Hashimoto's Encephalopathy

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Introduction

Background

In 1966, Brain and colleagues [1] reported the case of a 48-year-old man who developed fluctuating encephalopathy several months after he was diagnosed with Hashimoto's autoimmune thyroiditis. For the first year after his Hashimoto's diagnosis, he had at least 12 episodes of acute-onset stroke-like symptoms that localized to different vascular distributions. These episodes were interspersed between periods of prolonged delirium with hallucinations and waxing-and-waning levels of consciousness. Five years after his first presentation with neurologic symptoms, his illness resolved spontaneously, and he had no residual neurologic deficits. Based on the fluctuating, multifocal, and self-resolving nature of the patient's symptoms, as well as the temporal proximity of the neurologic disease to the patient's onset of Hashimoto's thyroiditis, Brain surmised that there may be an underlying autoimmune mechanism relating the patient's Hashimoto's disease with his neurologic symptoms.

Since Brain's initial report, more than 120 further cases of wide-ranging neurologic symptoms associated with thyroid autoantibodies have been reported [1–5]. These cases have since been grouped into a poorly defined syndrome with several names:

1. Hashimoto's encephalopathy (HE) [2], the most commonly used nomenclature that references Brain's 1966 report.
2. Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) [3], a term used to highlight the responsiveness of cases to immunomodulatory therapy.
3. Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) [4], a term used to distinguish the entity from central nervous system (CNS) vasculitis.
4. Neurological disorder associated with thyroid autoimmunity [5], a term used to broaden the syndrome to include non-encephalopathic neurologic symptoms.

This varied nomenclature highlights the challenge of defining a clinical syndrome that does not yet have a clear molecular or pathologic cause. For the purposes of this chapter, we will use the term Hashimoto's encephalopathy (HE) to denote a steroid-responsive encephalopathy associated with elevated thyroid autoantibodies, noting that most patients do not have active thyroiditis at presentation.

Definition

HE is an autoimmune disorder that is characterized by a combination of elevated thyroid antibodies and altered cognition that cannot be attributed to hypothyroidism or thyrotoxicosis. It is one of several subcategories of autoimmune encephalopathy, which include HE, paraneoplastic encephalopathy, autoimmune encephalitis with known antibodies, autoimmune encephalitis without known antibodies, primary central nervous system vasculitis, and systemic autoimmune diseases with CNS involvement. HE is a heterogeneous clinical syndrome for which multiple sets of diagnostic criteria have been proposed [2, 6–9]. While its definition has evolved with the identification of antibodies that cause autoimmune encephalopathy, the key central diagnostic criteria remain relevant. These criteria are detailed as follows (and summarized in Table 17.1):

Encephalopathy The diagnosis of HE requires patients to have cognitive dysfunction. This may manifest as disorientation, confusion, memory loss, changes in level of consciousness, psychosis, or other signs of encephalopathy. Patients with HE may also have additional neurologic

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T. A. Cho et al. (eds.), *Neurorheumatology*, https://doi.org/10.1007/978-3-030-16928-2_17

Table 17.1 Diagnostic criteria for Hashimoto's encephalopathy

Diagnostic criteria for Hashimoto's encephalopathy/SREAT
Encephalopathy
Presence of serum thyroid autoantibody
Euthyroid or mild hypothyroid status
Exclusion of non-autoimmune causes of encephalopathy with laboratory and radiologic studies
Exclusion of non-convulsive status epilepticus
Exclusion of known autoantibody syndromes
Improvement with immune suppression

symptoms beyond encephalopathy, including seizures, tremors or myoclonus, and focal findings.

Presence of Serum Thyroid Autoantibody Patients with HE have elevated serum levels of anti-thyroglobulin antibody (anti-TG, previously known as thyroid microsomal antibody) or anti-thyroperoxidase antibody (anti-TPO).

Euthyroid or Mild Hypothyroid Status Serum thyroid-stimulating hormone (TSH) level should be between 0.3 mIU/L and 5.0 mIU/L (euthyroid) or 5.1 mIU/L and 20.0 mIU/L (mildly hypothyroid) to ensure that any symptoms of encephalopathy cannot be explained by profound hypothyroidism or thyrotoxicosis, as both are known to cause neurologic symptoms.

Exclusion of Non-Autoimmune Causes of Encephalopathy with Laboratory Studies Infectious, toxic, metabolic, or neoplastic causes of encephalopathy must be ruled out with blood, urine, and cerebrospinal fluid (CSF) studies. Particular attention should be paid to ensure that the patient does not have viral encephalitis.

Exclusion of Neoplastic, Structural, or Vascular Causes of Encephalopathy with Radiologic Studies To diagnose HE, neuroimaging should exclude neoplastic, structural, or vascular etiologies of encephalopathy.

