

HASHIMOTO'S ENCEPHALOPATHY AND RARE CASES OF HYPERTHYROIDISM

(REVIEW AND CASE REPORT)

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Hashimoto's encephalopathy (HE) is an association of autoimmune thyroiditis with encephalopathy covering a great variety of neuropsychiatric symptoms. This term, though somewhat controversial, is still highly preferred over more scientific terms such as "encephalopathy associated to autoimmune thyroid disease" or SREAT (steroid responsive encephalopathy with antibodies to thyroperoxidase). Although in some patients the level of thyroid hormones and TSH may be still normal, that of thyroperoxidase antibodies (TPOab) is usually increased nearly in all cases, some of them being accompanied by increased TSH. In spite of that, the prevailing opinion shows that thyroid antibodies possibly do not have any pathogenic significance, though the speculations on their pathogenic role recently started. It is also believed that several species of antibodies directed against common brain-thyroid antigens represent the most likely etiologic pathway.

HE is a relatively very rare condition. Because of this as well as of unusual variety of presentation, there is a high risk that the patients with HE will be misdiagnosed and mistreated. Since the finding of TPOab in blood is one of the most frequent signs of HE, it is generally recommended as a powerful diagnostic tool namely in all cases of unexplained seizures, confusion, headaches, hallucinations, stroke-like episodes, coma,

impairment of cognitive functions, behavioral and mood disturbances, focal neurological deficits, epilepsy resistant to anticonvulsive treatment etc. Among other diagnostic tools the examination of cerebrospinal fluid, EEG, MRI, SPECT, neuropsychological examinations etc. are used depending on the spectrum of patient's presentation.

Once a firm HE diagnosis is made, corticosteroid treatment usually brings a dramatic recovery, but several adverse outcomes, relapses and also temporary or permanent spontaneous remissions were also reported. High effectiveness of corticoid treatment strongly supports the view on the common autoimmune origin of such broad spectrum of phenotypes.

In this review a special attention is being paid to very few HE cases associated with thyroid hyperfunction which possibly may appear a misleading diagnostic factor. Since the binding of antibodies raised against certain specific epitopes of TSH receptor results in the stimulation of TSH release, it is suggested that this may be the mechanism of HE associated with hyperthyroidism which is based on the strong autoimmune component as the main pathogenic characteristic of HE

BRAIN et al. (1966) described a case of 63 year-old man with seizures, disorientation, frequent episodes of alternating hemiparesis, high protein level in cerebrospinal

fluid and electrocardiographic abnormalities. However, that patient also had hypothyroidism, positive thyroid antibodies and biopsy proved autoimmune (Hashimoto's) thyroiditis. Nearly three decades later SHAW et al. (1991) collected five cases with similar symptoms and called them „Hashimoto's encephalopathy" (HE). Since that time few hundred similar cases were published, among them nearly each one with entirely different clinical presentation. From such reason CHONG et al. (2003) raised the question as to whether HE is a true syndrome or just a myth. Nevertheless, they concluded that, since several patients already presented with various signs of encephalopathy and high thyroid antibodies in serum together with the responsiveness to glucocorticoid therapy, such coincidence seems unlikely to result just from chance. It also appeared that there is no evidence of any specific pathogenic role for thyroid antibodies in the origin of such encephalopathy and several authors hypothesized that these are only markers of possibly unrelated autoimmune disease affecting the brain.

Nowadays, more than 200 of such cases may be found in the literature, most of them using the term Hashimoto's encephalopathy. Nevertheless, in the meantime it appeared that some cases of various impairments of short-term memory, cognitive disturbances, depressions etc. in patients with myxedema thus called "myxedema madness" (ASHER 1949) were described a long time before the above mentioned paper by BRAIN et al. (1966) and possibly should be also considered as HE patients.

Pathogenesis of HE

So far, several pathogenic components of such life threatening disease still have to be elucidated. However, considering a great variety of symptoms both the disseminated encephalomyelitis and possibly also autoimmune general cerebral vasculitis (HENCHEY et al. 1995; SHAW et al. 1999; WATEMBERG et al. 2006) are being supposed as underlying causes of HE which could result in a broad spectrum of functional symptoms and multifocal abnormalities resulting from impaired cerebral perfusion and metabolism (BARKER et al. 1996).

