

# Encephalopathy Associated With Hashimoto Thyroiditis: Pediatric Perspective

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## ABSTRACT

In recent years, neuropsychiatric symptoms associated with Hashimoto thyroiditis have been increasingly recognized in both adult and pediatric patients. This neurologic complication has been termed “Hashimoto encephalopathy,” and it can begin abruptly, in the form of seizures or agitation, with or without other neurologic complaints, or it can develop gradually, in a relapsing-remitting manner, including, among others, cognitive deterioration and psychiatric illness. The occurrence of Hashimoto encephalopathy is unrelated to the patient’s thyroid function status. Although the pathogenesis of this encephalopathy is not fully understood, evidence for both autoimmune and vasculitic mechanisms exists. Owing to a low index of suspicion, this encephalopathy is very likely underdiagnosed in children. The diagnosis of Hashimoto encephalopathy is based on detecting antithyroid antibodies in these patients, although there is no correlation between antibody levels and the severity of the illness. Cerebrospinal fluid analysis, electroencephalography, and neuroimaging studies do not show consistent findings to support the diagnosis. Physicians’ awareness of this complication is of great importance because most patients respond dramatically to corticosteroid therapy. Moreover, early recognition might also avoid an expensive diagnostic work-up in patients with unexplained encephalopathy (*J Child Neurol* 2006;21:1–5).

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Neurologic complications of thyroid disease have long been recognized, including dementia, psychosis, ataxia, seizures, and myxedema coma.<sup>1,2</sup> Hashimoto thyroiditis is the most common form of thyroiditis in children and adults. In patients with this form of thyroid inflammation, insidious, symmetric enlargement of the gland with few or no local symptoms occurs. Patients may be euthyroid or show evidence of hypothyroidism or hyperthyroidism and thyrotoxicosis. It occurs predominantly in females and is the most common cause of thyroid enlargement and hypothyroidism in children over 6 years of age in North America, affecting up to 1.2% of school-aged children.<sup>3</sup>

The term “Hashimoto encephalopathy” refers to a syndrome of persisting or fluctuating neurologic and neuropsychologic deficits associated with elevated blood concentrations of antithyroid antibodies. Affected individuals are usually euthyroid or mildly hypothyroid.<sup>4,5</sup> Although the combination of encephalopathy, high serum antithyroid antibody titers, and clinical response to glucocorticoid therapy is likely to represent a distinct neurologic condition, there is no evidence that such antibodies play an active role in the pathogenesis of the syndrome. In fact, these antibodies probably represent an immunologic marker of a disease that is caused by another, as yet unidentified autoimmune mechanism.<sup>6</sup> Hence, the term “corticosteroid-responsive encephalopathy associated with Hashimoto thyroiditis” has recently been proposed instead of Hashimoto encephalopathy.<sup>7</sup>

At least 22 pediatric cases of Hashimoto encephalopathy have been reported in the English medical literature in recent years. However, this condition is probably underdiagnosed in children.<sup>8–11</sup> Of the 22 cases, 18 have been girls. Although symptoms have appeared between 8 and 17 years of age, only two cases have been diagnosed under the age of 10 years.<sup>7–23</sup>

Since Hashimoto encephalopathy responds well to corticosteroids in early stages, prompt recognition of this complication can offer symptomatic relief, prevent a protracted clinical course, and markedly reduce the cost of diagnostic work-up in patients, who often undergo multiple, expensive tests in search of an etiology for their neurologic deterioration.

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The aim of this article is to review the current knowledge on Hashimoto encephalopathy, particularly its impact on the pediatric population.

## HISTORICAL ASPECTS

Encephalopathy as a complication of Hashimoto thyroiditis was first described by Brain and coworkers in 1966.<sup>24</sup> The patient, a 49-year-old man with Hashimoto thyroiditis and hypothyroidism, had slowly progressive impairment of consciousness, intermittent episodes of confusion and coma, and recurrent strokelike episodes involving different vascular territories. Interestingly, oral prednisone was not helpful. Years later, the patient developed splenic atrophy and Raynaud phenomenon and died in 1975 following acute cholecystitis. At autopsy, no evidence of brain infarction, old or new, was found.<sup>25</sup> Since then, the syndrome has been well documented in adults, but only rare pediatric cases have been reported.<sup>15</sup> However, in recent years, awareness of this neurologic complication has increased, particularly concerning the association between epilepsy and neuropsychiatric symptoms and Hashimoto thyroiditis.

