Hashimoto Encephalopathy
Syndrome or Myth?

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Background: Hashimoto encephalopathy has been described as a syndrome of encephalopathy and high serum antithyroid antibody concentrations that is responsive to glucocorticoid therapy, but these could be chance associations.

Objective: To study a patient with Hashimoto encephalopathy and to review the literature to determine whether Hashimoto encephalopathy is an identifiable syndrome.

Data Sources and Extraction: We searched the MEDLINE database to June 2002 for “Hashimoto” or “autoimmune thyroiditis” and “encephalopathy” and examined all identified articles and articles referenced therein, including all languages. We included all patients with noninfectious encephalopathy (clouding of consciousness and impaired cognitive function) and high serum antithyroid antibody concentrations. We excluded patients if they did not meet these inclusion criteria or if their symptoms could be explained by another neurologic disorder. We recorded clinical features and the results of imaging, electroencephalographic, thyroid function, and cerebrospinal fluid studies.

Data Synthesis: We identified 85 patients (69 women and 16 men; mean age, 44 years) with encephalopathy and high serum antithyroid antibody concentrations. Among these patients, 23 (27%) had strokelike signs, 56 (66%) had seizures, 32 (38%) had psychosis, 66 (78%) had a high cerebrospinal fluid protein concentration, and 80 (96%) had abnormal electroencephalographic findings. Thyroid function varied from overt hypothyroidism to overt hyperthyroidism; the most common abnormality was subclinical hypothyroidism (30 patients [35%]). Among patients treated with glucocorticoids, 66 (96%) improved.

Conclusions: The combination of encephalopathy, high serum antithyroid antibody concentrations, and responsiveness to glucocorticoid therapy seems unlikely to be due to chance. However, there is no evidence of a pathogenic role for the antibodies, which are probably markers of some other autoimmune disorder affecting the brain.

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tibodies, but whether either the antibodies or concomitant thyroid dysfunction contributes to the pathogenesis of the neurologic disorder is not known. Indeed, the existence of the disorder itself has been questioned because of the high frequency of high serum antithyroid antibody concentrations in asymptomatic people and because there is no evidence of a causal link between the antibodies and encephalopathy.

We describe a patient with encephalopathy and high serum antithyroid antibody concentrations. We also review all reported cases to determine whether the disorder is a definable entity.

REPORT OF A PATIENT

In 1996, a 63-year-old woman had an episode of presumed viral encephalitis with subacute onset of impaired memory, ataxia, and headache. She had no focal motor, sensory, cranial nerve, or cerebellar abnormalities. Magnetic resonance images of the brain were normal. Results of cerebrospinal fluid (CSF) studies for viral and bacterial infection were negative. She was treated with acyclovir, intravenously, for possible herpes simplex encephalitis, and she improved.

A few months later she developed tremor and cognitive dysfunction, which subsequently subsided. In 1999, cognitive dysfunction gradually recurred, she became increasingly confused, and she had a generalized seizure. Brain magnetic resonance images were normal. After a second seizure, she was given phenytoin, acyclovir, and ceftriaxone and was transferred to the Columbia-Presbyterian Medical Center, New York.

On hospital admission, she was comatose. Brainstem reflexes were present, and painful stimuli resulted in extensor posturing of all limbs. Brain magnetic resonance images revealed diffuse, nonenhancing white matter hyperintensity, sparing the posterior fossa and deep gray nuclei (Figure). Treatment with intravenous valproic acid, phenytoin, mannitol, and methylprednisolone resulted in rapid improvement. She became oriented to place and time but was inattentive. Cranial nerve function was normal except for bilateral sixth nerve palsy. Tendon reflexes were brisk, but there were no upper or lower motor neuron signs, and sensation was normal.

Hospital admission laboratory studies revealed a normal erythrocyte sedimentation rate; normal serum concentrations of lactate, angiotensin-converting enzyme, and complement; and negative test results for antinuclear, anti-DNA, antineutrophilic cytoplasmic, antitymulin-associated glycoprotein, anti-Yo, and anti-Hu antibodies. The CSF leukocyte count was 26 × 10^3/µL, the protein concentration was 0.098 g/dL, and viral and bacterial culture findings were negative. Serum thyrotropin and thyroxine concentrations were normal on hospital admission, but 2 weeks later her serum thyrotropin concentration was 5.6 mIU/L (reference range, 0.3-4.2 mIU/L) and her serum thyroxine concentration was 5.4 µg/dL (69 nmol/L) (reference range, 5.4-11.7 µg/dL [69-151 nmol/L]). She was not given levothyroxine. Serum antithyroglobulin antibodies were undetectable; serum antithyroid microsomal antibody concentrations were 400 and 1600 U/mL (reference, < 1 U/mL). Brain biopsy findings revealed no evidence of infection, demyelination, or tumor; the only abnormality was small perivascular cuffs of lymphocytic cells. No perivascular demyelination was seen, and axonal staining was normal.