Exclusion of Non-Convulsive Status Epilepticus By Electroencephalography (EEG) While patients with HE may have seizures, seizures are not the sole cause of encephalopathy in the syndrome. Thus, EEG should be obtained to rule out non-convulsive status epilepticus as a cause of encephalopathy before assigning a diagnosis of HE.

Exclusion of Known Auto Antibody Syndromes HE cannot be diagnosed in a patient who has positive serum antibodies to known neural antigens and pathologically defined types of autoimmune encephalitis. These include, but are not limited to, N-methyl-D-aspartate (NMDA) receptor antibody, voltage-gated calcium channel antibody syndromes, voltage-gated potassium channel complex antibody syndromes, and neuromyelitis optica (NMO) spectrum disease. By extension, systemic autoimmune diseases that can cause neurologic symptoms, such as lupus, Sjögren syndrome, neuro-Behcet's, and sarcoidosis, should be excluded.

Improvement with Corticosteroid Treatment A key feature of HE is its response to immunotherapy, usually within 1–4 weeks. This is a fundamental diagnostic criterion needed to distinguish HE, an autoimmune encephalopathy associated with anti-thyroid antibodies, from an unrelated encephalopathy with coincidental presence of serum anti-thyroid antibody. This criterion is similar to idiopathic Parkinson's disease, in which a patient's response to dopamine replacement can distinguish Parkinson's disease from other parkinsonian syndromes.

It is worthwhile to note that the patient in the original report by Brain and colleagues received steroids but did not improve and thus would not be diagnosed with HE by these criteria.

Pathophysiology

It is widely accepted that an autoimmune process causes HE. However, the pathophysiology of HE remains poorly understood. Proposed disease mechanisms include antibody-mediated effects on neurons and/or glia, alteration of cell metabolism, and disruption of cerebral blood flow. These mechanisms are illustrated in Fig. 17.1 and discussed as follows.

The Role of Anti-Thyroid Antibodies in Disease

Controversy surrounds the question of whether anti-thyroid antibodies in HE are pathogenic or whether they are a coincident marker of immune dysregulation and a bystander to a different autoimmune process.

Those who support the theory that thyroid antibodies are pathogenic point to evidence that anti-thyroid antibodies have been found in the cerebrospinal fluid of individuals with HE, but not in individuals with other neurologic diseases or individuals with elevated serum thyroid antibodies who do not have encephalopathy [10, 11]. A possible mechanism of pathogenesis is a shared antigen between thyroid and neural structures: two studies report binding of anti-thyroperoxidase (TPO), anti-thyroglobulin (TG), and anti-thyroid-stimulating hormone receptor (TSH-R) antibodies to astrocytes, vascular smooth muscles, and neurons, respectively [12, 13]. However, these