## CLINICAL MANIFESTATIONS

The clinical spectrum of Hashimoto encephalopathy is broad and includes cognitive impairment, psychiatric symptoms, varying degrees of consciousness impairment, involuntary movements, seizures, myoclonus, opsoclonus, generalized chorea or strokelike episodes, and myelopathy. The onset of symptoms is usually acute or subacute, followed by a progressive or relapsing-remitting course.<sup>5,6</sup>

Hashimoto encephalopathy has been described mostly in adults. This fact probably relates to the increased prevalence of thyroiditis in middle-age individuals. Moreover, thyroid disease is more likely to be considered in the differential diagnosis of encephalopathy and other neurologic complications in adults than in the pediatric population. Hence, Hashimoto encephalopathy is probably underdiagnosed in children.<sup>5,6</sup> Nevertheless, in a thorough *MEDLINE* database review by Chong et al, of 85 patients reported with Hashimoto encephalopathy, 19 were younger than 18 years of age.<sup>6</sup>

Kothbauer-Margreiter et al suggested two different clinical presentations: the vasculitic type, presenting as strokelike episodes with or without mental changes or alteration of consciousness, and the diffuse progressive type, which presents as progressive cognitive deterioration, dementia, lethargy, and coma.<sup>5</sup> Seizures (including isolated or recurrent episodes of status epilepticus), myoclonus, movement disorders, and tremor occurred in both types but were more common in the latter form.<sup>5</sup> However, further studies have shown that patients can follow a complex clinical course, often with multiple symptoms arising from different areas of the brain occurring in the same individual. Hence, Kothbauer-Margeiter et al's classification is generally not applicable.

As opposed to adult-onset encephalopathy, pediatric cases have generally been reported as case reports or as small series. Thus, it is very difficult to draw any conclusions as to whether the clinical presentation in children and adolescents differs from that seen in adults. Following is a summary of clinical data on children with Hashimoto encephalopathy<sup>4-23</sup>:

Between 1986 and 2004, 22 cases were reported in the English medical literature. Of these, 18 (82%) were female. The mean patient age was 13.8 years (median 14 years). Only two children under 10 years of age have been reported; in one, encephalopathy was the presenting symptom of thyroiditis.<sup>9</sup> Seizures are by far the most common symptom, occurring in 13 patients; 2 further cases presented with status epilepticus, 2 patients had recurrent hemiparesis, 1 had depression and hallucinations, and 1 depicted acquired attention deficit and learning difficulties. Acute episodes of altered mental status occurred at some point in 10 children. The remaining three patients presented with an admixture of symptoms. Ataxia, found in six patients, and psychiatric disturbances, found in five patients, constituted associated symptoms. Tremor, myoclonus, and headache were seen occasionally and did not occur as an isolated symptom. Despite the high proportion of seizures, very little has been described regarding their phenomenology and natural course.

Associated autoimmune disease was present in three cases: one patient had Addison disease, one suffered from renal tubular acidosis and pernicious anemia, and another had arthritis. Eleven children were hypothyroid at the time of diagnosis, whereas eight were euthyroid. Only one hyperthyroid patient was reported.

Neuroimaging studies were obtained in 20 of the 22 cases: 4 had computed tomography (CT) and 16 had magnetic resonance imaging (MRI). Studies were normal in 14 cases. Among the six abnormal MRI studies, five had prolonged (focal or multifocal) T<sub>2</sub>-weighted signals of the white matter and one had cerebellar atrophy. There was no correlation between radiologic abnormalities and specific clinical presentations.

Electroencephalography (EEG) was performed in 19 cases. Fourteen studies depicted various degrees of background slowing, two showed focal slowing, and one demonstrated focal epileptiform activity (periodic lateralized epileptiform discharges). Data on epileptiform discharges or ictal electrographic events are scarce. Two EEGs were normal. Cerebrospinal fluid was normal in eight cases. The most significant abnormality was mild protein elevation (usually below 100 mg/dL) in 12 patients. When measured, the opening pressure was normal.

