Hashimoto’s Encephalopathy

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Hashimoto’s Encephalopathy (HE) is a rare condition associated with Hashimoto’s disease. HE is seen mostly in women. Researchers considered HE to consist of two sub types. HE is diagnosed in patients with neurological findings (generalized seizures, myoclonus, ataxia, cognitive disorders, focal neurological disorders), by looking at the high titers of antithyroid antibodies and abnormal thyroid functioning tests, nonspecific EEG changes, nonspecific white matter changes and elevated CSF protein. There are serious positive evidences supporting an autoimmune etiology for the disease (more frequent in women, dramatic response is given to steroid treatment, seen concomitantly with other autoimmune diseases). The other pathologies that cause central nervous system vasculitis should be eliminated. The clinical, laboratory and biochemical findings support the presence of an underlying autoimmune event in patients with encephalopathy in association with autoimmune thyroid disease. Therefore, a good respond to treatments regulating the immune system are expected. If no specific etiology has been established in patients with acute and subacute encephalopathy, neurologic findings in these patients should be considered to be related to autoimmune thyroiditis. In Hashimoto’s encephalopathy diagnosis and treatment commences when the disease is first suspected.

Keywords: Hashimoto’s Disease, Hashimoto’s encephalopathy, autoimmune thyroid disease, Graves disease, Creutzfeldt-Jakob disease

Hashimoto’s Encephalopathy

Hashimoto’s Thyroiditis (HT) is a common form of chronic autoimmune thyroid diseases. Hashimoto’s Encephalopathy (HE) is a rare condition associated with Hashimoto’s disease. HE cases began to be reported in 1966 following the first report by Brain and colleagues about a 63 year-old patient with hemiparesis presenting itself as a vascular defect due to the presence of seizures (1). All other conditions leading to encephalopathy should be excluded to diagnose HE. HE is diagnosed in patients with neurological findings (generalized seizures, myoclonus, ataxia, cognitive disorders, focal neurological disorders), by looking at the high titers of antithyroid antibodies and abnormal thyroid functioning tests, nonspecific EEG changes, nonspecific white matter changes and elevated CSF protein. After the diagnosis has been made, corticosteroid treatment should be started, since these patients respond well to steroid treatment. Besides, spontaneous remission might also be seen.

HE patients might come up with different clinical pictures. The facts that most of the patients are female, the disease is seen together with other autoimmune diseases and its responsiveness to corticosteroid treatment, brings to mind that the disease might have nonautoimmune origin. In the examination of the CSF (Cerebrospinal fluid) of the first diagnosed subject, an increased protein level and transient anomalies in EEG were established. In this patient Hashimoto’s Thyroiditis was diagnosed relying on the findings of hypothyroidism, positivity of antithyroid antibodies and biopsy results. Patient demonstrated spontaneous improvement after the occurrence of 12 seizure attacks, and the antineuronal antibodies, which were checked later on, were determined to be negative (1).

Hashimoto’s Thyroiditis (HT) Pathogenesis

Up to date many genes associated with HT have been described. Hashimoto’s Thyroiditis (HT) causes a disease in the thyroid gland through a T-cell mediated immune mechanism in people with appropriate genetic type. Chronic autoimmune thyroiditis is seen in 8% of women, 3% of men and
in 10% of women above 55 years (2). Subclinical hypothyroid rates of 4.6% and clinical hypothyroid rates of 0.3% were documented in the NHANES III study where 17,353 healthy subjects above the age of 12 were studied (3). According to the results of a 20 years period of observation, the risk of developing hypothyroidism was found to be 4 times higher in women between 60-70 years, compared to women between 40-50 years (4).

HT can start as subclinical hypothyroidism (5). As it is the case in all autoimmune diseases, the commencement of HT can be affected by genetic and environmental factors. The environmental factors include: increased iodine intake (6,7), bacterial (Yersinia enterocolitica) (8) and viral infections (influenza B, rubella, retrovirus), cytokine therapy (9), and pregnancy. Infectious agents can affect the thyroid gland in various ways. The disease may manifest itself with mechanisms such as self-antigenic changes, antigenic similarities and increased polyclonal T cell activation. As a result, MHC expression on the thyroid cells increases and immune destruction begins (10). The role of dietary iodine is well known in animal trials (11).

