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Case report

Thyrotoxic autoimmune encephalopathy in a female patient: Only partial response to typical immunosuppressant treatment and remission after thyroidectomy

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Abstract

Hashimoto's encephalopathy (HE) is a rare immune-mediated encephalopathy developing in patients with high serum concentrations of anti-thyroid antibodies usually in an euthyroid or hypothyroid state. We report a 31-year-old female patient with thyrotoxic HE whose daughter has been followed up with the same diagnosis. Suboptimal response was observed with intravenous methylprednisolone (IVMP), intravenous immunoglobulin (IVIG) and plasmapheresis. Reduction of the anti-thyroid auto-antibody concentrations marked the patient's improvement in each episode. She relapsed under oral immunosuppressive therapy. After removing the thyroid tissue, full recovery has been achieved for the last 18 months. These data may contribute to clarification of the pathogenetic role of anti-thyroid antibodies in HE. Thyroidectomy can be considered as one of the treatment options especially in thyrotoxic HE patients with uncontrolled relapses. Our patient is the first reported HE case with a family history. Genetic background can underlie the etiopathogenesis of HE as is the case in other autoimmune disorders.

Keywords: Autoimmune; Encephalopathy; Family history; Genetic; Hashimoto's; Thyroiditis; Thyrotoxicosis

1. Introduction

Among the subacute encephalopaties of unknown origin, Hashimoto's encephalopathy (HE) has attracted growing attention as a treatable condition. High levels of serum anti-thyroid antibodies serve as a marker for the diagnosis of HE, in the presence of steroid responsive progressive or relapsing encephalopathy with seizures, hallucinations, tremors, myoclonus and cerebellar syndrome [1–3].

Since it was first described by Lord Brain et al. over 120 cases have been reported [3–4]. However, the pathogenetic mechanisms underlying HE remain unclear. The possible mechanisms proposed are autoimmune-mediated CNS vasculitis [1,2,5,6] in which the origin of the symptoms is attributed to disruption of cerebral microvasculature, and humoral immunity by anti-neuronal antibodies possibly recognizing a common antigen in the thyroid gland and in the brain [2,3,7].

We here describe a rare female case of HE with thyrotoxic Hashimoto's thyroiditis (HT) which was partially responsive to typical immunosuppressant treatment used in HE and eventually responded to thyroidectomy. The presence of a family history, with the patient's daughter apparently suffering from HE as well, has not been previously reported. The treatment options in HE have been also discussed by reviewing the recent literature.

2. Case report

On March 2005, a 34-year-old woman was referred to our hospital with complaints of weight loss, palpitations,

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unsteadiness, tremor and involuntary jerks. Memory disturbances and personality changes were also reported by her sister. She had been receiving per oral methimazole and acebutolol for hyperthyroidism since December 2004.

Her past medical history held great interest in terms of autoimmune diseases. From 1985 to 1996 she had been intensively investigated for suspected diagnosis of systemic vasculitis when she began to experience episodic attacks with multiple symptoms including high fever, abdominal pain, vomiting, hematemesis, melena and hematuria beginning at the age of 14 years. She reported having suffered from Raynaud's phenomenon, arthralgia, alopecia, photosensitivity and joint pain at that time. She had received prednisolone and cyclophosphamide therapy with colchicine until 1991, with a diagnosis of segmentary mesengial glomerulonephritis. She stated that she had benefited from those treatments. A series of relevant laboratory studies that had been performed had not met the criteria for systemic vasculitis. Between 1991 and 1996 she had shown remission. In 1996 she had been evaluated again for recurrent hematuria and had been treated with prednisolone and mycophenolate mofetil for 2 years. She was reported to have been well until her latest symptoms.

