Hashimoto's Encephalopathy

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Hashimoto's encephalopathy (HE) is a controversial neurological disorder that comprises a heterogenous group of neurological symptoms that manifest in patients with high titers of antithyroid antibodies. Clinical manifestations of HE may include encephalopathic features such as seizures, behavioral and psychiatric manifestations, movement disorders, and coma. Although it has been linked to cases of Hashimoto's thyroiditis or thyroid dysfunction, the most common immunological feature of HE is the presence of high titers of antithyroglobulin or anti-TPO (antimicrosomal) antibodies. At present, it is unclear whether antithyroid antibodies represent an immune epiphenomenon in a subset of patients with encephalopathic processes or they are really associated with pathogenic mechanisms of the disorder. The significance of classifying encephalopathies under the term HE will be determined in the future once the relevance of the role of antithyroid antibodies is demonstrated or dismissed by more detailed experimental and immunopathological studies. The responsiveness of HE to steroids or other therapies such as plasmapheresis supports the hypothesis that this is a disorder that involves immune pathogenic mechanisms. Further controlled studies of the use of steroids, plasmapheresis, or immunosuppressant medications are needed in the future to prove the concept of the pathogenic role of antithyroid antibodies in HE.

Key words: **Hashimoto's encephalopathy; dementia; seizures; encephalitis; steroids**

Introduction

Hashimoto's thyroiditis (HT), also known as lymphadenoid thyroiditis and lymphocytic thyroiditis, is an autoimmune disorder in which antithyroid-specific antibodies mediate an attack against the thyroid gland that generally results in hypothyroidism.[1] This disorder was first described by Hakaru Hashimoto (Fig. 1), a Japanese surgeon who was working in Berlin in 1912.[2] The antibody-mediated injury of the thyroid gland in HT may present initially as transitory hyperthyroidism, but it usually evolves in hypothyroidism that develops slowly and manifests as fatigue, lethargy, mental slowing, and myxedema. Myxedema, a frequent clinical sign of hypothyroidism, presents clinically as a boggy face with puffy eyelids, enlarged tongue, and edematous hands and feet. Myxedema results from accumulation of proteoglycans in the extracellular matrix. This appearance is particularly important because it is one of the few clinical features other than thyromegaly that physicians were able to use to diagnose HT before laboratory antibody and thyroid hormone testing. The term "Hashimoto's encephalopathy" (HE) was first coined by Lord Brain in 1966 who described a patient with various neurologic manifestations in the setting of fluctuating thyroid levels.[3] Since then, the term has been loosely applied to a variety of patients who have elevated titers of antithyroid antibodies with various clinical presentations, neuroimaging findings, thyroid hormone levels, and cerebrospinal

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Ann. N.Y. Acad. Sci. 1142: 254–265 (2008). © 2008 New York Academy of Sciences.
doi: 10.1196/annals.1444.018

Figure 1. Hakaru Hashimoto. (Courtesy of Wellcome Trust Images.)

fluid (CSF) findings. The term has also been used interchangeably with other terms such as Hashimoto's encephalitis,[4] steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT),[5] and nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM).[6] The lack of clinical diagnostic criteria, uniformity in the clinical presentation, and most importantly a solid understanding of etiological and pathophysiological mechanisms have resulted in a dazzling array of case reports entitled "Hashimoto's encephalopathy," the consequences being an ever-expanding definition of the term and application to any encephalopathic or psychiatric condition associated with antithyroid antibodies.

History

The first reference to an autoimmune etiology for HT occurred in 1956 when Roitt *et al.* suggested that "the raised γ-globulin levels, their delayed return to normal after thyroidectomy, and the infiltration of the thyroid with lymphoid tissue, lymphocytes and numerous plasma cells suggested that an immune response might be involved in this disease."[1] In the next decade, there were several attempts to link the disease to other systemic disorders such as polymyositis, liver cirrhosis, myasthenia gravis, pernicious anemia, and systemic lupus erythematosus with various, often conflicting, outcomes.[7,8]

The involvement of thyroid disease in nervous system disorders was suggested for the first time in 1880 with the publication of a case report entitled "Myxoedema and its Nervous Symptoms" by G.H. Savage in which he described psychiatric and neurologic findings in patients with hypothyroidism/myxoedema:

> "One very important question to be decided is, whether the mental dulness [*sic*] is due . . . to the padding of the peripheral extremities of the nerves so that the constant healthy nerve stimulation is cut off, a kind of central nerve starvation, or whether the mental symptoms are due to primary disease of brain. . . ."[9]

Several other reports on nervous and psychiatric symptoms appeared in 1888 at a meeting of the Clinical Society of London investigating myxoedema.[10] Despite the many advances we have made in the past 130 years, the fundamental questions in thyroid-related encephalopathies clearly have not changed.