Antigen presenting cells present autoantigens to T cells, and later they lead to clonal expansion and activation. Therefore the maturation and clonal expansion of autoreactive T and B lymphocytes occurs in the lymph nodules at the onset of the disease. In animal models, autoimmune thyroiditis is seen together with the presentation of tissue antigens and expansion of autoreactive lymphocyte cloning, following the breaking down of immunologic self-tolerance. This immune defect occurs particularly in the presence of MHC class 2, however it can also occur in the presence of the other immune regulator genes (for example, CTLA-4 and others) (12).

Immune tolerance defects can occur through different ways. Central tolerance interaction (autoreactive T cell loss at the thymus), and abnormalities in peripheral tolerance might occur. There must be an insufficiency in the regulatory and suppressory T cell subpopulations for the development of autoimmune diseases in predisposed individuals and in patients with autoimmune thyroiditis. In autoreactive T cells there is activation in the absence of anergy and depletion, there is also the possibility of triggering an autoimmune event following T cell tolerance loss (13). Antigen presenting cells convey the message to T cells and thus activate them after the excess expression of MHC molecules and the identification of these cells by antigen presenting cells (14). Excess expression of MHC class II is supported by studies on mice. Researchers have demonstrated that a type of Grave’s disease had developed following the intravenous injection of TSH receptor and MHC class II. They also demonstrated that there is an increase in the production of class II and TPO antibodies in fibroblast after the injection (15,16).

HE is a rare but potentially fatal autoimmune disease, which can mimic many different neurological diseases. Although this is a treatable disease, it is essential that the physician recognizes and treats the illness on time. After exclusion of the other conditions causing brain damage in patients with subacute encephalopathy, elevated autoimmune antibody levels might be related with HE (17). At this point, it is essential to observe the antibodies since the addition of steroids will lead to remission (18).

**Epidemiology of Hashimoto’s Encephalopathy (HE)**

HE is seen mostly in women. Most of the reported cases are adult patients. However incidences in children have also been reported (19).

In the study made by Oide and colleagues 150.000 people were analyzed in terms of neurological findings, and antithyroid antibodies were searched in symptomatic individuals. Antithyroid antibodies were found to be high in 12 of these patients and HE was documented in 9 of the patients. Based on these results the prevalence of HE was determined to be 2.1/100.000. No correlation was established between the level of antithyroid antibodies determined in the examination of CSF and the clinical picture of HE (20).

**Clinical Aspects of Hashimoto’s Encephalopathy (HE)**

Hashimoto’s Encephalopathy (HE) is believed to be a complication of Hashimoto’s Thyroiditis (HT). It was first defined in 1966 by Brain and colleagues, and in this case HE was accompanied by myasthenia gravis (1). HT is commonly seen together with the other autoimmune diseases such
as Type I diabetes, celiac disease, rheumatoid arthritis, multiple sclerosis and vitiligo (21). Since 1966 there has been an increase in the incidence of HE cases in Hashimoto patients. Approximately 100 cases have been reported from the time it was initially defined until 2002 (22).

Researchers considered HE to consist of two sub types. The first is an insidious, recurrent vasculitic type, demonstrating stroke-like attacks concomitant with impairment of consciousness, and the second is progressive and the more commonly seen form of encephalopathy, which presents itself with confusion, psychosis, somnolence and coma (57,71).

Among the clinical findings associated with HE are: stroke-like symptoms (23,24), confusion (25), focal or generalized seizures (23,26-32), psychosis (23,32), amnesia (33,34), myoclonus(35,36,44,61) and cerebellar syndrome (37). It may manifest itself through different neurological symptoms such as fluctuating confusion states, suppression of cognitive functions, tremors (38,39), hallucinations (40,44,61), depression (41,42) and fever (43).

