Clinical Worsening Despite Various Imunotherapy In Hashimoto-Antibodies-Associated-Encephalopathy

J.C. Bier[*,1], H. Slama[2], S. De Breucker[3], L. Victoor[4], S. Goldman[5] and M. Vokaer[1]

[1]*Department of Neurology,* [2]*Department of Neuropsychology,* [3]*Department of Geriatric Diseases,* [4]*Department of Psychiatry,* [5]*PET/Biomedical Cyclotron Unit, Erasme Hospital, ULB, Brussels, Belgium*

Abstract: *Background*: In 1966, first description of a "Steroid-Responsive Encephalopathy Associated with autoimmune Thyroiditis (SREAT)" syndrome was described. Since then, lots of cases emerged with two major kinds of presentations: "vasculitic" and "diffuse progressive". Patients respond variably to corticoids. Methotrexate, plasmatic exchange or intravenous imunoglobulins (IvIG) have only been anecdotically used.

Case Report: A 63 years old man presented with mild words finding difficulties evolving for 5 years in 2000. He lost appetite and was tired despite sleeping 10 hours/day for 3 years. He presented bradypsychia and his MMSE was 28/30. Diagnosis of depression was made and treated. At this time, he fell asleep while eating or watching TV. EEGs and usual blood investigations were normal. During the next three years, he presented left extinction and extra-pyramidal gait followed by spontaneous myoclonus. Both lumbar puncture and brain MRI were normal despite atrophy. Diagnosis of cortical posterior atrophy due to possible corticobasal degeneration was then set up. Cognitive decline rapidly progressed and anti-TPO antibodies were positive at >3000 UI/ml. Treatment by oral methylprednisolone (64mg/day during 1 month) was then initiated and followed by a delirious major depressive disorder requiring hospitalization. Over the next years, cognitive decline persisted and treatments by methotrexate, prednisolone and even IvIG were all followed by worsening of myoclonus and psychosis relapses.

Conclusion: This case of clinical worsening after immunotherapy highlights the necessity to cautiously study the response of SREAT to immune-therapies.

BACKGROUND

The first description of a "Steroid-Responsive Encephalopathy Associated with autoimmune Thyroiditis (SREAT)" syndrome was dated from 1966 [1]. In 1974, two new cases were described [2]. All three presented with episodic subacute, progressive encephalopathy with cortico-sensitive remissions. Since then, lots of cases emerged with two major kinds of presentations: "vasculitic" and "diffuse progressive". However, in some peculiar presentations, monosymptomatic cases have been described as isolated progressive myelopathy, psychosis, cerebellopathy, paraparesthesia, epilepsy, headache or dementia. Typically, the diffuse progressive form of SREAT showed progressive dementia accompanied by depressive disorders, cerebellopathy and extrapyramidal signs [3]. Progressive aphasia, apraxia, amnesia, or all of them are other presentations of the syndrome with asthenia and headaches as classical supporting symptoms.

