

Hashimoto's Encephalopathy: A Review

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Abstract

The condition "Hashimoto's encephalopathy" (HE) refers to a cerebral dysfunction syndrome with elevated antithyroid peroxidase antibody titers that is thought to have an autoimmune cause. Similar to autoimmune thyroid illness, women are more likely than men to develop HE. It has been documented in adult, geriatric, and pediatric populations worldwide. The clinical appearance may be recurrent and remitting, with myriad symptoms involving myoclonus, seizures, episodes resembling strokes, cognitive deterioration, and neuropsychiatric symptoms. Clinically and biochemically, thyroid function is often normal. Although HE seems to be a rare disorder, it should be taken into consideration when treating "investigation negative encephalopathies" because it responds to corticosteroid treatment. The results of neuroimaging frequently do not help to clarify the diagnosis. High titers of antithyroid antibodies, specifically antithyroid peroxidase antibodies, are diagnosed in the setting of the usual clinical picture. Corticosteroid treatment is nearly always successful, although relapses are common. Other immunomodulatory treatments, like intravenous immunoglobulin and plasma exchange, are often effective as well. Despite a statistical correlation to autoimmune thyroid illness, the cause of HE is not well understood. Research is still needed to fully understand the connections between clinical images, thyroid disease, auto-antibody pattern, and brain pathology. It's possible that over time, a class of nonvasculitic autoimmune inflammatory meningoencephalopathies will include HE. Some writers have proposed severing all connections to Hashimoto and calling the illness, SREAT - "steroid responsive encephalopathy associated with autoimmune thyroiditis".

Keywords: Cerebrospinal fluid, Computed tomography, Electroencephalography, Hashimoto's encephalopathy, Hashimoto's thyroiditis, Lumbar puncture, Magnetic resonance imaging, Positron emission tomography

Abbreviations: HE: Hashimoto's Encephalopathy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography; CSF: Cerebrospinal Fluid; LP: Lumbar Puncture; PET: Positron Emission Tomography; HT: Hashimoto's Thyroiditis; EAE: Experimental Allergic Encephalomyelitis; ADEM: Acute Disseminated Encephalomyelitis

Introduction

The clinically heterogeneous illness known as Hashimoto's encephalopathy (HE) is characterized by a corticosteroid-responsive encephalopathy with elevated blood antithyroid antibody titers that do not include aberrant thyroid hormone levels. Hashimoto's encephalopathy is the name given to a condition that Lord Brain and associates reported in 1966 [1]. This concerned a 49-year-old man who had episodes of stroke-like symptoms involving several vascular regions, hallucinations, fluctuating awareness, and cognitive impairment. His diagnosis of Hashimoto's autoimmune thyroiditis (HT) was confirmed. There was an increase in CSF protein as well as high titers of anti-thyroglobulin (anti-TG)

and antithyroid microsomal antibodies. This patient, however, was clinically hypothyroid, did not react to prednisolone treatment, and ultimately seemed to heal with thyroxine treatment alone, demonstrating the heterogeneity of HE. Since then, there has been a lot of interest in the connection between antithyroid antibodies, autoimmune thyroid illness, and corticosteroid-responsive encephalopathy. As a result, over 175 instances have been documented in the literature. In consideration of the historical and case report bias in the literature, the term "Hashimoto's encephalopathy" will be used to refer to the present state of knowledge on this type of encephalopathy, as this article aims to provide an overview of it. Future directions for nosology will be discussed in the conclusion section.

Inclusion and Exclusion Criteria

To identify articles and reviews and journals pertaining to Hashimoto's encephalopathy, we used two sources of information: PubMed (National library of medicine) and Google scholar. We limited candidate articles, reviews, and journals to those having the term Hashimoto's encephalopathy in their titles. No specific time period was followed as our understanding of the disease is quite limited and we wanted to encompass as much information as possible in this review. We excluded articles that were not written in English.

Criteria	Inclusion	Exclusion
Publication type	Original research, Reviews, Case reports, full text articles	Letters, editorials
Language	English	Any other language
Time period	Every year	-

Epidemiology

Since HE is an uncommon disorder, it might be challenging to estimate its incidence and prevalence. According to one prospective investigation, the incidence of detectable antithyroid antibodies in patients of unexplained encephalopathy was estimated to be 2.1/100,000 participants [2]. Cases in adult [3], elderly [4], and pediatric populations have been recorded globally [5]. The average age of onset is between 45 and 55 years old, with ages ranging from 9 to 86 years old, as shown in **Table 1**. With a female to male ratio of almost 5 to 1, there is a definite female majority in the adult population [3,6]. Pediatric samples typically show similar gender distribution, despite their tiny size [3,7]. HE is linked to other autoimmune illnesses. In a study of 20 patients with HE, 30% had a co-morbid autoimmune condition, including type 1 diabetes, systemic lupus erythematosus, and Sjogren's syndrome [8]. A bigger, literature-based analysis identified fewer connections of this sort, although only a few of the 85 cases had thorough antibody testing for connective tissue illnesses [3]. While there is evidence that autoimmune thyroid illness can run in families, no examples of familial HE has been described [9,10].

Table 1. Epidemiology of Hashimoto's encephalopathy.	
Prevalence Approximately	2/100 000
Mean age of onset	45–55y
Age range	9–86y
Female to male ratio	5 : 1
Associated autoimmune disorders	Autoimmune thyroid disease, systemic lupus erythematosus, type 1 diabetes mellitus, Sjogren's syndrome

Pathophysiology

It is uncertain what causes HE. There is little evidence to support a common mechanism at the microscopic level between patients with HE. The pathological findings *in vivo* are varied and have only been obtained from a limited number of patients; the most common result is mild lymphocytic infiltration of tiny capillaries [11,12]. The brain biopsy taken from animal models after inducing experimental allergic encephalomyelitis by sensitization to myelin basic proteins also showed intense perivascular round cell infiltrates in white matter [13]. It is debatable whether these characteristics indicate intracerebral vasculitis, especially as the CNS and other organs do not appear to exhibit vessel wall damage and transmural infiltration typical of vasculitis [3].

In contrast to other autoimmune neurological disorders like myasthenia gravis or paraneoplastic syndromes, where antibodies play a role in pathogenic mechanisms by disrupting cell signaling pathways (e.g., anti-Hu antibodies) or blocking specific neurotransmission functions (e.g., anti-acetylcholine receptor antibodies) [14], the role of thyroid antibodies in the pathogenesis of HE is still unknown. Antithyroid antibodies may indicate genuine etiopathogenic variables that cause such encephalopathies by functional or cytotoxic effects, or they may simply be an autoimmune epiphenomenon in the context of encephalopathic processes of various etiologies. The existence of antithyroid antibodies designates a group of neurological illnesses under the name Hashimoto's encephalopathy, regardless of the part that these antibodies may play in the pathophysiology of CNS problems.