In a study of 9 diseases in the HE series 7 of the patients were found to have generalized seizures together with focal neurological findings. These neurological findings included headache, mental alterations, grand mal epilepsy, myoclonus, ataxia, tremors, focal parenthesis and heat loss. The average age of these 9 patients (4 men, 5 women) was 54, the number of neurological attacks suffered was 2-4, average duration of the neurological picture appeared to be 1.5 years (45).

Stiff-limb syndrome is a condition characterized by stiffness and contractions in the extremities. The stiff-limb syndrome is also associated with autoimmune diseases. Calvet and colleagues presented a 70-year-old HE patient with stiff-limb syndrome. Encephalopathy findings of the patient improved rapidly following the corticosteroid treatment and after 12 months the subject went into remission totally (46).

Neurological system involvement is frequently seen in Thyroid diseases. The occurrence of neurological findings in patients with hypothyroidism and hyperthyroidism is a well-known condition (47). Patients with thyroid disease, who also manifest a clinical picture of encephalopathy, should receive endocrinological consultation. The encephalopathy picture accompanied by these neurological findings might totally be associated with the level of thyroid hormone. Therefore the clinical picture might be completely improved by normalizing the levels of thyroid hormone. This event is completely different from the clinical picture of HE (48).

HE has no relationship with the clinical picture of hypothyroidism or thyroid functional tests; it is generally seen in euthyroid (49) patients. HE cases seen together with the clinical picture of hyperthyroidism have also taken their place in medical literature (50,51).

The generally accepted point is that the underlying mechanism in both HE and HT is autoimmunity. From this point of view two possible mechanisms were put forth in the development of HE. The first of these might be the result of edema and reduction in the vasculature due to autoimmune mediated central nervous system vasculitis together with impairment of the microvascular structure. The other is the formation of antineural antibodies and cross-reaction due to a common antigen of both the thyroid gland and the brain. In some of the cases the vasculitic theory gains weight due to the presence of perivascular lymphocytic infiltration. Besides, there is a moderate infiltration in most cases and the presence of a genuine vasculitis has not been clearly demonstrated in the previously reported cases of HE.

Seo and colleagues reported a Graves case with a high TRab level, multifocal myoclonus and a picture of subacute progressive encephalopathy. A decreased cerebral glucose metabolism was demonstrated in this patient using PET imaging. In graves disease there are two different routes in the mechanism of encephalopathy. The first is the increase in the level of thyroid hormones due to the effect of TRab, which might lead to neurological signs. This picture can improve only after thyroid hormone levels are normalized following anti-thyroid treatment, however no remission of this sort was seen in the patient presented by Seo and colleagues. Dexamethasone treatment was begun in the patient and a rapid response was obtained. Finally the symptoms of this patient were reduced after a short period following the onset of dexamethasone treatment and the symptoms improved completely with the continuous application of high doses of steroid treatment. The clinical course of
this patient diagnosed with Graves disease and the response he gave to steroid treatment, supports the presence of an autoimmune mechanism (52).

HE associated with thyrotoxicosis was reported only in two cases and these cases responded dramatically to corticosteroid treatment (45,53). One of these patients was diagnosed with Graves whereas the diagnosis of the other was not clear. The central nervous system finding of thyrotoxicosis is mostly psychosis or impairment of reasoning. Mental confusion, seizures, manic or depressive dispositions might occur in some thyrotoxic patients, and these symptoms might respond to corticosteroid treatment or plasmapheresis (54,55). In this context, TRab (TSH receptor antibody) is either low or not evaluated in thyrotoxic patients with encephalopathy; as a result, it is difficult to eliminate the possibility of an autoimmune mechanism in thyrotoxic patients (56).

Patients presenting a clinical picture of encephalopathy associated with HT, Graves, Graves’ ophthalmopathy and hypothyroidism were examined at the Mayo Clinic between 1950 and 1996. Clinical, laboratory and neurologic imaging techniques were used for the diagnosis of HE associated with AIT (autoimmune thyroiditis). Patients demonstrating one or more of the clinical signs such as hallucination, myoclonus, generalized tonic-clonic seizures or focal neurologic symptoms, were recruited in the study. 188 patients were investigated in this study and HE associated with Hashimoto’s thyroiditis was determined in 9 of them (45).

