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Hashimoto's Encephalopathy: Case Series and Literature Review

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Abstract

Purpose of Review To describe the clinical manifestations of Hashimoto's encephalopathy (HE) and discuss its pathogenesis in light of recent research.

Recent Findings The pathogenesis of HE is uncertain. Available evidences point towards an autoimmune etiology due to vasculitis or other inflammatory process. Detection of thyroid antibodies — antithyroid peroxidase and anti-thyroglobulin are essential for diagnosis. Autoimmune encephalitis including Anti-IgLON5 disease needs to be excluded in suspected cases with appropriate tests for neuronal surface antibodies. Detection of thyroid autoantibodies is nonspecific, as these can be detected in some normal individuals and in other autoimmune diseases. In recent years, attention has turned to an aggressive form of Hashimoto's thyroiditis accompanied by elevated serum IgG4 levels in younger males with very high levels of thyroid antibodies. The role of the thyroid autoantibodies in the central nervous system (CNS) tissue damage remains unclear and these can act only as markers for diagnosis. Conversely, they have a role to play in determining the thyroid pathology — more glandular fibrosis associated with thyro-peroxidase antibody than with the thyroglobulin antibody.

Summary HE is a syndrome characterized by altered mental status, confusion, hallucinations, delusions, and sometimes seizures, in association with high serum anti-thyroid antibody concentration that is usually responsive to glucocorticoid therapy. Diagnosis requires the exclusion of other causes of encephalopathies and encephalitis including autoimmune encephalitis associated with neuronal surface antibodies and paraneoplastic ones. Diagnosis also is dependent on the demonstration of thyroid autoantibodies in serum. Since there is no direct pathophysiologic link between antithyroid antibodies, Hashimoto thyroiditis and the cerebral syndrome, the nomenclature HE could be misleading. The response to steroids led to a renaming of the syndrome to steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), though some cases do not respond to steroids. In recent years, attention has turned to an aggressive form of Hashimoto's thyroiditis accompanied by elevated serum IgG4 levels (IgG4-related disease). This is characterized by a higher incidence in men (5:1) than in women, onset at a younger age, more intense thyroid inflammation and higher antithyroid antibody titers. Such patients have excessive production of IgG4 + plasmacytes, which infiltrate various organs leading to their fibrosis and sclerosis, sometimes resulting in inflammatory tumors. HE is treated with corticosteroids along with treatment of the dysthyroid condition, if any. There are yet no guidelines regarding steroid dose and/or duration.

Keywords Hashimoto's thyroiditis · Hashimoto's encephalopathy, Anti-thyro-peroxidase antibody · Anti-thyroglobulin antibody · Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) · IgG4 related disorders

Introduction

Hashimoto's Encephalopathy (HE) is a syndrome characterized by altered mental status, hallucinations, delusions, and sometimes seizures, in association with high serum anti-thyroid antibody concentration that is usually responsive to glucocorticoid therapy [1••]. Diagnosis requires exclusion of other identifiable causes of encephalopathy [2, 3••]. Brain MRI and cerebrospinal fluid (CSF) studies are normal or non-specific [4••]. HE is believed to be immune-mediated

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[5••]. Three cases of HE are described herein followed by remarks and a review of the currently available literature.

Case Studies

Case 1

A 43-year-old man was admitted to a different institution in 2017 for evaluation of 2-month history of progressive behavioral changes characterized by being withdrawn gradually, getting irritable over trivial matters, progressively forgetful for recent events, inability to recognize family members and having complex visual hallucinations. In addition, he had five to six generalized tonic–clonic seizures and had been having jerky movements of his arms mostly. He also had some degree of truncal and appendicular ataxia. After admission, his Mini Mental Status Examination (MMSE) score was 20/30. No focal neurological or meningeal signs were detected. Visual acuity and eye movements were normal. He was afebrile. MRI brain with and without contrast was essentially normal. Routine hematological and biochemical parameters were within normal limits. TSH was mildly elevated. HIV status was negative. CSF study showed a raised protein content to 90 mg% and a mild lymphocytic pleocytosis (10 cells/cmm). CSF study for HSV1 was negative. Serum for anti-NMDAR, anti-VGKC and anti-LGI1 autoantibodies, were negative. EEG showed marked generalized slowing without any epileptiform features, periodic features, triphasic waves or FIRDA. The corresponding author was consulted for opinion regarding the high suspicion of a prion disease like Creutzfeldt Jakob disease (CJD). The only previously overlooked finding had been a goiter. This prompted checking on thyroid auto-antibodies. The anti-thyroglobulin antibody was undetected but the anti-TPO antibody level was raised to 300 mUnits/dL. This confirmed the diagnosis HE. He was given methylprednisolone 250 mg intravenously three times daily for 10 days and then switched to oral prednisolone 60 mg daily. He was reviewed after about 1 month when there had been no recurrence of seizures, no myoclonic jerks were seen and his cognition improved. EEG normalized, and the anti-TPO antibody level came down, though still elevated.