Autoimmune reaction to antigens shared by the thyroid gland and CNS

There is no empirical evidence to support the theory that the pathogenicity of antithyroid antibodies may be attributed to the cross-reactivity of CNS and thyroid gland epitopes. No proteins found in the central nervous system have been shown to share structural similarities with thyroglobulin and thyroperoxidase proteins. Although there is little evidence to support a shared thyroid/brain antigen, a recent study found that anti-TPO antibodies bind specifically to cerebellar astrocytes in HE patients but not in HT patients [15]. This finding may lend credence to the theory that antibodies that affect neuroglial function may be responsible for neuronal dysfunction. Paradoxically, seroepidemiological research has revealed that antithyroid antibodies are present in 10–20% of the healthy population and rise with age >65 [16], particularly in women [17]. Antithyroid antibodies have also been linked to peripheral neuropathy, myopathy, chronic fatigue syndrome, fibromyalgia, mood and anxiety disorders, depression, borderline personality disorder, Alzheimer's disease, Wegener's granulomatosis, juvenile idiopathic arthritis, and 34%–41% of patients with fibromyalgia [18]. Given that thyroid antibodies have been associated with a wide range of disorders and

have been observed in the general healthy population, it is unlikely that there is a distinct antigen in the brain that thyroid antibodies share and are therefore not necessarily disease-specific.

Autoimmune vasculitis

Neuroimaging SPECT results that typically demonstrate focal or global hypoperfusion [3] and the identification of anti- α -enolase antibodies—which are highly expressed in endothelial cells and have been linked to other vasculitic disorders including Kawasaki disease—support this theory [19]. Like the antibodies, it is unclear if the perivascular lymphocytic infiltration detected in five out of seven pathology reports is a nonspecific finding or indicative of the onset of a “true vasculitis”. Perivascular cuffing, however, is also frequently observed as a neuropathological “fingerprint” of neuroinflammatory conditions such as encephalitis, multiple sclerosis, and uncommon types of epilepsy like Rasmussen's syndrome [20,21].

Toxic effects of thyrotropin-releasing hormone

The theory behind the toxic effects of thyrotropin-releasing hormone (TRH) is that elevated cerebral TRH is the source of the encephalopathic symptoms of Huntington's disease (HE), including myoclonic and ataxic symptoms. The hypothalamus releases TRH, which causes the pituitary to produce more TSH, which in turn causes the thyroid to produce more thyroid hormone [22]. There has only been a single trial where TRH infusion successfully caused myoclonus and tremor that resembled the patient's symptoms during an exacerbation in a patient with HE.

Clinical Presentation/Symptomatology

Behavioral abnormalities, disorientation, cognitive decline, stroke-like episodes, amnestic syndrome, ataxia, seizures, myoclonus [23,24] and psychiatric manifestations are only a few of the many symptoms that can accompany HE [25-27]. Epilepsy, encompassing focal and focalized seizures [3,28] and myoclonus are the most common manifestations in adulthood, accounting for 60–66% of affected patients, according to reports [22]. The most frequent type of seizures in children are generalized tonic-clonic seizures, which are followed by partial complex seizures. Additional prevalent symptoms have been documented to include cognitive impairment (84.6% of affected patients) and psychiatric symptoms (38.5% of affected patients), such as depression, mania, psychosis, and hallucinations [25-27]. Although it is uncommon in adult HE patients, children who present with coma and generalized tonic-clonic seizures have been reported to have status epilepticus (SE). Anti-epileptic medications do not work well for these patients [29]. The primary complication of HE in children has also been documented to be recurrent status epilepticus, with frontal brain involvement being linked to

these symptoms [30]. Adult HE patients have also been linked to multiple anti-epileptic drug (AED) hypersensitivity and temporal epilepsy [31].

In older HE patients, subacute dementia with a subtle onset and schizophrenia-like symptoms has been reported [32]. There is a case study of a 60-year-old woman who had a history of HT for more than 40 years and presented with symptoms of schizophrenia-like illness. It took 40 years for this patient's diagnosis to be made following the onset of her schizophrenia-like symptoms [28]. In certain HE patients, the onset of psychosis has also been seen during corticosteroid therapy [33]. Opsoclonus, or erratic saccadic eye movements, is linked to ataxia before encephalopathy develops and can potentially appear as an early HE symptom [34]. There have been proposed to be two clinical subtypes of HE [35]. The first subtype is episodic, characterized by stroke-like symptoms that have a relapsing-remitting history and are associated with vasculitis [32]. The second subtype exhibits a more advanced course with an inflammatory beginning, a notable reduction in cognitive function, and memory loss [36,37].

Diagnosis/Testing/Imaging/Evaluation

Antibodies that define HT and HE

The existence of antithyroid antibodies that specifically target distinct thyroid gland epitopes is one of the main laboratory characteristics of HT and HE. There is a lot of disagreement regarding the importance of their existence and role in the etiology of HE. David Sinclair wrote a great assessment on the drawbacks of antibody testing in HT [38]. Graves' disease is caused by antithyrotropin antibody, also known as anti-thyroid stimulating hormone (anti-TSH), which is aimed at the thyrotropin receptor [39]. The literature on HE only has one case report in which the patient exhibited considerably higher levels of thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG) but only marginally raised levels of anti-TSH [1]. Antibodies directed against microsomes, which are produced from injured thyroid cells, are known as anti-TPO or originally antimicrosomal antibodies. These are the antibodies in the majority of HE cases and are most commonly linked to hyperthyroidism and hypothyroidism [18,40,41]. Nevertheless, they have also been detected in a small number of euthyroid individuals (14.4% of men and 25.8% of women), rheumatoid arthritis [42], insulin-dependent diabetic mellitus, and rheumatoid arthritis [43]. There is a lot of variation in the sensitivity of available laboratory techniques and kits, as well as in what is regarded as the “normal” reference range, which makes utilizing this antibody as a diagnostic criterion for HE and HT problematic [38]. The target of anti-TG antibodies is thyroid cell-resident thyroglobulin, also referred to as “colloid” [44]. These antibodies do not significantly outperform anti-TPO antibodies because they are not as prevalent in HE cases as anti-TPO antibodies [45]. About 10% of the 13,344 participants in the Third National Health and Nutrition Examination

Study (NHANES III) who were free of illness, pregnant, not using steroids, or lacking biochemical hyperthyroidism or hypothyroidism showed anti-TG antibodies [18]. Recently, proteomic investigations have revealed anti- α -enolase antibodies in the blood of patients with HE as a possible antibody more specific for HE than HT [46]. A further investigation revealed that patients with HE were more likely than HT or control subjects to recognize the amino-terminal region of α -enolase [47]. The high expression of α -enolase in the endothelium provides support to the vasculitic explanation of HE, as demonstrated by these investigations [12,48]. Nevertheless, anti- α -enolase has also been detected in other autoimmune disorders such as rheumatoid arthritis and inflammatory bowel disease [49,50].

