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High prevalence of serum autoantibodies against the amino terminal of α-enolase in Hashimoto's encephalopathy

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Abstract

Recently, we discovered autoantibodies against the amino (NH_2)-terminal of α-enolase (NAE) in patients with Hashimoto's encephalopathy (HE) (83.3%; 5/6) [Fujii, A., Yoneda, M., Ito, T., Yamamura, O., Satomi, S., Higa, H., Kimura, M., Suzuki, M., Yamashita, M., Yuasa, T., Suzuki, H., Kuriyama, M., 2005. Autoantibodies against the amino terminal of α-enolase are a useful diagnostic marker of Hashimoto's encephalopathy. J. Neuroimmunol. 162, 130–136]. We further investigated the anti-NAE autoantibodies in 25 patients who fit the diagnostic criteria for HE, based on the presence of anti-thyroid antibodies and responsiveness to immunotherapy. In this study, we demonstrated a high prevalence (68%, 17 of 25) and high specificity of anti-NAE autoantibodies in patients with HE, and clarified the clinical features of HE. This result demonstrated that anti-NAE autoantibodies, in addition to anti-thyroid autoantibodies, are emphasized as useful serological diagnostic markers of HE.

Keywords: Hashimoto's encephalopathy; Autoantibodies; NAE; Clinical features

1. Introduction

Hashimoto's thyroiditis (HT) is the most common disorder affecting the thyroid gland. In 1966, Brain et al. reported the first case of encephalopathy associated with HT, who presented with recurrent neuropsychiatric symptoms accompanied by serum anti-thyroid antibodies in euthyroid states (Brain et al., 1966). Hashimoto's encephalopathy (HE) therefore was recognized as a nomenclature of new disease, distinct from myxoedema encephalopathy associated with hypothyroidism (Behan et al., 1988; Shaw et al., 1991; Chaudhuri and Behan, 2003; Chong et al., 2003).

Autoimmune mechanism has been proposed as an underlying pathogenesis (Brain et al., 1966; Chaudhuri and Behan, 2003; Chong et al., 2003), and immunotherapy such as steroids, immunosuppressants and/or intravenous injection of immunoglobulin (IVIg)/plasmapheresis was successfully administered (Shaw et al., 1991; Boers and Colebatch, 2001; Chaudhuri and Behan, 2003). Over 100 accumulated cases (Shaw et al., 1991; Chaudhuri and Behan, 2003; Chong et al., 2003) reported mainly by neurologists, emphasized this potentially treatable encephalopathy associated with HT in the differential diagnosis of unknown etiology of encephalopathy, and suggested the risk of under-diagnosis of HE (Ghika-Schmid et al., 1996; Maydell et al., 2002).

Several diagnostic criteria for HE have been proposed based on encephalopathy, the presence of anti-thyroid antibodies and/or responsiveness to immunotherapy including steroids (Shaw et al., 1991; Peschen-Rosin et al., 1999). Endocrinologists however argued against the terminology of HE because of the wide spectrum clinical features in patients with HE and the high prevalence of anti-thyroid antibodies in the normal population, which are usually subclinical (Sawka et al., 2002; Fatourechi, 2005).

To resolve such debates on the nomenclature and nature of HE, more specific diagnostic markers are needed (Chong et al., 2003; Fatourechi, 2005). Very recently, we discovered autoantibodies against the amino (NH_2)-terminal of α-enolase (referred to as NAE) that were highly specific in sera from a limited number of HE patients (83%, 5 of 6 with HE; 11%, 2 of 17 with HT without any neuropsychiatric features; none of controls [50 individuals] including those with other neurological or immunological conditions involving encephalopathy [25 individuals]) (Fujii et al., 2005). Thus, the anti-NAE autoantibodies are a potential tool for the diagnosis of HE and resolving the debate

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over HE described above. We further investigated the prevalence and specificity of anti-NAE autoantibodies, and clarified the clinical features in a large number of patients with HE in this study.

