Hashimoto Encephalopathy or Neurosarcoidosis? A Case Report

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Abstract

Hashimoto encephalopathy (HE) is a rare autoimmune disease characterized by symptoms of acute or subacute encephalopathy associated with increased antithyroid antibody levels. Neurosarcoidosis is also a rare entity that occurs in less than 5% of patients with systemic sarcoidosis. Neurosarcoidosis usually presents with cranial neuropathies, myelopathy, or new-onset seizure. We report a case of a 49-year-old caucasian woman, previously healthy, who initially presented for a workup of a new-onset seizure. She had a gradually progressive course with neurocognitive decline and recurrent partial seizures refractory to conventional anti-epileptic drugs. Her seizures responded well to a course of intravenous immunoglobulin. She was subsequently diagnosed with HE and pulmonary sarcoidosis based on serological and pathological studies. She improved neurologically once the seizures were controlled. Hashimoto encephalopathy is a rare condition that is potentially treatable and presents with various neuropsychiatric manifestations. It is a diagnosis of exclusion that requires a strong clinical suspicion and is often underrecognized.

Keywords

autoimmune diseases of the nervous system, epilepsy, encephalitis, central nervous system infections, neuroimmunology, clinical specialty

Introduction

Hashimoto encephalopathy (HE) is a rare neurologic syndrome associated with Hashimoto thyroiditis. It was initially described in 1966.¹ Hashimoto encephalopathy is thought to be an autoimmune disease and is known to be associated with other immunologic disorders (myasthenia gravis, glomerulonephritis, primary biliary cirrhosis, pernicious anemia, and rheumatoid arthritis). The inflammatory findings in cerebrospinal fluid (CSF) and response to treatment with steroids support the autoimmune theory.² More recently, high titers of anti- α -enolase antibodies were significantly detected in patients with HE having excellent corticosteroid sensitivity compared to low or negative titers in those with poor corticosteroid responsiveness and controls, respectively.³ Some authors suggest that HE may represent an autoimmune cerebral vasculitis resulting from either endothelial inflammation or immune complex deposition.⁴ Clinical findings are variable and nonspecific. In this case report, we present the case of a patient with a new-onset seizure and subsequent progressive neurocognitive decline in a setting of refractory partial seizures. To our knowledge, this is the first reported case of HE in association with pulmonary sarcoidosis and serum glutamic acid decarboxylase antibodies.

Case Presentation

A 49-year-old caucasian woman was transferred from a small community hospital after intubation for respiratory failure from a new-onset generalized tonic-clonic seizure (GTCS). She had received a loading dose of 1 g of levetiracetam and was continued on 500 mg twice a day. Initial history was primarily obtained from the family who reported a recent emergency department (ED) visit a week prior for symptoms of dizziness associated with gait imbalance and intermittent slurred speech. She was being treated with ciprofloxacin and meclizine for presumed labyrinthitis diagnosed during that visit. The family also mentioned spells of slurred speech and hand shaking, which led to the current ED visit. She had her first GTCS while in the ED, leading to intubation. Her vital

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Figure 1. Magnetic resonance imaging (MRI) of the brain showing dural enhancement Post Lumbar puncture (post-LP) (Axial).

Figure 2. Magnetic resonance imaging (MRI) of the brain showing dural enhancement Post Lumbar puncture (post-LP) (coronal).

signs and electrolytes were normal. The initial neurological evaluation was limited due to sedatives and intubation. She was arousable to voice off sedatives, was able to follow simple commands, pupils were symmetric and reactive with normal extraocular movements and some end gaze nystagmus, motor and sensory examination were normal, and there was no involuntary movement, automatisms, appendicular dysmetria, or myoclonus. Her history and family history included no psychiatric disease, seizures, or other chronic medical problems. The initial computed tomography (CT) of the head without contrast was unrevealing. The CSF results were significant for elevated protein of 82 mg/dl and a normal cell count and glucose levels. Cultures of blood, sputum, urine, and CSF were sterile. The CSF examination for herpes zoster (herpes simplex virus) HSV I & II PCR (CSF) I and II and cryptococcal antigen was negative. Subsequent magnetic resonance imaging (MRI) of the brain with and without contrast revealed smooth dural enhancement, which likely related to her recent lumbar puncture. Electroencephalogram (EEG) showed non-specific slowing without any electrographic seizures or epileptiform discharges. Once she regained complete consciousness, mechanical ventilation was discontinued. She was neurologically and cognitively at her baseline and remained seizure free throughout her hospital stay. Given the negative workup so far the risk of recurrent seizure was low, and therefore levetiracetam was discontinued. As more history became available it became apparent that she had significant unintentional weight loss over the past several months along with vague memory and concentration difficulties over the prior 3 weeks. This led us to entertain the differential of

