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Case Report Open Access

Mixed Clinical Response After Total Thyroidectomy in Two Patients with Hashimoto's Encephalopathy

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Abstract

Importance: Hashimoto's encephalopathy (HE) is currently treated with medical therapy. Only one case of thyroidectomy as treatment for HE has been presented in the literature. We present two patients with distinct manifestations of (HE) who underwent thyroidectomy after minimal response to medical management.

Observations: Patient 1 is a 71 year-old female who presented with motor restlessness. She had persistently elevated antithyroid antibodies. After thyroidectomy, her symptoms were only mildly improved. Iodine-123 thyroid scan revealed a small remnant of thyroid tissue. Her antithyroid antibodies remained elevated. Patient 2 is a 60 year-old female with previous diagnosis of (HE) who presented with recurrent seizures. She had a history of elevated antithyroid antibodies. After thyroidectomy, she no longer had seizures, and her antithyroid antibodies normalized.

Conclusions and relevance: Patient 1 did not improve as quickly as patient 2. A possible explanation for this is the thyroid tissue remnant found in the first patient during a follow-up iodine-123 thyroid scan; the remnant could be responsible for persistently elevated antithyroid antibodies. The degree or pattern of preoperative antithyroid antibody elevation does not seem to be predictive of postoperative response. Thyroidectomy is a reasonable treatment option for the severely symptomatic patient who has failed medical therapy with steroids, IVIG, and plasmapharesis.

Keywords: Hashimoto's encephalopathy; Creutzfeld-jacob disease; Electroencephalogram

Introduction

Hashimoto's encephalopathy (HE) is a rare disorder first characterized by Brain et al. in 1966 [1]. With only a few hundred reported cases, its etiology is not entirely understood but is believed to be related to the autoimmune mechanism of Hashimoto's thyroiditis. Generally, patients diagnosed with HE demonstrate a progressive encephalopathy in the setting of elevated antithyroid antibodies. They may display cognitive deterioration, seizures, stroke-like events, hallucinations, focal neurologic deficits or movement disorders, and a clinical response to corticosteroid therapy [2].

The current first-line treatment is steroid therapy, with intravenous immunoglobulin (IVIG) and plasmapharesis reserved for refractory cases. Only one case of thyroidectomy as treatment for (HE) has been presented in the literature, which resulted in a full recovery [3]. We present two patients with distinct manifestations of (HE) who underwent thyroidectomy with mixed results after minimal response to medical management.

Case 1

A 71-year old female presented with agitation and abnormal movements of two weeks duration. During that time, the patient had increased motor and behavioral restlessness as well as spontaneous movements of all limbs. Examination at the time of presentation revealed an awake and alert woman who was oriented only to self. Other pertinent findings included resting tremor and mild rigidity in the extremities. Earlier in the year, the patient was admitted for an episode of rapidly progressive dementia, and was presumptively diagnosed with Hashimoto's encephalopathy based on persistently elevated antithyroglobulin antibody (up to 1125 IU/mL) and thyroid peroxidase antibody (up to 110 IU/mL). Neck ultrasound at that time revealed various small nodules and a left thyroid nodule (2.7×2.7×2.7 cm) with cystic and solid components. Fine needle aspiration of the nodule revealed findings consistent with benign nodular goiter. She underwent treatment with intravenous steroids followed by oral steroids in addition to IVIG, which yielded questionable improvement of her symptoms.

During her second admission, the patient was found to have elevated antithyroglobuin antibody (173 IU/mL) but a normalized thyroid peroxidase antibody level. Her thyroid function tests were normal. Cerebrospinal fluid (CSF) analysis was significant for elevated protein, with no evidence of disseminated Lyme disease or neurosyphilis. Brain magnetic resonance imaging (MRI) revealed mild atrophy and small vessel disease. An Electroencephalogram (EEG) performed on admission was normal. In the days following admission, the patient was evaluated by neurology for frontotemporal dementia and Creutzfeld-Jacob Disease (CJD). CSF analysis for 14-3-3 protein, which is elevated in CJD, was not performed because the specimen was not handled properly. Brain biopsy was declined by neurosurgery as prion disease had not been ruled out. In the following week, the patient's agitation improved, but she remained unable to cooperate and follow directions during an exam. Otolaryngology was then consulted, and examination at that time revealed aeuthyroid patient with no overt thyromegaly. The option for total thyroidectomy was discussed with the family as a possible measure to improve her mental status, and the family consented to the procedure. The surgery was performed on the 13th

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day of hospitalization. Surgical pathology revealed chronic thyroiditis with Hurthle cell changes and nodular hyperplasia, without evidence of malignancy (Figure 1). Within one week of surgery, her thyroglobulin antibody remained elevated (245 IU/mL), and her thyroid peroxidase antibody remained normal.

