

## CASES

## Progressive impairment of cognition and motor function: Hashimoto encephalopathy

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A 48-year-old woman arrived at the emergency department with a decreased level of consciousness after having had a generalized tonic-clonic seizure for the first time. Her score on the Glasgow Coma Scale was 8. Her vital signs were stable, and her blood glucose was normal. Mechanical ventilation was started. A computed tomography scan of her head showed no evidence of intracranial bleeding or space-occupying lesions. No other abnormalities could be seen. She was admitted to the intensive care unit.

The patient's medical history included gastroesophageal reflux disease. She did not take any medications regularly, and she had no known allergies. Her family history included a maternal grandmother with hypothyroidism. According to her family, the patient lived independently, worked at a job requiring high cognitive function, had a 40 pack-year history of smoking, drank minimal amounts of alcohol socially and did not use illicit drugs.

Over the past year, she had been seeing a neurologist for progressive confusion and unsteadiness. Recent falls had caused her to start using a walker. The neurologist had noted some features in her presentation that were consistent with Parkinson disease: bradykinesia, mask-like facies, vague and slow responses to all general questioning, some resting tremor of her left hand, cogwheel rigidity and difficulty tapping her left foot. Magnetic resonance imaging of her brain and cervical spine had not shown demyelination, atrophy or changes in the basal ganglia. An electroencephalogram had shown slow and poorly reactive background activity. The neurologist had started a trial of ropinirole (a dopamine agonist), but the patient's symptoms had worsened. Although she was subsequently given sinemet (carbidopa-levodopa), no significant improvement was noted in either her tremor or her bradykinesia. She had recently been referred to the regional movement disorder clinic with a possible diagnosis of young-onset Parkinson disease.

During her stay in the intensive care unit, the patient's level of consciousness improved spontaneously, and mechanical ventilation was stopped. However, she remained confused and was not oriented to time, person or place. The only abnormality detected by initial laboratory tests was an elevated level of thyroid-stimulating hormone (14 [normal 0.5–5.0] mIU/L); her levels of free triiodothyronine and thyroxine were normal. The patient's cerebrospinal fluid was unremarkable, except for an elevated level of protein (1.21 [normal 0.15–0.45] g/L). No growth was seen in a culture of her cerebrospinal fluid.

We considered Hashimoto encephalopathy because of the patient's progressive confusion and unsteadiness and her elevated level of thyroid-stimulating hormone. She was given high doses of steroids (prednisone, 100 mg daily), and her confusion diminished within 24 hours of starting treatment. She was discharged with home care support one week later. Laboratory tests later showed that the patient had extremely elevated levels of antibodies against thyroglobulin (24300 IU/L, normal < 40 IU/L) and thyroid peroxidase (3056 IU/L, normal < 40 IU/L).

Over the next few months, the patient continued the steroid treatment (prednisone, 50 mg daily) and showed marked improvement in her steadiness. Her cognition also improved, and she contemplated returning to work. Laboratory investigations showed a decrease in her titres of antibodies against thyroglobulin (5400 IU/L) and thyroid peroxidase (440 IU/mL).

**Competing interests:** None declared.

This article has been peer reviewed.

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**CMAJ 2011. DOI:10.1503/cmaj.100007**

### KEY POINTS

- Hashimoto encephalopathy is a rare condition associated with elevated titres of antithyroid antibodies.
- Elevated titres of antithyroid antibodies and the exclusion of other causes of encephalopathy support the diagnosis of this disorder.
- Corticosteroids or other immunosuppressants are effective treatments for Hashimoto encephalopathy.
- Delaying diagnosis or treatment can result in permanent cognitive impairment.

Because the patient began to show cushingoid features, her prednisone dose was gradually tapered by 10 mg every 4–6 weeks. Her cognition and movement began to slow down, and increases were noted in her levels of antibodies against thyroglobulin (50 892 IU/mL and thyroid peroxidase (3862 IU/mL). Her steroid dose was increased, and azathioprine (50 mg once daily) was added to her treatment regimen.