CASE REPORT

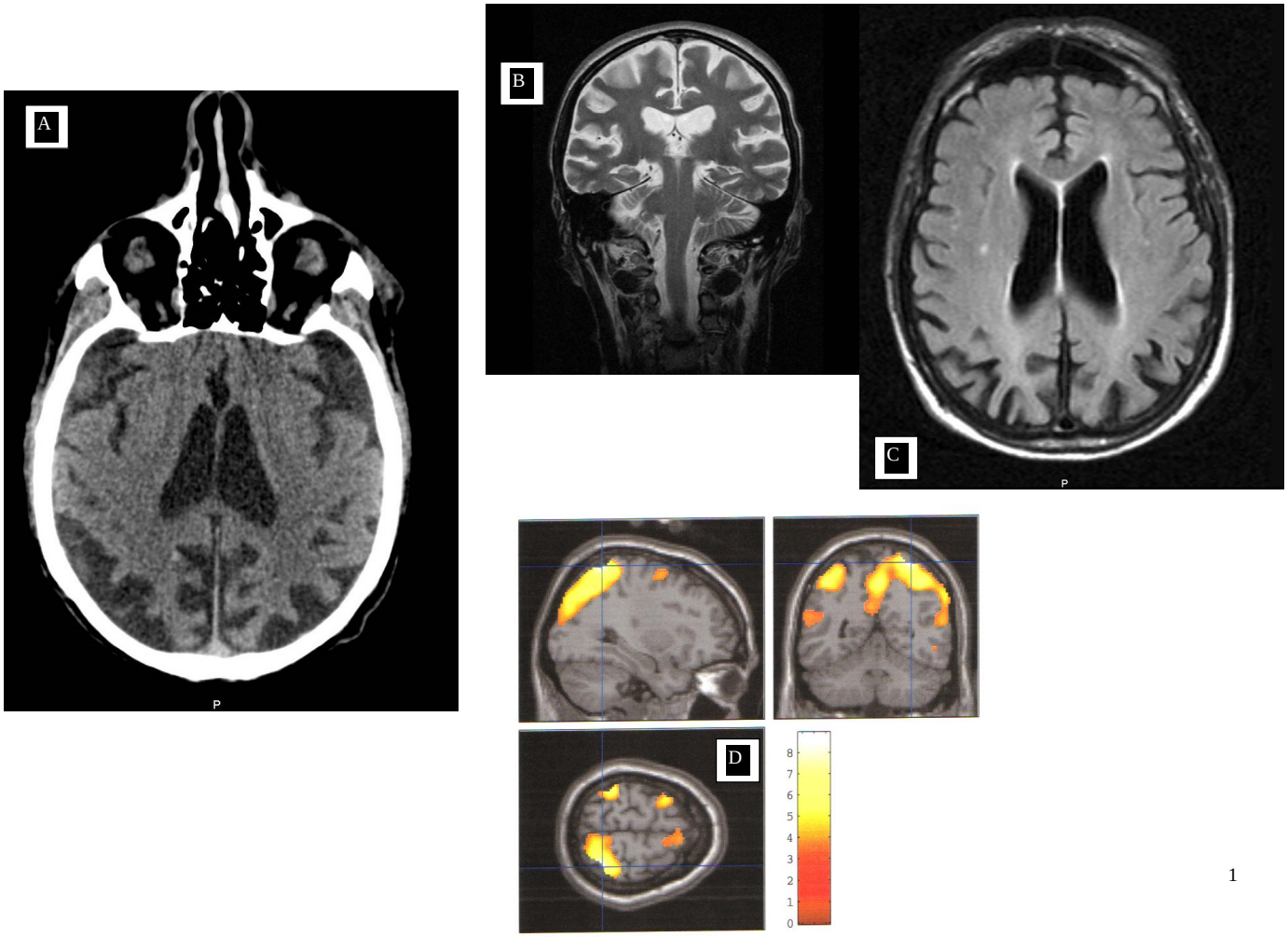
In early 2000, a French-speaking, right handed, 63 years old commercial representative, presented with mild words finding difficulties evolving for 5 years. His weight was 70 kg and he was 180 cm tall. He smoked 25 cigarettes/day. He lost appetite and was tired despite sleeping 10 hours/day for 3 years. He drove his car more cautiously than before and complained about difficulties in parking. His family history revealed various cancers with mother deceased at 94 years, father at 76 while his brother at 58. Personal medical history consisted in arteriopathy requiring left femoral percutaneal dilatation with stenting in 1996, appendicectomy and chirurgically treated anal fistula. He presented hypercholesterolemia, hypertension and seborrhoeic hyperkeratosis. He was treated with Amlodipine 5 mg/day; acetylsalicylic acid 100 mg/day and pravasine 20 mg/day. He also tried pyracetam 2400 mg/day for a few months but stopped it for subjective inefficiency. He presented bradypsychia with a MMSE score of 28/30. A diagnosis of depression was proposed and treated with citalopram 20 mg/day for four months with none observed benefit. At this time, he fell regularly asleep while eating or watching TV. Cerebral Ct scan showed no structural lesion. Multiple electroencephalographies (EEG) were normal with an occipital alpha rhythm of 8-9 Hz. Blood investigations were all normal including sedimentation rate, C-reactive protein, haematology, chemistry, lactate, coagulation, lipids, liver functions, renal function, calcium, magnesium, thyroid stimulating hormone, riboflavine, folates, antinuclear antibodies, ANCA, proteins and immune-electrophoresis, cholestéanol, long chain fat-acids, amino-acids profile, ceruloplasmine & cupper, iron function, syphilitic serology, HIV serology, HCV serology, HBV serology, ... Urinary examination was normal too with no protein and no porphobilinogen or delta-aminolevulinic acid. During the next three years, he presented left extinction, extra-pyramidal gait, followed by spontaneous myoclo-