In the early part of the 20th century, there were a few reports of central nervous system (CNS) involvement in thyroid disease[11] and evidence of electroencephalogram (EEG) abnormalities[12]; however, the subject was revived in 1962 in an article entitled "Fits, Faints, Coma and Dementia in Myxoedema," in which Dr. E.H. Jellinek described 56 case reports of patients displaying psychiatric symptoms and neurologic problems associated with myxedema as well as their EEG findings.[13]

Three years later he became a coauthor on a report in which these psychiatric and neurologic manifestations were first described

as "encephalopathy" by Lord Brain. They described a 48-year-old man with HT confirmed by antithyroid antibodies and biopsy with inflammatory features who developed a waxing–waning neurologic course that progressed from aphasia, hemiplegia, and blindness to coma. Throughout the course of his disease, he had varying levels of hypothyroidism with myxedema as well as euthyroid periods, did not respond to steroid therapy, and eventually stabilized with thyroxin treatment.[3] Thus, the first case of HE did not appear to satisfy the criteria of steroid responsiveness or consistent euthyroidism and appears to have been nothing other than yet another case of "mental dullness" in the setting of abnormal thyroid function originally described by Dr. Savage in 1880 but with the addition of identification of antithyroid antibodies. Nevertheless, for lack of a better diagnosis, the controversial term HE has been embraced by neurologists worldwide to encompass any neurologic or psychiatric manifestation in the setting of thyroid antibodies with or without thyroid hormone fluctuations.[14]

Clinical Aspects of HE

Neurological abnormalities are found within the entire repertoire of thyroid hormone dysfunction, which ranges from hypothyroid/myxedematous to euthyroid to thyrotoxic. Although it is commonly done, it is not possible to strictly define HE as occurring solely in euthyroid conditions because there is considerable overlap within the spectrum of thyroid hormone effects on the brain. Although most HE cases reported occur under the condition of hypothyroid and euthyroid conditions, there are also cases of altered mental states in hyperthyroidism, with EEG changes and antithyroid antibodies.[15–17] These have sometimes been dubbed "thyrotoxic Hashimoto's encephalopathy."[15]

By definition, encephalopathy should be included within the clinical picture of HE, although this guideline is not always followed.[18,19] Other neurologic signs that have been attributed to the disease include strokelike episodes,[3] transient aphasia, tremor, ataxia, sleep disturbance, headache, psychosis/paranoia[5] as well as visual hallucinations, seizures, and myoclonus.[14] Presentations similar to Creutzfeldt–Jakob disease (CJD) have also been described.[4,20] In an effort to clarify and categorize the diverse clinical characteristics, one report divided HE into two classes: a vasculitic presentation including strokelike events and a diffuse progressive form that includes dementia and seizures.[21]

Encephalitis/encephalopathy with other autoantibodies has also been found in other autoimmune diseases such systemic lupus erythematosus,[22] Sjögren's disease,[23] myasthenia gravis,[24] encephalitis associated with *N*-methyl-D-aspartate receptor antibodies,[25] and a subset of encephalopathies associated with paraneoplastic syndromes.[26] With this in mind, some investigators have proposed that HE be renamed SREAT (steroid-responsive encephalopathy associated with autoimmune thyroiditis).[5] Their criteria for HE include response to corticosteroids,[27] slightly ironic because Brain's original patient with HE did not respond to corticosteroids.[3] Likewise, another coined term that defines this spectrum of encephalopathic disorders is "nonvasculitic autoimmune inflammatory meningoencephalitis" (NAIM),[6] which further broadens the umbrella to all autoimmune diseases and still includes responsiveness to steroids in the criteria. Although it may be convenient to name a disease by its response to a specific remedy, doing so is slightly analogous to naming a bacterial infection by its effective antibiotic and simply adds to the ever-expanding confusion in the literature. However, as Drs. Chong and Rowland noted: "Sometimes, an eponym is a useful admission of ignorance about etiology or pathogenesis; under these circumstances, the familiar eponym is shorter, easier to remember, and fosters communication more effectively than longer, seemingly more accurate names with acronyms that may be awkward."[28]