On admission, besides her aggressive behavior and psychomotor restlessness, spontaneous and stimulus induced myoclonic jerks, postural tremor and ataxia were also observed. Cognitive testing showed verbal memory deficits and impaired attention. Physical examination revealed sinus tachycardia and mild thyromegaly. Serum free T_3(fT_3) and free T_4(fT_4) levels were found to be high, that is 32.55 pg/ml (*N*: 2.3–4.2) and 7.7 ng/dl (*N*: 0.8–1.8), respectively. The level of TSH was 0.06 μIU/ml (*N*: 0.4–5.5). Anti-thyroglobulin antibody (TGAb) and anti-thyroperoxidase antibody (TPOAb) were positive at high levels of 394 IU/ml (*N*: 0–115) and 600 IU/ml (*N*: 0–35), respectively. The level of TSH receptor antibody necessary to exclude Basedow-Graves was defined as 5.5 U/L ($N<9$). Bilaterally non-homogeneneous activity and low uptake were determined by means of thyroid scintigraphy. Thyroid ultrasound detected heterogeneity and pseudo-nodules. She was diagnosed as thyrotoxic Hashimoto's thyroiditis and oral prednisolone (60 mg daily) with beta blocker drug (metoprolol) was initiated. Propylthiouracil was also prescribed in order to prevent the conversion of the pro-hormone T_4 to bioactive T_3 in the periphery.

On the third day of her hospitalization, she developed a progressive organic brain syndrome characterized by impaired cognitive abilities and a confusional state with disinhibited behavior. During follow-up, besides tonic clonic generalized seizures, frequent brief attacks with asymmetric posturing and bizarre motor automatisms with minimal postictal state, resembling frontal seizures, were also observed. EEG showed generalized slowing of the background rhythm and intermittent bursts of delta and theta activity. Cranial magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) revealed normal findings. Reduction in perfusion was detected in the left parietal area by means of single photon emission computed tomography (SPECT) imaging (Fig. 1). CSF analysis showed a moderate increase in protein level (68 mg/dl; *N*: 0–45) with no cells. Blood and CSF examinations to detect viral, bacterial and fungal agents were found to be normal. Collagen vascular screening including serum Ig GAM, protein electrophoresis, immune fixation electrophoresis, antinuclear antibody (ANA), antimicrosomal antibody (AMA), anti-smooth muscle antibody (ASMA), liver–kidney microsomal antibody (LKM), gastric parietal cell auto-antibody (GPC), ethanol ANCA C and P, formalin ANCA, Anti-ds DNA, rheumatoid factor, Anti-Ro antibody, Anti-La antibody, anticardiolipin (aCL) antibody, anti-SCL70, anti-U1RNP, Anti-Jo, Anti-SM antibodies were within normal limits except for a high level of serum IgG (2224 mg/dl, *N*: 650–1000). Lip biopsy and Schirmer test showed no abnormality with regard to Sjogren disease. After exclusion of other causes of subacute encephalopathy, the patient was diagnosed as HE [1–3] and intravenous methylprednisolone (IVMP) 1 g daily was initiated for 7 days, followed by 60 mg daily oral prednisolone. After 5 days of IVMP administration, except for a high fT_4 level (10.9 ng/dl, *N*: 0,8–1.8), TGAb and TPOAb and fT_3 levels returned to normal with marked clinical improvement. She became cooperative and orientated, and neurological exam was normal. However, the seizures did not respond to IVMP or antiepileptic medication with sodium valproat and topiramate. Repeated thyroid functions after 1 week showed a euthyroid state with increasing TGAb and TPOAb levels, namely 374 IU/ml (*N*: 0–115) and 590 IU/ml (*N*: 0–35), respectively. Although intravenous immunoglobulin (IVIG) treatment with a dose of 2 g/kg over 3 days was begun, her seizures persisted. As her neurological exam was normal between the seizure and her confusional state responded well to IVMP and IVIG, anti-thyroid and beta blocker drugs were suspected to cause the lowering of seizure threshold and were gradually stopped. Seizures ceased within 3 days. After IVIG administration, within 3 weeks, TGAb and TPOAb levels also returned to normal limits, that is 96 IU/ml (*N*: 0–115) and 32 IU/ml (*N*: 0–35), respectively.