## PATHOGENESIS

The pathophysiology of Hashimoto encephalopathy is still unclear. However, certain progress has been made in recent years in our understanding of the syndrome. As previously mentioned, the clinical course of the disease is not uniform among patients: some (probably most) cases present in a relapsing-remitting manner, whereas in other cases, the course is either continuous or progressive. In some instances, there might be only one acute, nonrecurrent encephalopathic event. Moreover, different central nervous system structures can be affected at various stages of the disease. Finally, there does not seem to be a relationship between the status of thyroid function and the development of symptoms; patients are either euthyroid or hypothyroid and, rarely, hyperthyroid.<sup>6</sup>

Pathophysiologic processes that can cause this broad range of clinical presentations and neurologic involvement include autoimmune disease, vasculitic disease, cerebral hypoperfusion, and infection.

### Autoimmune Disease

Patients with Hashimoto thyroiditis have antibodies to various thyroid antigens, the most frequently detected being antithyroid peroxidase, antithyroglobulin, and, to a lesser extent, thyroid-stimulating hormone receptor-blocking antibodies. Nevertheless, a small percentage of patients with Hashimoto thyroiditis (~10–15%) can be antibody negative. The pathogenesis of thyroid autoimmunity is a multistep process: environmental factors can cause thyroid cell damage and the subsequent formation of potential autoantibodies. Autoreactive T and B lymphocytes accumulate in large numbers and infiltrate the thyroid parenchyma. Interestingly, the eventual clinical syndrome appears to depend on whether the predominant T helper lymphocyte is of the T helper 1 type or the T helper 2 type. Thus, T helper 1 predominance leads to Hashimoto thyroiditis, whereas T helper 2 predominance is associated with Graves disease and atrophic thyroiditis.<sup>26</sup>

Hashimoto thyroiditis can be associated with other autoimmune diseases, such as Addison disease, autoimmune gastritis (pernicious anemia), rheumatoid arthritis, systemic lupus erythematosus, celiac disease, and type 1 diabetes mellitus.<sup>27</sup> Moreover, nonvasculitic, autoimmune-mediated, inflammatory meningoencephalitis has been described in patients with Sjögren syndrome and systemic lupus erythematosus. Brain biopsy in some of the cases and one postmortem study demonstrated a panencephalitis with T- and B-cell infiltration and no evidence of vascular inflammation. Of note, some of the patients with this inflammatory condition have probably had Hashimoto encephalopathy.<sup>28</sup>

Ferracci et al detected antithyroid antibodies, namely antithyroglobulin and antiperoxidase antibodies and circulating immune complexes in the cerebrospinal fluid of 6 patients with Hashimoto encephalopathy but not in the cerebrospinal fluid of 21 controls.<sup>29</sup> Although the synthesis of autoantibodies and immune complexes was intrathecal, their concentration in the cerebrospinal fluid was independent of the patients' clinical status or therapy. Hence, the detection of antithyroid antibodies and immune complexes in the cerebrospinal fluid might be a distinctive marker of Hashimoto encephalopathy, although it might not be useful for assessing disease activity.<sup>30</sup> In fact, based on their case of a patient whose serum immunoglobulin G levels markedly decreased following treatment, Fatemi et al suggested the use of this antibody as a marker of disease activity.<sup>31</sup> Another finding that supports the role of autoimmune mechanisms in the pathogenesis of Hashimoto encephalopathy is that of a serum antineuronal autoantibody that reacted with the 36 kDa antigenic protein present in the human cerebral cortex.<sup>32</sup>

A striking new finding has been the discovery of  $\alpha$ -enolase as a novel autoantigen in Hashimoto encephalopathy.<sup>33</sup> This autoantigen exists in both the brain and the thyroid gland and appears to be highly relevant for Hashimoto encephalopathy, especially for patients with a multiphasic clinical course. The authors suggested that the detection of  $\alpha$ -enolase might imply a vasculitic process, because this autoantigen is found in several autoimmune vasculitic disorders, or it might be related to cerebral hypoperfusion through disruption of the cerebral microvasculature ( $\alpha$ -enolase is highly expressed in the endothelium).

