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REVIEW ARTICLE

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Hashimoto encephalopathy: literature review

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Hashimoto encephalopathy (HE) presents as an encephalopathy without central nervous system infection or tumor. HE is associated with autoimmune thyroiditis and is thus considered to be an autoimmune disorder. The prevalence of HE is low, but death and status epilepticus have been reported. HE manifests with a wide range of symptoms that include behavioral changes and confusion. Elevated thyroid antibodies are present in the majority of cases and are required for the diagnosis of HE. Normal brain MRI findings are found in the majority of patients diagnosed with HE. The most consistent CSF abnormality noted in HE patients is the presence of elevated protein. Most HE patients respond well to steroid therapy. Clinical improvements are also observed with IV immunoglobulin and plasmapheresis. In conclusion, it is now generally accepted that the diagnosis of HE must include encephalopathy characterized by cognitive impairment associated with psychiatric features, such as hallucinations, delusions, and paranoia. Autoimmune encephalitis and prion disease should be considered in the differential diagnosis due to the similarity of the clinical features of these conditions to those of HE.

KEYWORDS
Hashimoto encephalopathy, metabolic disorders, neuroendocrinology

1 | INTRODUCTION

Hashimoto encephalopathy (HE), also known as steroid-responsive encephalopathy, is associated with autoimmune thyroiditis and presents with encephalopathy and elevations in antithyroid antibodies without brain tumor, stroke, or infection of the central nervous system.[1] Brain and colleagues reported the first case of HE in 1966. This first case presented with hallucinations, tremor, agitation, altered mental status, and elevated thyroid antibodies. HE was eventually diagnosed after confirmation of Hashimoto's thyroid disease by biopsy.[2] Since then, more than 200 cases have been reported.[3,4] Although the majority of the cases have good outcomes,[3] death and status epilepticus due to HE have been reported.[5]

2 | PREVALENCE

The prevalence of HE is estimated to be 2:100 000.[6] Patients are predominantly female and in their 5–6th decades of life, and the reported gender ratio of this disease is 4.1 in favor of women.[3,4,6] The prevalence in pediatric populations is relatively lower than that in adults.[7]

3 | PATHOGENESIS

3.1 | Hashimoto's encephalopathy is considered to be an autoimmune disorder

The exact underlying pathogenesis of HE is still unknown. HE is considered to be an autoimmune disorder due to its close correlation with autoantibodies that interact with antigens shared by the thyroid and its good response to steroid treatment.[6,8] Additionally, serum antithyroid peroxidase antibody (anti-TPO antibodies) in the CSF has also been detected in adult patients diagnosed with HE along with autoimmune reactions of these antibodies with the cerebral vascular and brain cells that results in either vasculitis or damage to the brain cells[9–12] Furthermore,

the detection of other unknown pathogenic autoantibodies and immune complexes in HE patients has also been reported.[13–15]

3.2 | HE is induced by inflammation

The presence of perivascular lymphocytic inflammation in the brain tissue samples of some HE patients supports the hypothesis that HE may be induced by inflammation.[6,8]

4 | CLINICAL PRESENTATIONS

HE presents with a wide variety of symptoms that include behavioral changes, confusion, cognitive decline, stroke-like episodes, amnestic syndrome,[16] ataxia,[17] seizures,[18] myoclonus,[19,20] and psychiatric manifestations.[7,21,22]

Seizures, including both partial and generalized seizures,[3,23] and myoclonus have been reported to be the most frequent presentations (60–66% of affected patients) in adults.[24] Generalized tonic–clonic seizures are the most common seizures in children followed by partial complex seizures.[25] Cognitive impairment (84.6% of affected patients) and psychiatric symptoms (38.5% of affected patients) including depression,[26] mania,[27] psychosis, and hallucinations[7,21,22] have been reported to be additional common symptoms.