CSF findings

The most frequent observation in the CSF of patients with HE that has been reported is an increased protein content without pleocytosis [3,51,52]. Typically, the immunoglobulin G index falls within the reference range [51] and oligoclonal bands are occasionally, however not always, observed [53]. In one study, the CSF of HE patients included circulating immune complexes, anti-TG antibodies, and anti-TPO antibodies, but not the CSF of control patients [54]. There was no control group consisting of HT patients who did not have encephalopathy. According to the authors, their existence suggests intrathecal production.

Neuroimaging

In cases of HE, results from brain magnetic resonance imaging and computed tomography imaging have ranged from perfectly normal to different levels of nonspecific abnormalities. Cerebral atrophy [55], focal and confluent white matter abnormalities [3,56] cortical irregularities [57] and vasculitic alterations are among the findings [58]. Furthermore, results from magnetic resonance imaging can change over time in the same patient, decline with steroid use, and have a correlation with antibody levels. In patients with thyroid problems, single-photon emission computed tomography (SPECT) scanning has also been employed. Research utilizing SPECT on hypothyroidism-affected HT patients has revealed a notable change in the local cerebral blood flow [59,60]. These changes are observed in both euthyroid hypothyroid patients and hypothyroid individuals without neurologic symptoms [61]. The frontal lobes appeared to be most impacted in one study, which could account for the behavioral and psychiatric symptoms of HE that are frequently described. The findings of the HE patient case reports vary from normal to focal hypoperfusion to global [3].

EEG findings

The original 1966 paper by Lord Brain outlining the encephalopathic characteristics of his case included reports of EEG results. Between 1961 and 1966, the patient underwent

serial EEGs. Their condition deteriorated over time, beginning with bitemporal abnormalities and continuing to bilateral loss of α activity and θ discharges. After that, they took a varying path that eventually normalized by 1966 [1]. These results were comparable to the EEG studies on myxoedema patients that Jellinek, a collaborator on Brain's study, had published four years prior [13]. According to a review by Chong *et al.*, abnormal EEG results (most frequently diffuse slowing) were present in 98% of HE patients between 1966 and 2002 [3].

Neuropathology

Regretfully, there aren't many neuropathological reports for HE. Based on existing literature, the argument primarily divides into two categories: HE classified as a vasculitic or encephalitic process. The patient of Lord Brain passed away about ten years after he was first seen, and the postmortem report simply mentioned that the "central nervous system reported free from infarction, cerebral vessels congested, with a few atheromatous patches". There was hypertrophy and dilation of the left ventricle [62]. In 1992, there was a subsequent pathologic report that offered proof of a vasculopathic genesis for the illness. The walls of arterioles and venules displayed a localized region of lymphocytic infiltration in a stereotactic biopsy sample taken from a patient with HE [63]. A cerebral angiography in this instance was normal. A further example involving a patient with a lengthy history of HT revealed leptomenigeal venules invaded by T lymphocytes and a localized brain stem vasculitis [64]. Following the publication of this report, there was debate on the precise meaning of the term "vasculitis". Nolte *et al.* concluded that lymphocytic vasculitis is a pathogenic subtype that is well recognized and is defined by the presence of lymphocytes in the vessel wall. That being said, it does not follow that lymphocytic vasculitis does not exist only because the diagnosis is more challenging than for necrotizing arteritis [47]. A subsequent autopsy case from 2003 revealed a little lymphocytic infiltration in the venules and arterioles throughout the leptomeninges, cortex, white matter, and brainstem [65]. The literature also contains reports of pathologic abnormalities unrelated to vasculitis. The autopsy of a 27-year-old lady who had neurological encephalopathy that was fast progressing was documented by Striano *et al.*, showed no lymphocytic infiltration [6]. In 2004, Oide presented an additional report on a nonvascular etiology, describing antineuronal autoantibodies that immunohistochemically identified a 36-kDa antigenic protein present in the neurons of the human cerebral cortex [66]. It was absent from the control group or in an HT patient who is not experiencing encephalopathy. Vasculitis was not evident in the brain pathology; nevertheless, an autopsy was performed following the steroid therapy. Two sequential biopsies on a young woman with sensory complaints, no encephalopathy, and a steroid-responsive white matter lesion were reported in one final pathologic report. The results of the biopsy revealed "relative axonal preservation and discrete microscopic foci of demyelination with rare perivascular lymphocytes" [67].

The patient did not exhibit clinical signs of encephalopathy, according to their own criteria of "cognitive impairment with or without neuropsychiatric symptoms"; therefore it is still unclear if multiple sclerosis and ADEM (acute disseminated encephalomyelitis) are the correct diagnoses in this particular instance. These collections of neuropathological case reports only serve to highlight the illness we named HE's confusion and possible heterogeneity.

Differential Diagnosis

Systemic lupus erythematosus (SLE)

Seizures, acute confused states, affective and psychotic disorders, as well as cognitive difficulties, are examples of neuropsychiatric symptoms of SLE [68]. Thus, this could be a phenotype of the encephalopathy caused by Hashimoto's. Serum antibody profiles and a prior diagnosis of SLE may be used to distinguish it. Low titers of anti-TPO antibodies as well as anti-neuronal, antiphospholipid, and anti-DNA antibodies may be observed [69,70]. Since thrombotic disease is frequently associated with CNS signs of SLE (especially when antiphospholipid antibodies are present), neuroimaging evidence of venous thrombosis or infarction may help to explain the neurological characteristics of SLE and help to distinguish it from Hashimoto's encephalopathy [69,71,72]. Nonfocal symptoms, however, can be produced by more diffuse processes, and a diagnosis cannot be made based solely on the pathophysiology and antibody correlations of cognitive dysfunction or psychiatric symptoms [69].

Sporadic Creutzfeldt Jacob disease (sCJD)

The symptoms of sCJD include a marked myoclonus, psychotic characteristics, and a dementia that progresses quickly. With this disease, ataxia, abnormal gait, personality changes, and seizures are also possible outcomes. Regular investigations are usually not very noteworthy. Periodic, triphasic sharp-wave complexes on the EEG and the finding of 14-3-3 protein in the CSF is used to confirm the diagnosis [73]. These results set sCJD apart from HE, as does the unremittingly fast decreasing course and absence of corticosteroid reactivity.

Vasculitis

As a differential diagnosis, isolated or primary CNS vasculitis should be taken into account. This is an uncommon kind of large-vessel vasculitis that manifests as encephalopathy, headaches, and, less frequently, ischemic stroke during a subacute phase. In as many as 50% of instances, angiography may be normal, MRI may be normal, and inflammatory markers may not be raised [74-76]. HE cannot occur if antithyroid antibodies are not present. Corticosteroids and cyclophosphamide can also be effective in treating this illness; nevertheless, a brain biopsy is frequently necessary to provide a final diagnosis [77].

