Pearls & Oy-sters: Hashimoto encephalopathy

PEARLS

• A diagnosis of Hashimoto encephalopathy (HE) should be considered when a combination of encephalopathy and elevated antithyroid antibody levels are seen in a patient in whom other more common infectious, metabolic, and toxic causes of encephalopathy have been thoroughly excluded. Diagnosis should prompt early corticosteroid therapy, which leads to favorable outcomes in the majority of cases.

• The presentation of HE is highly variable with fulminant, acute, subacute, and even chronic patterns of altered mental status across pediatric, adult, and elderly patient populations. Commonly reported clinical manifestations of HE include stroke-like symptoms, dementia, focal or generalized seizures, status epilepticus, myoclonus, tremor, and neuropsychiatric symptoms.

OY-STERS

• HE should not be confused with myxedema coma and the neurologic complications associated with Hashimoto thyroiditis, although the name suggests a connection. There is no conclusive evidence that HE represents a state of dysthyroidism. However, the majority of evidence today and patients’ clinical response to corticosteroids does suggest that the underlying pathogenesis of HE is autoimmune.

• The clinical picture of a relapsing and remitting encephalopathy characterized by stroke-like episodes, seizures, myoclonus, tremor, and neuropsychiatric disturbances particularly in a young female patient should warrant investigation into HE. An encephalopathic EEG with normal neuroimaging and nonspecific inflammatory CSF findings supports the diagnosis, and detection of antithyroid antibodies confirms the diagnosis.

• Early diagnosis of HE and prompt institution of corticosteroid therapy can often lead to seizure control where antiepileptic drug therapy is ineffective.

CASE REPORT

A 30-year-old previously healthy, right-handed woman was admitted to an outside hospital for new-onset seizures preceded by a flu-like prodrome for a week. After admission, she was noted to have frequent events consisting of a sudden blank stare with associated hand fumbling, lip smacking, and postictal confusion and amnesia. She experienced occasional tonic-clonic seizures, preceded by these staring events with head version to the left or right side. An estimated 100 seizures occurred during her first 4 days of admission. She was placed on video EEG monitoring which demonstrated bitemporal electrographic seizure onset. Apart from persistent disorientation and lethargy, her general and neurologic examination including vital signs were normal.

Initial workup showed normal blood counts, electrolytes, and liver and renal function panels, and negative urine toxicology. Mild hypothyroidism with a serum thyroid-stimulating hormone of 7.25 mIU/mL (normal range 0.350–5.500 mIU/mL) but normal free thyroxine fT4 (1.0; normal range 0.9–1.8 ng/dL) was noted.

Basic CSF analysis on the first day of admission showed 3–4 white blood cells (WBCs) with normal pressure, glucose, and protein, and without erythrocytes or other atypical cells. A repeat analysis on day 4 was normal except for a lymphocytic pleocytosis of 134 WBCs, which was thought to either represent an inflammatory etiology or a reaction to the ongoing seizure activity. Neuroimaging including CT, MRI, magnetic resonance angiography, and magnetic resonance venography were unremarkable and showed symmetric hippocampi on volume acquisition sequences.

A diagnosis of limbic encephalitis was entertained and serum, CSF, and urine studies were sent to in-
vestigate for a possible infectious, paraneoplastic, or autoimmune process, as outlined in detail in the table. Viral, bacterial, and paraneoplastic CSF studies were all normal. Notably, PCR detection of CSF herpesvirus DNA was negative. Extensive serum evaluation for paraneoplastic and the predominantly nonparaneoplastic autoimmune limbic encephalitis was negative. CT chest, abdomen, and pelvis in pursuit of a primary neoplasm was also unrevealing. The patient failed phenytoin, valproic acid, lamotrigine, and levetiracetam. She was discharged 3 weeks following admission to a rehabilitation facility on a final regimen of phenobarbital and carbamazepine. A working diagnosis of nonspecific, most likely rare viral, limbic encephalitis was made.

Five weeks following discharge, the patient continued to show cognitive impairment and experienced a recurrence of seizures. Topiramate was added but she developed psychosis the next day and was readmitted. At this time, antithyroid peroxidase antibody (anti-TPO-Ab) was obtained, exhibiting extremely elevated titers (354.4 IU/mL; normal range <9.0 IU/mL) in the setting of persistently elevated serum thyroid-stimulating hormone (4.67 mIU/L; normal range 0.350–5.500 mIU/mL) and normal free thyroxine fT4 (0.9; normal range 0.9–1.8 ng/dL). Thyroid sonography was performed and showed no abnormalities. The diagnosis of HE was suspected and the patient was given a 3-week titration course of 20 mg PO/day prednisone. Her seizure frequency and mental status improved significantly over the 3-week course. However, she never completely returned to baseline, exhibiting mild concentration and memory problems, and continuing to have weekly focal seizures and monthly convulsions.