With glucocorticoid therapy, she gradually improved; 15 months later, while taking prednisone (15 mg every other day), she was asymptomatic, and cognitive function was normal. Administration of the same dose of prednisone was continued, and she remained well at last evaluation (early 2002).

LITERATURE REVIEW

We conducted a MEDLINE search using the words “Hashimoto” or “autoimmune thyroiditis” and “encephalopathy.” We retrieved articles in all languages, and we reviewed references cited in these articles. We did not consider patients described in abstracts.

We diagnosed Hashimoto encephalopathy if patients had the following 5 findings: clouding of consciousness with reduced wakefulness, attention, or cognitive function; no CSF evidence of bacterial or viral infection, as determined by culture or molecular analysis; and positive test results for or a high serum concentration (or titer) of antithyroid microsomal, antithyroid peroxidase, or antithyroglobulin antibodies. Patients with stroke-like or postictal focal signs, seizures, dementia, or psychiatric symptoms were included if consciousness was depressed. Any CSF abnormality was acceptable as long as viral or bacterial infection was excluded. Any abnormalities in thyroid function and any thyroid or antithyroid therapy were acceptable as long as there was a high serum concentration (or titer) of antithyroid antibody. Patients were excluded if the case report did not contain adequate information to determine whether the illness met the inclusion criteria or if symptoms could be explained by brain tumor or stroke, as detected by imaging.

We found studies of 105 patients with brain dysfunction associated with possible Hashimoto thyroiditis. We excluded 3 patients who did not have encephalopathy and in whom CSF was not analyzed, 1 patient lacking examination of the CSF, 13 who had no encephalopathy, including 6 patients with a purely cerebellar syndrome, and 2 in whom serum antithyroid antibodies were not measured. Two patients were described twice but are included only as single cases.

Patients who met our criteria for the disorder were divided into subcategories based on the results of thyroid function tests (Table 1).

RESULTS

We identified 85 patients who met the inclusion criteria, including the patient described herein (Table 2). Their mean age at onset was 44 years (range, 9-78 years); 19 were boys or girls 18 years or younger. Among the adults, there were 53 women and 13 men.

NEUROLOGIC FEATURES

All patients had encephalopathy, as required. Additional findings were stroke-like signs in 23 patients (27%)
and seizures in 56 patients (66%) (Table 2), including status epilepticus (10 patients [12%]). The seizures were of all types—focal motor, tonic, generalized tonic-clonic, and myoclonic. Myoclonus was present in 32 patients (38%). Visual hallucinations or paranoid ideations were prominent in 31 patients (36%). The course was relapsing and remitting in 51 patients (60%). The findings were similar in patients of all ages.

**THYROID STATUS**

Thyroid status varied greatly (Table 1). Neurologic symptoms and signs were similar in patients with normal serum thyroxine and thyrotropin concentrations (excluding patients taking levothyroxine); those being treated with levothyroxine on hospital admission and who therefore had been hypothyroid in the past; those with sub-
clinical hypothyroidism and overt hypothyroidism on admission; and all patients (Table 2).

The serum concentrations of thyroid antibodies also varied widely. Multiple antibodies were measured in 60 patients (71%); the value for 1 antibody was normal in 20 patients (24%). There was no relationship between the neurologic symptoms and signs and the type or serum concentration of antithyroid antibodies.

NEUROLOGIC STUDIES

In 65 patients (76%), the CSF contained 0 to 3 nucleated cells/mm³; in 3 patients (4%), it contained more than 100 cells/mm³. The CSF protein concentration was high in 66 patients (78%), exceeding 0.01 g/dL in 18 patients (21%).

Brain computed tomography or magnetic resonance imaging was performed in 82 patients (96%), of whom 40 (49%) had some abnormality: 11 had cerebral atrophy, 13 had nonspecific subcortical focal white matter abnormality, 8 had diffuse subcortical abnormality, 7 had focal cortical abnormality, and 1 had transient bilateral narrowing of a middle cerebral artery. Single-photon emission computed tomography findings were normal in 2 patients and showed focally decreased uptake in 8 and global hypoperfusion in 1.

Electroencephalography was performed in 82 patients; 80 (98%) had some abnormality, most commonly diffuse slowing.

OTHER AUTOIMMUNE DISEASE

Few patients were tested for autoantibodies other than thyroid antibodies. Fourteen patients (16%) had nonspecific abnormalities: a high erythrocyte sedimentation rate, a high serum C-reactive protein concentration, or a high serum antinuclear antibody concentration. One patient had psoriatic arthritis and sicca syndrome,56 and 1 had sarcoidosis.