paraneoplastic limbic encephalitis, and serum and CSF antibodies were sent. However, the serum and CSF paraneoplastic antibodies, which included antineuronal nuclear antibodies, anti-Purkinje cell cytoplasmic antibody, anti-amphiphysin antibody, anticollapsin response-mediator protein 5 immunoglobulin G, anticalcium channel antibody, antigial nuclear antibody, anti-N-methyl-D-aspartate receptor antibody, and neuronal (V-G) K channel antibody, were negative. A CT of the thorax abdomen and pelvis was pursued simultaneously to look for occult malignancy. Significant findings were mediastinal and bilateral hilar lymphadenopathy. Serum and CSF angiotensin-converting enzyme levels were 65 U/L (range 12-68 U/L) and 2.1 U/L (range 0.0-2.5 U/L), respectively. Thyroid-stimulating hormone (TSH) levels were elevated at 10.65 μ IU/mL; however, free T3 and T4 levels were normal. Pulmonary sarcoidosis was a possible diagnosis for which she was scheduled for an outpatient bronchoscopy with a pulmonologist (Figures 1 and 2).

Approximately 2 weeks later, she had a recurrent seizure and was started on levetiracetam 500 mg twice a day. However, she continued to worsen and was readmitted for progressive neurocognitive decline. The family described episodic disorientation, poor short-term memory, and poor concentration sometimes associated with episodic tonic posturing of both lower extremities lasting seconds. Family members were concerned as they felt all her symptoms worsened after the addition of levetiracetam. In about 4 weeks since the initial presentation, she declined to a point where she required assistance with activities of daily living. The neurological examination was significant for drowsiness, disorientation to time

and place, and impairment of attention and concentration without any cranial nerve or motor and sensory deficits or any involuntary movements such as tremor or myoclonus.

The levetiracetam was stopped, and lacosamide 200 mg twice a day was started. A repeat MRI of the brain with and without contrast was normal. Electroencephalogram was suspicious for nonconvulsive status epilepticus (NCSE). Given her high TSH levels, serum antithyroid antibodies and antiglutamic acid decarboxylase (anti-GAD) antibodies were sent out to a referral laboratory (there was a significant time lag in obtaining final results).

She continued to have a fluctuating course with episodic confusion and encephalopathy with intermittent tremulousness but without obvious tonic-clonic activity. As long-term continuous EEG monitoring capacity was lacking, a repeat EEG on day 3 of admission was obtained, which was consistent with NCSE. Fosphenytoin was added to her antiepileptic drug (AED) regimen. An endobronchial lymph node aspiration was pursued, the pathology results of which were nondiagnostic.

There was no clinical or electrographic improvement, despite being on 2 AEDs with therapeutic plasma levels. She was started with intravenous immunoglobulin (IvIG) on day 5 of admission and was continued on the AEDs. After 2 days of IvIG, she started showing improvements in regard to her cognition and overall encephalopathy. On day 5, thoracoscopy was performed with a right lower lobe wedge resection and mediastinal lymph node sampling. The pathological finding of nonnecrotizing granulomatous inflammation with a negative AFB, fungal, and nocardia stain was consistent with a diagnosis of pulmonary sarcoidosis. She finished 5 days of IvIG and continued to improve. Previously sent thyroid microsomal antibody and thyroglobulin antibody came back elevated at 128 and >3000 IU/mL, respectively. Serum anti-GAD antibody (anti-GAD-Ab) titers were also elevated at 8.40 U/mL.

She was subsequently started on immunosuppression with prednisone and azathioprine. She remained clinically and electrographically seizure free on phenytoin and lacosamide. The antimicrosomal antibody and thyroglobulin antibody continued trending down to 95 and >3000 IU/mL, respectively, a month later and 64/1031 IU/mL 2 months later.

Discussion

Hashimoto encephalopathy is a rare cause of rapidly progressive dementia. A recent systematic review of the literature in 2010 found only 130 patients who met the criteria for diagnosis of HE.⁵ The disorder occurs more frequently between the ages of 44 and 46 years, with a female to male ratio of 4 to 1.⁶

It is likely immune mediated and is not simply a manifestation of the cognitive changes associated with hyperthyroidism or hypothyroidism. A Significant proportion of patients have concurrent extrathyroid immune abnormalities.⁶ To our knowledge, this is the first reported case of HE in a patient with subclinical pulmonary sarcoidosis.