*Address correspondence to this author at the Hôpital Erasme, Service de Neurologie; 808 route de Lennik, 1070 Bruxelles, Belgium; Tel: +32-2-555-46-22; Fax: +32-2-555-39-42; E-mail: jbier@ulb.ac.be

1874-8279/08

nies and increasing bradykinesia. In August 2002 ophtalmoscopic examination was normal. Left visual field was first impaired but controlled two months later normal. Cervical ultrasonography showed carotidal intimae thickening evaluated in its maximal broad to 1,8 mm. Transthoracic echocardiography and 24 hour's electrocardiogram were both normal. Asthenia progressed and audition decreased due to a beginning presbyacousy revealed by audiometry. A neuropsychological examination showed a severe cognitive alteration of the visuospatial processing (see Table **1**) with abnormal performance in visuospatial working memory (block-tapping test), visual-constructive skills (Rey's complexe figure), visual selective attention (3 matrixes), visuospatial reasoning (PM38). We also found an alteration of executive functions (Stroop test) and mental calculation. Pictures naming, verbal episodic memory and verbal fluencies were globally preserved. In December 2002, left elbow rigidity was evaluated by the UPDRS quotation to ¼ and to 2/4 on the right. Dermal biopsy showed chronicle lesions of eczema with lymphocytic infiltration. Two lumbar punctures were normal. The first one showed no leucocytes and nine red cells by millimetre cube. The second one demonstrated one polyneutrophylic and 115 red cells by millimetre cube. There was no malignancy cell. Proteins, glycorachy and lactic acid were systematically normal. There was no band on electrofocusing and albumin-immunoglobulin index was normal. Brain MRI was normal despite a diffuse atrophy with a slight predominance in the posterior areas and no focal lesion (Fig. **1**).

In view of progressive dressing apraxia, left neglect, myoclonies and unsymmetrical extrapyramidal signs, a diagnosis of Posterior Cortical Atrophy probably due to Cortico-Basal Degeneration was set up. A ^{18}FDG-PET-scan of the brain showed predominantly posterior cortical hypometabolism, suggestive of a degenerative disorder. In order to confirm the visual PET data evaluation, PET data were analyzed using a voxel-based method, Statistical Parametric Mapping (SPM99) (Fig. **1**). Treatment by rivastigmine 6 mg/day was then associated with a stabilisation of 8 months. Memantine 20 mg/day was added helping view of increasing dressing apraxia (Table **1**). In April 2004, Bromocriptine 10 mg/day



1

Fig. (1). (**A**) cerebral Ct scan slice showing diffuse cortical atrophy with predominance in the posterior areas (February 2006); (**B**) MRI T2 sagital slice illustrating the absence of focal lesion in the posterior areas (July 2005); (**C**) MRI T1 coronal slice showing diffuse cortical atrophy with a slight predominance in the posterior areas (July 2005); (**D**) Results of the subtractive SPM analysis comparing the regional cerebral glucose metabolism of our patient with that of a control group. This analysis revealed the existence of a significant bilateral, predominantly right, parieto-occipital hypometabolism. Slight bilateral frontal involvement is observed (December 2002).