2. Patients and methods

2.1. Patients

In this study, we selected 25 patients with HT, who presented with encephalopathy and fit the diagnostic criteria for HE, based on the presence of anti-thyroid antibodies and responsiveness to immunotherapy such as steroids, immunosuppressants and/or IVIg/plasmapheresis. These 25 patients included our own 8 cases and 17 cases from other institutions. Neurological specialists carefully excluded other possible causes of encephalopathy including infections, other autoimmune conditions, vitamin deficiency, intoxication, cerebrovascular diseases, neoplasms and Creutzfeldt–Jakob disease and so on, and the detailed clinical information of each patient was obtained from the attending physician. The ethics committee of the University of Fukui approved this research, and written permission was obtained from each patient.

The clinical profiles of all patients were summarized in Table 1 and Fig. 1. The sex ratio of patients examined was 7:18 (male:female). The mean age was 60 years old (range: 23 to 83). All patients showed the responsiveness to steroids in variable degrees. We categorized the patients into three clinical forms such as acute encephalopathy (AE)-form, subacute psychiatric (SP)-form and others. AE was the most common clinical form (76%; 19 of 25), SP was much less frequent (16%; 4 of 25), and others were 8% (2 of 25). Four of 25 patients demonstrated recurrence (16%). Five of 25 patients had a history of HT before encephalopathy appeared (20%). All patients carried anti-thyroid antibodies (both of anti-thyroglobulin [Tg] and anti-thyroid peroxidase antibodies [TPO], 48%, 12 of 25; anti-Tg, 32%, 8 of 25; anti-TPO, 20%, 5 of 25). Most of the patients were in euthyroid states (72%, 18 of 25), except for a few patients in mild hypothyroid states treated with thyroxin (16%, 4 of 25) or transient hyperthyroid states (thyrotoxicosis) (12%, 3 of 25). All of the patients showed neuropsychiatric symptoms after recovery from dysthyroid states.

Table 1
Clinical features and anti-NAE autoantibodies in patients with Hashimoto's encephalopathy

Patient	Age/ gender	Clinical form	Anti-thyroid	Immunotherapy (response)	Anti-NAE	Neurological manifestation					Abnormal EEG	Abnormal brain MRI	Elevated CSF/ IgG protein
						C	S	C/P	I	A			
1	44, F	AE	TPO [a]	PSL (excellent)	Positive	+	+	+	Chorea	−	+	−	+
2	34, M	AE	TPO, Tg	mPSL/PSL (excellent)	Positive	+	+	+	−	−	+	−	−
3	71, F	AE [b]	TPO, Tg [a]	mPSL/PSL (excellent)	Positive	+	+	+	−	−	+	−	+
4	45, F	AE	TPO, Tg	mPSL (excellent)	Positive	+	+	−	Tremor	−	*n.d.*	−	−
5	60, F	AE	Tg	PSL (excellent)	Positive	+	−	+	−	−	+	−	+
6	78, F	AE	Tg [c]	PSL (excellent)	Positive	+	+	−	Myoclonus	−	+	−	+
7	32, F	AE (LE)	TPO,Tg	mPSL/PSL (excellent)	Positive	+	+	+	−	−	+	L	−
8	57, F	AE [b]	TPO [a]	PSL (excellent)	Positive	+	+	+	Chorea	+	+	−	−
9	78, F	AE	Tg	PSL (excellent)	Positive	+	−	+	Tremor	−	+	−	+
10	83, F	AE	TPO, Tg	mPSL/PSL (good)	Positive	+	+	−	−	−	+	−	−
11	76, M	AE	TPO, Tg [c]	PSL (good)	Positive	+	+	−	Myoclonus	−	+	−	+
12	79, F	AE	TPO, Tg [c]	PSL (good)	Positive	+	−	+	Chorea	−	+	−	−
13	36, F	AE	Tg	mPSL/PSL (good)	Positive	+	+	+	−	−	+	−	−
14	71, F	AE [b]	Tg	mPSL (fair)	Positive	+	+	+	Myoclonus	−	+	WM	*n.d.*
15	56, M	AE	Tg [d]	mPSL/PSL (good)	Negative	+	+	+	−	−	+	−	+
16	74, M	AE	Tg [d]	mPSL/PSL (good)	Negative	+	+	−	−	−	*n.d.*	−	+
17	69, M	AE (LE)	TPO	mPSL/PSL (good)	Negative	+	+	+	Myoclonus	−	+	L	−
18	58, F	AE (LE)	TPO, Tg [d]	mPSL (good)	Negative	+	+	+	Myoclonus	−	+	L	−
19	61, F	AE (LE)	TPO, Tg [d]	mPSL/PSL (fair)	Negative	+	+	+	−	−	−	L	−
20	69, F	SP	TPO [a]	PSL (good)	Positive	−	−	+	−	−	*n.d.*	−	+
21	60, M	SP	TPO, Tg	PSL (fair)	Positive	−	−	+	−	−	+	−	+
22	69, F	SP	TPO	PSL (fair) IVIg (excellent)	Positive	−	−	+	Myoclonus	−	+	−	*n.d.*
23	61, M	SP	TPO, Tg	PSL (excellent)	Negative	−	−	+	−	+	+	−	+
24	63, F	CJD [b]	Tg [a]	mPSL/DX/azathioprine (excellent)	Negative	+	+	+	Myoclonus	+	+ (PSD)	−	+
25	23, F	IVM	TPO, Tg	PSL (excellent)	Negative	−	−	−	Myoclonus	−	−	−	−

