)
Cirrhosis	8 (16.0)
Systemic autoimmune disease	11 (22.0)
Current infection	27 (54.0)
Investigations	
Abnormal thyroid function (n=40)	28 (70.0)
Elevated ESR	41 (82.0)
ANA positive	17 (34.0)
CSF analysis (n=28)	
• CSF protein elevated	21 (75.0)
• CSF pleocytosis	13 (46.4)
EEG abnormalities (n=29)	26 (89.7)
Antibodies status	
Anti-TPO positive	14 (28.0)
Anti-TG positive	10 (20.0)
Autoimmune encephalitis assays positive	1 (2.0)

ESR=erythrocyte sedimentation rate; ANA=antinuclear antibody; CSF=cerebrospinal fluid; EEG=electroencephalogram; TPO=thyroid peroxidase; TG=thyroglobulin; SD=standard deviation; IQR=interquartile range

Table 2. Etiologies of encephalopathy of non-autoimmune encephalopathic patients (n=50)

Etiologies	n (%)
CNS infection	7 (14.0)
Metabolic encephalopathy	29 (58.0)
Uremic encephalopathy	8 (16.0)
Hepatic encephalopathy	4 (8.0)
Endocrine and electrolyte abnormalities	3 (6.0)
Hypoxic encephalopathy	1 (2.0)
Septic encephalopathy	7 (14.0)
Toxic encephalopathy	4 (8.0)
Hypertensive encephalopathy	2 (4.0)
Others	14 (28.0)
Creutzfeldt-Jakob disease	3 (6.0)
Brain metastasis	2 (4.0)
Ischemic stroke	1 (2.0)
NCSE from remote epilepsy	2 (4.0)
Psychosis	2 (4.0)
Delirium	2 (4.0)
Unknown*	2 (4.0)

CNS=central nervous system; NCSE=nonconvulsive status epilepticus

* Possible autoimmune etiology which incompatible with diagnostic criteria but showed response to treatment with immunotherapy

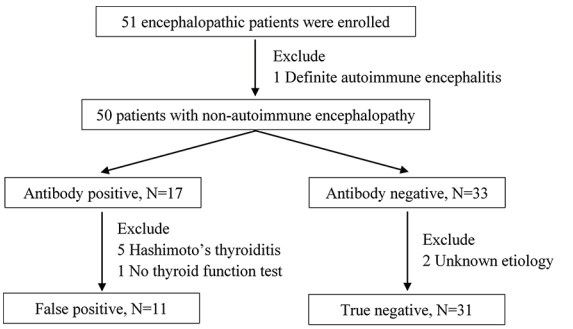

Figure 1. Study diagram.

the emergency room was significantly shorter in the false-positive group than the true-negative group (p=0.029). There was no significant difference in other clinical characteristics including age, liver and renal status, preexisting cancer, and concurrent infection. However, patients in false-positive group tended to have preexisting systemic autoimmune disease including inflammatory myositis, adult-onset still disease, myasthenia gravis, immune thrombocytopenic purpura, and Sjögren syndrome. Analysis of laboratory data, detail of treatment, etiology, and outcome also showed no significant difference. However, patients with severely impaired renal function with a GFR of 15 or less, or receiving renal replacement therapy, tended to have an association with false positive antibodies but it did not reach statistical significance (p=0.120).

Regarding the false-positive group, four patients were dead, in which three patients from systemic infection and one from decompensated cirrhosis. Regarding true-negative group, six patients were

Table 3. Characteristics of non-autoimmune encephalopathic patients with anti-thyroid antibodies positive

No.	Sex	Age (year)	AIE Ab	Anti-TPO (IU/ml)	Anti-TG (IU/ml)	Thyroid function interpretation	Hashimoto's thyroiditis	Diagnosis	Treatment	Outcome
1	F	50	-	– (1.1)	+ (384.0)	Normal	No	Brief psychotic disorder	Antipsychotic drug	Improved
2	M	77	-	+ (17.6)	+ (2,166.0)	Nonthyroidal illness	No	PRES	Antihypertensive	Improved
3	F	88	-	+ (26.4)	– (<10.0)	2°hypothyroid	No	Uremic encephalopathy	Hemodialysis	Improved
4	M	88	-	– (3.6)	+ (116.0)	Normal	No	Symptomatic hyponatremia	Isotonic saline	Improved
5	M	44	-	+ (6.0)	+ (155.0)	No thyroid function test done	No	Chikungunya encephalitis	Supportive	Improved
6	F	67	-	+ (64.9)	– (29.9)	Nonthyroidal illness	No	Uremic encephalopathy	Supportive	Dead
7	F	60	-	+ (10.4)	– (16.8)	Nonthyroidal illness	No	Bacterial meningoencephalitis	Antibiotic	Dead
8	F	71	-	– (2.5)	+ (848.0)	Nonthyroidal illness	No	Acyclovir induced encephalopathy	Supportive	Improved
9	M	63	-	+ (98.4)	+ (390.0)	Normal thyroid function was reported prior and post studied period, no thyroid medication used*	No	Hypoxic ischemic encephalopathy	Supportive	Improved
10	F	71	-	+ (30.0)	– (93.0)	Nonthyroidal illness	No	Septic encephalopathy with NCSE	Antiepileptic drugs, antibiotic	Improved
11	F	69	UNCA	+ (17.8)	+ (1352.0)	Nonthyroidal illness	No	Hepatic encephalopathy, HCV cirrhosis	Lactulose	Dead
12	F	85	-	+ (74.4)	– (<10)	Nonthyroidal illness	No	Bacterial meningoencephalitis	Antibiotic	Dead
13	F	60	-	+ (2,087.0)	– (0.3)	1°Hypothyroid	Yes	Viral encephalitis, mycobacterium brain abscess	Antibiotic	Improved
14	M	65	-	+ (>1,000)	+ (779.0)	1°Hypothyroid	Yes	PRES	Antihypertensive	Improved
15	F	63	-	+ (29.1)	– (<10)	1°Hypothyroid	Yes	Breast cancer with brain metastasis	Supportive	Dead
16	M	78	-	+ (97.9)	+ (>4,000)	1°Hypothyroid	Yes	Septic encephalopathy	Antibiotic	Improved
17	F	76	-	+ (>1,000)	+ (>4,000)	Nonthyroidal illness	Yes**	Bacterial meningoencephalitis	Antibiotic	Dead