Actually, there are several reasons to suspect also the participation of autoimmune component in the pathogenesis of this disease (such as the majority of cases in female patients, fluctuating course, association with other autoimmune diseases). In spite of that the presence of thyroid antibodies definitely appears an important diagnostic tool, MAHMUD et al. (2003) claimed they did not find any evidence on causative link between thyroid

autoimmunity and encephalitis. However, FERRACI et al. (2004) and KATOH et al. (2007) found thyroid antibodies in cerebrospinal fluid of HE patient and, interestingly enough, the latter authors observed their decrease in parallel with clinical improvement of the patient.

At the same time BLANCHIN et al. (2007) attempted to explore the neurological targets of thyroperoxidase antibodies (TPOab) in HE patients and, among the cohort consisting of 10 HE patients, 33 patients with unrelated neurological symptoms, 12 patients with Hashimoto's thyroiditis and 4 healthy adults, TPOab in cerebrospinal fluid were detected only in HE patients. In immunofluorescent assay such antibodies reacted with monkey cerebellar cells and normal human astrocytes which, together with the above mentioned paper by KATOH et al. (2007) possibly suggested a novel role of thyroid antibodies in the pathogenesis of HE.

A new autoimmune antigen in the brain of HE patients – NH₂ terminal of alpha-enolase (NAE) – was found by OCHI et al. (2002) who observed a high level of antibodies against this antigen in patients with Hashimoto's thyroiditis., while any similar antibodies were not detected in patients with other neurological diseases. FUJII et al. (2005) found the presence of such NAE antibodies in 83.3 % of patients with HE. Later YONEDA et al. (2007) confirmed high prevalence and high specificity of NAE antibodies in 68 % HE patients (17 cases of 25) and recently Matsunaga and Yoneda (2009) specified the prevalence of NAE antibodies to be 44 % in larger cohort of 84 patients and emphasized that, together with thyroid antibodies, also NEA is a useful diagnostic marker of HE. It was repeatedly suggested that such antibodies may be also associated with the pathogenesis of HE. In serum of two HE patients OIDE et al. (2004) detected also anti-neuronal antibodies which immunohistochemically labelled neurons of mouse and human cerebral cortex and reacted with the 36-kDa antigenic protein present in a soluble fraction obtained from human cerebral cortex.

Interesting finding was published by ZETTINIG et al. (2003) who, in the group of 41 patients with Hashimoto's thyroiditis, but with normal detailed neurological history and normal actual neurological findings, observed impaired cerebral perfusion by SPECT as compared to 35 healthy controls. They assumed that such impaired cerebral perfusion in patients with autoimmune thyroiditis could result from cerebral vasculitis which could be present in several patients with autoimmune (Hashimoto's) thyroiditis and thus could be considered as a pathogenic model of HE.

Symptomatology, diagnostics and treatment

So far, perhaps about 200 cases of this syndrome were published with about the same number of various clinical presentations. It still seems to be outside of the attention of endocrinologists and is better known to neurologists or psychiatrists. It must be repeatedly stressed that, in most cases, such serious disease remains undiagnosed or misdiagnosed and thus mistreated. From this reason it is recommended that basic thyroid tests be performed in all unexplained cases with a variety of nonspecific neuropsychiatric symptoms, generalized or partial seizures, hallucinations, status epilepticus etc.

HE appears in all age groups including children (VASCONCELLOS et al. 1999; ALINK and DE VRIES 2008) and 70-80 % of patients are women and girls. It was repeatedly underlined that very often such encephalopathy remains unrecognized, namely in children (MAYDELL et al. 2002; JANES et al. 2004; WATEMBERG et al. 2006). On one hand, HE appears as a clear thyroid disorder, mostly as hypofunction, while it shows the most different neuropsychiatric signs on the other. Such signs usually continue or even show a worsening after the thyroid treatment which is generally considered one of the most important signs of HE, since some neuropsychiatric problems usually accompanying each thyroid disorder disappear after the treatment by thyroxine.