Case 2

A 65-year-old woman was first seen in October 2019. She complained of gradually progressive difficulty in walking for the past 1 year. Later, her family members noticed that she was not speaking as clearly as before. She had history of arterial hypertension, diabetes mellitus and hypothyroidism for more than 5 years before she was first seen. She had been on thyroid replacement therapy for the latter condition.

On examination, she was dysarthric and her MMSE score of 27/30. Extra-ocular movements were full and she had no nystagmus. She had bilateral abnormal finger nose finger test (right more than left) and bilateral knee-heel-knee ataxia. Gait was also ataxic and short-stepped. She also had mild bradykinesia of both upper and lower limbs. She had already been on Levodopa and amantadine by the time she first presented. Action tremors, but no rest tremors, were noted on both hands, left more than right. Muscle stretch reflexes were normal, except for absent ankle reflexes. Plantar responses were flexor. There was no family history of a similar disturbance.

Based on the presence of a slowly progressive cerebellar ataxia with extrapyramidal features, a provisional diagnosis of Multiple System Atrophy cerebellar type (MSA-C) was made. All routine blood investigations, including thyroid profile, were normal, apart from raised blood sugar. Brain MRI showed prominence of the cerebellar folia. Gait and balance control exercises were advised.

When seen 1 year later, a prominent decline in her neurological status was observed. In addition to her bilateral cerebellar signs, she now had marked bradykinesia and rigidity which were more noticeable in her left hand. She needed support to walk. No upper motor neuron signs were elicited. A postural drop in her systolic blood pressure of 40 mmHg was noted at this time which supported the initial clinical impression of MSA. She was also noted to be more forgetful of recent events which was not consistent with her initial clinical diagnosis of MSA-C.

This prompted re-check of her thyroid profile along with anti-thyroid antibodies. The free T3, T4 and TSH levels were normal. But significantly high anti-TPO and anti-thyroglobulin antibodies levels (> 1000 units/ml) were reported. Other routine hematological and biochemical parameters were normal. Based on these high antibody titers, the diagnosis of HE was considered. However, before embarking on steroid therapy, full encephalitic and paraneoplastic autoantibody profiles were ordered and these yielded normal results. She was admitted and daily intravenous injections of methyl prednisolone (500 mg) was administered for five consecutive days. This was followed by oral tapering dosage of prednisolone 60 mg daily to start with and reducing the dose by 10 mg/day every fortnight.

Improvement in her clinical condition was noted on completion of her intravenous regime and this continued while on oral steroids as well. When reviewed 6 weeks later and on a dosage of prednisolone 30 mg daily, her memory returned to normal and her gait and appendicular ataxias were substantially reduced. Slight dysarthria persisted. There had been a drop of around 50% of the antibody titers but they still remained raised. One year later, she was walking normally and her antibody titers returned to normal. Steroids were discontinued and she remains well.

Case 3

This 60-year-old woman had been under care of the corresponding author for more than past 12 years for combined epileptic and non-epileptic seizures. The epileptic seizures had been of partial type with secondary generalization with loss of awareness and sudden falls. A left posterior parietal focal onset was suggested once in an interictal EEG record. The psychogenic non-epileptic attacks were all eye shut spells of slow falls and unawareness for 30 min and once an ictal EEG failed to show any epileptiform activity. In addition at times, she had some form "speech arrests" which again appeared to be psychogenic in origin. She was always euthyroid. Fortunately, all forms of the spells were kept under full control on a combined regime of carbamazepine, levetiracetam, clobazam and sertraline for over 2 years. She was last seen in 2018. Following this, she defaulted from our clinic for about 4 years (which included the COVID-19 pandemic period) but continued her medicines regularly and did not have any further attacks of any kind. She retired from governmental services in December 2021. Following this, relatives noted her to be progressively much withdrawn, talking and eating much less and having a marked weight loss. She developed increased speech problems (which was later noted to be non-fluent aphasia with intact comprehension), reading and writing difficulties and profound loss of recent memory. Her walking became unsteady and she attempted to pass urine at inappropriate places. Soon thereafter, she became incontinent of both urine and feces.