She was discharged from the hospital in May 2005 with complete recovery and showed remission for 2 months upon treatment with immunosuppressant medication. She had taken 60 mg daily oral prednisolone for a period of 3.5 months, and 100 mg/day per oral azathiopirine (AZA) for a period of 2 months. On June 2005, she suffered a clinical episode coinciding with thyrotoxicosis and high serum concentrations of anti-thyroid antibodies that is to say her TGAb and TPOAb levels were 196 IU/ml (*N*: 0–115) and 415 IU/ml (*N*: 0–35), respectively. Serum free T_3(fT_3) and free T_4(fT_4) levels were found to be 39.22 pg/ml (*N*: 2.3–4.2) and 12.9 ng/dl (*N*: 0.8–1.8), respectively. The levels of TSH and TSH receptor antibody were 0.03 μIU/ml (0.4–5.5) and 7.5 U/L ($N<9$), respectively. The patient, who was known to partially respond to IVIG and IVMP therapy, received plasmapheresis (1800 ml/day for 3 days) this time and after

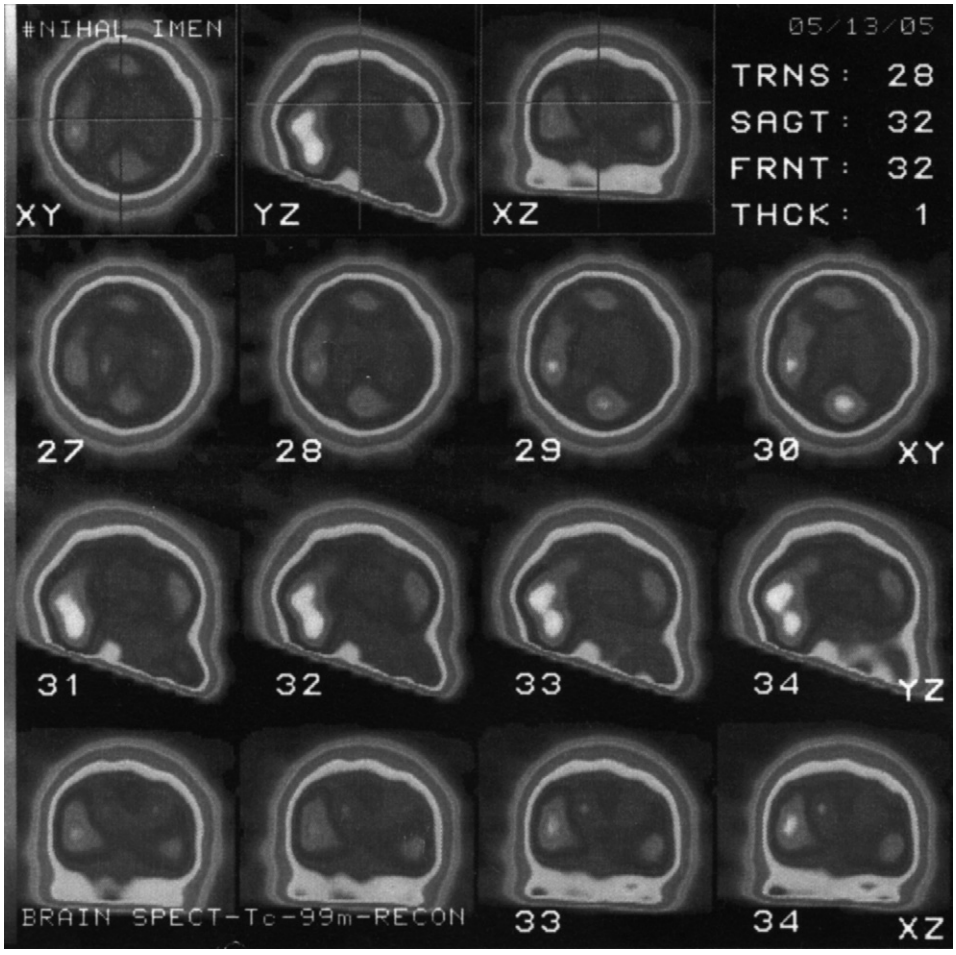
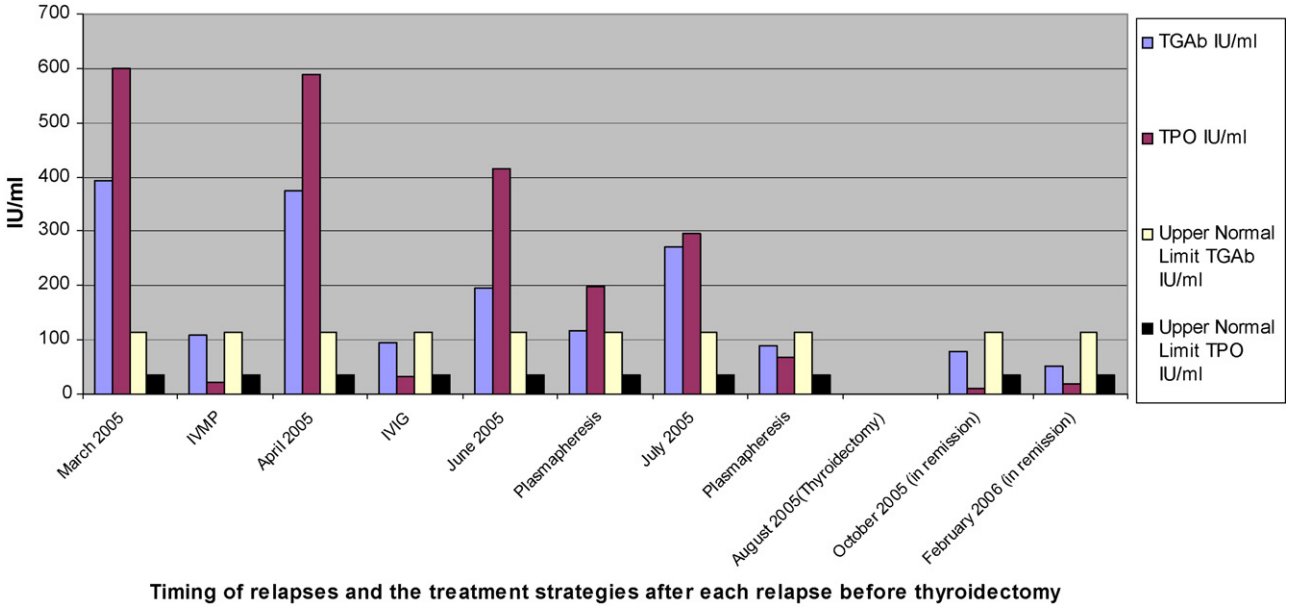


Fig. 1. Focal hypoperfusion in the left parietal area is shown on brain ^{99m}Tc-HMPAO SPECT. Row 2: axial view, row 3: sagittal view, row 4: coronal view.