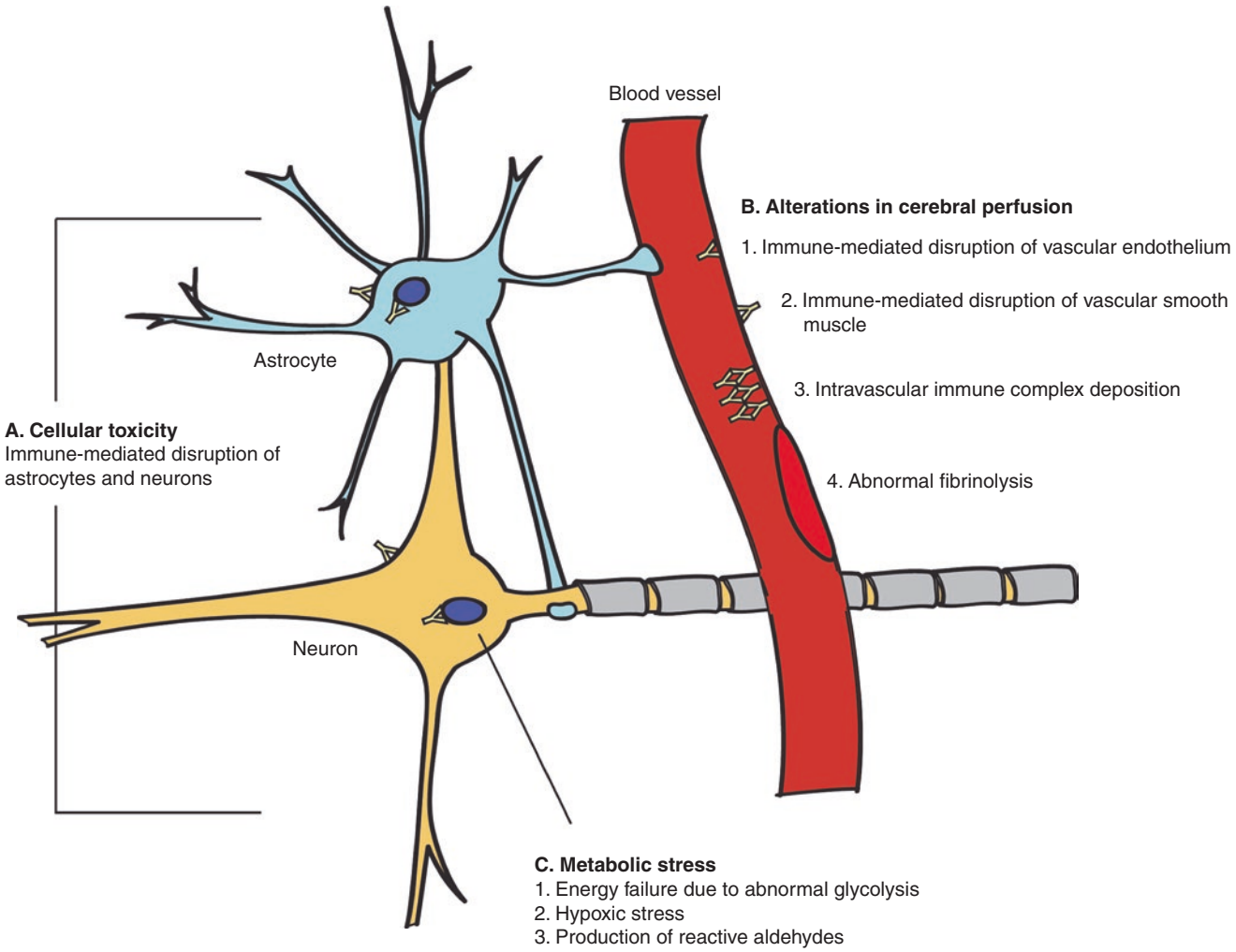

Fig. 17.1 Proposed mechanisms of Hashimoto's Encephalopathy

studies have not been replicated, and they also do not demonstrate a causal link between anti-thyroid antibodies and neuronal dysfunction. The evidence is inadequate to confidently support a pathogenic role of the anti-thyroid antibodies in HE.

The opposing theory hypothesizes that serum thyroid antibodies are nonpathogenic markers of autoimmunity that coincidentally coexist with a separate autoimmune neurologic disease process. Proponents of this theory point to the high prevalence of anti-thyroid antibodies in the general population and contrast it with the rarity of HE: approximately 10–12% of the healthy population in the United States have detectable anti-thyroid antibodies [14], but the estimated prevalence of HE is 2.1/100,000 [7, 15]. Indeed, the serum concentration of anti-thyroid antibodies does not correlate well with the severity of encephalopathy symptoms in previously reported cases of HE [16], which argues against their pathogenicity.

Other Autoantibodies in Hashimoto's Encephalopathy

A small number of studies have highlighted other antibodies that could be associated with HE. Two proteomic screens of serum and CSF from patients with HE identified anti-dimethylargininase-I (DDAHI) and anti-aldehyde reductase I (AKRIAI) as potential markers of the disease [17, 18]. DDAHI is involved in the regulation of nitric oxide synthesis [19] and was found to bind to endothelial cells in venules of the CNS. AKRIAI is involved in the metabolism of reactive aldehydes [20], and antibodies against this protein bind to endothelial cells, glial cells of white matter, and cortical gray matter. While intriguing, these studies have small sample sizes, have not been replicated, and have not demonstrated a causal link between antibodies and neuronal dysfunction.

One promising potential biomarker of HE is an antibody against α-enolase, a glycolytic enzyme that has multiple

functions that include plasminogen binding, response to hypoxic stress, and microtubule organization [21]. Three studies measured the presence of serum α-enolase antibodies in a total of at least 31 patients with clinical HE, 71 patients with Hashimoto's thyroiditis without encephalopathy, and 78 control individuals [22–24]. The combined studies found antibodies to α-enolase in 60–83% of patients with clinical HE, 6–12% of patients with Hashimoto's thyroiditis without encephalopathy, and 0% of the control patients.

Despite this preliminary evidence, α-enolase antibody assays remain experimental and have not become standard in clinical practice. It remains unclear how specific these antibodies are for HE; α-enolase antibodies have been reported in rheumatologic disorders such as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, lupus nephritis, primary sclerosing cholangitis, and autoimmune hepatitis, among others [20]. It also remains unclear how antibodies to α-enolase may be involved in the pathogenesis of HE. Anti-α-enolase antibodies may represent a nonspecific predilection to autoimmune disease. Alternatively, α-enolase could be involved in the pathogenesis of HE via energy failure due to aberrant glycolysis, intravascular immune complex deposition, and disturbance of fibrinolysis leading to disruption of cerebral blood flow and cerebral hypoperfusion.