AE, acute encephalopathy form; SP, subacute psychiatric form; LE, limbic encephalopathy-like clinical feature; CJD, Creutzfeldt–Jakob disease-like clinical feature; IVM, involuntary movement dominant-form; TPO, anti-thyroid peroxidase antibodies; Tg, anti-thyroglobulin antibodies; mPSL, methylprednisolone; PSL, prednisolone; DX, dexamethasone; IVIg, intravenous administration of immunoglobulin G; C, consciousness disturbance; S, seizures; C/P, cognitive impairment/psychiatric symptoms; I, involuntary movements: A, ataxia; PSD, periodic synchronized discharge-like paroxysmal discharges; L, limbic lesions; WM, white matter lesions. *n.d.* not determined. Patients 1, 3, 8, 14, 20 and 24 were very briefly reported (Fujii et al., 2005).

[a] Known history of Hashimoto's thyroiditis before the onset of encephalopathy.

[b] Positive history of recurrence.

[c] Transient hyperthyroidism (thyrotoxicosis).

[d] Hypothyroidism treated with thyroxin.

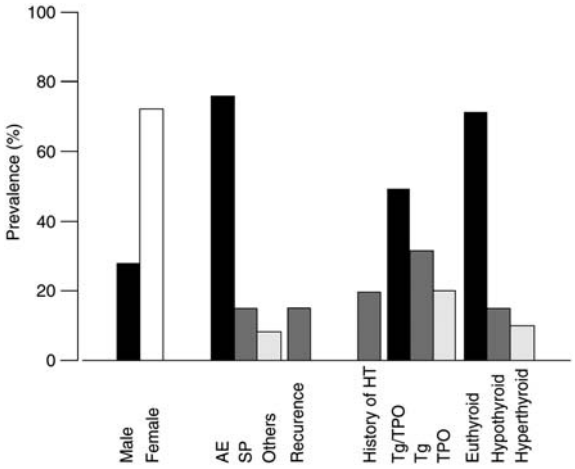

Fig. 1. Clinical profiles of patients. AE, acute encephalopathy form; SP, subacute psychiatric form; HT, Hashimoto's thyroiditis. Tg, anti-thyroglobulin antibodies; TPO, anti-thyroid peroxidase antibodies.

We examined anti-thyroid antibodies (anti-Tg and anti-TPO), steroid-responsiveness, clinical features (consciousness disturbance [C], seizures [S], cognitive impairment/psychiatric symptoms [C/P], involuntary movements [I], ataxia [A]), electroencephalogram [EEG], brain MRI and protein/immunoglobulin G in CSF, and compared these between patients with anti-NAE autoantibodies [referred to as NAE(+)] and without [NAE(−)]. Steroid-responsiveness was evaluated in three degrees: excellent, good, and fair.