Clinical manifestation may be characterized as fluctuating encephalopathy. Among the most frequently observed signs belong cognitive disorders, focal or generalized seizures, cognitive decline, stroke-like episodes, myoclonus, tremor, choroid movements, central nystagmus, gait disorders, ataxia and hallucinations. In addition, sometimes also the transient aphasia, somnolence, confusion, cephalalgia, fatigue and reversible amnesia may appear. CHONG et al. (2003) summarized 105 cases and concluded that, in most cases, the diagnosis was based on the disturbed consciousness, negative finding of bacterial or viral infection in cerebrospinal fluid and high level of thyroid antibodies, the latter being found in 100 % cases. Moreover, high protein level in CSF appeared in 78 %, EEG abnormalities in 98 %, various and mostly unspecific abnormalities by MR in about 50 %. With the aid of MRI Song et al. (2004) observed ischemic areas, multiple tumours or granulomas or various degenerative processes in 60 %. SPECT examinations and showed decreased perfusion in cortical areas or basal ganglia.

Among 20 HE patients who presented within 1995-2003 (among them 14 females) CASTILLO et al. (2006) found tremor (16), transient aphasia (16), myoclonus (13), walking impairments (13), seizures (12) and sleeping disorders (11). All such patients originally presented with false diagnosis such as viral encephalitis (5), degenerative dementia (4), Creutzfeld-Jacob (3) and most frequent laboratory findings were increased activity of liver enzymes (11), increased TSH (11), increased RBC sedimentation (5). They underlined that clinical, laboratory and radiological findings are very varying and that such syndrome should be always suspected in spite of normal TSH, normal RBC sedimentation, negative cerebrospinal fluid findings and negative neurological findings.

Recently, when attempting to review all published HE cases in children, ALINK and de VRIES (2008) found 25 patients (median age 14, range 9-18 years; 85.8 % girls) among them the most frequent symptoms being seizures (80 %), confusion (52 %), headache (40 %), ataxia (36 %) and hallucinations (32 %). TPOab were found in all cases and 55 % of patients showed complete recovery after treatment with steroids.

The diagnosis of HE is based on detecting thyroid antibodies in these patients, although some correlation between antibody levels and the severity of the illness still remains to be definitely elucidated. Cerebrospinal fluid analysis, electroencephalography, and neuroimaging studies do not show consistent findings to support the diagnosis. Physicians' awareness of this complication is of great importance because most patients respond dramatically to corticosteroid therapy. Moreover, early recognition might also avoid an expensive diagnostic work-up in patients with unexplained encephalopathy.

Although a great majority of described cases showed neural symptoms for months before the acute onset, in some cases a dramatic acute onset appeared. When trying to elucidate the onset question, CHEN et al. (2000) reviewed 30 patients and concluded that two types of clinical presentation can be observed, e.g. that with acute or insidious onset. Nevertheless, recently also a third type of onset and clinical course of a variety of neurologic complications has been defined as „relapsing-remitting manner“, including the cognitive deterioration and psychiatric illness (WATEMBERG et al. 2006).

Clinical experience obtained so far shows that, in spite of unusual variety of symptoms, nearly all patients were successfully treated with corticosteroids.

Mosaic of selected literary cases

Possibly more about HE symptomatology and diagnostic problems could be learned from the overview of some recently published cases. Thus, for instance, FERLAZZO et al. (2006) reported a patient with repeated generalized convulsive status which was resistant to various antiepileptic treatments, but improved after methylprednisolone. They underlined the fact that only the finding of positive thyroid antibodies resulted in appropriate diagnosis and treatment. Similarly, a decisive role of positive thyroid antibodies finding has been stressed by AIDIN-OZEMIR et al. (2006) who successfully treated one 37-year-old male patient with a severe multifocal motoric status epilepticus, body ataxia, semirhythmic convulsions and impaired signals in precentral cortex at MR examination. Bz intravenous corticoids

It seems paradoxical that 36-year-old female patient with 10 year history of autoimmune thyroiditis presented symptoms of encephalitis during the treatment of hepatitis type C with interferon alpha-2b and ribavirin. An objective causality assessment revealed that the HE was probably caused by the patient's medications and thus it was concluded that HE may rarely be triggered by interferon alpha therapy in susceptible patients (DEUTSCH et al. 2005).