Hashimoto’s encephalopathy can also occur before HT develops. Peschen-Rosin and colleagues reported the case of a patient having generalized seizures and myoclonic symptoms. Initially, the patient’s MRI and thyroid tests were not studied. Oligoclonal bands were demonstrated in the CSF examination. Patient’s symptoms improved a short period after the administration of high doses of prednisolone treatment. Hyperthyroidism developed in the patient following the 5th myoclonic attack, and the levels of antimicrosomal antibodies investigated seemed to be high. The special thing about this case is that before the development of HE, Hashimoto’s thyroiditis was not known; and HT and the associated HE diagnosis was made after the development of neurologic symptoms, when examinations revealed increased levels of antithyroid antibodies (59).

Autoimmune Mechanism

There are serious positive evidences supporting an autoimmune etiology for the disease. The disease is more frequent in women. It might be seen concomitantly with other autoimmune diseases (58). Also, a dramatic response is given to steroid treatment (60,63). Apart from corticosteroids, other immune modulation treatments were also used, including azathioprine (62), methotrexate (62), cyclophosphamide, hydroxychloroquine sulfate and plasmapheresis (64,71,78), intravenous immune globulin (62,79) and success was achieved in most of the patients.

Apart from the clinical findings, antithyroid antibodies are high. Its association with autoimmune vasculitis and the accumulation of immune complexes is likely to form the bases for pathogenesis. Visualization problems in the brain and metabolic abnormalities tend to occur as a result of these immune events.

One of the evidences supporting autoimmunity is that 2 years ago a homogeneous increase was determined in the Gd DTPA (Gd-diethylenetriaminepentaacetic acid) evaluation of a female patient diagnosed with HT, who came in with seizures; 2 weeks later malignancy was suspected upon the discovery of a lesion enlargement in control CT, and thus biopsy specimen was obtained and consequently it was seen that most parenchymal vessels were infiltrated with lymphocytes. A complete improvement in the lesion was noted following the corticosteroid treatment. The special thing about this case is that its histopathology and improvement with immunomodulated treatment, supports the significance of vasculitis (isolated vasculitis) in the pathogenesis of HE (63). Apart from this one, other data in the literature also support the autoimmune phenomenon (64).

In the 9 HE patient series examined by Oide and colleagues, two of the cases demonstrated lymphocytic infiltration in the brain vessels (20). The demonstration of vasculitis using angiography supports the diagnosis in these patients. Recently, an experimental explanation to support vasculitic pathogenesis has been the identification of the autoantigen, α-enolase, in Hashimoto’s encephalopathy. Anti α-enolase antibodies in systemic lupus erythematosus and ANCA associated vasculitis are expressed in great amounts in the
endothelium (65). When the presence of antibodies against \( \alpha \)-enolase was compared with a group of 10 healthy controls, none was found to be present in the control group, whereas 4 (19%) of 21 Hashimoto patients and 1 (8%) of 12 Grave’s disease patients had these antibodies (66).

Caselli and colleagues presented 5 patients under the title of non-vasculitic autoimmune inflammatory meningoencephalitis, with abnormal CSF findings and a good response to steroid treatment. Postmortem brain biopsy was performed in most of these patients and moderate leptomeningeal perivascular lymphocytic inflammation was demonstrated. Nonvasculitic autoimmune mediated meningoencephalitic Sjogren’s syndrome, systemic lupus erythematosus, and recently Hashimoto’s disease have also been described (67).