Cerebral Hypoperfusion in Hashimoto's Encephalopathy

Cerebral perfusion changes may be a mechanism of disease in HE. Several case reports of individuals with HE who had single-photon emission computed tomography (SPECT) scans demonstrated global brain hypoperfusion at the time of diagnosis. Perfusion subsequently improved with treatment and resolution of the clinical syndrome [25, 26]. In addition, a SPECT study of seven individuals with both HE and serum α-enolase antibodies showed decreased perfusion in the bilateral anterior cingulate areas and left prefrontal cortex compared to controls [27]. However, it is important to note that some case series of individuals with HE also show normal cerebral perfusion on SPECT scans [15].

Interestingly, a study that compared the brain SPECT images of patients with autoimmune thyroiditis compared to healthy individuals found evidence of cerebral hypoperfusion in patients with autoimmune thyroiditis, even in the absence of neurologic symptoms [28]. This study raises the intriguing possibility that there may be a unifying vascular process linking autoimmune thyroiditis and HE.

Clinical Syndromes

Epidemiology

HE is a rare disorder. Its estimated prevalence is 2.1/100,000 [15]. Like most autoimmune disorders, HE has a female predominance with a female-to-male ratio of 4:1 [5]. It is primarily a disorder of adulthood; the mean age of presentation ranges between 44 and 56 years [3]. However, HE has been reported in patients from the ages of 34 months to 86 years, and between 14% and 20% of cases are pediatric patients [5, 29, 30].

Clinical Presentation

HE can manifest in a variety of ways, though clinical presentations generally fall under two major phenotypes [31]. The first type is a "vasculitic" presentation, in which patients have recurrent, discrete, stroke-like episodes with focal findings such as hemiparesis, hemisensory deficits, aphasia, or ataxia. The other type is an indolent "diffuse progressive" presentation, in which patients develop insidious encephalopathy that may mimic rapidly progressive dementia such as prion disease. These patients may also have symptoms of psychosis, hallucinations, or changes in level of consciousness. There is significant overlap between these categories, and patients can present with both types during different phases of disease. Patients may also have seizures, tremors, or myoclonus in both types of presentations. In both presentations, the hallmark feature is a nonspecific encephalopathy that can include alterations in consciousness, confusion, impaired cognitive function, or delirium. Symptoms are often subacute and may fluctuate; they rarely can present acutely.

The common clinical features outside of encephalopathy have been reported in several case series and reviews. They are summarized in Table 17.2 [2, 3, 5, 32]. The wide range in reported prevalence is a result of different sample sizes in different studies.

Table 17.2 Common clinical features of Hashimoto's encephalopathy

Clinical symptom	Prevalence (% reported)
Seizures	52–66
Altered consciousness	36–85
Focal deficits, including aphasia	18–80
Myoclonus	32–65
Tremor	28–84
Ataxia or gait disturbances	28–65
Psychosis and/or hallucinations	25–36
Headache	13–50

Modified from [2, 3, 5, 32]

In addition to the typical features of HE previously described, there are also rare case reports of other neurologic symptoms described in the setting of HE, including encephalopathy associated with subacute cerebellar syndromes [33, 34], choreiform movements [35], sensory ganglionopathies [36], or peripheral neuropathies [37]. However, in cases of suspected HE with atypical features, it is important to rule out concurrent autoimmune or paraneoplastic disorders leading to rare presentations of disease.

Laboratory Features

By definition, patients with HE are euthyroid or have mild hypothyroidism. Also by definition, patients with HE have thyroid antibodies present in the serum. As there is no disease-specific minimum antibody titer required for diagnosis, the antibody titer can range from slightly above the upper limit of normal to markedly elevated.

The most commonly found thyroid antibody is anti-TPO, which has been reported in the serum of 86–100% of patients in HE case series [2, 3, 5]. Anti-TG antibodies are less prevalent and are found in 60–73% of these cases. It is important to remember that while antibodies are required for diagnosis, their presence is not specific for the disease because they are found in 10–12% of the normal population [14].

The CSF findings of patients with HE vary from normal to mildly inflammatory. The most common abnormality is mildly elevated CSF protein, which has been reported in 70–85% of cases. While CSF cell count can be mildly inflammatory in a fraction of HE cases, the majority (approximately 75%) of patients with HE have a normal CSF cell count. CSF glucose is usually normal. Oligoclonal bands are rare in HE, but their presence has been reported [2, 3, 5]. A marked CSF pleocytosis should be a signal for caution and may point away from HE and toward an alternative diagnosis such as infectious encephalitis.