When examined on the last week of March 2022, her MMSE score was 17/30 and she was obviously aphasic. She was conscious but disoriented and her awake EEG revealed grossly slowed background with dominance of delta activity but no paroxysmal features. This prompted the diagnosis of an encephalopathy rather than a rapidly progressive dementia of fronto-temporal or primary aphasic type. Non-contrast brain MRI revealed left parieto-temporal lobar atrophy with dilatation of the left lateral ventricle. Compared with a brain MRI done in 2017, the findings were essentially unchanged. Routine hematological and biochemical profile were normal. Thyroid functions were normal. Anti-TPO antibody titer was well within normal limits but her anti-thyroglobulin antibody level was well above 500 U/ml. Serum encephalitic and paraneoplastic auto-antibody profile was negative.

She was given 5 doses of intravenous methylprednisolone of 500 mg each for 5 days following which oral prednisolone on a very slow tapering dosage was instituted. When assessed, while on a daily dosage of prednisolone 30 mg/day, her speech, memory and gait, all seemed normal. There had been progressive improvement in the EEG background activity as well with normalization. Ultrasound examination of the thyroid gland revealed no fibrosis.

An unexpected event occurred at this stage. She developed subacute intestinal obstruction due to a band from a previous gynecological surgery and needed surgery under general anesthesia. Going back home, her speech, memory and gait all started deteriorating and the anti-thyroglobulin antibody level rose to above 300 U/ml. It seemed likely that while in a different hospital, perhaps her dosages were missed out or not adequately increased as generally practiced in the par- or post-operative period. She was put back on 60 mg of prednisolone daily and after 6 weeks, there was remarkable improvement in all fronts. The thyroglobulin antibody level dropped below 100 U/ml but the anti-TPO antibody levels never showed a rise.

Discussion and Review

Of the three cases cited above, two presented with rapidly progressive dementing syndromes with the possibility of an ongoing encephalopathy. The second patient had many features suggestive of a MSA-like syndrome with combined extrapyramidal, cerebellar and autonomic features. Onset of cognitive decline in this case had been a subtle but significant pointer towards consideration of an ongoing encephalopathic process. Such encephalopathic features led to appropriate investigations leading to the correct diagnosis. The typical features of HE (cognitive and psychiatric involvement, altered sensorium and seizures) were not present in the second patient [6•, 7••, 8]. However, HE encompasses a wide spectrum of neurological features. Cerebellar involvement [9, 10•] and extrapyramidal features [4, 11] in the form of tremors and myoclonus have been reported, as also autonomic features [12]. HE has been known to present with a pure, progressive, cerebellar syndrome with normal cognitive function and intellectual performance [13••]. Cognitive decline and psychosis/hallucinations would suggest a form of limbic encephalitis [14]. Stroke-like symptoms, myoclonus and tremors are also frequently seen, either alone or as part of a syndrome [15]. Sometimes, HE can present with an acute encephalopathy []. This diagnosis is usually considered in patients with the above neurological symptoms, accompanied by either a euthyroid state or mild hypothyroidism [16, 17] normal or non-specific MRI and CSF findings, increased serum levels of thyroid antibodies (anti-TPO and/or anti-TG) [18], a robust clinical response to steroids and exclusion of other possible causes. In the first two cases described herein, there had been rise in the anti-TPO antibody levels along with a rise in the anti-thyroglobulin levels in the second case. The third case, where presentation had been one of rapidly progressive dementia, had persistent high levels of anti-thyroglobulin antibodies but never any rise in the TPO antibodies. The exact cause for this discrepancy is not clear but the possibility of any

correlation with clinical features needs to be looked into in large series of patients []. Also, this small case series highlights the need for checking both thyroglobulin and TPO antibodies for exclusion of HE in patients with suggestive clinical features.