A 15-year-old HE patient with Hashimoto’s thyroiditis demonstrating a clinical picture of autoimmune thyrotoxicosis was reported. This patient was diagnosed with distal renal tubular acidosis at the age of 5, pernicious anemia at the age of 9 and encephalopathy at the age of 12. Thyroid hormone levels were found to be within normal ranges at the time when neurologic signs had developed. Cognitive functions improved following the corticosteroid treatment, however the mental condition continued to deteriorate. A progressive symmetric atrophy was discovered in repeated cerebral CT examinations, without the presence of any infacts in the white matter. These findings bring to mind an antineuronal antibody mediated reaction in HT associated HE (51). In the previous studies it was thought that the toxic effects of TRH could cause HE, however a sufficient amount of data could not be gathered in relation to this (68).

In a patient with a clinical picture and laboratory findings of HE, a biopsy specimen was obtained and immunohistochemical studies with western blot analyzes were performed on it. This was compared with purified IgG obtained from other patients diagnosed with HE. Findings of vasculitis and other reasons were not discovered in brain biopsies. This IgG type antibody reacted with a soluble protein (36kDa) found in the cortex of men and mice. These results support the fact that antineuronal antibodies may be responsible for the pathogenesis of HE. This antigen did not show any reaction in the control group and the patient group of HT without antigen encephalopathy (69).

Central nervous system vasculitis causes multifocal cerebral dysfunction, whereas corticosteroid treatment is mostly useful in focal brain damages. The second theory involves the direct influence of antineuronal antibodies. This appears to be a possible pathogenesis for HE, because the nonfocal neurologic symptoms and widespread slowness of EEG brings to mind a diffuse encephalopathy. The imaging techniques are also either abnormally or completely normally diffuse and symmetrical. These findings support humoral autoimmunity. Recently, Ochi and colleagues defined \( \alpha \)-enolase (48 kDa protein) as an autoantigen in HE patients. Though in small numbers, there was a weak reaction against alpha-enolase in 95% of the HT patients. This reaction was also tested in healthy groups and found to be negative (65).

Fujii and colleagues investigated auto antibodies associated with Hashimoto’s thyroiditis in HE patients. They demonstrated that the amino terminal region recombinant of \( \alpha \)-enolase in human cell culture was high in most HE patients associated with HT (83.3 %; 5/6 patients). On the other hand, apart from HE, the percentages were determined to be 11.8% (2/17) for any group of patients with neurologic disease and 0 % (0/50) for the control group. As a result it was emphasized that the antibodies formed against the amino terminal of alpha enolase, can be used as indicators in the diagnosis of HE (70).

High levels of antithyroid antibodies were previously used for the diagnosis of HE. However apart from Hashimoto’s, antibodies were also found to be positive in the other thyroid diseases. The use of only antithyroid antibodies for the diagnosis of HE can lead to false positive results (20). In spite of this, the increase in the level of antithyroid antibodies in the serum, can show itself as depression in the clinical picture of HE (72). On the other hand, it is necessary for antibodies to be demonstrated in patients with unexplained neurologic symptoms. The relationship between the increased serum antibodies and HE is unclear.

Laske and colleagues reported the case of a 74-year-old patient with severe depression attacks who could not respond to treatment with citalopram, 40 mg/day and venlafaxine, 150 mg/day. In a detailed EEG examination aimed at diagnosis, abnormality, high antithyroid antibodies and thyroditis related findings in the thyroid ultrasonography were documented. This patient was
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diagnosed with HE and began to be treated with prednisolone, 70 mg/day. The dose was gradually reduced and treatment was continued with antidepressant drugs. On the 4th week of treatment, in addition to the achievement of normal EEG results, depressive episodes also disappeared and the antithyroid antibody level decreased. It should be taken into consideration that depression might be one of the early findings in the clinical picture of HE. HE should be suspected during refractory depressive conditions, these cases might respond to treatment with steroids (42).

Diagnosis

Information that might be beneficial in the diagnosis of HE:

1- Recurrent illness (generalized seizures, myoclonus, ataxia, cognitive defects, focal neurologic defects),
2- Abnormal thyroid functional tests,
3- High antithyroid antibodies,
4- Nonspecific EEG changes,
5- Nonspecific white matter changes,
6- Elevated CSF proteins

HE is an abnormality, which responds to treatment with steroids and it is frequently accompanied by diffuse abnormal EEG and seizures. EEG findings were examined in 7 patients with HE; there was generalized slowness and frontal rhythmic slowness in 5 of the patients, triphasic waves in 2 of the patients, periodic sharp waves in one of the patients, and focal temporal slowness in 3 of the patients. There were different clinical and EEG findings in HE (82).