Table 1.

Test		VIII 2002	I 2003	III 2003	IX 2003	XII 2003	III 2004	VI 2004	V 2005	VII 2005	XI2005	II 2006	V 2006	IX 2006
MMSE		28/30	**23**/30	26/30	26/30	**24**/30	26/30	**20**/30	**19**/30	**14**/30	**16**/30		**15**/30	
Digit span / Block tapping test		4 / **2**												
Verbal learning:	**Semantic Encoding**	16 / 16												
	Immediate Recall	13 / 16												
	Free Recall (3 trials)	6-6-6 / 16												
	Cued Recall (3 trials)	14-14-14 / 16												
	Delayed Free Recall	**5** / 16												
	Delayed Cued Recall	13/ 16												
	Recognition	16 / 16												
Rey's complexe figure		**impossible**												
Fluencies P/R/Animals/ Fruits		19/14/23/12												
Bachy- Langedock		45/45												
Mental Calculation		**Impossible**												
PM38		**Impossible**												
3 matrixes (digits cancellation)		**21**/60												
Stroop (Informatics items by items)		**5** NC for **190''** (interference)												
ACE				**73**/100	84/100		**72**/100							
KATZ			**7**/24 (Dressing)	**7**/24 (Dressing)	**8**/24 (Dressing)			**11**/24 (Dressing)	**11**/24				**17**/24	**23**/24
LAWTON			**26**/36	**26**/36	**27**/36			**32**/36	**32**/36				**33**/36	**36**/36
NPI			25 /144	13 /144	20 /144			44 /144	46 /144				31 /144	31 /144
NewQ			Rivastigmine	Escitalopram	Memantine	Bromocriptine	STOP Memantine Escitalopram	STOP Bromocriptine	MPS (PO)	Mirtrazapine		Azathioprine		MPS (IV) + IVg STOP Azathioprine
TSH ***Free T3*** ***Free T4***		1,9 mIU/ml 4,2 pg/ml 1,3 ng/dl				2,6 mIU/ml 1,18 ng/dl			1,3 mIU/ml			**4,12** mIU/ml	1,51 mIU/ml	1,8 mIU/ml 3,2 pg/ml 1,4 ng/dl
ANTI TRG ***ANTI TPO***						**93 IU/ml** **>3000IU/ml**			**219 IU/ml** **343 IU/ml**			**189 IU/ml** **>1300IU/ml**	**168 IU/ml** **>1300IU/ml**	**204 IU/ml** **260 IU/ml**
THYROGLOBULINE						< 0,5 ng/ml							< 0,2 ng/ml	

Test	I 2007	VI 2007	XI 2007
MMSE	08/30	05/30	✝
KATZ	24/24		
LAWTON	36/36		

ACE: addenbrook's cognitive examination; MMSE: minimal mental state examination; NPI: neuropsychiatric inventory; ϴ: treatment; TSH: Thyréostimuline; T3: Tri-iodothyronine; T4: Tétra-iodothyronine; TRG: thyroglobulin; TPO: Thyreoperoxidase; IU: international unit; MPS: methylprednisolone; PO: per os; IV: intravenous; IVg: gammaglobulins; ✝: death owing to pneumonia.