Other signs of systemic inflammation may be evident in patients with HE, such as positive serum antinuclear antibody, elevated erythrocyte sedimentation rate, elevated C-reactive protein, and mildly elevated liver aminotransferases [3].

Radiological/Electrophysiological Features

Brain magnetic resonance imaging (MRI) abnormalities have been noted in less than half of reported cases of HE [2, 3, 6]. Indeed, MRI is most useful in ruling out other structural or inflammatory causes of the patient's clinical syndrome. When MRI abnormalities are present, they are nonspecific and can include diffuse white matter signal abnormalities, leptomeningeal enhancement [3], and atrophy [38]. As with other causes of autoimmune encephalopathy, brain fluorodeoxyglucose-positron emission tomography (FDG-PET) may disclose metabolic abnormalities in patients with normal brain MRI (Fig. 17.2). In some cases, imaging abnormalities reverse following immunosuppressive therapy [3, 39].

Electroencephalography (EEG) is commonly abnormal in patients with HE (82–98% in case series), but there is no specific EEG pattern [2, 5]. The most common EEG abnormality is generalized background slowing in the delta range (Fig. 17.3) [5]. Other abnormalities seen in HE include focal slowing, triphasic waves, periodic lateralized epileptiform discharges, frontal intermittent rhythmic delta or theta activity, and epileptiform abnormalities. These abnormalities are often reversible with treatment [40].

Pathology

The most common pathologic finding in brain biopsy and autopsy specimens from patients with HE is a chronic perivascular lymphocytic infiltration in arterioles and venules [41]. There can also be inflammation within the brain parenchyma, with tissue samples showing microglial activation and chronic gliosis with prominent astrocytes. There has been no pathologic evidence of central nervous system demyelination in HE.

Treatment

Treatment guidelines are based on expert opinion because no randomized clinical trials for treatment of autoimmune encephalopathy exist.

Acute Therapy

Steroids

The initial treatment of patients with suspected HE is high-dose corticosteroids because of their rapid action and favorable risk-to-benefit ratio in acute autoimmune disorders. A commonly used empiric course for HE is intravenous methylprednisolone (IVMP) 1000 mg daily for 5 days. Following this course, patients often require a period of maintenance steroid treatment and slow steroid taper. Suggested regimens include daily prednisone therapy with an initial dose of 1–2 mg/kg/day, followed by a slow taper over 6–12 weeks; alternatively, IVMP 1000 mg may be given weekly for 6–12 weeks. Patients should be monitored for side effects including hyperglycemia, hypertension, osteoporosis,