Autoimmune hypophysitis

Pituitary hypofunction, hyperprolactinemia, diabetes insipidus, and sellar compression—which causes headaches and abnormalities in the visual field—are the hallmarks of autoimmune hypophysitis (AH) [78]. When there are metabolic disturbances brought on by endocrine dysfunction, encephalopathy may develop (such as hyponatraemia). Given that AH is often linked to Hashimoto's thyroiditis, anti-TPO antibodies may also be raised [79]. In these cases, a diagnosis of HE may be made. The diagnosis of AH can be supported by electrolyte problems, MRI findings of an intrasellar mass lesion, endocrine evidence of adrenocorticotrophic hormone (ACTH) deficiency, and, less precisely, antipituitary antibodies [80].

Paraneoplastic limbic encephalitis (PLE)

While seizures and focal neurological abnormalities are less common compared to HE, significant cognitive and behavioral changes can be observed in patients with paraneoplastic limbic encephalitis (PLE). It is believed that PLE is an autoimmune sub-acute encephalopathy associated with an underlying neoplasm, most frequently a breast, lung, or testicular tumor. Both the condition and the underlying cancer are associated with specific serum antineuronal antibodies. For example, antibodies against Hu, Ma1, Ma2, and CRMP/CV2 are linked to PLE caused by small cell carcinoma of the lung. For this disease, the underlying neoplasm and related antibodies must be found. There are no antithyroid antibodies found. More successful than corticosteroids or other types of immunomodulation is the treatment of the neoplasm [81].

Non PLE

Another diagnostic factor is non-PLE. Although complex partial seizures and sleep disturbances are more common than variations in conscious state and psychosis, the clinical symptoms of this condition are comparable to those of PLE [82]. Serum anti-voltage-gated potassium channel antibodies are linked to this type of limbic encephalitis [83], but not antithyroid antibodies. MRI observations of unilateral or unilateral enlarged temporomesial structures that are hyperintense on FLAIR and T2-weighted sequences may aid in diagnosis, in contrast to HE [84,85]. Furthermore, bitemporomesial hypermetabolism can also be seen using fluorodeoxyglucose-PET [86]. Similar to HE, corticosteroid therapy is remarkably successful.

Rapidly progressing dementias

Fast-moving dementia represents a significant category of differential diagnosis. Alzheimer's disease is characterized by a nonfluctuating conscious state unless there is concomitant delirium, and it rarely manifests with myoclonus [87]. However, in elderly individuals suspected of having HE, delirium atop a longer-standing dementia is a crucial factor to take into account. Correspondence from family members

or caregivers in detail can often shed light on these issues. DLB can cause parkinsonism, variable cognitive impairments, sleep disorders, and visual hallucinations in addition to altered conscious states [88,89]. Also documented is myoclonus [62,90], and the presentation of DLB can resemble that of sCJD [91]. Hashimoto's encephalopathy can be distinguished from DLB by the presence of antithyroid antibodies, Parkinsonian characteristics, and the lack of seizures or stroke-like episodes. Corticobasal ganglionic degeneration also occasionally presents psychotic symptoms, myoclonus, and dementia [92]. HE frequently results in stroke-like events, which can be mimicked by unilateral cortical symptoms. Unilateral cortical hypoperfusion or hypofunction may be seen on functional imaging; however, other characteristics that distinguish this disorder from HE includes progressive, asymmetric rigidity and apraxia, nonfluent aphasia, alien limb syndrome, and frontal lobe pattern of dementia [93].

Treatment and Monitoring

The first line therapy–Corticosteroids

It is advised to use prednisone (50–150 mg daily, or 1-2 mg/kg/d). It has also been used to administer high-dose IV methylprednisolone (500–1000 mg/d) [94,95]. About half of the cases had comprehensive response to the use of corticosteroids [96]. Following the initial course of corticosteroid medication, up to 40% of patients achieve total remission [97]. A tiny percentage of patients relapse in their mental symptoms and show resistance to steroid medication [98]. The length of corticosteroid treatment and the rate of taper should be adjusted in accordance with the clinical response [67,95,99]. Improvements in MRI and clinical outcomes show that brain lesions resolve well with early treatments [100].

HE resistant to corticosteroids may be treated with immunosuppressive medications

Combination therapy with immunosuppressive drugs such as methotrexate, cyclophosphamide, and azathioprine is advised for patients who are resistant to corticosteroids [97,101]. Early interventions with these immunosuppressive medications should be initiated if HE recurs in any patient. Adjunct therapy with immunosuppressive drugs, such as rituximab and an anti-CD20 monoclonal antibody, has also shown promise in treating HE patients who exhibit paraneoplastic opsoclonus syndrome [102]. An ideal treatment for HE would be natalizumab, a monoclonal antibody developed against an adhesion molecule (integrin). Natalizumab prevents inflammatory breakdown in the blood brain barrier and appears to be the most effective treatment currently available for EAE, the animal model for ADEM [13].

Patients who are unable to tolerate or take corticosteroids or immunosuppressant may be treated with plasma exchange and IVIG. Significant clinical improvements have

been documented in both adults and children receiving IV immunoglobulin therapy. It has been demonstrated that plasma exchange can eliminate antithyroid peroxidase antibodies (anti-TPO) [96,103,104]. However, despite notable drops in anti-TPO antibodies in HE patients, no change in neurophysiologic or clinical parameters has been noted [99].

Seizures prevention

The anti-epileptic drug called levetiracetam is used to treat specific kinds of seizures [105]. Studies conducted *in vivo* have demonstrated the anti-inflammatory properties of this medication [106]. When used with other medications, like diabetes, levetiracetam can effectively treat people with HE who cannot tolerate steroids. It also has anti-inflammatory and antiseizure properties. In two diabetic HE instances, levetiracetam was reported to be a successful treatment [107]. More research is needed to confirm its targeted benefit in HE patients.

Prognosis

The majority of patients show full remission and a good response to steroid treatment. Some people get better even without steroid therapy [108]. Twelve percent of patients experience relapses, twelve percent show no improvement, and sixty percent have relapsing-remitting courses [3]. Cognitive decline is one of the aftereffects, and youngsters are more likely to experience recurring refractory seizures [5]. Higher serum TPO-Ab titers at the beginning were linked to better results [109]. It is thought that autoimmune encephalitis, including anti-NMDAR encephalitis, is a paraneoplastic condition. It is unknown if HE is a paraneoplastic condition as well. Because HE is a rare disease, there are no published data on the cancer prevalence in HE patients to our knowledge. Research on the incidence of cancer in HE patients is required.