a period of 1 week, improved with marked reduction in the levels of anti-thyroid antibodies as TGAb and TPOAb levels were found to be 118 IU/ml (*N*: 0–115) and 197 IU/ml (*N*: 0–35), respectively. Thyroid hormone levels were also normalized. Four weeks after the administration of plasmapheresis, she was readmitted to our clinic for a relapse characterized by a confusional state, myoclonus and seizures. Analysis performed at this time again showed thyrotoxicosis (fT_3: 20 pg/ml, *N*: 2.3–4.2 and fT_4:1 2.2 ng/dl, *N*: 0.8–1.8) and high serum concentrations of anti-thyroid antibodies (TGAb: 271 IU/ml, *N*: 0–115 and TPOAb: 297 IU/ml, *N*: 0–35). Plasmapheresis was administered for the second time, and after 2 weeks, a decrease in anti-thyroid antibody levels was also noted with clinical improvement (Graphic 1) She then underwent thyroidectomy in an euthyroid state in August 2005. Histopathological examination of the tissue sample was compatible with Hashimoto's thyroiditis. Steroid therapy was tapered within 2 months. After thyroidectomy, the patient has been asymptomatic, having normal cognitive status, for the last 18 months under treatment with azathioprine, levothyroxine. The levels of her anti-thyroid antibodies and thyroid hormones remain within the normal limits at her last exam on February 2007.