ARCHAMBEAUD et al. (2001) presented three females and one male with the same type of convulsions, psychotic episodes, disturbed consciousness and hallucinations and, at the same time, with negative findings by EEG, MR and CT. However, all of them had light hypothyroidism with high level of thyroperoxidase antibodies. In spite of the substitution with thyroid hormones still the disturbances persisted, but definite improvement was found only after the treatment by corticoids.

Unique improvement of HE in 65-year-old male with cognitive disorders and repeated acute convulsions after selective treatment of Hashimoto thyroiditis only was described by GUNTHER and KOPF (2004). One of unusual cases was also observed by MAHMUD et al. (2003) who described a 14-year-old girl suffering from visual and auditory hallucinations since her age of 9. On the walls around she was seeing the pictures of people unknown to her or pictures of animals and she was hearing voices giving her various orders which resulted in her fear and bad mood. She had negative EEG finding and has been treated by psychotropic drugs for 6 months. MRI showed disseminated focuses in frontal lobe, SPECT

showed decreased perfusion in left temporal lobe, basal ganglia and frontal lobes. However, since her twin-sister had autoimmune (Hashimoto) thyroiditis, they finally checked also the thyroid of this patient and found TSH level of 77 mU/l and positive thyroperoxidase antibodies. After one month of treatment with 100 µg thyroxine daily partial improvement appeared, but definite improvement was found after long-term treatment with thyroxine and prednisone. MRI showed disseminated focuses in frontal lobe, SPECT showed decreased perfusion in left temporal lobe, basal ganglia and frontal lobes.

STEVENS et al. (2008) reported the female with type 1 diabetes who was two years after renal transplantation and presented with comatose state that had developed over the preceding 24 hours. She was 55-year-old and the cause of her coma appeared to be HE. The authors discussed a possibility that increased use of steroid-free immunosuppression after that renal transplantation and intensive lymphocyte depletion regimen possibly enhanced a possibility of de novo autoimmune disease onset.

Unusual case of 6-yr-old girl with progressive epilepsy resistant to anticonvulsive treatment and unclear encephalopathy in which finally also Hashimoto thyroiditis was found and thus her epilepsy was ameliorated by corticoids was reported by HOFFMAN et al. (2007). In nine infants YAMANOUCHI et al. (2006) observed acute encephalopathy involving bilateral frontal lobes with convulsive epileptic state and hyperpyrexia followed by a prolonged impairment of consciousness for 2-20 days. After recovery from consciousness, all infants manifested regression of verbal function and lack of spontaneity. In frontal lobes, the diffusion-weighted MR resonance showed a transient postictal edema and SPECT showed attenuated perfusion. The authors proposed a novel HE subtype to be called acute infantile encephalopathy affecting predominantly the frontal lobes.

Possibly the first case of AIDS dementia with HE was reported by WALTEREIT et al. (2007) in a senescent woman which was, however, resistant to steroid therapy.

Progressive spastic paraparesis and hyperintense signal in the spinal cord and brain was observed by GEORGE et al. (2007) in 35-year-old woman in which muscle biopsy showed perivascular lymphocytes around endomysial vessels, but she had also primary hypothyroidism and high level of thyroid antibodies which thus supported the association of both the spinal cord involvement and abnormal muscle biopsy with HE.

CAO et al. (2005) reported HE with prominent unsteadiness of gait consistent with a sensory gan-

glionopathy showed by nerve conduction studies and electromyographic findings which has been resolved with high-dose corticosteroids parallel with a decrease of thyroperoxidase antibodies

LEYHE et al. (2007) described 74-year-old patient with seizures and progressive cognitive deterioration. Since previous anti-epileptic treatment with carbamazepine, lamotrigine and topiramate had not been effective, they suspected HE and the treatment with prednisolone (100 mg/d over 6 months) resulted into a cessation of seizures and cognitive improvement. They concluded that HE should be a differential diagnosis in cases of epilepsy in the elderly. Late-onset seizures are frequently caused by cerebrovascular disease, head trauma, degenerative disorders or CNS tumors. In one-third of cases, the etiology remains obscure. In only 60-70% of adult-onset epilepsy is antiepileptic drug treatment successful. Although seizures are a well-known symptom of HE, it is rarely taken into consideration as differential diagnosis in epilepsy.