2.2. SDS-PAGE and immunoblotting

Anti-NAE autoantibodies were investigated in encephalopathic patients with HT and patients with other disorders including autoimmune conditions or collagen diseases. Immunoblotting analysis of the patient's serum against the NAE expressed in human cultured cells was carried out with 12% sodium lauryl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE) using a gel electrophoresis system (BE-220, BIO CRAFT, Tokyo, Japan), described previously (Fujii et al., 2005). The proteins on the gel were Western-blotted onto polyvinylidene difluoride (PVDF) membrane (Hybond-P, Amersham Biosciences, NJ) with a blotting apparatus (KS-8453, Oriental Instrument, Tokyo, Japan) at 0.3 mA/cm^2 for 8 h at 4 °C. For detection of the band specific to NAE, serum was applied to the membrane and incubated in 1% gelatin for 1 h at room temperature, then horseradish peroxidase (HRP)-conjugated anti-human goat IgG Fc (ICN Pharmateuticals, Inc., OH) was applied to the membrane as the secondary antibody, fluoresced, and developed on X-ray films (BioMax, Kodak, NY).

2.3. Statistical analysis

We used χ^2 test to assess the correlation between patients with encephalopathy with HT and anti-NAE antibodies.

3. Results

3.1. Anti-NAE autoantibodies

The clinical profiles of patients and immunological characters were summarized in Table 1 and Fig. 1. Of the 25 patients with encephalopathy with HT examined here, 68% of them were NAE(+) (17 of 25) ($p<0.001$, compared to patients with HT without encephalopathy [10%, 2 of 20], supplemented by additional data from 3 patients of HT without encephalopathy to our previous study) (Fujii et al., 2005). To our knowledge, there

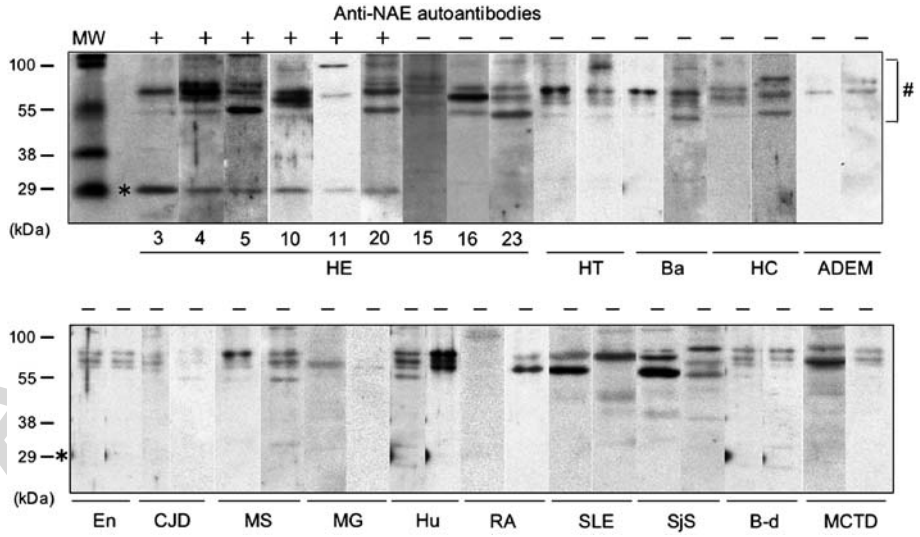

Fig. 2. Immunoblotting of the recombinant NAE with sera from patients with encephalopathy with HT, HT without encephalopathy, Basedow's disease or other neurological disorders including autoimmune conditions, or from controls. HE, Hashimoto's encephalopathy; 3–23, patients 3–23 with HE in Table 1; HT, Hashimoto's thyroiditis without encephalopathy; Ba, Basedow's disease; HC, healthy controls; ADEM, post-infectious acute disseminated encephalomyelitis; En, viral encephalitis; CJD, Creutzfeldt–Jakob disease; MS, multiple sclerosis; MG, myasthenia gravis; Hu, paraneoplastic syndrome associated with Hu-antigen; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SjS, Sjögren syndrome; B-d, Behçet disease; MCTD, mixed connective tissue disease. MW, molecular weight marker. *The position of the recombinant NAE. #Derivatives from human cultured cells for expression, which showed non-specific reactions with sera.