AIE Ab=autoimmune encephalitis antibodies; F=female; M=male; UNCA=unclassified neuronal specific antibody; HCV=hepatitis C virus; PRES=posterior reversible encephalopathy syndrome; NCSE=nonconvulsive status epilepticus

* The patient assumed to had normal thyroid function, ** Diagnosis of Hashimoto's thyroiditis was made by endocrinologist prior to the study

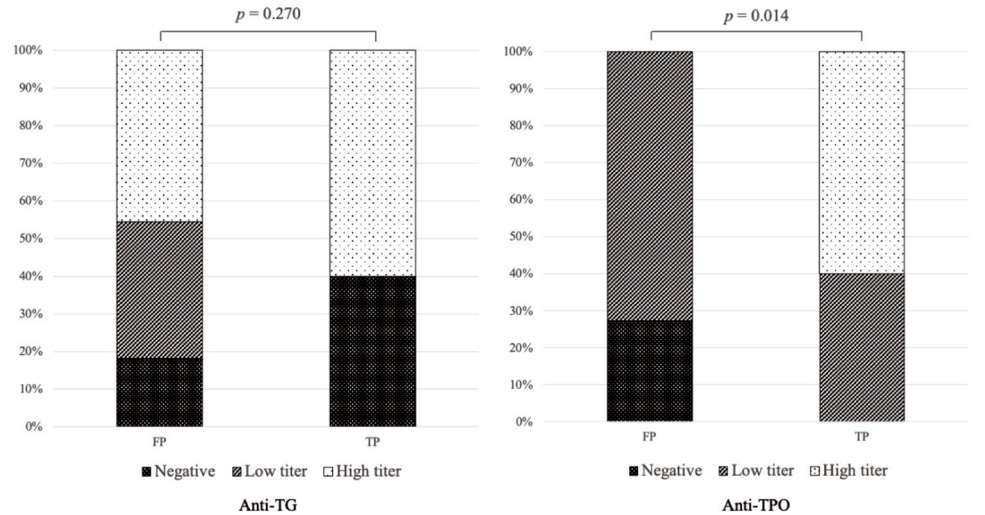

Figure 2. Comparison of levels of anti-thyroid antibodies in patients with anti-thyroid antibodies positive between the false-positive (FP) and true-positive (TP) groups.

Table 4. Comparison between false-positive and true-negative groups

Characteristics	FP; n (%)	TN; n (%)	p-value
Patients	11	31	-
Female	8 (72.7)	15 (48.4)	0.291
Age (years); mean±SD	71.7±12.0	68.2±16.1	0.507*
Duration (days); median (IQR)	1 (1, 3)	3 (1, 14)	0.029**
Clinical characteristics			
Altered mental status	10 (90.9)	22 (70.9)	0.245
Psychiatric symptom	1 (9.1)	7 (22.6)	0.657
Language impairment	1 (9.1)	5 (16.1)	1.000
Memory impairment	1 (9.1)	3 (9.7)	1.000
Seizure	3 (27.3)	7 (22.6)	1.000
Fever	6 (54.6)	13 (41.9)	0.504
Coexisting conditions			
Cancer	2 (18.2)	9 (29.0)	0.696
Chronic kidney disease	5 (45.5)	7 (22.6)	0.243
Cirrhosis	2 (18.2)	5 (16.3)	1.000
Systemic autoimmune diseases	5 (45.5)	5 (16.1)	0.094
Current infection	7 (63.6)	16 (51.6)	0.726
Investigations			
Abnormal thyroid function, n=35	8 (80.0)	15 (60.0)	0.434
Elevated ESR	9 (81.8)	25 (80.7)	1.000
ANA positive	3 (27.3)	10 (32.3)	1.000
CSF analysis, n=21			
• CSF protein elevated	4 (80.0)	11 (68.8)	1.000
• CSF pleocytosis	2 (40.0)	6 (37.5)	1.000
EEG abnormalities, n=24	6 (85.7)	16 (94.1)	0.507
Etiologies			0.186
CNS infection	2 (18.2)	2 (6.5)	
Metabolic encephalopathy	8 (72.7)	19 (61.3)	
Others	1 (9.1)	10 (32.6)	