Conclusion

HE is thus a relatively uncommon condition that manifests with myriad neurological symptoms like cognitive dysfunction, psychiatric symptoms, myoclonus and seizures. It is presumed to be an autoimmune condition despite lack of clear causality from a definite source. The treatment is relatively straightforward in most cases due to the use of steroids with great responsiveness seen. Collaborative management between internists, neurologists and psychiatrists is often necessary. It is necessary to consider this condition in patients presenting with unspecified causes of encephalopathy, especially with the presence of other signs of neurological dysfunction. The presence of other autoimmune disorders may also be a useful diagnostic clue. Testing modalities are often limited in utility, other than the exception of lab tests which are strongly supportive and EEG which is often abnormal without any pathognomic findings. Prompt neurological consultation is often imperative to enable timely diagnosis and minimize morbidity from this condition. Greater

Summary Table.	
Aspect	Current Status
Definition	Cerebral dysfunction syndrome with elevated antithyroid peroxidase antibody titers that is thought to have an autoimmune cause.
Etiology	- Autoimmune reaction to antigens shared by the thyroid gland and CNS - Autoimmune vasculitis - Toxic effects of thyrotropin releasing hormone - Antithyroid antibodies may indicate genuine etiopathogenic variables that cause such encephalopathies by functional or cytotoxic effects, or they may simply be an autoimmune epiphenomenon in the context of encephalopathic processes of various etiologies.
Symptoms	- Most frequent symptoms • Seizures and lost consciousness (51%) • Cognitive deterioration and loss memory (48%) • Myoclonus (32%) • Hallucinations and psychosis (26%) • Stroke-like episodes (21%) • Tremors and involuntary movements (12%) • Language and fluency impairment (8%) • Ataxia and gait impairment (6%) • Behavioral changes (6%) • Sensory deficits (6%) - Other symptoms • Anxiousness • Apraxia • Depression and bipolar affective disorder • Dizziness • Headache • Insomnia • Muscle hypertonus • Mydriasis • Nystagmus
Diagnosis	- Antibodies- anti TPO antibody, anti TG antibody, anti alpha enolase antibody - CSF findings • Increased protein content without pleocytosis. • Oligoclonal bands occasionally observed. • Normal IgG index. • May include circulating immune complexes and related antibodies. - Neuroimaging • Brain MRI- Cerebral atrophy, focal and confluent white matter abnormalities, cortical irregularities, vasculitic alterations • SPECT- change in frontal lobe cerebral bloodflow -EEG- Bitemporal abnormalities continuing to bilateral loss of alpha and theta discharges. -Neuropathology • Dense perivascular lymphocytic infiltrate of both artery and venules of brain parenchyma. Immunostaining showing T cells. • Foci of demyelination and vacuole formation seen with relative axonal preservation.

Treatment	- 1st line therapy – IV corticosteroids - Steroid unresponsive cases – Immunosuppressive medications like methotrexate, cyclophosphamide, azathioprine, rituximab and natalizumab can be used. - If both corticosteroids and immunosuppressants can't be used – plasma exchange and IVIG can be used. - Levetiracetam- used in case of seizure episodes.
Prognosis	- Majority show full remission and good response to steroid therapy. - Some show remission even without steroid therapy. - 12% patients relapse, 12% patients don't show improvement and 60% patients show relapsing-remitting course.
Research	Ongoing to better understand the pathogenesis and improve treatments.

awareness of this condition among medical professionals of different fields would enable faster diagnosis and limit delays in evaluation and morbidity to patients. The future direction of our understanding of this disease should be aimed at finding the exact cause of HE and the underlying mechanism. A universally accepted diagnostic criteria for HE can prevent underdiagnosis and misdiagnosis. We must also look into the different treatment modalities that can be used in patients who don't respond to corticosteroids and those who show remission.

Author Contributions

Both authors were involved in research, writing, and final collation of the manuscript. Both of them have read and approved the final version of the manuscript.

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Both authors confirm that the information contained in this manuscript has been obtained ethically and is consistent with correct and ethical standards of research and scientific publishing.

References

1. Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. The Lancet. 1966 Sep 3;288(7462):512-4.

2. Ferracci F, Bertiato G, Moretto G. Hashimoto's encephalopathy: epidemiologic data and pathogenetic considerations. Journal of the Neurological Sciences. 2004 Feb 15;217(2):165-8.

3. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth?. Archives of Neurology. 2003 Feb 1;60(2):164-71.

4. Galluzzi S, Geroldi C, Zanetti O, Frisoni GB. Hashimoto's encephalopathy in the elderly: relationship to cognitive impairment. Journal of Geriatric Psychiatry and Neurology. 2002 Sep;15(3):175-9.

5. Vasconcellos E, Piña-Garza JE, Fakhoury T, Fenichel GM. Pediatric manifestations of Hashimoto's encephalopathy. Pediatric Neurology. 1999 May 1;20(5):394-8.

6. Chaudhuri A, Behan PO. The clinical spectrum, diagnosis, pathogenesis and treatment of Hashimoto's encephalopathy (recurrent acute disseminated encephalomyelitis). Current Medicinal Chemistry. 2003 Oct 1;10(19):1945-53.

7. Byrne OC, Zuberi SM, Madigan CA, King MD. Hashimoto's thyroiditis—a rare but treatable cause of encephalopathy in children. European Journal of Paediatric Neurology. 2000 Nov 1;4(6):279-82.

8. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Archives of Neurology. 2006 Feb 1;63(2):197-202.

9. Tomer Y, Davies TF. Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. Endocrine Reviews. 2003 Oct 1;24(5):694-717.

10. Ban Y, Tomer Y. Genetic susceptibility in thyroid autoimmunity. Pediatric Endocrinology Reviews: PER. 2005 Sep 1;3(1):20-32.

11. Shovman O, Gilburd B, Zandman-Goddard G, Sherer Y, Shoenfeld Y. Pathogenic role and clinical relevance of antineutrophil cytoplasmic antibodies in vasculitides. Current Rheumatology Reports. 2006 Jul;8(4):292-8.

12. Paulus W, Nolte KW. Neuropathology of Hashimoto's encephalopathy. Journal of Neurology, Neurosurgery & Psychiatry. 2003 Jul 1;74(7):1009.

13. Behan PO, Currie S. Clinical Neuroimmunology. United Kingdom: Saunders; 1978. p. 34-60.

14. Vincent A, Rothwell P. Myasthenia gravis. Autoimmunity. 2004;37(4):317-9.

15. Blanchin S, Coffin C, Viader F, Ruf J, Carayon P, Potier F, et al. Anti-thyroperoxidase antibodies from patients with Hashimoto's encephalopathy bind to cerebellar astrocytes. Journal of Neuroimmunology. 2007 Dec 1;192(1-2):13-20.

16. Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid: thyroid deficiency in the Framingham study. *Archives of Internal Medicine.* 1985 Aug 1;145(8):1386-8.
17. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *The Journal of Clinical Endocrinology & Metabolism.* 2002 Feb 1;87(2):489-99.
18. Pamuk ÖN, Çakir N. The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms. *Clinical Rheumatology.* 2007 Jan;26:55-9.
19. Chun JK, Lee TJ, Choi KM, Lee KH, Kim DS. Elevated anti- α -enolase antibody levels in Kawasaki disease. *Scandinavian Journal of Rheumatology.* 2008 Jan 1;37(1):48-52.
20. Kornek B, Lassmann H. Neuropathology of multiple sclerosis—new concepts. *Brain Research Bulletin.* 2003 Aug 15;61(3):321-26.
21. Pardo CA, Vining EP, Guo L, Skolasky RL, Carson BS, Freeman JM. The pathology of Rasmussen syndrome: stages of cortical involvement and neuropathological studies in 45 hemispherectomies. *Epilepsia.* 2004 May;45(5):516-26.
22. Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Usuki S. Thyrotropin-releasing hormone-induced myoclonus and tremor in a patient with Hashimoto's encephalopathy. *The American Journal of the Medical Sciences.* 1995 Nov 1;310(5):202-05.
23. Arya R, Anand V, Chansoria M. Hashimoto encephalopathy presenting as progressive myoclonus epilepsy syndrome. *European Journal of Paediatric Neurology.* 2013 Jan 1;17(1):102-4.
24. Gücüyener K, Serdaroğlu A, Bideci AY, Yazman Y, Soysal AŞ, Cinaz P. Tremor and myoclonus heralding Hashimoto's encephalopathy. *Journal of Pediatric Endocrinology and Metabolism.* 2000 Sep;13(8):1137-41.
25. Mahmud FH, Lteif AN, Renaud DL, Reed AM, Brands CK. Steroid-responsive encephalopathy associated with Hashimoto's thyroiditis in an adolescent with chronic hallucinations and depression: case report and review. *Pediatrics.* 2003 Sep 1;112(3):686-90.
26. Gómez-Bernal GJ, Reboreda A, Romero F, Bernal MM, Gómez F. A case of Hashimoto's encephalopathy manifesting as psychosis. Primary care companion to the *Journal of clinical psychiatry.* 2007;9(4):318-9.
27. Wilcox RA, To T, Koukourou A, Frasca J. Hashimoto's encephalopathy masquerading as acute psychosis. *Journal of Clinical Neuroscience.* 2008 Nov 1;15(11):1301-4.
28. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Archives Of Neurology.* 2006 Feb 1;63(2):197-202.
29. Hilberath JM, Schmidt H, Wolf GK. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): case report of reversible coma and status epilepticus in an adolescent patient and review of the literature. *European Journal of Pediatrics.* 2014 Oct;173:1263-73.
30. Visée H, Mabiglia C, Vanderspoilden V, Gazagnes MD, Glibert G. Recurrent status epilepticus associated with Hashimoto's encephalopathy. *Epilepsy & Behavior Case Reports.* 2013 Jan 1;1:113-7.
31. Sadan O, Seyman E, Ash EL, Kipervasser S, Neufeld MY. Adult-onset temporal lobe epilepsy, cognitive decline, multi-antiepileptic drug hypersensitivity, and Hashimoto's encephalopathy: Two case studies. *Epilepsy & Behavior Case Reports.* 2013 Jan 1;1:132-5.
32. Jamrozik Z, Janik P, Kiljański J, Kwieciński H. Hashimoto's encephalopathy. Case report and literature review. *Neurologia i Neurochirurgia Polska.* 2004 Jan 1;38(1):55-9.
33. Sirois F. Steroid psychosis: a review. *General hospital psychiatry.* 2003 Jan 1;25(1):27-33.
34. Hernández Echebarría LE, Saiz A, Graus F, Tejada J, García JM, Clavera B, et al. Detection of 14-3-3 protein in the CSF of a patient with Hashimoto's Encephalopathy. *Neurology.* 2000;54:1539-40.
35. Salazar R, Mehta C, Zaher N, Miller D. Opsoclonus as a manifestation of Hashimoto's encephalopathy. *Journal of Clinical Neuroscience.* 2012 Oct 1;19(10):1465-6.
36. Lee SW, Donlon S, Caplan JP. Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) or Hashimoto's Encephalopathy: a case and review. *Psychosomatics.* 2011 Mar 1;52(2):99-108.
37. Canelo-Aybar C, Loja-Oropeza D, Cuadra-Urteaga J, Romani-Romani F. Hashimoto's encephalopathy presenting with neurocognitive symptoms: a case report. *Journal of Medical Case Reports.* 2010 Dec;4:337.
38. Sinclair D. Analytical aspects of thyroid antibodies estimation. *Autoimmunity.* 2008 Jan 1;41(1):46-54.
39. Smith BR, Sanders J, Furmaniak J. TSH receptor antibodies. *Thyroid.* 2007 Oct 1;17(10):923-38.
40. Mariotti S, Pinchera A, Vitti P, Chiovato L, Marcocci C, Urbano C, et al. Comparison of radioassay and haemagglutination methods for anti-thyroid microsomal antibodies. *Clinical and Experimental Immunology.* 1978 Oct;34(1):118-25.
41. Mocellin R, Walterfang M, Velakoulis D. Hashimoto's encephalopathy: epidemiology, pathogenesis and management. *CNS Drugs.* 2007 Oct;21:799-811.
42. Atzeni F, Atzeni F, Doria A, Ghirardello A, Turiel M, Batticciotto A, et al. Anti-thyroid antibodies and thyroid dysfunction in rheumatoid arthritis: prevalence and clinical value. *Autoimmunity.* 2008 Jan 1;41(1):111-5.
43. Zöphel K, Saller B, Wunderlich G, Grüning T, Koch R, Wilde J, et al. Autoantibodies to Thyroperoxidase (TPOAb) in a Large Population of Euthyroid Subjects: Implications for the. *Clin. Lab.* 2003;49:591-600.
44. Goudie RB, Anderson JR, Gray KG. Non-Precipitating Antithyroglobulin Studied by the Ouchterlony Technique. *Immunology.* 1959 Oct;2(4):309-21.