Laboratory and Paraclinical Studies in HE

Antibodies That Define HT and HE

The central laboratory features of HT and HE are the presence of antithyroid antibodies that target different thyroid gland epitopes. There is a great degree of controversy about the significance of their presence and involvement in the pathogenesis of HE. An excellent review on the pitfalls of antibody testing in HT was written by David Sinclair.[29]

Antithyrotropin antibody (anti–thyroid stimulating hormone [anti-TSH]) is directed at the thyrotropin receptor and results in Graves' disease.[30] There is only one reported case in the literature in relation to HE in which the patient had slightly elevated levels of anti-TSH but also had significantly higher levels of antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG).[31]

Anti-TPO, originally described as antimicrosomal, antibodies are directed at cell organelles called microsomes, which are released from damaged thyroid cells. These antibodies are the most frequently associated with hypothyroidism and hyperthyroidism[32,33] and are reported in almost all HE cases.[34] However, they have also been found in rheumatoid arthritis,[35] insulin-dependent diabetes mellitus,[36] and a low percentage of euthyroid subjects (14.4% in men and 25.8% in women).[37] One of the pitfalls of using this antibody as a diagnostic criterion for HE and HT is that there is extensive variability in the sensitivity of available laboratory techniques and kits as well as what is considered the "normal" reference range.[29]

Anti-TG antibodies are directed against thyroglobulin (formerly known as "colloid") that is within thyroid cells.[38] These antibodies are also present in many HE cases but not to the extent of anti-TPO antibodies and thus do not present any significant advantage over anti-TPO antibodies.[39] In the Third National Health and Nutrition Examination Study (NHANES III) survey, approximately 10% of the 13,344 people surveyed who were disease free, pregnant, not taking steroids, or had no biochemical hypothyroidism or hyperthyroidism had anti-TG antibodies.[32]

Anti–α-enolase antibodies in the serum of patients with HE have recently emerged in proteomic studies as a potential antibody specific more for HE than for HT.[40] A further study identified that the amino-terminal region of α-enolase was recognized more by patients with HE than HT or control subjects.[41] These studies support the vasculitic theory of HE because α-enolase is abundantly expressed in the endothelium.[42,43] However, anti–α-enolase has also been found in other autoimmune diseases such as inflammatory bowel disease[44] and rheumatoid arthritis.[45]

CSF Findings

Generally, the most consistent finding in the CSF of patients with described HE has been an elevated protein level without pleocytosis.[5,14,46] The immunoglobulin G index is usually within reference limits[5] and oligoclonal bands are occasionally found, although not consistently.[17] In one study, anti-TPO antibodies, anti-TG antibodies, and circulating immune complexes were found in the CSF of HE patients but not in the CSF of control patients.[47] They did not have a control group of HT patients without encephalopathy. The authors suggest that their presence indicates intrathecal production.

Neuroimaging

Brain magnetic resonance imaging and computed tomography imaging in HE has run the gamut from entirely normal to various degrees of nonspecific abnormality. Findings include cerebral atrophy,[48] white matter abnormalities—both focal[49] and confluent,[14,50] cortical irregularities,[51] and vasculitic changes.[52] In addition, magnetic resonance imaging findings may vary over time in the same patient,[53] decrease with steroids, and may correlate with antibody levels.[50]

Single-photon emission computed tomography (SPECT) scanning has also been used on patients with thyroid abnormalities. Studies using SPECT on HT patients with hypothyroidism have shown a significant alteration in regional cerebral blood flow.[54,55] These changes are seen not only in hypothyroid individuals but also in euthyroid HT patients with no neurologic manifestations.[56] In one study the frontal lobes appeared to be most affected, which may explain the often-reported psychiatric and behavioral components of HE. Of the HE patient case reports, the results range from normal to focal hypoperfusion to global.[14]