There is no correlation between the antithyroid antibody titer and the severity and clinical picture of encephalopathy. There is no correlation between thyroid functions of the patients and HE either. In patients with Hashimoto’s thyroiditis, in the occasion of encephalopathy, antibody presence should be investigated because excellent results are being obtained with corticosteroid treatment (20,73,83).

During a SPECT study, brain perfusion findings of euthyroid HT patients and healthy control subjects were compared. A high prevalence of abnormal brain perfusion findings in HT patients was demonstrated. Moreover these results were found to be similar to those of severe HE patients. Therefore, it is emphasized that HE can occur in autoimmune thyroiditis patients more frequently than it was previously thought (84).

HE can sometimes mimic a cerebrovascular disease. In this regard Utku and colleagues reported a 45-year-old patient who had sub-acute encephalopathy associated with Grave’s disease. Intracerebral great vessel occlusion was identified in this patient using MR angiography (MRA) findings. The neurologic picture improved dramatically following the administration of high doses of methylprednisolone and plasmapheresis. Three months later there was a regression in the control MRA findings (85).

Antithyroid antibodies were positive in almost all of the patients. Thus it is not enough to make a diagnosis only due to its high levels. CSF protein was found to be high in 75% of the patients in the CSF examination. In 27% of these patients oligoclonal bands were found to be increased in the CSF examination, and a protein increase in correlation with mononuclear pleocytosis was established. Glucose values were within normal limits in CSF. Nonspecific findings were obtained from the EEG examinations. Intermittent slow wave appearances could be visualized. Increased signals of subcortical density could be seen in the T2 images using the imaging method of MR in approximately 60% of the patients. CT imaging is less sensitive than MR and thus abnormalities are discovered in 29% of the patients. In these patients, correct results will be obtained using angiography and Doppler examinations (86,87).

Differential Diagnosis

The other pathologies that cause central nervous system vasculitis should be eliminated. Lymphocytic vasculitis shows itself by the presence of lymphocytes on the vessel walls and can appear together with the Wegener’s disease, systemic lupus erythematosus and Behçet’s disease (74).

During differential diagnosis, Creutzfeldt-Jacob disease (CJD) should also be taken into consideration. HE and Creutzfeldt-Jacob disease both have similar clinical aspects. It is important to differentiate between these two diseases because while HE responds to corticosteroid treatment, Creutzfeldt-Jacob disease does not and it is progressive (45). HE cases similar with CJD are present in the literature (76). In a separate study, a CJD patient with high antithyroid antibodies, and having similarities to HE was reported; the
diagnosis of this patient’s clinical course was made following autopsy (75). The symptoms of Creutzfeldt-Jacob disease include rapidly progressive dementia, myoclonus, pyramidal, extrapyramidal and cerebral symptoms (77). It is generally a rare disease seen between the ages of 60 and 70 (1 case/1000 000 persons/year). It is more frequently seen in women than in men. Death occurs in a few months following the onset of the disease. Diagnosis is made relying on clinical suspicion, EEG and CSF examinations (78,79). No effective treatments are presently performed.

The 14-3-3 protein belongs to the family of acidic proteins and in mammals it is made up of 7 isoforms (β, γ, ε, σ, ζ, τ, η). The 14-3-3 protein interacts with more than 200 phosphoserine dependent and independent proteins. There is limited knowledge on these interactions, and continuous studies are being made in this regard. The 14-3-3 protein which is positive in CJD was investigated in CSF in the previous articles during the differentiation of HE from CJD and such a patient was described (75). The 14-3-3 protein controls the cell cycle, growth, differentiation, apoptosis, migration and diffusion. The new mechanism of action of this protein has been a call for concern in the latest studies. The 14-3-3 protein, together with its isoforms, can have a direct association with human cancer. In the occasion of DNA abnormality, the 14-3-3 protein itself makes arrangements over p53 (80). Sensitivity and specificity of this protein was demonstrated to be high in a study made on CJD patients (sensitivity 97% and specificity 87%) (92).