45. Baker BA, Gharib H, Markowitz H. Correlation of thyroid antibodies and cytologic features in suspected autoimmune thyroid disease. *The American Journal of Medicine.* 1983 Jun 1;74(6):941-4.
46. Ochi H, Horiuchi I, Araki N, Toda T, Araki T, Sato K, et al. Proteomic analysis of human brain identifies α -enolase as a novel autoantigen in Hashimoto's encephalopathy. *FEBS Letters.* 2002 Sep 25;528(1-3):197-202.
47. Fujii A, Yoneda M, Ito T, Yamamura O, Satomi S, Higa H, Kimura A, Suzuki M, et al. Autoantibodies against the amino terminal of α -enolase are a useful diagnostic marker of Hashimoto's encephalopathy. *Journal of Neuroimmunology.* 2005 May 1;162(1-2):130-136.
48. Servettaz A, Guilpain P, Camoin L, Mayeux P, Broussard C, Tamby MC, et al. Identification of target antigens of antiendothelial cell antibodies in healthy individuals: a proteomic approach. *Proteomics.* 2008 Mar;8(5):1000-8.
49. Vermeulen N, Arijis I, Joossens S, Vermeire S, Clerens S, Van den Bergh K, et al. Anti- α -enolase Antibodies in Patients with Inflammatory Bowel Disease. *Clinical chemistry.* 2008 Mar 1;54(3):534-41.
50. Saulot V, Vittecoq O, Charlionet R, Fardellone P, Lange C, Marvin L, et al. Presence of autoantibodies to the glycolytic enzyme α -enolase in sera from patients with early rheumatoid arthritis. *Arthritis & Rheumatism.* 2002 May;46(5):1196-1201.
51. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Archives of Neurology.* 2006 Feb 1;63(2):197-202.
52. Shaw PJ, Walls TJ, Newman PK, Cleland PG, Cartlidge NE. Hashimoto's encephalopathy: A steroid-responsive disorder associated with high anti-thyroid antibody titers—report of 5 cases. *Neurology.* 1991 Feb;41(2):228-33.
53. Peschen-Rosin R, Schabet M, Dichgans J. Manifestation of Hashimoto's encephalopathy years before onset of thyroid disease. *European Neurology.* 1999 Feb 19;41(2):79-84.
54. Ferracci F, Moretto G, Candeago RM, Cimini N, Conte F, Gentile M, et al. Antithyroid antibodies in the CSF: their role in the pathogenesis of Hashimoto's encephalopathy. *Neurology.* 2003 Feb 25;60(4):712-4.
55. Ghika-Schmid F, Ghika J, Regli F, Dworak N, Bogousslavsky J, Städler C, et al. Hashimoto's myoclonic encephalopathy: an underdiagnosed treatable condition?. *Movement disorders: official journal of the Movement Disorder Society.* 1996 Sep;11(5):555-62.
56. Bohnen NI, Parnell KJ, Harper CM. Reversible MRI findings in a patient with Hashimoto's encephalopathy. *Neurology.* 1997 Jul;49(1):246-7.
57. Sawka AM, Fatourehchi V, Boeve BF, Mokri B. Rarity of encephalopathy associated with autoimmune thyroiditis: a case series from Mayo Clinic from 1950 to 1996. *Thyroid.* 2002 May 1;12(5):393-8.
58. Becker H, Hofmann M, Von Einsiedel H, Conrad B, Sander D. Circumscribed vasculitis with posterior infarct in Hashimoto encephalopathy. *Der Nervenarzt.* 2002 Apr 1;73(4):376-9.
59. Kaya M, Cermik TF, Bedel D, Kutucu Y, Tuglu C, Yigitbasi ON. Assessment of alterations in regional cerebral blood flow in patients with hypothyroidism due to Hashimoto's thyroiditis. *J Endocrinol Invest.* 2007 Jun;30(6):491-6.
60. Bertoni M, Falcini M, Sestini S, Niccoli L, Nannini C, Cantini F. Encephalopathy associated with Hashimoto's thyroiditis: an additional case. *European Journal of Internal Medicine.* 2003 Nov 1;14(7):434-7.
61. Piga M, Serra A, Deiana L, Loi GL, Satta L, Di Liberto M, et al. Brain perfusion abnormalities in patients with euthyroid autoimmune thyroiditis. *European Journal of Nuclear Medicine and Molecular Imaging.* 2004 Dec;31:1639-44.
62. Jellinek EH, Ball K. Hashimoto's disease, encephalopathy, and splenic atrophy. *The Lancet.* 1976 Jun 5;307(7971):1248.
63. Shibata N, Yamamoto Y, Sunami N, Suga M, Yamashita Y. Isolated angiitis of the CNS associated with Hashimoto's disease. *Rinsho Shinkeigaku= Clinical Neurology.* 1992 Feb 1;32(2):191-8.
64. Nolte KW, Unbehau A, Sieker H, Kloss TM, Paulus W. Hashimoto encephalopathy: a brainstem vasculitis?. *Neurology.* 2000 Feb 8;54(3):769-770.
65. Duffey P, Yee S, Reid IN, Bridges LR. Hashimoto's encephalopathy: postmortem findings after fatal status epilepticus. *Neurology.* 2003 Oct 28;61(8):1124-26.
66. Oide T, Tokuda T, Yazaki M, Watarai M, Mitsunashi S, Kaneko K, et al. Anti-neuronal autoantibody in Hashimoto's encephalopathy: neuropathological, immunohistochemical, and biochemical analysis of two patients. *Journal of the Neurological Sciences.* 2004 Jan 15;217(1):7-12.
67. Mahad DJ, Staugaitis S, Ruggieri P, Parisi J, Kleinschmidt-Demasters BK, Lassmann H, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis and primary CNS demyelination. *Journal of the Neurological Sciences.* 2005 Jan 15;228(1):3-5.
68. Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 1. Clinical syndromes: a literature investigation. *Rheumatology (Oxford).* 2002 Jun;41(6):605-18.
69. Bruns A, Meyer O. Neuropsychiatric manifestations of systemic lupus erythematosus. *Joint Bone Spine.* 2006 Dec 1;73(6):639-45.
70. Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. *Rheumatology.* 2002 Jun 1;41(6):619-30.
71. Sanna G, Bertolaccini ML, Mathieu A. Central nervous system lupus: a clinical approach to therapy. *Lupus.* 2003 Dec;12(12):935-42.
72. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. *The Journal of Rheumatology.* 2003 May 1;30(5):985-92.