### Vasculitis

As previously mentioned, the original patient described by Brain et al presented with strokelike episodes.<sup>24</sup> Although no evidence

of parenchymal damage was detected on autopsy 10 years later, this clinical presentation was suggestive of vasculitis as the underlying mechanism of disease. Further observations in small patient series seemed to support this view,<sup>5</sup> with strokelike events occurring in up to 27% of cases.<sup>6</sup> Evidence of vascular inflammation was suggested in a few cases in which the brain pathology was analyzed: one autopsied case showed prominent T-cell infiltration of the leptomeningeal veins of the brainstem and mild to moderate infiltration in the leptomeninges of the cerebrum, cerebellum, and brain stem (a 77-year-old woman with long-standing Hashimoto thyroiditis who died of cardiac failure and bronchopneumonia),<sup>34</sup> whereas brain biopsy showed lymphocytic infiltration of the walls of small arterioles and venules in one case<sup>35</sup> and perivascular cuffs of lymphocytes in another.<sup>6</sup> Nevertheless, in some cases, these findings could, in fact, be associated with the recently described nonvasculitic autoimmune inflammatory meningoencephalitis.<sup>28</sup>

One particularly interesting pediatric case was reported by Balestri et al: a 14-year-old cognitively normal boy with sudden-onset alternating hemiplegia and no evidence of ischemic lesions in the brain and normal angiography.<sup>21</sup> Serum antimicrosomal antibodies were markedly elevated, and thyroid-stimulating hormone levels were moderately increased. A diagnosis of alternating hemiplegia of childhood was contemplated, and the child was successfully treated with flunarizine for 28 months. The authors, however, concluded that Hashimoto encephalopathy was the probable cause of the hemiplegic events.

### Cerebral Hypoperfusion

This mechanism was suggested by Forchetti et al, who found reversible global cerebral hypoperfusion on a single photon emission computed tomographic (SPECT) study of a 59-year-old patient,<sup>36</sup> and by Kalita et al, who demonstrated decreased perfusion of the right temporal region in a 42-year-old man.<sup>37</sup> A disruption of cerebral microvasculature owing to autoantibody or immune complex deposition was suggested as the mechanism underlying the hypoperfusion (Forchetti et al<sup>36</sup>). Thus,  $\alpha$ -enolase expression in the endothelium might actually represent a common denominator for both autoimmune and vasculitic processes in the pathogenesis of Hashimoto encephalopathy.<sup>32</sup>

## DIAGNOSIS OF HASHIMOTO ENCEPHALOPATHY

A high index of suspicion is required to establish the diagnosis of Hashimoto encephalopathy in children.<sup>8–10</sup> Physicians caring for adult patients are more likely to seek thyroid disease or autoimmune conditions in patients with encephalopathy, refractory epilepsy, and cognitive or psychiatric impairment. However, given the prevalence of Hashimoto thyroiditis in school-aged children (over 1%), the encephalopathy associated with this disease is very likely underdiagnosed.<sup>8</sup>

### Antithyroid Antibodies

The diagnosis of Hashimoto encephalopathy is clinical and based on the triad of (1) neuropsychiatric symptoms, often affecting more than one area of the central nervous system; (2) the detection of antimicrosomal or antithyroglobulin antibodies in serum; and (3) the elimination of other potential etiologies.<sup>5,6</sup> Elevation of cerebrospinal fluid protein is suggestive. A clinical response to corticosteroid therapy is also supportive of the diagnosis. As previously

mentioned, serum levels of antithyroid antibodies do not correlate with neurologic disease activity, inasmuch as many patients with Hashimoto thyroiditis have elevated antibody titers with no neurologic symptoms.