One unusual female patient who presented with goiter, recurrent encephalopathy and elevated thyroid peroxidase antibodies, while she apparently responded to steroid therapy has been described by CHAN et al. (2007). However, magnetic resonance imaging was atypical for HE, and she was diagnosed with MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). Although such syndrome can present with apparent steroid-responsive encephalopathy and also with elevated thyroid peroxidase antibodies thus mimicking HE, but even in such cases MELAS should be suspected if stroke-like episodes are present together with lactic acidosis in cerebrospinal fluid and blood and typical features are detected on magnetic resonance imaging.

Another unusual case of spontaneous complete remission of HE without corticosteroid treatment was observed by KATO et al. (2007) in a 85-year-old man. He had positive autoantibody against the amino terminal region of alpha-enolase and his neuropsychological manifestations (personality change and progressive cognitive impairment) gradually improved over approximately 6 weeks after onset of disease in parallel with a spontaneous decrease in the anti-thyroglobulin antibody (TGab) in the cerebrospinal fluid. Such finding of TGab in CSF perhaps appears a new important diagnostic tool and perhaps also pathogenetic factor, since it was not detected in blood. Thus, the authors suggested that HE should be considered as a possible diagnosis even in elderly patients with neuropsychiat-

ric symptoms, particularly when a previous history of thyroid disease is present.

The report by BISMILLA et al. (2007) described a case of HE in an 11-year-old girl presented with features typical for HE such encephalopathy, seizures, and neuropsychiatric symptoms. Hypothyroid stage of autoimmune thyroiditis was supported by elevated TSH level, low T4 level and positive TPOab. Since her response to levo-thyroxine treatment was incomplete, an additional therapy with valproic acid and methylprednisone was started. Since also acute psychosis developed, the treatment with risperidone resulted in the resolution of her psychosis and improvement in neuropsychiatric symptoms. The authors underlined that antipsychotic therapy has not been previously described in the pediatric population with HE and suggested the need of guidelines for the management of such rare disorder.

SPORIS et al. (2007) showed that HE also can manifest with purely psychiatric symptoms such as in their patient with history of rheumatoid arthritis – a 38-year old female – who was treated with psychotropic drugs for a couple of years in psychiatric structures because of depressive symptoms, psychotic like manifestations and impairment of cognitive functions. The EEG was characterized by general slowing with high voltage (2 to 3 Hz) delta biphasic and triphasic waves. However, after a firm HE diagnosis was made, corticosteroid treatment resulted in resolution of her psychiatric symptoms, marked EEG improvement, and partial improvement in her cognitive functions. Since they did not find autoimmune thyroiditis in this patient, they assumed that possibly also some other autoimmune disease - such as rheumatoid arthritis – could be related to HE and thus they recommend to suspect HE in young females with history of autoimmune disorders and EEG abnormalities.

In a 37-year-old woman memory disturbance and seizures were preceded by headache and high fever (SHINDO et al. 2007). She presented with persistent high fever, confusion, neck stiffness, anterograde and retrograde amnesia and disorientation. In CSF the pleocytosis, normal glucose level, and negative herpes simplex virus DNA on PCR were found. The fluid attenuated inversion recovery (FLAIR) MRI of the brain demonstrated nearly symmetric high signal intensity areas in the bilateral mesial temporal lobes. The tentative clinical diagnosis was non-herpetic acute limbic encephalitis (NHLE), and administration of methylprednisolone improved her conditions. Mild hypothyroidism was also found with high level of serum TPOab and TGab which supported

autoimmune (Hashimoto's) thyroiditis. In addition, antibodies against amino terminal of alpha-enolase and against glutamate receptor (GluR) epsilon 2 in serum and CSF were positive. The present case suggests that NHALE-like clinical manifestation can be produced by autoimmune-mediated encephalopathies related to HE associated also with GluRepsilon2 antibody.