In the days following thyroidectomy, the patient's mental status did not improve from baseline. The patient was eventually discharged to a nursing home with improved agitation but persistent altered mental status and inability to follow commands. Four months following surgery, she underwent an Iodine-123 thyroid scan prompted by persistently elevated antithyroid antibody levels, which was notable for mild uptake in the right thyroid bed, consistent with a small remnant of thyroid tissue. She was referred for radioactive iodine ablation but never presented to the appointment. Telephone conversation eight months later revealed the patient did not improve clinically, with further loss of independence of living.

Case 2

A 60-year woman with a previous presumed diagnosis of Hashimoto's encephalopathy diagnosed at another academic medical center presented to the emergency department with altered mental status and seizures. Prior to the current admission, the patient was managed with five antiepileptic medications, but she relapsed every 4-5 weeks, requiring recurrent hospital visits. During the current presentation, she was stuporous and did not follow commands on exam. Brain MRI showed lesions consistent with vasogenic edema in the left thalamus, right medial temporal lobe, right hippocampus, right occipital lobe, as well as an old right temporal lobe infarction. CSF analysis showed mildly elevated leukocyte count, decreased glucose, and elevated protein without organisms on gram stain or culture. A brain biopsy was performed and showed mild glial cell proliferation; there was no evidence of nuclear atypia, microorganism infiltration, or significant myelin loss. A muscle biopsy was performed to rule out mitochondrial disorders, and no abnormalities were found. Although labs on hospital admissions within the preceding six months showed elevated antithyroglobulin antibody (up to 639 IU/mL), thyroid peroxidase antibody (up to 98 IU/mL), and anti-GAD65 antibody (34 IU/mL), levels at this presentation were within normal limits. The patient received treatment with IVIG, prednisone, plasmapharesis, IV rituximab, and antiepileptics for her seizures. Her mental status showed minor improvements, but these improvements could not be consistently sustained. Additionally, she continued to have focal and generalized seizures, despite trials with multiple antiepileptics. Multiple

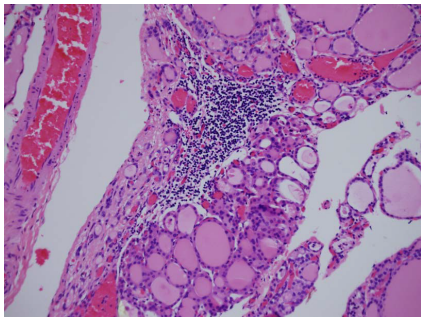

Figure 1: Pathology from case 1
Description: Pathology from Case 1 exhibiting a lymphocyte aggregate adjacent to Hurthle cell changes. H&E stain, magnified at 400x Specimen type: Thyroid gland.

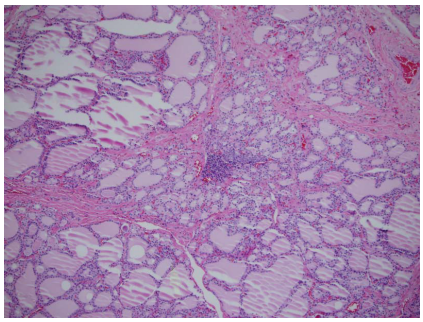

Figure 2: Pathology from case 2
Description: Pathology from Case 2 exhibiting lymphocyte aggregation with surrounding bands of fibrosis. H&E stain, magnified at 200x Specimen type: Thyroid gland.

EEGs were performed throughout the patient's hospitalization, which continued to show epileptiform activity, without a consistent period of remission.

When the patient finished her last round of plasmapharesis, thyroid antibodies were measured again, and her anti-thyroglobulin antibody level was 96 IU/mL, while her thyroid peroxidase antibody level remained normal. Otolaryngology was consulted to evaluate the patient for possible thyroidectomy. On exam, she was euthyroid with minimal thyromegaly and no thyroid tenderness. After discussion with the family, consent was given for thyroidectomy. Total thyroidectomy was performed without complication. Surgical pathology revealed chronic thyroiditis and nodular hyperplasia, without evidence of malignancy (Figure 2). EEGs performed postoperatively showed isolated epileptiform discharges, which were significantly improved. The patient did not have any further episodes of convulsive epilepsy. On post-operative day six, she was discharged home to her family's care. At that time, she was oriented only to self, could follow simple commands, was not able to repeat simple words, and was able to name a pen. She was discharged with four antiepileptic medications.

The patient presented to her follow-up appointment two months after discharge. At that time, her family reported that the patient had not had any seizures. On exam, the patient was oriented only to self, could follow simple commands, was able to repeat simple words, and was able to name common objects. Her antithyroglobulin antibody decreased to less than 20, while her thyroid peroxidase antibody remained normal. At her five-month follow up, the patient was eating by mouth and was able to converse appropriately with clinicians.