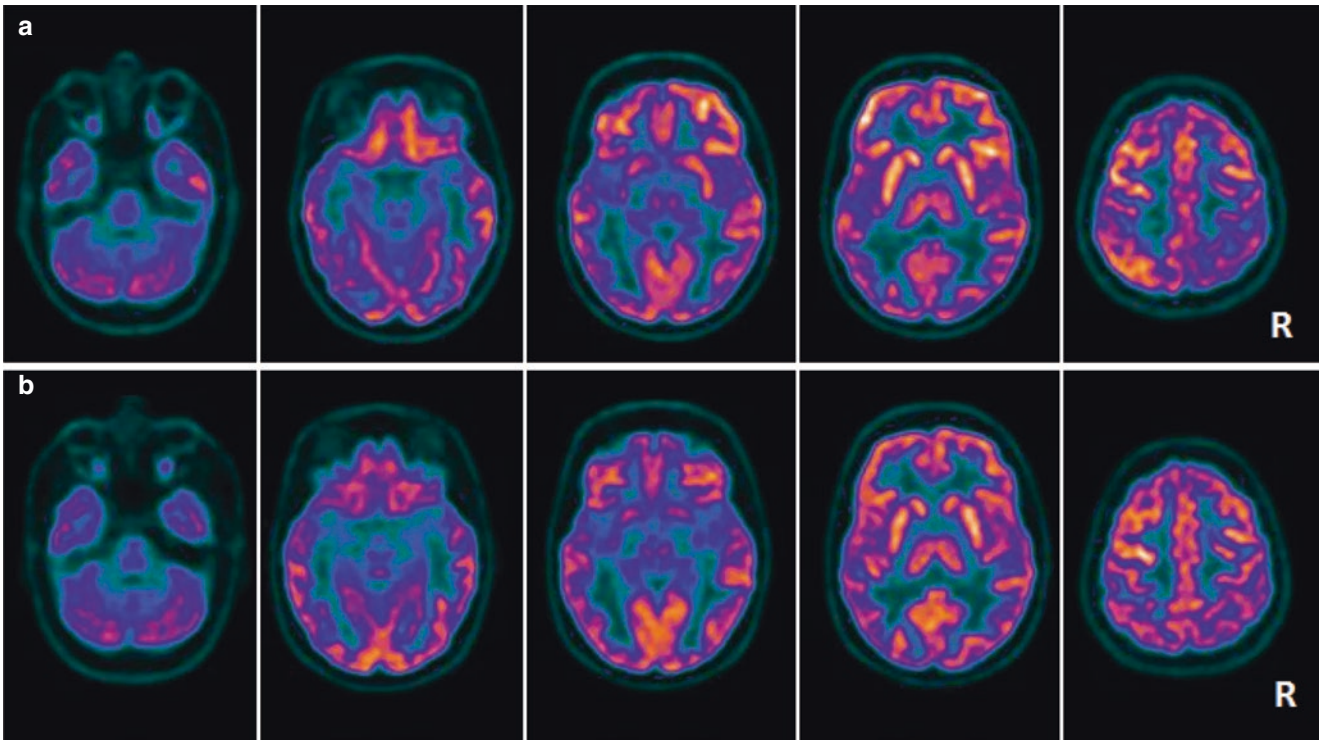

Fig. 17.2 (**a**) 18F-FDG brain PET showing hypometabolism in the left temporal lobe, insula, and ipsilateral temporo-occipital junction and in the right superior parietal lobule. (**b**) 18F-FDG brain PET documenting a normalization of brain glucose metabolism 3 months after the treatment with plasmapheresis. (Reprinted with permission from Pari Pari et al. [45])

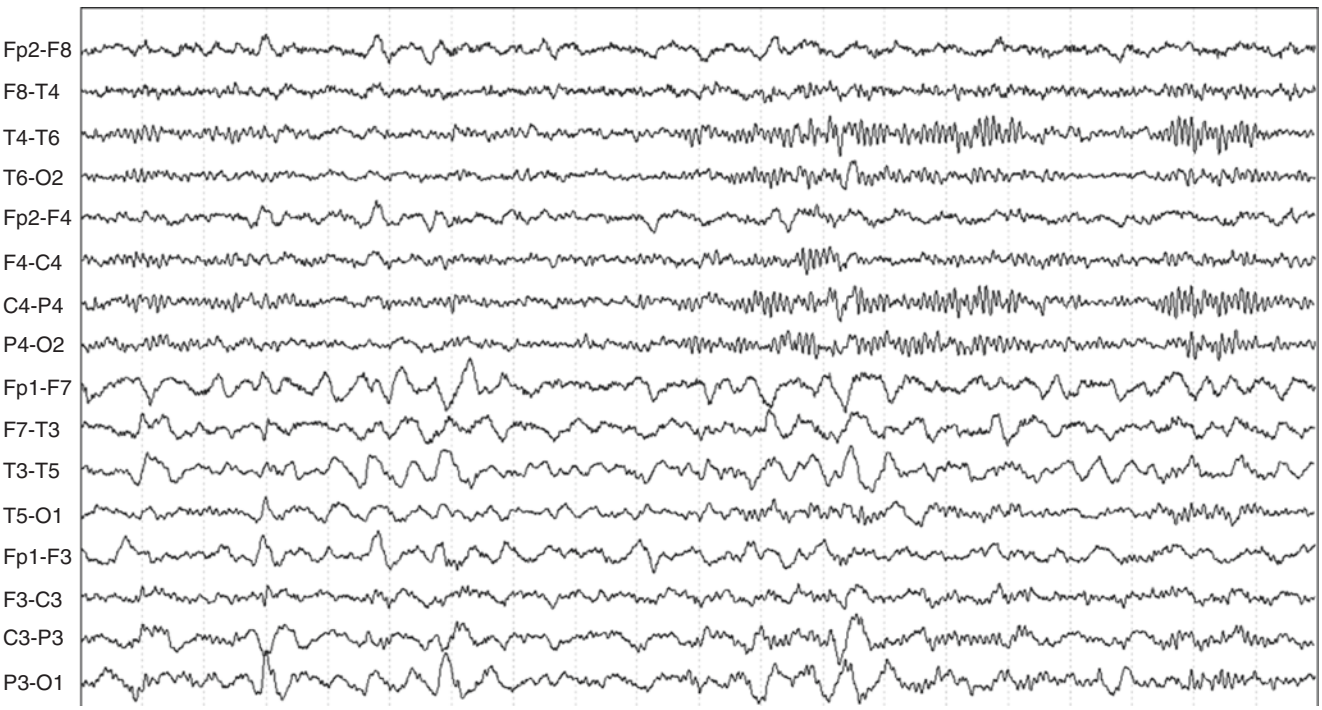

Fig. 17.3 EEG showing continuous high-amplitude rhythmic lateralized delta waves in the frontotemporal regions, with a defined prevalence over the left hemisphere. Neurological examination revealed global aphasia with dysgraphia as well as dyslexia. (Reprinted with permission from Pari et al. [45])

Cushingoid changes, weight gain, and infections. Calcium with vitamin D should be used in all patients, and *Pneumocystis jirovecii* prophylaxis should be given to patients who will be taking moderate-dose steroids long term (>16 mg prednisone for 8 or more weeks [see Chap. 28]).