EEG

EEG findings were reported in Lord Brain's original 1966 article describing the encephalopathic features of his patient. Serial EEGs were conducted on the patient between 1961 and 1966. They showed progressive deterioration starting with bitemporal abnormalities and progressing to bilateral loss of α activity and θ and Δ discharges throughout. Thereafter they followed a fluctuating course, with normalization by 1966.[3] These findings were similar to the EEG reports in myxoedema patients published 4 years earlier by Jellinek, a coauthor on Brain's report.[13] Abnormal EEG findings (most commonly diffuse slowing) have been found in 98% of HE cases from 1966 to 2002, as reviewed by Chong *et al*.[14]

Neuropathology

There exists, unfortunately, a paucity of neuropathological reports for HE (Table 1). From what is currently in the literature the debate essentially falls into two categories—is HE a form of encephalitic or vasculitic process? In his original report Lord Brain's patient died approximately 10 years after his presentation, and the only mention of the brain on autopsy stated "central nervous system reported free from infarction, cerebral vessels congested, with a few atheromatous patches. The left ventricle was dilated and hypertrophied."[57]

The next documented pathologic report was in 1992, which provided evidence for a vasculopathic etiology of the disease. A stereotactic biopsy sample of a patient with HE showed a focal area of lymphocytic infiltration of the walls of arterioles and venules.[49] In this case a cerebral angiogram was normal. A following case on a patient with a long history of HT showed a localized brain stem vasculitis with leptomeningeal venules infiltrated by T lymphocytes.[58] A discussion ensued after this report over the actual definition of a "vasculitis," with Nolte *et al.* stating that "Lymphocytic vasculitis is a generally accepted pathological subtype . . . characterized by the presence of lymphocytes within the vessel wall. That the diagnosis is more difficult than for necrotizing arteritis does not, however, imply that lymphocytic vasculitis does not exist."[42] A following autopsy case in 2003 showed mild lymphocytic infiltrate within the arterioles and venules throughout the brainstem, white matter, cortex, and leptomeninges.[59]

Reports of nonvasculitic pathologic findings are also in the literature. Striano *et al.* described the autopsy of a 27-year-old woman with a rapidly progressive neurological encephalopathy that showed no lymphocytic infiltration.[60]

Another report of a nonvascular etiology was published by Oide in 2004 that described antineuronal autoantibodies that immunohistochemically labeled a 36-kDa antigenic protein within the neurons of the human cerebral cortex.[61] It was not found in the control or in a patient with HT without encephalopathy. The brain pathology showed no evidence of vasculitis—however, autopsy was conducted after the administration of steroids.

One final pathologic report described two consecutive biopsies on a young woman with sensory symptoms, no encephalopathy, and a steroid-responsive white matter lesion. Biopsy showed "discrete microscopic foci of demyelination with rare perivascular lymphocytic cuffs

TABLE 1. Neuropathological Studies in Hashimoto's Encephalopathy

Author	Case	Steroids	Angiogram	Pathology
Brain 1966	Original description of HE; anti-TG	No improvement	Bilateral carotid angiogram "unremarkable" but followed by confusion/extensor plantar responses	Autopsy done 1975: "Central nervous system reported free from infarction, cerebral vessels congested, with a few atheromatous patches. The left ventricle was dilated and hypertrophied" (Jellinek *et al.* 1976).
Shibata 1992	69-year-old woman	Improved	No abnormality	Biopsy: dense infiltration of the entire walls of many small parenchymal vessels, both arterioles and venules by lymphocytes.
Nolte 2000	77-year-old woman; anti-TPO	Improved	Not done	Prominent lymphocytic infiltrates within leptomeningeal but not parenchymal vessel walls. Only found in veins and venules, not arterioles/arteries. Restricted to brain stem.
Becker 2002	52-year-old woman; elevated TSH and anti-TPO, anti-TG	Unknown	Stenosis of proximal segment left posterior cerebral artery	None.
Doherty 2002	57-year-old woman; euthyroid, anti-TPO	Improved	Not done	Focal evidence of rare vacuoles abutting neurons, gliosis, perivascular lymphoid cells/macrophages (mimic CJD).
Duffey 2003	40-year-old man, elevated TSH, anti-TPO	No improvement, could not suppress seizures	Not done	Mild lymphocytic infiltrate around venules and arterioles throughout the brain. Immunostaining showed T cells.
Mahad 2005	32-year-old woman, euthyroid, elevated anti-TPO	Improved	Not done	"Discrete foci of demyelination with rare perivascular lymphocytic cuffs and relative axonal preservation."
Oide 2004	51-year-old man; elevated TSH, anti-TG	Improved	Not done	"No evidence of vasculitis in cerebral parenchyma/leptomeninges. Cerebral parenchyma well preserved, no infiltrates" + antineuronal antibody.
Striano 2006	27-year-old woman; euthyroid, anti-TPO	No improvement	Not done	No lymphocytic infiltrates by immunohistochemical staining.