LOPEZ-GIOVANELI et al. (2007) observed two very rare patients in which there was a considerable gap of 10 to 20 years between the proof of autoimmune thyroiditis and neurological symptoms. After several relapses total recovery was confirmed 3 years after the end of steroid treatment. HUETE et al. (2007) reported a patient with HE presenting as long-standing episodes of aphasia associated with migraine and aura. She had normal thyroid hormone levels, but high level of antithyroid antibodies.

Recently NAGAMINE et al. (2008) reported one patient in which HE was apparently induced by lithium used to relieve depressive symptoms, while SHINAGAWA et al. (2008) described HE case induced by morphine sulfate used for the management of cancer pain.

Rare cases of HE with hyperthyroidism and their possible pathogenesis

Actually, most HE cases reported so far occur under the conditions of hypothyroid or euthyroid state resulting from the presence of thyroperoxidase antibodies which, at the same, contribute to the destruction of thyrocytes leading to hypothyroidism. In contrast, however, perhaps the first patient with "Hashimoto's encephalopathy" and pronounced thyrotoxicosis was a 49 year old women who presented with progressive left sided weakness and was successfully managed with steroids, carbimazole and propranolol (BARKER et al. 1996). Similarly, 39 year old women with repeated episodes of generalized convulsions and hyperthyroidism who responded to steroids was reported by PESCHEN-ROSIN et al. (1999). Another patients with encephalopathy accompanied by Graves' disease who responded to corticoid treatment has been described by CANTON et al. (2000) who, from such reason, instead of "Hashimoto's encephalopathy" proposed the term "*encephalopathy associated to autoimmune thyroid disease*" as more appropriate for this syndrome. After careful revision of the literature CHONG et al. (2003) found a total of 105 HE patients, but analyzed only 85 of those which were presented with most complete data. Among them they found 4 patients with hyperthyroidism (i.e. with low TSH and

high thyroxine level) and 2 patients with subclinical hyperthyroidism (i.e. with low TSH and normal thyroxine level). At the same time SEO et al. (2003) presented another HE patient with hyperthyroidism. Recently YUCEYAR et al. (2007) observed a 31-year-old female with thyrotoxic HE, whose daughter has been followed up with the same diagnosis. Suboptimal improvement was observed with intravenous methylprednisolone, intravenous immunoglobulin and plasmapheresis. Decreased blood level of thyroid antibody resulted in an improvement of patient's status and she relapsed under oral immunosuppressive therapy. However, full recovery has been achieved only after thyroidectomy. These data may contribute to the clarification of pathogenetic role of thyroid antibodies in HE and thyroidectomy may be considered as one of the treatment options especially in thyrotoxic HE patients with uncontrolled relapses. In addition, this patient possibly has been the first reported HE case with a family history. Genetic background can underlie the etiopathogenesis of HE as also known in other cases of autoimmune disorders. DIHNE et al. (2007) reported a patient in which HE developed after thyroid radiotherapy with 131-iodine for Graves' disease. Few patients with HE and thyrotoxicosis were recently reported from Japan (SAITO et al. 2002; SAKURAI et al. 2008) and from Korea (SEO et al. 2003).

The pathogenesis of rare HE cases associated with thyrotoxicosis may be explained by different epitopes of TSH receptor located on the membrane of thyroid epithelial cells. Thus, extracellular A subunit is recognized by thyroid stimulating antibodies whilst the subunit B which is located much nearer to the cell surface, shows the affinity to TSH receptor blocking antibodies (CHAZENBALK et al. 2004; SINCLAIR 2008). Thus, since a strong autoimmune background participates in the etiology of HE, it appears obvious that, in some cases, the antibodies may be directed predominantly to the stimulatory epitope of TSH receptor thus resulting in thyrotoxicosis.