HE was first described by Lord Brain and colleagues in 1966 in a case report of a 49-year-old man with Hashimoto's disease and encephalopathy [19••]. The patient, previously diagnosed with Hashimoto thyroiditis, developed a neurologic illness consisting of altered mood and consciousness, along with stroke-like episodes causing transient aphasia, right or left hemiparesis, hemisensory symptoms, hemianopia and monocular blindness. These were followed by episodes of hallucinations, confusion, and involuntary movements (tremor and athetosis). CSF studies showed raised protein content with mild pleocytosis. Carotid angiography was normal, EEG showed generalized slowing. He was treated with prednisone and anticoagulant therapy with inconsistent response and ultimately resolved while taking only levothyroxine. Lord Brain et al. [••] summarized the case as one of a "*stuttering brain disorder of an unusual kind with concurrent rise in the level of thyroid antibodies",* and concluded, showing remarkable foresight, *"antibody studies in future cases of unexplained encephalopathy should show whether we have described a syndrome or a coincidence*."

Since 1966, many cases of HE have been reported with varied presentations —fulminant, acute, subacute or chronic patterns of altered mental status — occurring across all ages. The syndrome is relatively rare with an estimated prevalence of 2/100,000. Epidemiologically, HE is 4–5 times more common among females than males. The mean age at onset is 41–48 years [20, 21•]. However, it has been reported in pediatric populations as well [2, 22•]. Common clinical features include relapsing and remitting episodes of encephalopathy along with stroke-like symptoms, dementia, focal or generalized seizures, status epilepticus, myoclonus, tremor, and neuropsychiatric symptoms [23]. Two patterns of HE have been described, one showing predominantly stroke-like and focal symptoms, and another comprising progressive course of cognitive disorder with psychotic manifestations. Seizures, myoclonus, and tremor can occur in both types [24•]. Clinical features of HE are varied, but since the condition is treatable, the diagnosis has to be kept in mind in certain clinical situations.

Seizures are common occurring in about 2/3 of the patients. Diagnosis of HE should be considered in unexplained episodes of focal or generalized seizures, refractory to common antiepileptic drugs, with cognitive impairment and neuropsychiatric symptoms. New onset status epilepticus (SE), including epilepsia partialis continua (EPC), and nonconvulsive SE (NCSE) have been reported [25••, 26–28]. A limbic encephalitis-like presentation with subacute onset memory deficits, decreased level of consciousness, seizures, and behavioral change can also occur [15]. Autoimmune encephalitis including Anti-IgLON5 disease [29••] needs to be excluded in such cases with appropriate tests for neuronal surface antibodies. Anti-IgLON5 disease is a complex neurological disease, the clinical features of which consist of a sleep disorder with non-rapid eye movement (REM) sleep parasomnia, REM behavior disorder, obstructive sleep apnea syndrome, stridor bulbar symptoms, gait abnormalities, extrapyramidal features, autonomic disturbances and cognitive dysfunction.

HE can cause progressive cognitive deterioration with dementia, neuropsychiatric symptoms, and impaired consciousness [30, 31]. This is seen more in older patients and HE should be considered in the differential diagnosis of rapidly progressive dementia, especially CJD. Even in patients with apparent degenerative dementias like Alzheimer's disease, Lewy body dementia, frontotemporal dementia, and cortico-basal degeneration, HE needs consideration if the course is too rapid or atypical.

Elevated thyroid antibodies, including anti-TPO (thyroid peroxidase) or antithyroglobulin are present in majority of cases, and are required for diagnosis. In a review of 105 patients with HE, anti-TPO antibodies were elevated in 100%, and antithyroglobulin antibodies in 48% [32•, 33•]. Thyroid-stimulating hormone antibodies may also be present. However, the titer of antibodies does not correlate with disease activity. Moreover, the presence of thyroid antibodies is not specific, as about 10% of general population has raised serum anti-TPO [34•, 35]. There are some reports of raised thyroid antibodies in the CSF, but the sensitivity and specificity are unclear. Antibodies against amino terminal domain of alpha enolase (NAE) have been proposed as a more reliable marker of HE [36•]. However, these antibodies have been described in a few reports, and have been found in a patient with CJD as well, casting doubt on its specificity [37].

Thyroid status varies from overt hypothyroidism to overt hyperthyroidism. But most patients with HE are either euthyroid or have subclinical hypothyroidism.

The majority of patients with HE have normal or nonspecific MRI findings. Abnormal MRI findings include ischemic lesions, demyelination, edema, atrophy, and abnormal signals in the hippocampus or temporal lobe [38–42].

CSF studies show abnormalities, usually mild, in 80% of patients. Most common abnormality is raised protein content in around 75% of patients. Protein levels more than 100 mg/dl are uncommon, occurring in 20%. A mild lymphocytic pleocytosis is present in 10 to 25% [43].