were no sera from 33 patients with 2 Basedow's disease, 4 post-infectious acute disseminated encephalomyelitis (ADEM), 2 viral encephalitis, 2 Creutzfeldt–Jakob disease, other autoimmune disorders or collagen diseases with neurological symptoms, including 4 multiple sclerosis, 4 myasthenia gravis, 2 paraneoplastic neurological syndrome associated with Hu-antigen, 2 rheumatoid arthritis, 3 systemic lupus erythematosus, 3 Sjögren syndrome, 3 Behçet disease, 2 mixed connective tissue disease that showed any immunological reaction to the recombinant NAE (Fig. 2). This confirmed our recent finding that anti-NAE autoantibodies were highly specific to HE.

3.2. Neurological manifestations

The neurological manifestations of patients are summarized in Table 1 and Fig. 3. There is no significant difference in the responsiveness to steroid between NAE(+) (excellent, 9; good, 5; fair 3) and NAE(−) patients (excellent, 3; good, 4; fair 1) but a bit better response in NAE(+) (Table 1 and Fig. 3). Consciousness disturbance appeared most frequently (80%, 20 of 25; 82%, 14 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Seizures were also common (68%, 17 of 25; 64%, 11 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Cognitive impairments/psychiatric symptoms such as memory disturbance, abnormal behaviors or hallucination occurred in 76% (19 of 25; 76%, 13 of 17 in NAE(+), 75%, 6 of 8 in NAE(−)). Involuntary movements including myoclonus/tremor and chorea were also present (52%, 13 of 25) with no difference between NAE(+) (52%; 9 of 17) and NAE(−) (50%; 4 of 8). Ataxia was much less frequent (12%, 3 of 25 in total; 5%, 1 of 17 in NAE(+); 25%, 2 of 8 in NAE(−)).

3.3. Laboratory and MRI findings

The laboratory and MRI findings of patients were summarized in Table 1 and Fig. 4. EEG abnormalities such as slow background activities and/or episodic spikes/slow waves showed very high prevalence (90%, 20 of 22) in patients examined, with

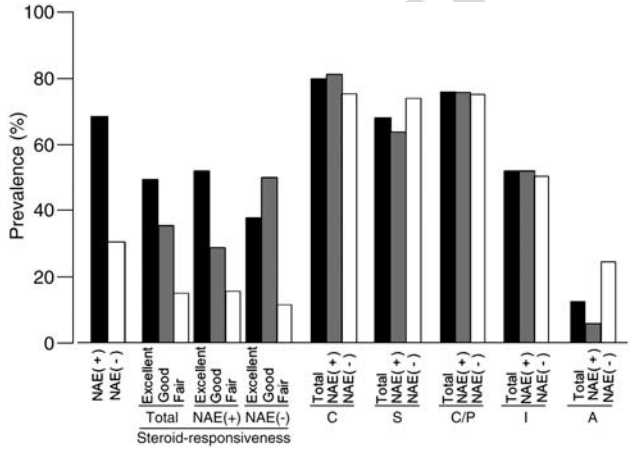

Fig. 3. Neurological manifestations compared between patients with and without anti-NAE autoantibodies. NAE(+), presence of anti-NAE autoantibodies; NAE(−), absence of anti-NAE autoantibodies. C, consciousness disturbance; S, seizures; C/P, cognitive impairment/psychiatric symptoms; I, involuntary movements: A, ataxia.