Similarly, her daughter had a history of a confusional and aggressive state preceded by complex partial seizures at the age of 9. She was intensively investigated in the Child Neurology Unit of another hospital in January 2004. Her medical history was unremarkable. Physical examination revealed mild thyromegaly and sinusal tachycardia (115 beats/min). Thyroid function tests showed decreased TSH concentration of 0.01 μIU (*N*: 0.4–5.5), high fT_3 level of 14 pg/ml (*N*: 2.3–4.2) and high fT_4 level of 48 ng/dl (*N*: 0.8–1.8) with elevated levels of TGAb (333 IU/ml, *N*: 0–115), and TPOAb (1363 IU/ml, *N*: 0–35). The level of TSH receptor antibody was at a normal level of 7.6 U/L (*N*: <9). Thyroid ultrasound was compatible with HT. EEG showed a generalized slowing of the background rhythm. CSF studies showed normal results except for elevated protein levels. Although cranial MRI revealed normal findings, SPECT showed findings of focal hypoperfusion in the cerebral cortical areas. Her seizures and encephalopathy persisted despite anti-thyroid medication (propylthiouracil and metoprolol), used for a period of 2 weeks, but eventually responded dramatically to IVMP (for 3 days) and thereafter oral prednisolone (for 3 months). With the high level of anti-thyroid antibodies and full response to corticosteroid, she had been diagnosed



Graphic 1. Correlation of the patient's serum anti-thyroid antibody levels with the stages of the disease. Note the increase in anti-thyroid antibody levels with clinical relapse and the reduction or normalization of antibodies levels with clinical improvement induced by treatment. After thyroidectomy, long term remission has been achieved with normal anti-thyroid antibody levels.

as hashitoxic HE after exclusion of other causes. She has remained free of symptoms and relapse for the last 3 years while taking only anti-thyroid medication.

Analysis of HLA alleles of Class I and Class II genes of our patient and her daughter was performed by means of PCR technique. Both of them had HLA A*2, A*11, B*51, Cw*07, DRB1*15, DRB1*05, DQB1*06 haplotypes in common.

3. Discussion

This study may represent some other aspects of HE. Our case demonstrated features of recurrent encephalopathy with seizures after each episode of hashitoxicosis accompanied by high levels of anti-thyroid antibodies. Although sub-clinical hypothyroidism and euthyroidism were the most common abnormalities in HE [1–4], steroid-responsive thyrotoxic autoimmune encephalopathy has also been reported in a limited number of patients with either hashitoxicosis [3,8,9] or Graves' disease (GD) [9,10]. In fact, extreme excess or deficiency of the thyroid hormones may produce metabolic states that aggravate cortical instability. Neuropsychiatric disorders such as confusion, psychosis, seizures, manic and depressive mood changes can also be observed with overt hyperthyroidism without HE which can be radically improved by normalizing the thyroid function [11–13]. It is important to try to distinguish between the neuropsychiatric symptoms commonly seen in euthyroid HE and those commonly seen in overt hyperthyroidism without HE [2,8]. Nevertheless, it is difficult to eliminate the possibility of an autoimmune pathogenesis as anti-thyroid antibodies have not been evaluated in most of these patients [11,12]. Although thyrotoxicosis associated with high anti-thyroid antibody levels preceded our patient's relapses, persistence of her neuropsychiatric symptoms despite the high dose anti-thyroid treatment and existence of symptoms even when she was in an euthyroid state lead to conclude that concomitant thyroid dysfunction alone cannot account for the encephalopathy although it may be implicated. The relapsing nature of the disease, response to immunosuppressive therapy with a decrease in the titers of antibodies and relevant medical and family history are clues to an autoimmune aetiology of the encephalopathy. Focal hypoperfusion seen by means of brain SPECT and elevated CSF protein in both our patient and her daughter were also compatible with HE [3,6].