## Discussion

Hashimoto encephalopathy is a rare neuroendocrine disease. It is likely mediated by the immune system and is not simply a manifestation of the cognitive changes associated with hyperthyroidism or hypothyroidism. It is also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis.<sup>1,2</sup>

Hashimoto encephalopathy can be acute, subacute, chronic or relapsing–remitting. Two patterns of presentation are seen: a diffuse, progressive, cognitive impairment that can involve dementia, confusion, hallucination and drowsiness; and a stroke-like pattern of recurrent episodes of focal neurologic deficits, with varying degrees of cognitive impairment and altered consciousness.<sup>1,3,4</sup>

Other signs that may be seen in either presentation include focal or generalized tonic–clonic seizures, diffuse hyper-reflexia and other disorders of the pyramidal tract, psychosis (visual hallucinations and paranoid delusions) and myoclonus or tremor.<sup>1,4</sup>

The pathophysiology of the disease is unknown. There is evidence that autoimmune vasculitis or depositions of immune complexes may disrupt the cerebral microvasculature.<sup>1,3</sup> Biopsies of the brain at autopsy have shown lymphocytic infiltration of some of the small vessels.<sup>4</sup> Many patients have normal thyroid function at presentation, so the disease is probably not directly related to thyroid dysfunction. As with systemic lupus erythematosus and myasthenia gravis, Hashimoto encephalopathy may be an autoimmune disease that is associated with disorders of the thyroid.<sup>4,5</sup>

## Investigations

Laboratory tests need to be done to exclude the usual causes of delirium. Infectious causes need to be ruled out because the usual treatment of Hashimoto encephalopathy is immunosuppression.

The results of laboratory investigations typically show elevated levels of antibodies against thyroid peroxidase and thyroglobulin. However, these findings are not specific to Hashimoto encephalopathy, since they can be seen in a small number of healthy people.<sup>4,5</sup>

Tests for thyroid function can yield normal results in patients with Hashimoto encephalopathy. Previous findings have shown that, in 85 patients, 38% had normal thyroid function at presentation, 35% had subclinical hypothyroidism, 20% had overt hypothyroidism and 7% had hyperthyroidism.<sup>4</sup>

An elevated concentration of protein in the cerebrospinal fluid has been reported in many instances, and the glucose concentration is usually normal.<sup>1</sup>

Electroencephalograms typically show non-specific abnormalities with slowing of background activity; focal spikes, sharp waves and transient epileptic activity may be seen. Most of these abnormalities will resolve with treatment.<sup>1,5</sup>

Magnetic resonance images are usually normal, but some images have shown cerebral atrophy or nonspecific  $T_2$  signal abnormalities in subcortical white matter. These findings may resolve with treatment.<sup>1,4</sup>

There are no clinical or investigative findings specific to Hashimoto encephalopathy. The diagnosis is made when the clinical history suggests it, when there are elevated titres of antithyroid antibodies and if a response to immunosuppression is seen. As mentioned previously, other causes of encephalopathy, delirium and dementias need to be excluded.<sup>6–8</sup>

## Treatment

Most patients respond to steroids or other immunosuppressant treatments. Treatment regimens usually include 50–150 mg of prednisone daily, gradually tapered over two years. Azathioprine or cyclophosphamide has been used when patients were unable to tolerate steroids or during relapses.<sup>1,3</sup>

Most patients have a good prognosis unless there is a delay in diagnosis or treatment. Persistent cognitive impairment has been reported in up to 25% of patients in whom the disease remained untreated for a long time.<sup>5</sup> Reports of long-term follow up indicate that most patients remain free of symptoms for many years after steroid therapy has ended.<sup>5</sup>

## Gaps in knowledge

The pathogenesis of Hashimoto encephalopathy is not yet understood. Recently, an autoantibody against the amino-terminal of  $\alpha$ -enolase was found in serum from a small number of patients with the disease when no such antibody was found in serum from a control group.<sup>9</sup> Further research is needed to determine whether this test should be included in the diagnostic criteria. As well, antineuronal autoantibodies have been found in the serum from patients with

Hashimoto encephalopathy.<sup>10</sup> Again, as with the other autoantibodies that have been detected in patients with this condition, it is not yet known whether they are the cause of the disease or whether they merely coexist with the autoantibodies that are directly involved in the disease's pathogenesis. The roles of these newly discovered autoantibodies, as well as those of the previously described antithyroid antibodies, require further clarification.

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**Contributors:** Both authors contributed equally to the drafting and writing of the manuscript and approved the final version submitted for publication.

The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Generally, up to five references are permitted and visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Written consent from patients for publication of their story is a necessity and should accompany submissions. See information for authors at [www.cmaj.ca](http://www.cmaj.ca).