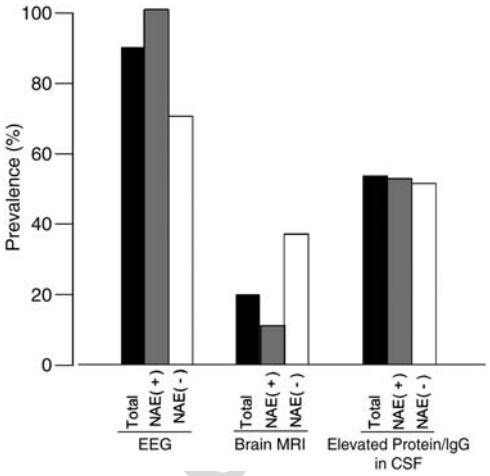

Fig. 4. Laboratory and MRI findings in patients.

a difference between NAE(+) (100%, 15 of 15) and NAE(−) (71%, 5 of 7) ($p<0.05$). By contrast, abnormalities on brain MRI were much less frequent (20%, 5 of 25), with no difference between NAE(+) (11%, 2 of 17) and NAE(−) (37%, 3 of 8). The elevated protein/immunoglobulin G in CSF was present (54%, 12 of 23), with no difference between NAE(+) (53%, 8 of 15) and NAE(−) (50%, 4 of 8).

4. Discussion

After Brain et al. reported the first case of encephalopathy associated with HT, there has been a debate on the nosology and nature on HE, despite the accumulation of over 100 reported cases (Behan et al., 1988; Chaudhuri and Behan, 2003; Chong et al., 2003). It is because of the wide spectrum clinical features in patients with HE, the high prevalence of anti-thyroid antibodies in the normal population (e.g. 5–10% in male, 10–25% in female in Japan), and the lack of specific diagnostic marker. HE patients presented with a variety of clinical features such as acute encephalopathy, psychosis/cognitive impairment, ataxia, recurrent acute disseminated encephalomyelitis (ADEM), involuntary movements (chorea, myoclonus or tremor) and Creutzfeldt–Jakob disease-like clinical features (Behan et al., 1988; Chaudhuri and Behan, 2003; Chong et al. 2003; Ferracci et al., 2004; Fatourechi, 2005).

In this study, the patients who presented with encephalopathy and fit the criteria for HE based on the presence of anti-thyroid antibodies and the responsiveness to immunotherapy such as steroids, immunosuppressants and/or IVIg/plasmapheresis, demonstrated a high prevalence of anti-NAE autoantibodies in their sera (68%; 17/25; $p<0.001$, compared to patients with HT without encephalopathy [10%, 2/20]). This strongly supported our previous finding of a high prevalence (83%, 5 out of 6) of anti-NAE autoantibodies in patients with HE (Fujii et al., 2005). There were no sera from patients with other disorders including autoimmune conditions or collagen diseases that showed any immunological reaction to recombinant NAE, suggesting a high specificity of anti-NAE autoantibodies to encephalopathy with HT. One third of patients examined here did not have anti-NAE

autoantibodies in their sera. NAE(−) patients can be associated with different autoantibodies because our preliminary study demonstrated other possible autoantibodies detected in NAE(−) patients (data not shown, in progress).

In the neurological features of the patients examined here, consciousness disturbance (80%), seizures (68%), cognitive impairment/psychiatric symptoms (76%) and involuntary movements (52%) were common in HE, while ataxia (12%) was much less frequent. As the clinical form, acute encephalopathy (AE) was the most common (76%). Chaudhuri and Behan investigated 18 cases of HE clinically and immunologically, and indicated that headaches (90%), seizures (67%), focal neurological deficit (67%), stupor/coma (67%), psychosis (50%) were common and ataxia (16%) and hemiparesis (16%) were rare (Chaudhuri and Behan, 2003). Although Chaudhuri and Behan emphasized myelopathy as a common clinical feature in HE with a similarity to ADEM, myelopathy was not observed in patients examined in our study. In addition, the anti-NAE autoantibodies were not detected in 4 patients with post-infectious ADEM in our study, suggesting that the clinical form of ADEM appeared relatively less frequent than Chaudhuri and Behan supposed.