Six months after disease onset, the patient came to our institution for elective video EEG because of persistent mild cognitive symptoms and refractory seizures, and was subsequently admitted and treated with a 7-day course of plasmapheresis followed by a 4 days of 1 g IV/day methylprednisolone. Her EEG was notable for continuous generalized slowing, independent bitemporal interictal epileptiform discharges, and electrographic seizure activity arising from both temporal lobes. Her serum carbamazepine level was 8.6 μg/mL, phenobarbital level was 18.8 μg/mL, and anti-TPO-Ab titer was 237 IU/mL prior to immunotherapy. Half of her recorded seizures occurred in sleep and were associated with central apnea and oxygen desaturations as low as 62%. The patient was discharged to complete a 40-day 60 mg PO/day prednisone course. At the end of the steroid taper, serum anti-TPO-Ab titer had fallen to 79 IU/mL and CSF sent at the time for anti-TPO-Ab

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency, %</th>
</tr>
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<tbody>
<tr>
<td>Symptomatology</td>
<td></td>
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<tr>
<td>Encephalopathy</td>
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<tr>
<td>Relapsing and remitting course</td>
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<tr>
<td>Seizures (focal, generalized, status epilepticus)</td>
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<tr>
<td>Stroke-like focal neurologic deficits</td>
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<tr>
<td>Myoclonus</td>
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<tr>
<td>Tremor</td>
<td>28</td>
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<td>Psychiatric symptoms</td>
<td>30</td>
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<tr>
<td>Hallucinations</td>
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<tr>
<td>Antithyroid antibodies</td>
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<tr>
<td>Elevated titer of anti-TPO antibodies</td>
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<tr>
<td>Elevated titer of anti-TG antibodies</td>
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<td>Mild lymphocytic pleocytosis</td>
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<td>Positive antithyroid antibodies</td>
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<tr>
<td>EEG</td>
<td></td>
</tr>
<tr>
<td>Abnormal (typically nonspecific background slowing)</td>
<td>85</td>
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<tr>
<td>Neuroimaging</td>
<td></td>
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<tr>
<td>Abnormal CT or MRI (typically nonspecific changes)</td>
<td>45</td>
</tr>
</tbody>
</table>

**Recommended workup for limbic encephalitis**

**Serum studies**

- Hashimoto encephalopathy
  - Anti-TPO and anti-TG antibodies
- Viral encephalitis
  - Anti-B burgdorferi/Lyme antibodies, anti-HIV antibodies, Arbovirus panel: anti-West Nile, anti-California, anti-St. Louis, anti-Eastern Equine, and anti-Western Equine antibodies
- Paraneoplastic limbic encephalitis
  - Paraneoplastic panel: anti-Hu (small-cell lung cancer), anti-CRMP5/CV2 (small-cell lung cancer, thymoma), anti-Ma2 and anti-Ma1 (testicular tumors, breast cancer), and anti-amphiphysin antibodies (ovarian teratoma, testicular tumors)
- Autoimmune limbic encephalitis
  - Anti-VGKC, anti-NMDA, anti-GABA, and anti-AMPA receptor antibodies
- Vasculitis with CNS involvement
  - Perinuclear and cytoplasmic antineutrophil antibodies, antinuclear antibody panel: anti-double-stranded DNA, anti-Smith, anti-Ro/SSA, anti-La/SSB, antiribonucleoprotein, antistriate, antitopoisomerase 1/Scl-70, anticientromere, and anti-Jo1 antibodies
- CSF studies
  - PCR detection of herpes simplex virus, varicella zoster virus, human herpesvirus 6, and Epstein-Barr virus DNA

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was undetectable. However, she continued to experience focal and generalized seizures every 1–3 weeks and had persistent mild cognitive impairment. Five months later, the patient was found deceased in her bed one morning. An autopsy including detailed pathological investigation of her brain found no alternative cause of death, confirming sudden unexpected death in epilepsy (SUDEP) as the cause.

**DISCUSSION**

Since it was originally described in 1966, HE has remained an elusive yet fortunately treatable cause of “investigation-negative” encephalopathies. While it is thought to be a rare syndrome, HE is likely underdiagnosed given that its clinical, laboratory, electroencephalographic, and radiographic features are highly variable and often misleading, as in the aforementioned case.