Non-specific EEG abnormalities are observed in over 90% of patients, usually showing background slowing. Focal spikes or sharp waves, triphasic waves, and frontal intermittent rhythmic delta activity (FIRDA) have also been described. EEG may have some role in monitoring treatment

response and there are reports of EEG abnormalities improving rapidly with steroid treatment [44•, 45]. The EEG also helps to exclude other conditions, such as CJD, in patients with rapidly progressive encephalopathy and myoclonus. Diagnostic criteria for HE are shown below in Table 1.

HE is treated with corticosteroids along with treatment of dysthyroid condition, if any. Since HE is rare, there are no guidelines regarding corticosteroid dose and/or duration. Oral prednisone 50–150 mg daily has been used. High dose intravenous methylprednisolone has been given in some patients. Most patients respond to steroid therapy with improvement occurring over weeks to months. Duration of therapy and tapering of steroids are adjusted according to the clinical response. Some patients require treatment to be continued for up to 2 years. Immunosuppressive medications, including azathioprine and cyclophosphamide, have been used in patients who do not tolerate corticosteroids, do not respond, or relapse during steroid tapering. There are some reports of good and prolonged response with rituximab. Intravenous immunoglobulin treatment produces significant improvement in both adults and children, but the efficacy of plasma exchange is doubtful, despite removal of antithyroid antibodies [48•, 49, 50, 51•].

The prognosis of HE is usually good. Patients can improve even if treatment is delayed for months or years after onset of symptoms. Residual cognitive improvement occurs in around 25% of patients with long-standing untreated disease. Patients usually remain disease-free after steroid tapering, but some relapse and require further courses of steroids and sometimes immunosuppressive therapy. There are some reports of spontaneous recovery as well [52, 53•].

The pathogenesis of HE is uncertain [1••]. Overt hypothyroidism can cause cerebral dysfunction, but there is no evidence that thyroid hormone dysregulation has any role in the pathogenesis of HE, as majority of the patients are euthyroid at presentation [54••]. The available evidences point towards an autoimmune etiology, causing encephalopathy due to vasculitis or other inflammatory process. As in most autoimmune conditions, the disease is more common in women. In more than 1/3 of patients, there is comorbidity with other systemic or organ-specific autoimmune diseases like SLE, Sjögren's syndrome, pernicious anemia, sarcoidosis, and myasthenia gravis [5]. Most patients with HE respond to steroids or other immunosuppressive therapies. Elevated thyroid antibodies are consistent with an autoimmune process, though it is unlikely that these antibodies have a direct pathogenic role. The thyroid antibodies are diagnostic markers rather than etiologic agents. Pathologic examination at autopsy or brain biopsy in a few patients has shown lymphocytic infiltration around small arterioles or venules [24•]. Because of the uncertainty regarding its etiopathogenesis, HE has remained a controversial entity. A review by Chong et al. [53••] (2003) was titled *"Hashimoto Encephalopathy – syndrome or myth?"* The review concluded that *"the combination of encephalopathy, high serum antithyroid antibody concentrations, and responsiveness to glucocorticoid therapy seems unlikely to be due to chance. However, there is no evidence of a pathogenic role for the antibodies, which are probably markers of some other autoimmune disorder affecting the brain*." Since there is no direct pathophysiologic link between antithyroid antibodies, Hashimoto thyroiditis and the cerebral syndrome, the nomenclature Hashimoto's Encephalopathy could be misleading. The response to steroids led to a renaming to steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), though some cases do not respond to steroids including Lord Brain's original patient. Another nomenclature is non-vasculitic autoimmune inflammatory meningoencephalitis (NAIM), but it probably does not reflect the neuropathology with accuracy [55•].

Most reports of HE appeared before the spectrum of autoimmune encephalitis was recognized and so tests for other autoantibodies were not done or done in a limited way. It is possible that some of the cases thus reported were actually autoimmune encephalitis patients, who are also responsive to steroids and immunosuppressive therapy, and the raised TPO antibody titer was just an incidental finding. In a recent review, Mattozzi et al. [14••] looked at 24 patients meeting the accepted diagnostic criteria for HE and lacking coexisting serum or CSF anti-glial or anti-neuronal antibodies. The patients had four clinical subtypes including rapidly progressive psychiatric syndrome in 29%, encephalopathy/cognitive impairment in 29%, new-onset refractory status epilepticus in 25%, and limbic encephalitis in 17%. There were