The pathogenesis is postulated to be a neuroimmunological phenomenon with disruption of cerebral microvasculature secondary to autoantibody or immune complex deposition in the vascular endothelium. There is indeed significant indirect evidence supporting this theory, given HEs association with other autoimmune diseases and abnormal single-photon emission CT/isotope brain findings.^{3,5} However, there is no evidence that thyroid autoantibodies react with brain tissue and affect neuronal function, and the level of circulating autoantibodies is not correlated with the severity of neurological manifestations or with the response to treatment.⁷ So far neuron-specific autoantibodies have not been identified in this group of patients.

There are 2 distinct forms of presentation described in the literature: a subacute progressive course either with cognitive impairment presenting as dementia or confusion or a psychiatric manifestation with hallucinations and psychosis and an acute presentation with seizures or stroke-like presentation with focal neurologic deficits, with varying degrees of cognitive impairment and altered consciousness.⁸

Most patients are euthyroid at presentation but with positive serum antithyroid antibodies. Positive antithyroid peroxidase (anti-TPO) antibody titer is more common compared with antithyroglobulin antibody.⁴ High protein is the most common abnormal CSF finding. Oligoclonal bands were present in 1/3 of the patients tested (only 22 were tested out of 130). There are some reports of positive antithyroid antibodies in CSF.⁴ The EEG findings are nonspecific with the most common reported abnormality being generalized slow waves.⁴ Data on MRI are limited with a majority of cases without any abnormalities. The most common abnormal MRI finding was T2/fluid-attenuated inversion recovery hyperintensity, which is very nonspecific.⁴

Our patient had subclinical hypothyroidism and an elevated antimicrosomal antibody titer similar to other described cases. Although a gold standard confirmatory test would be demonstration of intrathecal synthesis of antimicrosomal antibodies,⁹ we were unable to do so due to logistical difficulties. However, unlike other cases in literature, our patient showed decreasing antibody titers with clinical improvement. The variable association of sarcoidosis and thyroid autoimmunity has been reported by several studies. In a case-control study of patients with sarcoidosis, the prevalence of anti-TPO positivity in female patients was 34%. However, none of the patients met the criteria for diagnosis of HE.¹⁰ Neurosarcoidosis (NS) can present with new-onset seizure; however, cranial neuropathies and myelopathy are the more common presentations. The MRI is usually abnormal with meningeal enhancement and enhancing parenchymal lesions being the most common findings. Our patient had 3 contrast-enhanced brain MRI that were completely normal, therefore, we do not think she had NS. Anti-GAD antibodies are described in stiff-person syndrome and also in a cerebellar ataxia and epilepsy. However, positive GAD-Ab titers are also prevalent in patients with other organ-specific antibodies and autoimmune diseases such as myasthenia gravis, thyroiditis and pernicious anemia,

Figure 3. Precontrast magnetic resonance imaging (MRI) of the brain.

and insulin-dependent diabetes mellitus.^{11,12} High titers of GAD-Ab have been associated with cases of temporal lobe epilepsy (with or without hippocampal sclerosis) and extra-temporal epilepsy (with cortical dysplasia or without lesion) as well as with juvenile myoclonic epilepsy.³⁻⁶ However, prevalence studies have shown no major association between GAD-Ab positivity or titers and the severity of epilepsy. Given the nonspecific nature of anti-GAD-Ab, the pathophysiological importance of GAD-Ab in these patients and our patient is not clear (Figure 3).

There are no formal studies of the treatment of HE; most reports have shown that immunosuppression especially with glucocorticoids are effective.⁵ recommend the use of intravenous methylprednisolone (500-1,000 g/d) for 3 to 5 days, with oral prednisone at a high initial dose (1-2 mg/kg/d), followed by gradual reduction based on clinical improvement with or without additional immunosuppressive drugs, such as azathioprine. In their review 114 (87.6%) patients had complete remission of symptoms; 8 (6.2%) did not show any improvement; 4 (3.1%) had partial improvement and in 4 cases (3.1%) there was no information available on outcome.

In conclusion, HE is a rare autoimmune syndrome that requires a strong clinical suspicion for diagnosis. The diagnosis involves fulfilling the following criteria: (1) presence of high titers of antithyroid antibodies in the serum or CSF, (2) no change in CSF indicative of an infectious, SAH, or neoplastic

etiology, (3) nonspecific MRI or CT scans,⁴ and (4) a good response to immunosuppressive therapy (steroid or IvIG).

Declaration of Conflicting Interests

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