We suggest that patients undergo cognitive testing and ancillary testing (such as EEG) to establish a neurologic baseline before the initiation of therapy, if possible. Most patients with HE respond to treatment within 1 week, and almost all will have responded within 4 weeks [42]. If patients do not respond to steroids with quantitative improvement within the first 4 weeks, alternative diagnoses should be reconsidered before committing the patient to long-term immunosuppressive therapy.

Intravenous Immunoglobulin

For patients who have contraindications to steroid therapy, intravenous immunoglobulin (IVIG) may be used as an alternative immunomodulatory agent [16]. A typical dose is 0.4 g/kg/day for 3–5 days. This may also be followed by 0.4 g/kg weekly IVIG for 6–12 weeks. Patients should be monitored for side effects, which can include transfusion reactions, arterial and/or venous thrombosis, and acute kidney injury.

Plasmapheresis

Plasmapheresis, or plasma exchange, can be used in HE in patients with contraindications to steroid therapy [43, 44]. The standard dosing for plasmapheresis in this context is a 1–1.5 plasma volume exchange every other day for five treatments. Potential adverse effects include complications of central venous catheter placement, transfusion reactions, hypocalcemia, hypokalemia, coagulopathy, interactions with medications such as angiotensin-converting enzyme inhibitors, or removal of other immunomodulatory medications.

Maintenance Therapy

While some patients may recover after one clinical episode of HE, relapse of symptoms is common and patients often require steroid-sparing maintenance immunomodulatory therapy. Table 17.3 summarizes the common maintenance therapies. In our practice, we use mycophenolate as a first-line steroid-sparing agent and find that it is generally effective and well tolerated. We use azathioprine or methotrexate as alternate agents to mycophenolate, depending on patient comorbidities. These agents are typically continued for 1 year before a tapering trial. If clinical relapses recur with medication taper, we may continue these agents for 2 or more years. Patients with recalcitrant disease who do not

Table 17.3 Maintenance treatment of Hashimoto's encephalopathy/steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT)

Agent	Mechanism of action	Side effects	Dosing
Mycophenolate	Inosine monophosphate inhibitor Disrupts purine synthesis and depletes B- and T-cells	Gastrointestinal upset Myelosuppression Hypertension Increased risk for malignancy or infection	Starting dose: 250 mg twice a day Increase as tolerated to 1000 mg twice a day
Azathioprine	Amidophosphophoribosyl-transferase inhibitor Disrupts purine synthesis and depletes B- and T-cells	Hepatitis Rash Hypersensitivity Pancreatitis Myelosuppression Increased risk for malignancy or infection	Starting dose 2–3 mg/kg/day divided twice a day
Methotrexate	Dihydrofolate reductase inhibitor Disrupts purine synthesis and depletes B- and T-cells	Nausea, abdominal pain Hepatotoxicity Ulcerative stomatitis Myelosuppression Increased risk for infection and malignancy	Starting dose 7.5 mg per week Increase as tolerated to 15–20 mg a week Supplement with folic acid 1 mg daily
Rituximab	Anti-CD20 monoclonal antibody Depletes B-cells within 3 weeks	Infusion reaction Myelosuppression Reactivation of latent tuberculosis Reactivation of hepatitis B Rare PML Increased risk of infection	Loading dose: doses of 1000 mg IV, 2 weeks apart Maintenance doses can be repeated every 6 months and are guided by clinical relapses rather than serum CD 19/20 levels
Cyclophosphamide	Nitrogen mustard alkylating agent Depletes T-cells	Nausea, vomiting, diarrhea Infertility Hemorrhagic cystitis Increased risk of infection or malignancy Cardiac toxicity Pulmonary toxicity	Usual dose: 15 mg/kg, with maximum of 1200 mg per dose, given monthly for 6 months

IV intravenous, *PML* progressive multifocal leukoencephalopathy

respond to first-line therapy may then receive rituximab or cyclophosphamide to maintain disease remission [16]. Further medication adjustments are made based on continued assessments of risk and benefits of treatment effects versus clinical relapses, with any eye toward taper whenever possible.