73. Johnson RT, Gibbs Jr CJ. Creutzfeldt-Jakob disease and related transmissible spongiform encephalopathies. *New England Journal of Medicine.* 1998 Dec 31;339(27):1994-2004.
74. Calabrese L. Primary angiitis of the central nervous system: the penumbra of vasculitis. *The Journal of Rheumatology.* 2001 Mar 1;28(3):465-6.
75. Imbesi SG. Diffuse cerebral vasculitis with normal results on brain MR imaging. *AJR. American Journal of Roentgenology.* 1999 Dec;173(6):1494-6.
76. Wasserman BA, Stone JH, Hellmann DB, Pomper MG. Reliability of normal findings on MR imaging for excluding the diagnosis of vasculitis of the central nervous system. *American Journal of Roentgenology.* 2001 Aug;177(2):455-9.
77. Alrawi A, Trobe JD, Blaivas M, Musch DC. Brain biopsy in primary angiitis of the central nervous system. *Neurology.* 1999 Sep 1;53(4):858-60.
78. Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR. Autoimmune hypophysitis. *Endocr Rev.* 2005 Aug;26(5):599-614.
79. Miyake I, Takeuchi Y, Kuramoto T, Kaku H, Nakayama H, Takata K, et al. Autoimmune hypophysitis treated with intravenous glucocorticoid therapy. *Internal Medicine.* 2006;45(21):1249-52.
80. Rivera JA. Lymphocytic hypophysitis: disease spectrum and approach to diagnosis and therapy. *Pituitary.* 2006 Mar;9:35-45.
81. Mocellin R, Velakoulis D, Gonzales M, Lloyd J, Tomlinson EB. Weight loss, falls, and neuropsychiatric symptoms in a 56 year-old man. *The Lancet Neurology.* 2005 Jun 1;4(6):381-8.
82. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain.* 2004 Mar 1;127(3):701-12.
83. Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology.* 2004 Apr 13;62(7):1177-82.
84. Urbach H, Soeder BM, Jeub M, Klockgether T, Meyer B, Bien CG. Serial MRI of limbic encephalitis. *Neuroradiology.* 2006 Jun;48:380-6.
85. Sener RN. MRI and diffusion MRI in nonparaneoplastic limbic encephalitis. *Computerized Medical Imaging and Graphics.* 2002 Sep 1;26(5):339-42.
86. Fauser S, Talazko J, Wagner K, Ziyeh S, Jarius S, Vincent A, et.al. FDG-PET and MRI in potassium channel antibody-associated non-paraneoplastic limbic encephalitis: correlation with clinical course and neuropsychology. *Acta Neurologica Scandinavica.* 2005 May;111(5):338-43.
87. Caviness JN. Myoclonus and neurodegenerative disease—what's in a name?. *Parkinsonism & Related Disorders.* 2003 Mar 1;9(4):185-92.
88. McKeith IG, Burn DJ, Ballard CG, Collerton D, Jaros E, Morris CM, et al. Dementia with Lewy bodies. *Semin Clin Neuropsychiatry.* 2003 Jan;8(1):46-57.
89. Walker Z, Medicine DG, Stevens T. Dementia with Lewy bodies: clinical characteristics and diagnostic criteria. *Journal of Geriatric Psychiatry and Neurology.* 2002 Dec;15(4):188-94.
90. Caviness JN, Adler CH, Caselli RJ, Hernandez JL. Electrophysiology of the myoclonus in dementia with Lewy bodies. *Neurology.* 2003 Feb 11;60(3):523-4.
91. Tschampa HJ, Neumann M, Zerr I, Henkel K, Schröter A, Schulz-Schaeffer WJ, et.al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2001 Jul 1;71(1):33-9.
92. Dickson DW, Bergeron C, Chin SS, Duyckaerts C, Horoupian D, Ikeda K et.al. Office of Rare Diseases neuropathologic criteria for corticobasal degeneration. *Journal of Neuropathology & Experimental Neurology.* 2002 Nov 1;61(11):935-46.
93. Graham NL, Bak TH, Hodges JR. Corticobasal degeneration as a cognitive disorder. *Movement Disorders: Official Journal of the Movement Disorder Society.* 2003 Nov;18(11):1224-32.
94. Kothbauer-Margreiter I, Sturzenegger M, Komor J, Baumgartner R, Hess CW. Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment. *Journal of Neurology.* 1996 Aug;243(8):585-93.
95. Onesti E, Koudriavtseva T, Galiè E, Anelli V, Jandolo B. A possible case of Hashimoto's encephalopathy after surgery and radiometabolic therapy for thyroid carcinoma. *Neurol Sci.* 2013 Aug;34(8):1489-91.
96. Berger I, Castiel Y, Dor T. Paediatric Hashimoto encephalopathy, refractory epilepsy and immunoglobulin treatment-unusual case report and review of the literature Berger et al. Hashimoto encephalopathy and immunoglobulin. *Acta Pædiatrica.* 2010 Dec 1;99(12): 1903-5.
97. Vernino S, Geschwind M, Boeve B. Autoimmune encephalopathies. *The neurologist.* 2007 May 1;13(3):140-7.
98. Chang JS, Chang TC. Hashimoto's encephalopathy: report of three cases. *Journal of the Formosan Medical Association.* 2014 Nov 1;113(11):862-6.
99. Cook MK, Malkin M, Karafin MS. The use of plasma exchange in Hashimoto's encephalopathy: A case report and review of the literature. *Journal of Clinical Apheresis.* 2015 Jun;30(3):188-92.
100. Chen N, Qin W, Wei C, Wang X, Li K. Time course of Hashimoto's encephalopathy revealed by MRI: report of two cases. *Journal of the Neurological Sciences.* 2011 Jan 15;300(1-2):169-72.
101. Hussain NS, Rumbaugh J, Kerr D, Nath A, Hillis AE. Effects of prednisone and plasma exchange on cognitive impairment in Hashimoto encephalopathy. *Neurology.* 2005 Jan 11;64(1):165-166.
102. Pranzatelli MR, Tate ED, Travelstead AL, Longee D. Immunologic and clinical responses to rituximab in a child with opsoclonus-myoclonus syndrome. *Pediatrics.* 2005 Jan;115(1):e115-9.

103. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, Swanson J, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Archives of Neurology.* 2006 Feb 1;63(2):197-202.
104. Jacob S, Rajabally YA. Hashimoto's encephalopathy: steroid resistance and response to intravenous immunoglobulins. *Journal of Neurology, Neurosurgery & Psychiatry.* 2005 Mar 1;76(3):455-6.
105. Kim JE, Choi HC, Song HK, Jo SM, Kim DS, Choi SY, et al. Levetiracetam inhibits interleukin-1 β inflammatory responses in the hippocampus and piriform cortex of epileptic rats. *Neuroscience Letters.* 2010 Mar 3;471(2):94-9.
106. Stienen MN, Haghikia A, Dambach H, Thöne J, Wiemann M, Gold R, et al. Anti-inflammatory effects of the anticonvulsant drug levetiracetam on electrophysiological properties of astroglia are mediated via TGF β 1 regulation. *Br J Pharmacol.* 2011 Jan;162(2):491-507.
107. Wong LC, Freeburg JD, Montouris GD, Hohler AD. Two patients with Hashimoto's encephalopathy and uncontrolled diabetes successfully treated with levetiracetam. *Journal of the Neurological Sciences.* 2015 Jan 15;348(1-2):251-2.
108. Tang Y, Xing Y, Lin MT, Zhang J, Jia J. Hashimoto's encephalopathy cases: Chinese experience. *BMC Neurology.* 2012 Dec;12:1-7.
109. Litmeier S, Prüss H, Witsch E, Witsch J. Initial serum thyroid peroxidase antibodies and long-term outcomes in SREAT. *Acta Neurologica Scandinavica.* 2016 Dec;134(6):452-57.