PATHOLOGIC FINDINGS

Two patients underwent autopsy examination. The patient described by Brain et al1 was autopsied 10 years after the original study, but brain findings were not mentioned.39 Autopsy in the other patient revealed lymphocytic infiltration of the walls of the veins of the brainstem.35 Two patients underwent a brain biopsy; 1 had lymphocytic infiltration of the walls of many small arterioles and venules55 and the other (our patient) had perivascular cuffs of lymphocytic cells.

CLINICAL COURSE

Three patients died. The patient described by Brain et al had no neurologic symptoms at the time of death1.29; the 2 other patients died while being treated with glucocorticoids.4,35 Of 85 patients, 43 were treated with gluco-
corticoids (some were already taking levothyroxine), and 44 (98%) improved. Twenty-four patients were treated with glucocorticoids and levothyroxine, of whom 22 (92%) improved. Twelve patients were treated with levothyroxine alone; 8 (67%) improved. The clinical characteristics of the patients who improved in response to treatment with glucocorticoids, glucocorticoids and levothyroxine, and levothyroxine were similar (Table 3).

One patient was treated with glucocorticoids and carbimazole, 1 with anticonvulsant drugs, and 1 with plasma exchange (after failing glucocorticoid therapy); all 3 improved. Eight treated patients did not improve: 1 patient treated with glucocorticoids, 2 treated with glucocorticoids and levothyroxine, 4 treated with levothyroxine, and 1 treated with intravenous immunoglobulins. One patient received no treatment and did not improve.

**COMMENT**

The term “Hashimoto encephalopathy” is used by neurologists to describe a syndrome of cerebral symptoms in patients with serologic evidence of autoimmune thyroid disease. It is clear from our survey that the neurologic and thyroid abnormalities are diverse, so much so that some researchers have questioned whether the patients all have the same disorder.

In selecting case reports for review, we used simple criteria for diagnosis: encephalopathy and a high serum concentration of 1 antithyroid antibody, with no evidence of an infectious or other well-defined cerebral disorder. In patients who met these criteria, we then attempted to determine the variation in neurologic findings and whether these findings were related to different abnormalities of thyroid function.

The authors of most case reports included “Hashimoto encephalopathy” in the titles of their articles, but approximately 20% of the patients did not meet our diagnostic criteria. Either the patient did not have an encephalopathy or thyroid antibodies were not reported. On the other hand, the 85 cases are a minimum number because we did not search for the key word “encephalopathy” alone and therefore we could have missed cases if the researchers considered a high serum concentration of antithyroid antibodies to be an incidental finding in a patient with encephalopathy and therefore did not diagnose Hashimoto encephalopathy. Moreover, we do not know the number of patients with encephalopathy and normal serum concentrations of antithyroid antibodies, which would be the ideal comparison group.

**ENCEPHALOPATHY AND THYROID DISEASE**

Is Hashimoto encephalopathy a distinct entity or an idiopathic encephalopathy in a patient who has a high serum concentration of antithyroid antibodies? Could the encephalopathy be caused by hypothyroidism, which is common in patients with high serum antithyroid antibody concentrations? Overt hypothyroidism can cause cerebral dysfunction, including decreases in alertness, mood, and cognition, and even psychosis (“myxedema madness”) and coma. It can also cause low-amplitude electroencephalographic changes and high CSF protein concentrations. All these changes improve with levothyroxine therapy. Subclinical hypothyroidism has less, if any, effect on cerebral function, the electroencephalo-

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**Table 3. Response of Patients With Hashimoto Encephalopathy to Therapy With Glucocorticoids, Glucocorticoids and Levothyroxine, and Levothyroxine**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Improved With Glucocorticoid Therapy</th>
<th>Improved With Glucocorticoid and Levothyroxine Sodium Therapy</th>
<th>Improved With Levothyroxine Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated, No.</td>
<td>45</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>Patients improved, No.</td>
<td>44</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>39 (89)</td>
<td>16 (73)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>50 (12-78)</td>
<td>41 (14-76)</td>
<td>34 (12-59)</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>15 (34)</td>
<td>3 (14)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Seizures</td>
<td>29 (66)</td>
<td>15 (68)</td>
<td>5 (62)</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>21 (48)</td>
<td>4 (18)</td>
<td>5 (62)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>19 (43)</td>
<td>5 (23)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Relapsing-remitting course</td>
<td>25 (57)</td>
<td>16 (73)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>High CSF protein concentration</td>
<td>34 (77)</td>
<td>18 (82)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Abnormal imaging findings</td>
<td>20/43 (47)</td>
<td>14/21 (67)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Abnormal EEG findings</td>
<td>42/43 (98)</td>
<td>21/21 (100)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Goiter</td>
<td>13/20 (65)</td>
<td>5/12 (42)</td>
<td>1/3 (33)</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>15 (34)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Euthyroid with thyroid therapy</td>
<td>7 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>12 (27)</td>
<td>10 (45)</td>
<td>5 (62)</td>
</tr>
<tr>
<td>Overt hypothyroidism</td>
<td>3 (7)</td>
<td>9 (41)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>3 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonthyroidal illness</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Unclear thyroid status</td>
<td>2 (5)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory marker</td>
<td>5 (11)</td>
<td>5 (23)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalographic.