was intended without any clinical impact. Blood endocrine investigations revealed >3000 IU/ml anti-myeloperoxidase antibodies discovered in May 2005. Diagnosis of SREAT was thus proposed and treatment by methylprednisolone 64 mg/day initiated. A few months later, in July 2005, the patient developed delirium with paranoia and sadness, had visual and auditory hallucinations and cried a lot. His weight had drawn to 59 kg. Methylprednisolone was stopped and mirtrazapine 30 mg/d initiated. His EEG showed Frontal intermittent rhythmic delta activity (Fig. **2**). Brain CT-scan and MRI both showed cortical atrophy with no structural lesion (Fig. **1**). Lumbar puncture remained normal. Despite initiation of methotrexate in February 2006, nocturnal shaking and myoclonies increased dramatically in May. Azathioprine was increased to 100 mg/day, followed in September 2006 by new episodes of delirium, paranoia and hallucinations requiring hospitalization. He weighted 48 kg in January 2007 and unfortunately, 5 days of IvIG 400mg/kg.day were not clinically efficient. He died in November 2007 owing to pneumonia due to oropharyngeal dysphagia. Unfortunately, no autopsy was performed.

DISCUSSION

The SREAT syndrome is heterogeneous and includes various descriptions. There are, even at least, three cases suffering from peripheral neuropathies associated with autoimmune thyroiditis [4-6]. In all described cases, elevated levels of antibodies are the only constancy. Even cerebrospinal fluid analysis remains controversial. Some studies suggest an intrathecal synthesis of autoantibodies while others argue against it [3]. Usually, EEG is non-specifically abnormal, brain CT scan or MRI may be normal and PET or SPECT imageries seem not more specific [3]. One unconfirmed case of SREAT's MRI-spectroscopy revealed frontal reduction of N-acetylaspartate (arguing for a neuronal disease) with an increase of cholines (arguing for a glial one), disappearing after treatment with corticoids [7]. All but one of the few reported pathological examinations, revealed perivenular and arteriolar, predominantly T-type, lymphocytic infiltration within the leptomeninges and parenchyma [3]. The patient described by Oide *et al.* had negative autopsy [8]. Similarly, the therapeutic response may vary a lot. Some patients improved spontaneously with or without relapses [3]. Flunarizine helped in one case reported while methotrexate, plasmatic exchange or intravenous immunoglobulins (IvIG) have only been anecdotically used [3, 9]. To date, pathogenic mechanisms of SREAT remain unclear. A direct impact of the Thyrotropin-releasing hormone has even been evoked. Occurring of cerebral oedema too [1], sometimes with a swelling effect on MRI [10]. Vasculitic phenomenon has regularly been described with myo-vascular modifications [10], immune-complex implication [2] or cerebral arterial calibre variations [11]. A mitochondrial origin has even been proposed [12]. More recently, a high prevalence of serum autoantibodies against amino terminal's alpha-enolase has been described in SREAT with an excel-