Discussion

Both of our patients demonstrated signs and symptoms that largely fit the HE diagnostic criteria proposed by Peschen-Rosin et al. in 1999 [4]. The criteria include the presence of unexplained myoclonus, generalized seizures, psychiatric disorders, or focal neurological findings, and three of the following: abnormal EEG, elevated thyroid antibodies, elevated CSF protein, response to steroid treatment, and unremarkable findings on brain MRI. HE symptomatology has been expanded to include tremor and cognitive impairment, among other findings [2]. It has been noted that only half of HE patients exhibit a complete response to corticosteroid therapy; therefore, unresponsiveness should not be used as an exclusion criterion [5]. The first patient's predominant symptoms would best be categorized as tremor and cognitive impairment, while the second patient's main manifestations were cognitive impairment and seizures. Both patients

Test	Patient 1	Patient 2	Reference Range
TSH	1.078 uIU/mL	2.369 uIU/mL	0.350 - 4.940 uIU/mL
Total T4	5.9 mcg/dL	Unmeasured	4.5 - 12.5 mcg/dL
Total T3	43 ng/dL	Unmeasured	45 - 137 ng/dL
Free T4	1.0 ng/dL	0.6 ng/dL	0.7 - 1.9 ng/dL
Free T3	1.7 pg/mL	2.1 pg/mL	1.5 - 3.5 pg/mL

Table 1: Thyroid Function Tests of Patient 1 and Patient 2.

had elevated thyroid antibodies at some point during presentation, elevated CSF protein on lumbar puncture, and nonspecific findings on MRI. It has been demonstrated that in the presence of extreme levels of thyroid hormone patients can manifest neuropsychiatric symptoms such as seizures, mood disorders, and psychosis [6,7]. However, both of our patients were found to be euthyroid. The two patients' thyroid function tests are listed in (Table 1).

In each case, the patient exhibited a minimal response to steroids, plasmapharesis, and IVIG. Both patients underwent total thyroidectomy after informed consent was given for the procedure. Their responses to the surgery, however, were mixed. The first patient continued to display neurological signs such as tremor and motor agitation, but this was slightly improved at the time of her discharge. Following release from the hospital, she continued to lose ability to care for herself independently. Her mental status and ability to follow commands never recovered. In contrast, the second patient's intractable seizures remitted completely after thyroidectomy including drastic improvement on EEG. In addition, her cognitive status improved as she reacquired the abilities of naming, repetition, and comprehension at later follow-up. A possible explanation for the difference in clinical improvement between patients is the thyroid tissue remnant found in the first patient during a follow-up iodine-123 thyroid scan. This finding confirms that not all thyroid tissue was removed during thyroidectomy, and the tissue remnant could be responsible for her persistently elevated anti-thyroid antibodies.

Hashimoto's encephalopathy is a rare disorder with an estimated prevalence of 2.1/100,000 [8]. Treatment of this condition with total thyroidectomy has been reported only once in the literature to date [3]. Yuceyar et al. [3] reported a 31-year-old female with HE who underwent thyroidectomy after partial response to medical treatment and achieved full recovery. A notable difference is that the patient was thyrotoxic in contrast to our patients who were euthyroid. The patient's thyroid peroxidase antibody (up to 600 IU/mL) was elevated to a much greater degree than both of our patients, but her anti-thyroglobulin antibody level (up to 394 IU/mL) was comparable. Given that this patient experienced full recovery after thyroidectomy, it does not seem that significant preoperative antibody elevation precludes a clinical response to thyroidectomy. Taking our two cases into account, the degree or pattern of preoperative antibody elevation does not seem to be predictive of postoperative response. It is worth noting that for both of our patients, the thyroid peroxidase antibodies remained significantly lower than anti thyroglobulin antibodies, while the converse was true in the previously reported case referenced above.

The exact role of antithyroid antibodies in Hashimoto's encephalopathy is unclear. While most patients with (HE) will eventually be diagnosed with Hashimoto's thyroiditis, the former can precede the latter by several years [4]. Tissue pathology from both of our patients revealed cellular changes very similar to those found in Hashimoto's thyroiditis (Figure 1 and 2). Both cases are examples of tissue changes in the thyroid preceding the onset of altered thyroid hormone levels or clinical symptoms.

Even though the elevation of anti-thyroglobulin and thyroid peroxidase antibodies is a key diagnostic factor for HE, the antibodies themselves have not been directly linked to mediating the neuropsychiatric symptoms of the disease. Furthermore, the correlation of antibody titers with the severity of disease symptoms have been investigated in patients, but a clear relationship cannot be elicited [9,10]. Because of the lack of a clear causal relationship, Canton et al. have proposed that a more appropriate term for the disease would be "encephalopathy associated to autoimmune thyroid disease" [10].

Given the unknown disease etiology and the limited reports of surgical treatment, the role for total thyroidectomy in Hashimoto's encephalopathy remains to be fully elucidated. At current, it seems to be a reasonable option for the severely symptomatic patient who has failed steroids, IVIG, and plasmapharesis. Otolaryngologists must weigh the usual risks of hypoparathyroidism, recurrent laryngeal nerve injury, and lifetime thyroid hormone replacement that follow thyroidectomy with the benefits of possible remission from an individual's manifestations of Hashimoto's encephalopathy.

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