Case report

We also observed a 27-year-old woman which apparently also belongs to that sprinkling of HE cases with hyperthyroidism as published in more detail previously (PAYER et al. 2007). About 4 months before the acute onset of neural symptoms the endocrinologist found low TSH, high FT4 and high thyroperoxidase antibodies (TPOab) and prescribed the treatment by carbimazol (2 x 5 mg/d). However, few weeks after she deliberately

withdrew from this drug and neural symptoms then started after 5 days of febrile status with headache and arthralgia treated by an antibiotic. That time her husband at night noticed irregular breathing and responsiveness only to painful stimuli. The emergency physician found roving eye movements, intermittent seizures and altered consciousness. She was admitted to the hospital and subjected to artificial pulmonary ventilation and analgesic-sedative medication. She had negative brain CT, stable BP and tachycardia, leukocytosis, increased C-reactive protein and hyperglycaemia (8.8 mmol/l). TSH level was decreased (0.02 mU/l) and FT4 level increased (53.6 pmol/l) which clearly showed thyrotoxicosis. The level of all thyroid antibodies against thyroperoxidase (TPOab), thyroglobulin (TGab) and thyrotropin receptor (TRab) was very high. CSF showed increased IgG, IgM, albumin and total protein. Since the first day after the admission she was treated by carbimazole (30 mg/d) and hydrocortisone (200 mg/d). After 6 days her status was stabilized, the dose of hydrocortisone was decreased to 100 mg/d and replaced by prednisone (15 mg/d). However, three days later her status was aggravated and consulting psychiatrist concluded that this possibly resulted from side effects of corticoid treatment. However, after the withdrawal of corticoids her status rapidly worsened. The dose of carbimazol was increased to 60 mg/d and hydrocortisone was started again (3 x 100 mg/d) which resulted in nearly complete restitution of psychological functions within 3 days. Nevertheless, after the next withdrawal of corticoids the progressive aggravation of psychological functions and epileptic-like seizures appeared again. We finally concluded that her symptoms including thyrotoxicosis with low TSH, high FT4 and TRab, as well as repeated worsening of her condition after withdrawal from corticoids are compatible with the diagnosis of Hashimoto's encephalopathy. However, since the beginning, a misleading circumstance was namely the thyrotoxic status since our brief survey of the literature only showed HE cases with a hypothyroid or euthyroid state. She is permanently on peroral carbimazol (2x5 mg/d), prednisone (60 mg/d) and her long-term status appears fully stabilized. Thin

needle biopsy showed signs of chronic exacerbated Hashimoto's thyroiditis and some follicles with hypertrophic cells which is compatible with frequently used term "hashitoxicosis" in several thyrotoxic patients. SPECT examination showed normal accumulation in both hemispheres.

In conclusion, it appeared that few patients were presented with Hashimoto's encephalopathy combined with thyrotoxicosis which, in some cases, may be a misleading circumstance preventing to establish the appropriate diagnosis and treatment. Since a great majority of reported HE patients was hypothyroid, our above described patient prompted us to focus on the explanation of possible pathogenesis of very rare HE cases with thyrotoxicosis. Actually, it is well known that two main thyroid disorders – Hashimoto thyroiditis with hypothyroidism and Graves' disease with hyperthyroidism – are of autoimmune nature, the former being caused by thyroperoxidase (TPOab) and/or thyroglobulin antibodies (TGab), while the latter results from the effect of thyrotropin receptor stimulating antibodies (TRSab). Very rare thyroid patients may present with fluctuating thyroid function such as with one of these disorders at one time and with the other one at another time. Thus, TAKASU et al. (1990) reported eight cases of hypothyroidism due to Hashimoto's disease who developed Graves' disease and later OHYE et al. (DOI: 10.2169/internalmedicine.45.1506) reported four cases of Graves' disease after painful Hashimoto's thyroiditis. Since our patient described above had high levels of thyroperoxidase and thyroglobulin antibodies on one hand and thyrotropin receptor antibodies on the other, it may be hypothesized that such hyperthyroid state (supported by high free thyroxine and low TSH level) developed from preexisting Hashimoto thyroiditis. In addition, thin needle biopsy showed exacerbated Hashimoto thyroiditis and, at the same time, hypertrophic follicles with high follicular cells which further supported such hypothesis. From these findings it is suggested that possibly some of Hashimoto encephalopathy cases with hyperthyroidism may develop from preexisting hypothyroidism due to Hashimoto thyroiditis.

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