In HE cases with no or minimal response to steroids, plasmapheresis and IVIG may be applied [1–3]. Due to its relapsing nature, long term immunosuppression may be necessary [1–3]. Although our patient's neuropsychiatric symptoms responded well to IVMP, IVIG and plasmapheresis accompanying a decline in anti-thyroid antibodies, her seizures persisted during her first attack. Withdrawing of anti-thyroid and beta blocker drugs, which can lower the seizure threshold [14] may be responsible for the cessation of intractable seizures, although delayed response of IVMP or IVIG cannot not be excluded in the management of the seizures. Due to the existence of relapses despite oral immunosuppressive drugs and the serious side effects of anti-thyroid and beta blocker medication, she underwent thyrodectomy.

The pathogenetic role of anti-thyroid antibodies and autoimmune thyroiditis in HE has been questioned among

authors and some authors prefer the term "SREAT" (steroid responsive encephalopathy associated with autoimmune thyroiditis) or "neurological disorder associated with thyroid autoimmunity" as it reflects an association rather than a causative role [1–4,9]. Although the increase of the serum concentration of anti-thyroid antibodies is the serological abnormality recorded in all patients and mandatory for the diagnosis of HE, a controversial issue is whether the titers of antibodies correlates with the stage of the disease [3]. Some authors described the reduction or normalization of anti-thyroid antibodies after the remittance of symptoms either spontaneously or induced by immunosuppressant treatment [1,3,9]. However, contrary results have been also reported [3,6,9]. In our case, reduction and increase in antibody concentration marked the patient's improvement and relapse, respectively. The dramatic clinical response after removal of the thyroid tissue and the close correlation between the concentration of thyroid autoantibodies and the stage of disease suggest the presence of antibody-mediated autoimmune encephalopathy in this patient and may also support the hypothesis that humoral antibodies (possibly anti-thyroid antibodies) may have a role in the pathogenesis. It also raises the question of whether thyroidectomy can be a treatment option in HE patients with hashitoxicosis especially those having a relapsing nature and being only partially responsive to typical immunosuppresant treatment used in HE. In order to draw any conclusion, further experience with thyroidectomies in similar situations is needed.

HE can be seen in association with other autoimmune disorders [15]. Our patient's past medical history is an indicator of her high-risk genetic background for autoimmune diseases. She has not fulfilled any diagnostic criteria for systemic vasculitis during our follow-up.

As is the case in all autoimmune diseases, the commencement of HT may be affected by an interaction between susceptibility genes and environmental triggers. Family and twin studies point to a strong genetic influence on the development of autoimmune thyroid disease (AITD). Genome wide screening and linkage analyses have identified several chromosomal regions that are linked to AITD. The putative HT and Graves' disease susceptibility genes include both immune modifying genes (e.g. HLA, TLA-4, CD 40), and thyroid specific genes (e.g. TSHR, thyroglobulin gene) [16,17]. AITD is known to be clustered in families with a high prevalence in the siblings of affected children or adolescents. The disease may occur in the early ages of life in family members in whom autoimmune diseases are frequently seen [18]. It is logical to hypothesize that individuals who develop HE at an early age may represent a genetically high-risk population as in AITD. Genetic susceptibility is also an important issue in understanding the mechanism of HE and in assessing the risk of these conditions in pediatric patients. To our knowledge, our patient is the first reported HE case with a positive family history. Multifactorial aetiology determined by both genetic and environmental factors may underlie the pathogenesis of HE, as in other autoimmune disorders.

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