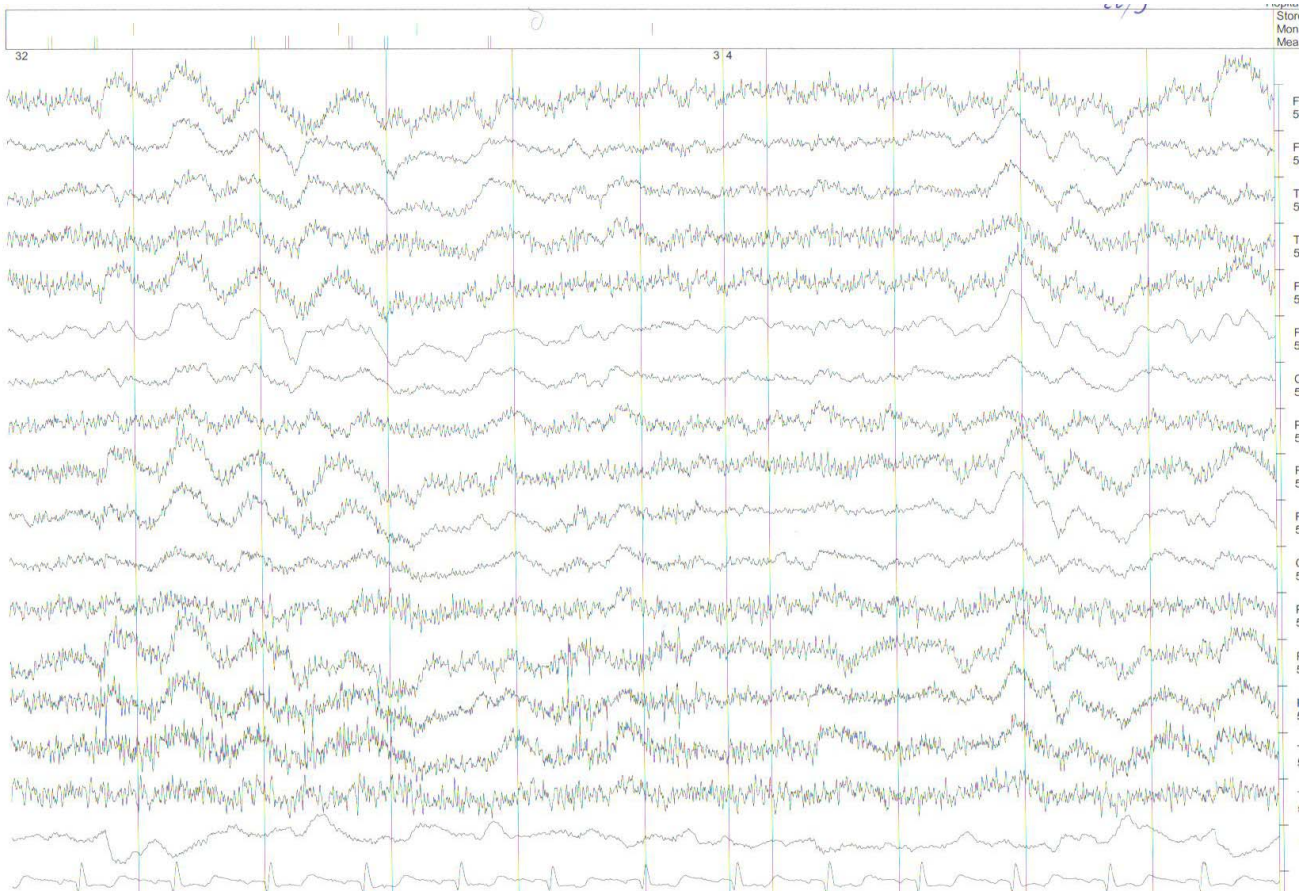


Fig. (2). EEG showing frontal intermittent rhythmic delta activity (July 2005).

lent specificity (80%) [9]. In 1991, Shaw *et al.* proposed the set of new SREAT diagnostic criteria [13]. These were revised in 1999 by Peschen-Rosin *et al.* as the presence of recurrent myoclonies, epilepsy, psychiatric troubles or any focal neurological signs associated with three of the five following points: 1/ abnormal EEG; 2/ elevated antithyroid antibodies; 3/ elevated proteinorachy; 4/ dramatic improvement with corticoids; 5/ no structural explication on MRI [14]. However, as discussed by Ferracci *et al.* [3], since 1999, lots of presentations have been described. Moreover, it could be interesting to reconsider the absolute necessity of antibodies in these criteria. Identically, thyroid function could be considered in these criteria. In our case, as classically described, thyroid function lab test was only once and lately proved to be abnormal. Clearly, a high titre of antithyroid antibodies associated with progressive encephalitis does not necessarily implicate a causal relationship. However, our case fulfil diagnostic criteria of SREAT with the presence of recurrent myoclonies, psychiatric troubles and multiple focal neurological signs associated with an abnormal EEG (Fig. **2**), an elevated antithyroid antibodies and no structural explication on MRI. Moreover, the history of his progressive encephalopathy and his laboratory examinations exclude any congenital aetiology. No structural lesions on brain imageries exclude vascular and traumatic aetiologies. Infectious and inflammatory origins are ruled out by blood exams and multiple lumbar punctures. Degenerative disorders and especially Posterior Cortical Atrophy (PCA) cannot be completely excluded. However, these degenerative syndromes are not characterized by its unequivoque pathology. Thus, SREAT and PCA are compatible and certainly not respectively exclusive. Creutzfeldt-Jakob disease is improbable in view of the clinical evolution and of EEGs. Clinic, MRI and biology excluded paraneoplastic and nonparaneoplastic limbic encephalitis [15]. Finally, our case, as others before [16], argues against definitive efficacy of corticosensitivity in SREAT. It could be said that, in most cases, SREAT would be diagnosed when antibodies are found in the absence of other well-defined aetiologies. Systematic report of all suspected cases and the study of their therapeutic response would be useful to better understand SREAT syndrome.