In neurogenerative diseases the 14-3-3 protein was found to be high in the CSF of human and animals (scrapie, bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jacob disease). Progressive neuronal defect is considered when this protein is discovered in the CSF of CJD patients. Besides, no isoforms of this protein was found to be present in the nonaffected neurons of CJD patients (81).

Different imaging results were presented for HE patients. The improvement in MR findings and the decrease in antithyroid antibodies were found to be related with the improvement in the clinical picture (88). MRI findings were normal, increased signals in the subcortical and mesocortical regions or widespread edema, and inflammation could be seen in the T2 sequence. SPECT (Single Photon Emission Computed Tomography) might show findings of hypoperfusion in many areas (52). Forchetti and colleagues related the presence of autoimmune vasculitis to multiple hypoperfusion discovered in SPECT; they also demonstrated an improvement in the low perfusion rates, following the improvement of defective areas (89). Besides, most HE patients have normal sedimentation rates and angiographic images. Only the vasculitic findings in the venules were described in the necropsy materials (90,91).

**Treatment**

The clinical, laboratory and biochemical findings support the presence of an underlying autoimmune event in patients with encephalopathy in association with autoimmune thyroid disease. Therefore, a good respond to treatments regulating the immune system are expected. HE patients might sometimes demonstrate spontaneous remission (76). They generally respond well to corticosteroid treatment, and the other immune suppressing agents (azathioprine, cyclophosphamide and intravenous immune globulin) might also be used. The initial dose of steroids varies between 50 mg and 150 mg of prednisone daily, usually slowly decreased over weeks to months, depending on the clinical course. However, the recommended treatment for H.E. is high dose (Immunosuppression) steroid treatment (1 gram intravenous methylprednisolone) for 3-4 day (91). Plasmapheresis (five cycles of 1800 ml of plasma) and intravenous immune globulin treatment have been used in those patients who do not respond to corticosteroid treatment (93). Neurologic functional defects were observed to improve rapidly following the treatment with plasmapheresis in HE patients who gave minimal response to steroid treatment (77,73).

Apart from corticosteroids, other immune modulation treatments were also used: azathioprine (27), methotrexate (27), cyclophosphamide, hydroxychloroquine sulfate and plasmapheresis (61,71,78), intravenous immune globulin (79) and success was achieved in most of the patients. S Jacob and colleagues reported the case in which a patient was resistant to treatment with steroids, but showed a good response to IVIG treatment (62). In the treatment of HE there is no change in the response to thyroid hormone replacement therapy (81).
Conclusion

If no specific etiology has been established in patients with acute and subacute encephalopathy, neurologic findings in these patients should be considered to be related to autoimmune thyroiditis. An autoimmune event should come to mind during the differential diagnosis of encephalopathy. This is because patients presenting a picture of encephalopathy associated with autoimmune thyroiditis respond well to corticosteroid and the other immune modulator treatments. Unfortunately, most of the time there are delays in the diagnosis and treatment of the disease, since this condition causes encephalopathy is skipped. When the diagnosis of Hashimoto’s thyroiditis has been made after having performed autoimmune thyroid tests, corticosteroid treatment should be started without delay. In cases where no response is given to corticosteroid treatments or where minimal response is given, the other immune modulator treatments can be performed. When a case thought to be encephalopathy is evaluated by both neurologists and endocrinologists in a multi-disciplinary fashion, time is not wasted for diagnosis and treatment. These patients can only have antithyroid antibody positivity, subclinical hypothyroidism or clinical hypothyroidism. There are rare cases in the literature in which an association with thyrotoxicosis has been reported. In Hashimoto’s encephalopathy diagnosis and treatment commences when the disease is first suspected.

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