*Data are given as number (percentage) except where noted otherwise. Percentages are based on patients who responded to treatment.
Among the 85 patients who met our inclusion criteria, 47 (55%) had subclinical or overt hypothyroidism; 8 (17%) of these 47 patients improved in response to levothyroxine therapy, and 19 (40%) improved in response to levothyroxine and glucocorticoid therapy. However, some patients with hypothyroidism did not respond to levothyroxine therapy. Furthermore, the neurologic findings were similar in patients who were euthyroid, with or without continuing levothyroxine therapy, and those with subclinical or overt hypothyroidism (Table 2). In addition, 6 patients with encephalopathy had overt or subclinical hyperthyroidism. Considering the inconsistency of thyroid function, hypothyroidism alone cannot account for the encephalopathy.

ENCEPHALOPATHY AND THYROID ANTIBODIES

What is the relationship between high serum concentrations of antithyroid antibodies and encephalopathy? Hashimoto thyroiditis (Hashimoto disease) was first described as struma lymphomatosa (lymphomatous goiter) in 1912; it is now defined clinically by the presence of antithyroid antibodies and encephalopathy? What is the relationship between high serum concentrations of antithyroid antibodies and the presence of antithyroid antibodies? Hashimoto thyroiditis, and virtually all patients with autoimmune diseases such as Sjogren syndrome and systemic lupus erythematosus.

ENCEPHALOPATHY AND GLUCOCORTICOID THERAPY

Most patients with Hashimoto encephalopathy improved in association with, but not necessarily because of, glucocorticoid treatment. The patients who responded had no distinguishing clinical characteristics, but too few were treated in other ways for meaningful comparison. We believe that it is generally unwise to define a condition by response to a particular therapy, especially if the treatment is not a replacement for a specific deficit or directed against a specific target, although other researchers have included a beneficial response to glucocorticoid therapy as a criterion for the diagnosis of Hashimoto encephalopathy.

ENCEPHALOPATHY AND OTHER AUTOIMMUNE DISORDERS

Many patients who have autoimmune diseases have high serum concentrations of 1 or more antibodies directed against tissues not affected by the particular autoimmune disease. For example, patients with myasthenia gravis may have high serum antithyroid antibody concentrations. The presence of high serum antithyroid antibody concentrations in patients with Hashimoto encephalopathy could be another example of the same phenomenon, rather than indicating that the antibodies have any direct relationship to the cerebral disease. Also, patients with one autoimmune disease are at risk for 1 or more other autoimmune diseases.

Several researchers have described patients with encephalopathy clinically similar to Hashimoto encephalopathy and high serum concentrations of antibodies to other self-antigens. One patient with myasthenia gravis had 2 episodes of unexplained encephalopathy. Five patients had an encephalopathy that improved with glucocorticoid therapy, but 1 of those patients had high serum antithyroid antibody concentrations compatible with Hashimoto encephalopathy; antithyroid antibodies were not mentioned in the other case reports. Four of the 5 patients had serologic evidence of another autoimmune disease, including high serum concentrations of rheumatoid factor, antinuclear antibodies, anti-RNA antibodies (SSA and SSB), or cardiolipin antibodies. Brain biopsy findings revealed only perivascular lymphocytic infiltration. The researchers postulated a syndrome of “nonvasculitic autoimmune inflammatory meningoencephalitis” associated with autoimmune diseases such as Sjogren syndrome and systemic lupus erythematosus.

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Based on this review of cases of Hashimoto encephalopathy, we believe that the constellation of clinical manifestations constitutes a clinical syndrome. High serum antithyroid antibody concentrations are unlikely to be a chance association. Although there is no evidence that high antithyroid antibody concentrations have a role in pathogenesis, they could be a marker of some other autoimmune disorder. Given the lack of a comprehensible pathophysiologic link between antithyroid antibodies or Hashimoto thyroiditis and the cerebral syndrome, “Hashimoto encephalopathy” could be a misleading term, the disorder being one of a larger group of autoimmune encephalopathies. However, until the pathogenesis is understood, the eponym seems to be the most appropriate name for the condition because it links the only known identifier, a high serum concentration of antithyroid antibodies or autoimmune disorder. Given the lack of a comprehensible chance association. Although there is no evidence that antithyroid antibody concentrations are unlikely to be a probable mechanism. Neurology. 1997;49:623-626.