CONCLUSION

This case of clinical worsening after immunotherapy highlights the necessity to cautiously interprete the current diagnostic criteria and to report all cases of suspect SREAT. Moreover, its responses to therapeutics require further assessment.

REFERENCES

[1] Brai L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. Lancet 1966; 2: 512-4.

[2] Thrush DC, Boddie HG. Episodic encephalopathy associated with thyroid disorders. J Neurol Neurosurg Psychiatry 1974; 37: 696-700.

[3] Ferracci F, Carnevale A. The neurological disorder associated with thyroid autoimmunity. J Neurol 2006; 253: 975-984.

[4] Cao NJ, Tselis AC, Li J, Gorman M. A case of Hashimoto's encephalopathy: association with sensory ganglionopathy. J Neurol Sci 2005; 238: 105-7.

[5] Kastrup O, Maschke M, Schlamann K, Diener HC. Hashimoto encephalopathy and neuralgic amyotrophy - causal link or chance association? Eur Neurol 2005; 53: 98-9.

[6] Sheng B, Lau KK, Li HL, Cheng LF. A case of Hashimoto's encephalopathy with demyelinating peripheral neuropathy. Eur Neurol 2005; 53: 84-5.

[7] Seo SW, Lee BI, Lee JD, *et al.* Thyrotoxic autoimmune encephalopathy: a repeat positron emission tomography study. J Neurol Neurosurg Psychiatry 2003; 74: 504-6.

[8] Oide T, Tokuda T, Yazaki M, *et al.* Anti-neuronal antibody in Hashimoto's encephalopathy: neuropathological, immunohistochemical, and biochemical analysis of two patients. J Neurol Sci 2004; 217: 7-12.

[9] Yoneda M, Fujii A, Ito A, Yokoyama H, Nakagaw H, Kuriyama M. Hih prevalence of serum autoantibodies against the amino terminal -enolase in Hashimoto's encephalopathy. J Neuroimmunol 2007; 185: 195-200.

[10] Forchetti C, Katsamakis G, Garron DC. Autoimmune thyroiditis and a rapidly progressive dementia: global hypoperfusion on SPECT scanning suggests a possible mechanism. Neurology 1997; 49: 623-6.

[11] Isik U, Tennison M, D'Cruz O. Recurrent encephalopathy and seizures in an adolescent girl. Clinic Pediatr 2001; 40: 273-5.

[12] Sue CM, Morris JGL. Another case of Hashimoto's encephalopathy. Mov Disord 1997; 12: 471-2.

[13] Shaw PJ, Walls TJ, Newman PK, Cleland PG, Cartlidge NEF. Hashirnoto's encephalopathy: A steroid-responsive disorder associated with high anti-thyroid antibody titers—report of 5 cases. Neurology 1991; 41: 228-33.

[14] Peschen-Rosin R, Schabet M, Dichgans J. Manifestation of Hashimoto's encephalopathy years before onset of thyroid disease. Eur Neurol 1999; 41: 79-84.

[15] Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. CNS Drugs 2007; 21: 799-811.

[16] Castillo P, Woodruff B, Caselli R, *et al.* Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 2006; 63: 197-202.

Received: September 23, 2008 Revised: October 8, 2008 Accepted: October 13, 2008