Status epilepticus (SE) is rare in adult HE patients but has been described in children who present with coma and generalized tonic–clonic seizures. These patients respond poorly to anti-epileptic medications.[28] Recurrent status epilepticus has also been reported to be the main complication of HE in children Frontal lobe involvement is implicated in these symptoms.[29] Temporal epilepsy and multi-antiepileptic drug (AED) hypersensitivity have also been reported in adult HE patients.[6]

Subacute dementia with insidious onset followed by schizophrenia-like syndrome has been described in elderly HE patients.[30] A case of a 60-year-old woman who manifested with schizophrenia-like syndrome and a history of Hashimoto's thyroiditis for more than 40 years has been reported. This patient's diagnosis was not established until 40 years after the presentation of her schizophrenia-like syndrome.[31] The development of psychosis has also been described during the course of corticosteroid therapy in some HE patients.[32]

Opsoclonus (i.e., chaotic saccadic eye movements) may also present as an early manifestation of HE[33,34] and is associated with ataxia prior to the development of encephalopathy.[34]

Two clinical subtypes of HE have been suggested. The first subtype is episodic and manifests as stroke-like symptoms described to be of the vasculitis type and with a relapsing–remitting course.[35] The second subtype has a more progressive course involving insidious onset, a significant decline in cognitive function and memory loss.[12,35]

5 | LABORATORY TESTS

5.1 | Thyroid antibodies and thyroid function

Abnormal elevations of thyroid antibodies, including either antithyroglobulin or anti-TPO (thyroid peroxidase antibodies), are present in the majority of cases and are required for HE diagnosis.[12] The most commonly detected antithyroid antibody is anti-TPO. In a retrospective review of 105 patients diagnosed with HE, anti-TPO antibodies were elevated in 100% of the cases followed, and antithyroglobulin antibodies were elevated in 48%.[12] Thyroid-stimulating hormone antibodies (anti-TSH) may also be observed.[12] It has also been shown that the titer of anti-TPO antibodies in HE patients is much higher than in Hashimoto thyroiditis (HT) patients.[36] However, the titer of plasma antithyroid antibodies does not correlate well with HE severity.[1,37,38] Furthermore, antithyroid antibody titers remain detectable after treatment.

However, high titer of plasma antithyroid antibodies has been detected in cancer patients treated with ipilimumab.[39] Furthermore, positive thyroid autoantibodies also correlate with hepatitis B, hepatitis C, delta hepatitis infection,[40,41] and *Helicobacter pylori* infection in patients with type 1 diabetes.[42] Therefore, the specificity of plasma antithyroid antibodies in diagnosing HE is low.

Although antithyroid antibodies are elevated in HE patients, 42% of the reported cases are euthyroid at the time of diagnosis.[43,44] The majority of the patients diagnosed with HE have Hashimoto's thyroiditis, and some HE patients are afflicted with Graves' disease. However, patients with Hashimoto's thyroiditis or Graves' disease manifest with similar clinical presentations of HE.[45] During the course of their disease, some HE patients developed hypothyroidism; however, very few patients who initially manifest with only HT subsequently develop HE.[36]

6 | MRI

The majority of patients with HE have normal MRI brain findings,[45] although abnormal MRI findings may include ischemic lesions, demyelination, edema, and atrophy.[46] Abnormal signals detected in the hippocampus or temporal lobe are thought to be related to memory loss or seizures in HE patients.[47]

7 | CEREBROSPINAL FLUID (CSF)

Elevation of cerebrospinal fluid (CSF) protein levels is found in 85% the affected patients[12] and decrease following the treatment of the disease.[30] Abnormal elevation of CSF thyroid antibodies is also found in 62–75% of diagnosed HE patients and may persist even after clinical improvement.[12,48] Due to the low specificity of plasma antithyroid antibodies in diagnosing HE, checking for the

elevation of antithyroid antibodies in both blood and CSF is recommended in suspected HE cases.[48]

8 | EEG

The most common EEG abnormality is mild to severe generalized slowing, which is observed in more than 95% of cases.[23,49,50] EEG findings reflect the degree of CNS involvement and may be used to monitor the response to steroid treatment.[49] The EEG is also useful in excluding other conditions, in particular, in patients with rapidly progressing encephalopathy and myoclonus, such as CJD.[49,50]

9 | OTHER BIOLOGICAL MARKERS

The amino-terminal of alpha-enolase (NAE) was an antigen identified in HE patients' brain tissue, and NAE antibodies were elevated in 68–83% of diagnosed HE patients.[14,15,51] Importantly, anti-ANE antibodies were not detected in patients with other neurological diseases.[14,15] This indicates its high specificity for HE. Anti-NAE antibodies together with antithyroid antibodies may be a useful biological marker in diagnosing HE.