In this study, relapsing was less frequent (16%) than that in Chaudhuri and Behan's study (67%). Chaudhuri and Behan carefully followed-up their patients with HE over a period of 16 years, and clarified the outcome of HE patients (Chaudhuri and Behan, 2003). The low frequency of relapse in our study seemed to depend on the short periods of the clinical courses examined (most patients were within one year). Thus, this short-term observation could have caused an underestimation of the relapse rate of HE in our study.

On laboratory/MRI findings in our study, EEG abnormalities were common (90%), compared to the low prevalence of abnormalities on brain MRI (20%). Elevation in CSF protein/IgG in our study was also a common feature (54%). Although there was no major difference in patients between NAE(+) and NAE(−) in the clinical features and laboratory/MRI findings in the present study, EEG abnormalities appeared at higher frequency and steroids tended to be more effective in NAE(+) patients.

Chaudhuri and Behan recommend immunosuppressants (e.g. azathioprine) as a potentially effective treatment besides steroids from the perspective of T-cell sensation to the antigen in HE (Chaudhuri and Behan, 2003). Although steroids have been widely administered to patients with HE in our study and others, steroid-responsiveness shows a temporally limited quality and other immunosuppressant agents are necessary to sustain long-term clinical response (Chaudhuri and Behan, 2003). Indeed, in our patient (Case 24) who showed an excellent steroid-responsiveness on the initial attack but poor response on the following attacks, this was successfully prevented from relapsing after the administration of an immunosuppressant (azathioprine) was started.

Chong et al. assumed that the combination of encephalopathy, presence of anti-thyroid antibodies and responsiveness to steroid administration seemed unlikely to be due to chance, and, however, there was no evidence of a pathogenic role for anti-thyroid antibodies in encephalopathy associated with HT (Chong et al., 2003). On the contrary, Ferracci et al. speculated that autoimmunity to neural antigens cross-reacting with thyroid antigens was the pathogenic basis of encephalopathy with HT (Ferracci et al., 2004). Additionally, the neuropathological finding of an autopsied case and brain perfusion studies in patients with HE suggested brain vasculitis, and supported the disease entity of HE (Nolte et al., 2000; Zettinig et al., 2003; Piga et al., 2004).

Sawka et al. searched for cases of encephalopathy associated with HT in Mayo Clinic from 1950 to 1996 years, and assumed that HE could be a rare autoimmune condition associated with a common autoimmune HT, in part with unknown origin (Sawka et al., 2002). In the present study, however, a large number of cases of encephalopathy associated with HT were still present, and two thirds of these patients carried anti-NAE autoantibodies even after neurological specialists had carefully excluded other possible conditions causing encephalopathy. Such discrepancy may be driven from differences between the profiles of patients treated by neurologists and compared to those treated by endocrinologists; i.e. neurologists see patients with neuropsychiatric symptoms of various causes while endocrinologists more frequently see patients with HT and less frequently encephalopathy.

Fatourechi et al. stated that a distinct clinical entity of encephalopathy associated with HT was present but the use of the term "Hashimoto's encephalopathy" was unfavorable until the pathogenesis of this condition was better defined (Fatourechi, 2005). Although the pathogenic role for anti-NAE autoantibodies in HE remained obscure, the present study demonstrated that anti-NAE autoantibodies were more specific to HE than anti-thyroid antibodies. This strongly suggests that "Hashimoto's encephalopathy" is a distinct clinical entity associated with HT although the underlying immunological condition should be better defined. Both the anti-NAE autoantibodies and anti-thyroid antibodies can be generated in the common immunological background related to HT, such as T-cell mediated antibody production (Weetman and McGregor, 1994; Stassi and De-Maria, 2002).

In conclusion, anti-NAE autoantibodies, in addition to anti-thyroid antibodies, are emphasized to as a useful serological diagnostic marker of HE, and should be included in the diagnostic criteria of this condition. Physicians must more attentively consider the possibility of HE, and test serum for anti-NAE autoantibodies as well as carefully excluding other conditions causing encephalopathy in patients with HT.

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