Clinical Case

A 50-year-old woman with Hashimoto's thyroiditis presented with a headache associated with confusion, memory loss, slurred speech, and fluctuating right-sided vision loss and numbness in her right face and arm. Her exam was notable for disorientation and inattentiveness. Her speech was fluent but her thought process was disorganized. Her responses to questions were inappropriate and peppered with confabulation. The remainder of her neurologic exam was normal.

The differential diagnosis at the time of presentation included seizures, CNS infection, Whipple disease, HE, CNS vasculitis, neuropsychiatric lupus, human immunodeficiency virus (HIV), paraneoplastic disease, rapidly progressive dementia, porphyria, and toxic or metabolic encephalopathy. An extensive laboratory evaluation revealed normal serum TSH, total T3, and free T4. Her anti-nuclear antibody (ANA) was 1:320, but antibodies to double-stranded DNA, Ro, La, Smith, and ribonucleoprotein (RNP) were negative. Studies for syphilis, Whipple's disease, HIV, and viral and bacterial encephalitis were negative. Her CSF was noninflammatory with 0 CSF leukocytes and a mildly elevated protein (94 mg/dL). A paraneoplastic encephalitis panel that included antibodies to VGKC, CV2, MATA, NMDAR, GAD, and amphiphysin was negative. Long-term EEG monitoring demonstrated intermittent diffuse slowing without epileptiform discharges.

HE was suspected when her thyroid peroxidase antibody was greater than assay (>1000 IU/mL, normal range <35 IU/mL). Her thyroglobulin antibody was 603 IU/mL (normal range <40 IU/mL). She was empirically started on oral prednisone 60 mg daily and rapidly improved within 48 h, leading to a diagnosis of HE. She was discharged home with a 2-week prednisone taper. Her mental status was normal in clinic 1 month later.

She remained well for 6 months off treatment until she had a relapse of symptoms. Prednisone 60 mg daily was restarted. Her mental status returned to baseline, and she remained well until prednisone was weaned after 1 month. Prednisone was restarted and methotrexate 15 mg weekly was added. Despite adjuvant therapy, she had a second relapse when prednisone was tapered, so she received IVIG (1.5 mg/kg divided over five doses) with return to her baseline mental status. She continued to receive IVIG infusions monthly.

One year after symptom onset, she was doing well with no neurologic deficits with monthly IVIG and weekly methotrexate. She successfully tapered prednisone to 20 mg daily. However, she had a third relapse when IVIG was stopped, and an increase in methotrexate to 20 mg weekly did not help. Therefore, she received rituximab (two doses of 1000 mg separated by 2 weeks, followed by two further doses 1 month later). Her mental status improved to near baseline with some residual mild emotional lability. She remained stable for a year.

Two and a half years after symptom onset, she had a fourth relapse with recurrent fluctuating mental status abnormalities. She received three doses of 1000 mg IV methylprednisolone followed by two doses of rituximab 1000 mg. Methotrexate was stopped because of ulcerative stomatitis. Her mental status returned to her previous baseline, and she was discharged home with a prednisone taper.

One month later, she had a fifth relapse in the setting of her prednisone taper. She had a witnessed tonic-clonic seizure at home and was hospitalized in the intensive care unit. She had a fever to 104 ° F and was comatose on admission. Extensive infectious evaluation was unremarkable. Her CSF had 0 white blood cells (WBC) and normal protein. Brain MRI showed susceptibility effect and T2 FLAIR hyperintensity, which were associated with mild leptomeningeal enhancement in the right precentral sulcus. She received 1000 mg IV methylprednisolone daily for 3 days, and her mental status rapidly improved. She was started on mycophenolate 250 mg twice daily. Rituximab was continued with two infusions of 1000 mg 2 weeks apart, dosed every 6 months.

Mycophenolate was slowly increased to 750 mg twice daily and rituximab continued every 6 months. On this regimen, she was able slowly to taper off prednisone over 1 year. She has not had another relapse in 18 months. Her neurologic exam at her most recent clinic visit (almost 4 years after symptom onset) was normal except for diabetic neuropathy that developed in the setting of diabetes from chronic steroid use. She was living independently.

Conclusion

HE is an exquisitely treatable condition that can mimic many other neurologic illnesses, including untreatable ones such as Creutzfeldt-Jakob disease. Thus, it is always worthwhile to screen for anti-thyroid antibodies in individuals with encephalopathy of unknown etiology. Most individuals with HE will respond to acute steroid therapy, and some will require long-term immunosuppression to prevent frequent relapses.

While HE's underlying pathophysiology is still being elucidated, clues point toward a reversible autoimmune vasculopathy. Disciplined definition of cases, as well as further research into the pathology and natural history of HE, will help provide targeted therapy for patients with the disease and minimize the risks of long-term treatment.

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