and relative axonal preservation."[19] However, by their own criteria of "cognitive impairment with or without neuropsychiatric symptoms" this patient did not have clinical evidence of encephalopathy, and the differential of multiple sclerosis and ADEM (acute disseminated encephalomyelitis) still remains debatable in this case. These sets of neuropathological case reports only confirm the confusion and perhaps the heterogeneity of the disorder we called HE.

Proposed Pathogenic Mechanisms in HE

Compared with other autoimmune neurological disorders such as myasthenia gravis or paraneoplastic syndromes in which antibodies are involved in pathogenic mechanisms either by blocking of specific neurotransmission function (e.g., anti–acetylcholine receptor antibodies)[62] or by disruption of cell signaling pathways (e.g., anti-Hu antibodies),[26] the role of antithyroid antibodies in the pathogenesis of HE remains uncertain. It is still unknown whether the presence of antithyroid antibodies is just an autoimmune epiphenomenon in the setting of encephalopathic processes of diverse etiology or they represent real etiopathogenic factors that trigger such encephalopathies by functional or cytopathic effects. Regardless of the role that antithyroid antibodies may play in the pathogenesis of CNS abnormalities, the presence of such antibodies defines a subset of neurological disorders under the term HE. Hypothesis about pathogenesis of HE are based on neuropathological observations or experimental studies and may be summarized as follows.

Autoimmune Reaction to Antigens Shared by the Thyroid Gland and CNS

The hypothesis of cross-reactivity of thyroid gland and CNS epitopes as a potential factor of pathogenicity of antithyroid antibodies has not been objectively supported. There have been no reports of any proteins within the CNS that are structurally similar to the thyroglobulin and thyroperoxidase proteins. Evidence to support a shared thyroid/brain antigen is slim; however, a recent study showed that anti-TPO antibodies bind specifically to cerebellar astrocytes in HE patients but not in HT patients,[63] an observation that may support the view that effects of antibodies of neuroglial function may produce neuronal dysfunction. Interestingly, seroepidemiological studies have shown that antithyroid antibodies are found in 10%–20% of the healthy population[64] and increase with aging,[65] especially in women.[32] Antithyroid antibodies have also been associated with myopathy,[66] chronic fatigue syndrome,[67] peripheral neuropathy,[68] mood and anxiety disorders,[69] borderline personality disorder,[70] depression,[71] Alzheimer's disease,[72] Wegener's granulomatosis,[73] juvenile idiopathic arthritis,[74] and 34%–41% of fibromyalgia patients.[75] Because antithyroid antibodies have been linked to such a large and variable group of disorders as well as appearing in the overall general healthy population makes it unlikely that there is any direct antigen within the brain that is shared by thyroid antibodies and are thus not necessarily disease specific.