Table 1 Diagnostic criteria for Hashimoto Encephalopathy (based on Graus et al.) [46••]

1. Encephalopathy with seizures, myoclonus, hallucinations or stroke-like episodes
2. Thyroid disease (subclinical or mild overt)
3. Brain MRI—normal or with nonspecific abnormalities
4. Serum thyroid antibodies present (no specific disease—cut-off value)
5. Absence of other neuronal antibodies in serum or CSF
6. Exclusion of alternative causes of encephalopathy by differential diagnosis

Comment: The inclusion of 'good response to corticosteroid treatment' as a necessary criterion in the criteria remains controversial. Recent studies suggest that such a response is achieved in only 32% of patients with HE [47]

no patients with stroke-like episodes. Surprisingly, only 32% responded to steroids. These patients were otherwise similar to those who did not respond, and it was not possible to distinguish them before treatment. TPO antibody levels were studied in two other groups, 74 with possible autoimmune encephalitis without neuronal antibodies, and 205 with different neuro-immunologic diseases. The frequency was around 8% in both groups, suggesting it is a non-specific finding, and of limited use in picking up possible HE cases in a group of patients with encephalopathy of unknown origin with negative neuronal antibodies.

Laboratory studies done so far have not yet confirmed any direct pathogenic effect of these antibodies (especially TPOAb) on the CNS. Autopsy and histopathological examinations have not shown the presence of antibodies in the structures of the nervous system, but only in the tissues of the thyroid gland [48•], even if these antibodies could be detected in high concentrations in the serum and sometimes in the CSF. Thyroid gland fibrosis evidenced by ultrasonography is more common in patients with anti-TPO antibody than with the anti-TG antibody [•]. This prompted some workers to question the value of anti-TG antibodies in the diagnosis of HE. Furthermore, no significant decrease in the levels of such antibodies could be detected in some patients after treatment with corticosteroids [56]. This is in contrast to our observations in two of the cases cited above.

So What is the Current Status of HE?

Is it a relatively benign variety of immune-mediated encephalopathy of unknown pathogenesis? Does testing for TPO antibody have any value? Till we have answers to the above questions, it seems reasonable to continue testing for TPO and TG antibodies and consider a diagnosis of HE in the clinical situations discussed — patients presenting with SE, NCSE, neuropsychiatric problems with altered consciousness and fluctuating course, and rapidly progressive dementia, with inconclusive brain imaging, CSF, blood biochemistry, and infective profile. Such patients are now routinely worked up for autoimmune encephalitis with antibody panel in blood and CSF, and treated appropriately if positive, and sometimes even if the results are negative if the clinical suspicion is high. Just as the antibody panel tests are expensive, so are the treatments, usually consisting of IVIG along with steroids. Considering the diagnosis of HE in patients with suggestive clinical presentations along with raised TPO and or TG antibodies, may suggest an inexpensive line of treatment with oral steroids, and at least some patients will benefit. This is particularly important in resource-poor settings.

Currently, an aggressive form of Hashimoto's thyroiditis accompanied by elevated serum IgG4 levels has been described. Features include a higher incidence in men (5:1) than in women, onset at a younger age, more intense thyroid inflammation and higher antithyroid antibody titers [57••, 58••]. Such subjects have excessive production of IgG4 + plasmocytes, which infiltrate various organs leading to fibrosis and sclerosis, and even inflammatory tumors [60]. Such cases are now classified with the IgG4-related disorders. Other members of the family include autoimmune pancreatitis, sclerosing cholangitis, interstitial nephritis, Sjögren syndrome, Reidel's goiter and hypertrophic pachymeningitis. In relation to HE, it is possible that the IgG4 fraction may be responsible for the CNS involvement causing encephalopathy [59–61].

Concluding Remarks

HE is a rare disease with non-specific clinical manifestation. It should be considered in the differential diagnosis in patients with acute or subacute features of encephalopathy, cerebellar and extrapyramidal features, autonomic failure, status epilepticus, NCSE as well as with rapidly progressive cognitive impairment and psychiatric symptoms of unclear aetiology. Taking into account the possibility of the coexistence of various autoantibodies, HE should, in some cases, be differentiated from other autoimmune encephalopathies and paraneoplastic syndromes. If elevated titers of antibodies to thyroid antigens are then demonstrated, corticosteroid treatment should be considered as soon as possible. Future research should look for a more specific marker for Hashimoto's encephalopathy.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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