FP=false-positive group; TN=true-negative group; ESR=erythrocyte sedimentation rate; ANA=antinuclear antibody; EEG=electroencephalogram; CSF=cerebrospinal fluid; CNS=central nervous system; SD=standard deviation; IQR=interquartile range

* Comparison was analyzed by Student t-test, ** Comparison was analyzed by Mann-Whitney U test

dead. Causes of death included systemic infection, lymphoma, Creutzfeldt-Jakob disease (CJD), and uncontrolled status epilepticus.

Further analysis of antibodies level between the patients with Hashimoto's thyroiditis and the patients without any thyroid disease was done. The exact anti-thyroid antibodies levels were masked by the upper limit of the testing kit. Thus, antibodies levels were categorized into three groups as the negative group, the low titer group, and the high titer group. The antibodies level of more than 200 IU/mL, as currently used in the criteria diagnosis of Hashimoto's encephalopathy, was defined as high titer for both anti-TPO and anti-TG. There was a significantly higher anti-TPO titer in the true-positive group than the false-positive group, p=0.014, while no difference detected in the anti-TG titer, p=0.270 (Figure 2).

Discussion

The present study showed a 22.0% false-positive rate of anti-thyroid antibodies in patients with encephalopathy. This finding was slightly higher than the prior published study. Anti-thyroid antibodies are reported in 13% of the normal population[11]. All subclasses of anti-NMDAR including IgA, IgM, and IgG have been reported in 17% of the dementing population, 10% of Alzheimer's disease, and 9% of the healthy population[9]. The higher false positive antibodies might be related to an inflammatory process that stimulated host immune system in both the innate and adaptive immune systems resulting in the production of antibody[12]. In encephalopathic state, inflammatory response is much higher than normal state, which may be one of the causes of an increase in antibodies detection[13]. Furthermore, preexisting autoimmune disorder appeared to be more common in the false-positive group in the study, supporting the role of inflammatory overreaction in the patients with non-autoimmune encephalopathy.

There was no statistically significant correlation between clinical characteristics and the presence of antibodies, except for the duration of symptoms that showed significantly higher false-positive results in more acute onset. The authors reckon that the patients who came to hospital early might have more severe symptom, which reflected more brain damage and inflammation. Thus, there might be a greater chance of antibodies detection during this phase.

The authors found only one false positive case of anti-neuronal antibody in the patient with hepatic encephalopathy. However, the application of this information was limited since the antibody detected was an unclassified pattern. Unlike anti-thyroid antibodies, which showed a greater false positive rate, might reflect the obviously low specificity of identifying etiology in encephalopathic condition.

Regarding to Hashimoto's encephalopathy, which is currently renamed as steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT), the diagnosis of this condition necessarily required the presence of anti-thyroid antibodies and exclusion of other possible conditions. Remarkable

response to steroid is the only strong evidence supporting that the pathogenesis may relate to immune process, whether by anti-thyroid antibodies or not. Moreover, some patients, who were previously diagnosed of SREAT, were subsequently identified to other autoimmune disorders after a long-term follow-up period[14]. Thus, anti-TPO and anti-TG antibodies might not be the true primary pathogenesis of disease, but they might be only the marker of other immunological pathology. These data were also supported by the studied patients who were positive for antineuronal antibodies. They also had non-clinical significant elevation of anti-TPO and anti-TG. However, the high level of anti-thyroid antibodies was more likely to relate to Hashimoto's thyroiditis. Further study is required to evaluate the cutoff point of antibody.

In summary, the study identifies relatively high frequency of false positive test of anti-thyroid antibodies in non-autoimmune encephalopathic patients. These data remind the clinicians to be more cautious in diagnose of Hashimoto's encephalopathy in clinical practice.

Limitation

The number of patients was limited by duration of the study, and it did not reach the appropriate number to have a power analysis. However, the present study was done in the different clinical setting by enrolling all patients admitted during the time of study instead, as a pilot study.

Conclusion

False positive tests for anti-thyroid antibodies appear to be more common in patients with acute non-autoimmune encephalopathy than previously thought. The occurrence of serum or CSF antibodies may associate with acute encephalopathy. However, the association does not imply that the presence of the specific antibodies is always the cause of the condition. Therefore, clinicians should be aware of the existence of the false positive test of the currently known antibodies. Diagnosis of autoimmune encephalopathy should be carefully made, gathering all the important clinical and laboratory data, and excluding all other possible causes.

What is already known on this topic?

The high false positive rate of autoimmune antibodies and anti-thyroid antibodies have been reported in various neurological syndromes and in normal population.

What this study adds?

The false positive antibodies can be found in patient with encephalopathy in the same magnitude as in other conditions. Almost all antibodies found are anti-thyroid antibodies. However, the level of the antibody detected may be related to true pathologic condition.

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Conflicts of interest

The authors declare no conflict of interest.

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