10 | DIAGNOSTIC CRITERIA

Due to the low prevalence, varied clinical presentations, and unidentified pathogenesis, there are no recognized and well-established diagnostic criteria for HE, and HE is a diagnosis of exclusion. The general accepted diagnostic criteria for HE are listed in Table 1.

It is generally accepted that the diagnosis of HE must include encephalopathy associated with cognitive dysfunction and psychiatric features, such as hallucinations, delusions, or paranoia.[2,8,36,52,53] Unexplained seizures or encephalopathic states, particularly in female adolescents, make the diagnosis of HE possible.[28] Additionally, antithyroid Ab testing should always be considered in these suspected patients,[29] the exclusion of other identifiable causes of encephalopathy and the improvement of symptoms with corticosteroid treatment (as listed in Table 1) are two of the other diagnostic criteria. In conclusion, a diagnosis of HE should always be considered in patients who present with neuropsychiatric behavioral disorder in association with Hashimoto's thyroiditis or Grave's disease.[31] Although the majority of HE patients respond to steroid treatment, it has been suggested that the lack of response to steroid treatment should not exclude the diagnosis of HE.[54] In addition, due to the low specificity of blood antithyroid antibodies in diagnosing HE, diagnostic tests such as MRI, CSF, or EEG studies, CSF antithyroid antibody and anti-NAE antibodies should all be included in the initial assessment.

TABLE 1 Diagnostic criteria for HE

Clinical presentations
Encephalopathy with cognitive impairment
Encephalopathy with psychiatric manifestation
Encephalopathy with partial or generalized seizures
Encephalopathy with focal neurological deficits or alteration of consciousness
Encephalopathy with dystonia
Laboratory test
Presence of high titer anti-TPO antibodies
Exclusion of neurological disease
Exclusion of neurological infection, toxic, and metabolic disorder
Response to treatment
Patient's neurological status return to baseline level after steroids therapy

11 | DIFFERENTIAL DIAGNOSIS

11.1 | Autoimmune encephalitis

Anti-N-methyl-D-aspartate receptor (Anti-NMDAR) encephalitis was reported in 2007 by Dalmau and colleagues[40] and is manifested by psychiatric symptoms with acute onset. This disease has several clinical features that are similar to those of HE and should be included in the HE differential diagnosis. Anti-NMDAR encephalitis is considered to be a paraneoplastic syndrome. The early recognition of anti-NMDAR encephalitis is thus essential for appropriate management and follow-up.

In the past 10 years, many new forms of autoimmune encephalitis associated with antibodies against neuron cell proteins have been described.[40,41] These include antibodies against neuron cell surface proteins or synaptic proteins (AMPA Receptor, GABAb receptor, mGluR5, DPPX, mGluR1, Dopamine 2 receptor16) [40,41] and antibodies against ion channels and other cell surface proteins such as the antileucine-rich, glioma-inactivated 1 (anti-LGI1), voltage-gated potassium channel (VGKC) antibody.[41] Careful evaluation of the clinical history of patients diagnosed with HE and the evaluation of encephalopathies mediated by antineuronal autoantibodies are crucial for ruling out other forms of autoimmune encephalitis in HE patients.[39]

11.2 | Irreversible prion disease

Notably, many cases of HE are initially mistakenly diagnosed as irreversible prion diseases, such as Creutzfeldt–Jakob disease (CJD), which is neurodegenerative disorder caused by a prion that leads to the rapid degeneration of brain tissue.[39] Therefore, prior to making the diagnosis of HE, one must thoroughly investigate and rule out other possible causes of neurodegenerative diseases such as CJD.