### Neuroimaging Studies

Most pediatric patients (70%) have normal CT or MRI studies at the time of diagnosis. In some cases, abnormal findings appeared as the disease progressed, particularly in cases in which the diagnosis was delayed.<sup>7,8</sup> When abnormal, MRI studies in children have mostly shown prolonged T<sub>2</sub>-weighted signals of the subcortical white matter, suggesting demyelination or inflammation.<sup>7,8,13,16,30</sup> These findings have also been described in adults and been shown to be reversible<sup>38,39</sup> or to change over time.<sup>40</sup> A few patients underwent magnetic resonance angiography, which was normal in most cases. In one case, it showed transient irregular areas of mild narrowing of both middle cerebral arteries. A repeat study 1 week later was normal.<sup>18</sup> A normal angiography was obtained in one child.<sup>11</sup>

SPECT scans were obtained in five pediatric cases.<sup>7,8,11,21</sup> In four patients, they showed various degrees of cerebral hypoperfusion, usually regional (frontal or frontotemporal). Where repeated, the SPECT scans returned to normal on clinical improvement. Positron emission tomography also showed reversible diffuse hypometabolic areas in one patient.<sup>8</sup>

### Cerebrospinal Fluid Analysis

By definition, infection is absent in these cases. About 60% of pediatric patients show a mild to moderate elevation of cerebrospinal fluid protein levels. Rarely, findings suggestive of demyelination, such as oligoclonal bands and myelin basic protein, have been reported, although the number of positive cases is too low to draw any significant conclusions.

### Neurophysiologic Studies

EEGs usually depict general or focal slowing of the background activity, suggesting various degrees of encephalopathy. On some occasions, the EEG has been normal during symptomatic periods.

### TREATMENT

Thyroid hormone replacement is used when indicated, although it has no influence on the neurologic symptoms. There appear to be enough anecdotal data to justify the use of glucocorticoids when Hashimoto encephalopathy is suspected. By far, the vast majority of reports on pediatric and adult patients describe a dramatic clinical response to either methylprednisolone pulse therapy or daily oral prednisone or prednisolone.<sup>6-8,10-13,17-20</sup> Nevertheless, owing to the lack of prospective, controlled studies, the exact doses and duration of treatment are unknown. Empirically, authors have continued corticosteroid therapy for months to 1 to 2 years, intermittently attempting medication tapering as tolerated by the patient. Albeit sporadically, other immunomodulatory means, such as plasmapheresis,<sup>41</sup> have been used successfully.

### OUTCOME

Although there are no clear data on the final outcome of the encephalopathy, most reports in pediatric and adult patients support the observation that Hashimoto encephalopathy is probably

a self-limited condition.<sup>6-8,10-20,29,30,36,37</sup> This observation is based on the fact that most patients can be successfully tapered from corticosteroids. However, a note of caution is needed because no data exist on long-term follow-up of these patients. Given the likelihood of autoimmune (with or without vasculitis) mechanisms being responsible for this syndrome, patients are probably prone to recurrences of the encephalopathy or to clinical presentations involving other body systems.

### CONCLUSIONS

Hashimoto encephalopathy is a highly variable neuropsychiatric condition affecting patients of all ages with autoimmune thyroiditis. Among children, adolescent females are more commonly diagnosed with this complication. The presence of unexplained bouts of confusion, agitation, refractory seizures, status epilepticus, motor deficits, cognitive decline, psychiatric symptoms, movement disorders, ataxia, or myelopathy should lead to evaluation of this disorder. These symptoms can occur even if the patient is euthyroid and do not respond to thyroxine. A high index of suspicion is required to diagnose this condition. Screening for antithyroid antibodies should be performed as the initial screening test. Ancillary diagnostic studies, such as neuroimaging, EEG, and cerebrospinal fluid analysis, can be supportive, although they are not diagnostic. Recent advances in the recognition of brain autoantigens such as  $\alpha$ -enolase might enable making a more precise diagnosis in the future.

Awareness of this underdiagnosed condition is of major importance because patients usually respond very well to corticosteroid therapy, and early recognition of this encephalopathy allows not only for prompt treatment and symptom relief but also for a more rapid, less costly diagnostic evaluation. Given the high frequency of seizures as a presenting symptom in children, Hashimoto encephalopathy should be considered in the differential diagnosis of new-onset epilepsy, particularly in adolescent girls with no apparent factors predisposing them to the development of seizures.

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