HE is a syndrome of encephalopathy, elevated serum antithyroid antibody concentrations, and response to corticosteroid therapy. These antithyroid antibodies include both anti-TPO-Abs and antithyroglobulin antibodies (anti-TG-Ab), with anti-TPO-Abs present in 100% of cases and anti-TG-Abs in up to 70%. Though the diagnosis of HE requires the presence of these antibodies, the neurologic disorder is not to be confused with the cognitive dysfunction associated with hypothyroidism, as in Hashimoto thyroiditis, or hyperthyroidism. Epidemiologically, HE is 4 to 5 times more likely to affect females, like most autoimmune disorders. The syndrome has no preponderance for age, with reported cases ranging from 8 to 86 years old, with a mean age at onset of 41–48 years.1,3

The pathophysiologic process of HE remains unknown, which fuels the controversy over whether this is an actual syndrome or an epiphenomenon related to an underlying autoimmune disorder. The majority of cases are euthyroid or subclinically hypothyroid at presentation.1,3 There has also been minimal experimental evidence that antithyroid antibodies react with human brain or nerve tissue directly. Recently, 1 small study of 5 human brains found antigenic targets for anti-TSH-receptor IgG on human cortical neurons and anti-TG IgG in cerebral vasculature.4 Another study identified antineuronal antibodies in the serum of a patient with HE that reacted with human brain tissue, but none from a control nor a patient with Hashimoto thyroiditis without encephalopathy.5 Therefore, the presence of antithyroid antibodies should be viewed as a diagnostic marker rather than the etiologic agent.

Unfortunately, recognition of HE and institution of therapy is complicated by its heterogeneous clinical presentation, including a fulminant onset like in our patient, acute, subacute, and even chronic disease patterns with relapsing and remitting or progressive courses. The syndrome has been previously described as 2 clinical subtypes: a vasculitic-like pattern characterized by multiple acute or subacute stroke-like episodes leading to focal neurologic deficits and variable degrees of cognitive dysfunction and impaired consciousness, or a diffuse progressive pattern characterized by gradual cognitive impairment with dementia, neuropsychiatric symptoms, and impaired consciousness.6 The latter is seen more in older patients and can be easily confused with Alzheimer disease, vascular dementia, or Lewy body dementia. The most common symptoms of HE are behavioral-cognitive changes, focal or generalized seizures, tremor, myoclonus, and stupor or coma (table).1–3 Status epilepticus is a rare presentation of HE although more cases are being reported in the literature since seizure response to steroid treatment has been recognized.1,2 Creutzfeldt-Jakob disease (CJD), acute disseminated encephalomyelitis, paraneoplastic and nonparaneoplastic limbic encephalitis, CNS vasculitis, and other encephalopathies associated with rapidly progressive dementia are often considered in the differential diagnosis for HE as outlined in the table. The neuropsychiatric manifestations of systemic lupus erythematosus in a young female patient could
paint a phenotypically similar clinical picture to HE and should be excluded.

Although the presence of antithyroid antibodies is the hallmark feature in making the diagnosis of HE, this laboratory finding is not specific as about 10% of the general population has elevated serum anti-TPO-Ab. Antibody type and levels do not necessarily correlate with the severity of neurologic symptoms and extent of recovery following treatment. The most common finding in CSF analysis is elevated protein concentration, seen in about 60%–85% of patients.1–3 The presence of a lymphocytic pleocytosis is less common and as in our case possibly related to ongoing seizure activity. The role of investigating the CSF specifically for antithyroid antibodies is unclear given limited patient data, though some very small studies have reported antibody positivity in more than half of suspected HE cases.3

Just as HE is clinically heterogeneous, it is not surprisingly electrophysiologically and radiographically heterogeneous as well. EEG abnormalities are nonspecific, most commonly diffuse background slowing consistent with encephalopathy.1,6 EEG resolution can lag behind the clinical improvement.7 CT and MRI brain in HE is typically normal but about half of patients demonstrate nonspecific changes.1,6

The current standard of care in HE management is oral or IV corticosteroids in addition to treatment of any concurrent dysthyroidism. Other therapeutic options have been found to be effective based on case reports in patients who failed or had insufficient response to steroid treatment, including plasmapheresis, as performed in our patient (table).2,5,6 The majority of patients respond favorably to steroids. Since the differential diagnosis for HE includes graver diagnoses like CJD and neurodegenerative disorders, we recommend a corticosteroid trial in suspected HE. Even in cases of fulminant HE, such as those presenting as our patient did with acute status epilepticus, IV steroids can lead to a favorable prognosis for acute seizure control. In 1 recent study, 5 of 7 reported cases of HE manifesting as status epilepticus responded to IV steroids when antiepileptic drug therapy proved ineffective.8

DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES
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