Other CNS infections (including encephalitis and meningoencephalitis), inflammatory conditions, such as systemic lupus and primary CNS vasculitis, paraneoplastic limbic encephalitis (PLE), tumors, and stroke should also be ruled out.[28]

12 | TREATMENT

12.1 | The first-line therapy is corticosteroids

Prednisone (50–150 mg daily, or 1–2 mg/kg/d) is recommended. High-dose IV methylprednisolone (500–1000 mg/d) has also been used.[8,42] Approximately 50% of cases exhibit complete responses to corticosteroid therapy.[54] Up to 40% of patients experience complete remission after the first course of corticosteroid therapy.[55] A small number of patients exhibit resistance to steroid therapy and relapse of psychiatric symptoms.[56] Based on the clinical response, the corticosteroid treatment duration and taper rate should be changed accordingly.[8,37,42] Early intervention results in a good resolution of brain lesions, as indicated by both clinical and MRI improvements.[46]

12.2 | HE resistant to corticosteroids may be treated with immunosuppressive medications

In patients resistant to corticosteroids, combination therapy with immunosuppressive medications, such as azathioprine, cyclophosphamide, and methotrexate, is suggested.[57–59] Relapse of HE even with high-dose IV methylprednisolone in some patients should prompt early interventions with these immunosuppressive drugs.[36] In HE patients who present with paraneoplastic opsoclonus syndrome, adjunct therapy with immunosuppressive medications, such as rituximab and an anti-CD20 monoclonal antibody, has also proven to be effective.[60]

12.3 | Patients who are unable to tolerate or take corticosteroids or immunosuppressant may be treated with plasma exchange and IVIG

IV immunoglobulin treatment has been observed to induce significant clinical improvements in both adults and children.[23,54,61] Plasma exchange has been shown to remove antithyroid peroxidase antibodies (anti-TPO). However, no improvement in either clinical or neurophysiologic parameters has been observed, despite significant reductions in anti-TPO antibodies in HE patients.[37]

12.4 | Levetiracetam

Levetiracetam is a new anti-epileptic medication used to treat some types of seizures.[62] This drug has been shown to have an anti-inflammatory effect in vivo studies.[63] Levetiracetam that has both anti-inflammatory and antiseizure effects may be an effective alternative treatment for patients with HE who are unable to tolerate steroids due to the presence of other diseases such as diabetes. Levetiracetam was reported to be an effective therapy in two HE cases who had diabetes.[64] However, further studies are needed to examine its effectiveness in treating HE.

13 | PROGNOSIS

Most patients respond well to steroid therapy and exhibit complete remission. Some patients improve without steroid treatment.[47] Among all patients, 12.5% have relapses, 12.5% exhibit no response,[3] and 60% are characterized as having a relapsing-remitting courses.[3] The sequelae include cognitive decline, and recurrent refractory seizures are more common in children.[25] Initial higher serum TPO-Ab titers associated with more satisfactory outcomes.[65]

Anti-NMDAR encephalitis and other autoimmune encephalitis are considered to be a paraneoplastic syndrome. Whether HE is also a paraneoplastic syndrome is not known. To our knowledge, there is no reported data on the cancer prevalence in HE patients due to the low prevalence of this disease. Study on cancer prevalence in HE patients is needed.

14 | CONCLUSION

Encephalitis patients presenting with behavioral disturbances, delirium, psychosis, hallucinations, and mood alterations, particularly females with familial histories of auto-immune disease, should be strongly suspected to have HE.[12,36,66] The diagnostic tests for HE include EEG and serum anti-TPO antibody levels. MRI and lumbar puncture are suggested to rule out infection, stoke and tumor. Steroid therapy is a specific treatment, and improvement with corticosteroids may confirm the diagnosis of HE.[4] Significant sequelae might occur in children with HE. HE should be considered in the differential of children with new onset seizures, particularly those with refractory seizures, hallucinations, confusion, and behavioral changes.[54] If anti-TPO antibodies are detected, early intervention with steroids should be initiated.[44]

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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