Autoimmune Vasculitis

This hypothesis is supported by neuroimaging SPECT findings that generally show focal or generalized hypoperfusion[14] and the discovery of anti–α-enolase antibodies, which are abundantly expressed endothelial cells and have been found in other vasculitic diseases such as Kawasaki disease.[76] Whether the perivascular lymphocytic infiltration found in five of seven of the pathology reports is, like the antibodies, a nonspecific finding or evidence of the beginnings of a "true vasculitis" remains debatable. However, perivascular cuffing is also a common neuropathological "fingerprint" of neuroinflammatory disorders such as encephalitis, multiple sclerosis, and rare forms of epilepsy such as Rasmussen's syndrome.[77,78]

Toxic Effects of Thyrotropin-Releasing Hormone

The hypothesis of toxic effects of thyrotropin-releasing hormone (TRH) is based on the idea that the encephalopathic—particularly myoclonic and ataxic—features of HE are caused by an increase in cerebral TRH.[79] TRH is released by the hypothalamus and stimulates TSH production in the pituitary, which subsequently stimulates thyroid hormone production in the thyroid. Only one trial of TRH in a patient with HE has been done that demonstrated that TRH infusion effectively produced myoclonus and tremor that were similar to the patient's symptoms during an exacerbation.[79]

Treatment

In the original report by Lord Brain, his patient received prednisone, anticoagulation therapy, and thyroxin. The patient worsened while on the first two while appearing to stabilize on the thyroxin combined with the tincture of time.[3] In nearly all HE case reports, steroids improved the encephalopathic symptoms; however, there are reports of patients dying while on steroids.[58,80] In a comprehensive review of 85 patients, 98% of those treated with steroids improved, 92% of those being treated with glucocorticoids and levothyroxine improved, and 67% of those treated with levothyroxine alone improved.[14] Keeping a low index of suspicion for the possible use of steroids in an unknown encephalopathy associated with thyroid antibodies is important. In a study of 20 patients at the Mayo Clinic in 2006, all patients were initially misdiagnosed at presentation with viral encephalitis, dementia such as Alzheimer's disease, CJD, or migraine.[5] In light of the fact that many patients improve or return to baseline with steroid administration, it is critical not to overlook the possible therapeutic benefit of a trial of steroids. However, our experience treating patients with other neurological and neuroimmune disorders with steroids suggests that the steroid effect is not strictly anti-inflammatory or directed against specific immune responses, and their beneficial effect may be associated with other non–anti-inflammatory mechanisms such as modulation of neuronal–neuroglial interactions and synaptic connectivity.

Other approaches in the treatment of immune-mediated neurological disorders appear to be effective in subsets of patients with HE. There are several reports of plasmapheresis helping patients with HE.[81] In one case, a 47-year-old man with HE improved suboptimally with steroids; however, he returned to his premorbid baseline with a course of plasmapheresis.[82] The improvement of neurological problems that follows plasmapheresis is a good demonstration of the potential pathogenic effect of antithyroid antibodies. Further controlled studies on the use of steroids, plasmapheresis, or immunosuppressant medications are needed in the future to prove the concept of the pathogenic role of antithyroid antibodies in HE.

Conclusion

In 2001 Sunil and Mariash wrote of HE: "This is a vague term, describing an association between presence of thyroid antibodies and encephalitis features. . . . This term has been loosely applied here and there and, over time, has become an established diagnosis, which is disturbing."[83] The best explanation for the variety of clinical pictures, pathology, and response to treatment lies in the idea that the constellation of patients diagnosed with HE represents a variety of different pathologic conditions that will eventually be identified individually. In the meantime, caution should be used in using HE as the default diagnosis in any patient with antithyroid antibodies who is afflicted with an unknown encephalopathy. In our view, regardless of the role that antithyroid antibodies may play in the pathogenesis of CNS abnormalities, the presence of such antibodies defines a

subset of neurological disorders that may be classified under the term HE. The significance of classifying such encephalopathies under the term HE will be determined only in the future once the relevance of antithyroid antibodies is demonstrated or dismissed by more detailed experimental and immunopathological studies. Despite the debates and contradictions in the literature regarding this disease, the one unifying feature and ultimate goal of every piece written is a worthy desire to relieve the anguish of an encephalopathic patient—thus a trial of steroids and/or plasmapheresis is always warranted in an encephalopathic patient with antithyroid antibodies in whom all other mimics have been ruled out.

Acknowledgments

Dr. Schiess is supported by a grant from the National Multiple Sclerosis Society. Dr. Pardo is supported by the Bart McLean Fund for Neuroimmunology Research—Project Restore and a National Institutes of Health–National Institute on Drug Abuse K08 award (DA 16160).

Conflicts of Interest

The authors declare no conflicts of interest.

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