

## Case Report

# Hashimoto's Encephalopathy

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### Abstract

Hashimoto's encephalopathy (HE) is a completely treatable but relapsing neuroendocrine disorder associated with Hashimoto's thyroiditis (HT). Though numerous neurological manifestations are often associated with thyroid disorder, this entity is less documented. We are reporting a case of HE in a 65 year old female presenting with sudden onset deep coma following an attack of mild fever and vomiting for two days. Patient was a known diabetic. Hypoglycemic coma, diabetic ketacidosis and hyperosmolar coma were excluded by laboratory investigations. High blood sugar was corrected with insulin. She had hyponatremia and hypokalemia which were corrected with electrolyte replacement. Liver function tests were normal, but serum ammonia was mildly raised. CSF study was normal. Despite correction of her metabolic derangements patient failed to regain her consciousness. CT scan of brain was normal. MRI of brain revealed diffuse brain atrophy. Patient's thyroid function tests were normal but anti-thyroid peroxidase (anti-TPO) antibody was highly raised. EEG showed diffuse slow wave pattern. Intravenous dexamethasone (24 mg/d) was started. Patient regained consciousness slowly over a period of one month. To reduce the toxicity of steroid, oral azathioprine 50 mg/day was added later with tapering of steroid dose. HE must be kept in mind in comatose patients when other metabolic, infective and structural neurological causes have been excluded. Proper and timely treatment can salvage the patient.

### Introduction

Hashimoto's encephalopathy (HE) is a rare relapsing neuroendocrine disorder. It is associated with Hashimoto's thyroiditis (HT) with high titers of anti-thyroid antibodies. The disorder is reported rarely in India as well as world literature.

### Case Report

A 65 year old Muslim female from Howrah district of West Bengal presented with sudden onset unconsciousness for two days with preceding history of mild fever with four episodes of vomiting two days back. She had no history of convulsion, focal loss of power of limbs, prior headache and visual disturbance. She was a known patient of hypertension and ischemic heart disease and was on multiple antihypertensive and anti-ischemic drug therapy (telmisartan, amlodipine, hydrochlorothiazide and aspirin). She had sleep disturbance for last one year, for which she was taking sedatives occasionally. She had mild loss of memory (especially recent memory) for the same period. She had no prior history of thyroid disorder or migraine. She was a known diabetic but was not getting any medication. Her family history was unremarkable.

On the day of admission, patient was completely comatose. Glasgow Coma Scale (GCS) score was 3/15. Her pulse rate was 82 / min, regular. Blood pressure was 156/90 mm of Hg. Respiratory rate was 22/min. Pallor, cyanosis and icterus were absent. On neurological examination, pupils were symmetrical and bilaterally reacting normally to light. There was no facial asymmetry. Light reflex, doll's eye reflex and gag reflex were normal. Neck rigidity was absent. Planter reflex was extensor in left side but flexor in right side. Deep tendon reflexes were preserved. There was no thyroid swelling in the neck. Examination of other systems revealed no abnormality.

Initial blood picture revealed hemoglobin 11.7 gm/ dl, total leucocyte count (TLC) 11300/ cu mm, with neutrophil 88 %,

lymphocyte 10 % and eosinophil 2%. ESR was 102 mm/hr. Biochemical tests revealed fasting blood sugar 216 mg/dl, serum urea 30mg/dl, creatinine 1mg/dl, sodium 120 mEq/l and potassium 2.1mEq/l. Hepatic profile was normal. Malaria parasite was not found. Widal test was negative. Urine analysis was normal. Chest X-ray revealed mild cardiomegaly. Electrocardiography showed antero-lateral ischemia. Ultrasonography of abdomen was normal. CT scan of brain revealed normal study. Cerebrospinal fluid (CSF) analysis showed clear fluid, 3 cells/ cu mm, all lymphocytes, sugar 97mg/dl, protein 29mg/dl. Gram stain and AFB stain of CSF revealed no micro-organism. In the mean time electrolyte abnormality was corrected with hypertonic saline and potassium chloride infusion. Antibiotic (Ceftriaxone) was given and repeat blood report on sixth day of admission revealed corrected biochemical profile (serum sodium 136mEq/l, potassium 3.6 mEq/l) but her TLC was 16100/cu mm with 80 % polymorphs. Antibiotic was changed to piperacillin-tazobactam and gentamicin. Gradually her blood count improved. But the patient's general condition did not improve, and her GCS score was still 3/15. This time planter reflex was bilaterally equivocal, other examination findings were similar to previous findings.

We started further investigations to find out the cause of encephalopathy. Serum ammonia was 89 µgm/dl (normal: 30 – 86 µgm/dl) and serum calcium was 8.9 mg/dl (normal 9–11 mg/dl). Thyroid profile revealed T<sub>3</sub> 0.8 ngm/ ml (normal 0.8-2.0 ngm/ ml), T<sub>4</sub> 6.15µgm/100 ml (normal 5.1-14.1 µgm/100ml) and TSH 3.3 µU/ml (normal 0.27-4.2 µU/ml). HIV serology was non reactive. Arterial Blood Gas analysis revealed no hypoxia. Magnetic resonance image (MRI) of brain revealed mild cerebral and cerebellar atrophic changes. Anti nuclear antibody was negative. Anti thyroid-peroxidase (ant-TPO) antibody was found positive with high titer (522 IU/ml, normal <34 IU/ml). Electro-encephalography (EEG) revealed characteristic diffuse slowing (without any focal epileptiform discharge) suggestive of encephalopathy (Figure 1). HE was suggested. Patient was started on intravenous dexamethasone (8 mg thrice daily) and she responded dramatically. Initially the eye opening returned and gradually motor response also improved. On fifth day of steroid therapy, spontaneous eye opening was present, on

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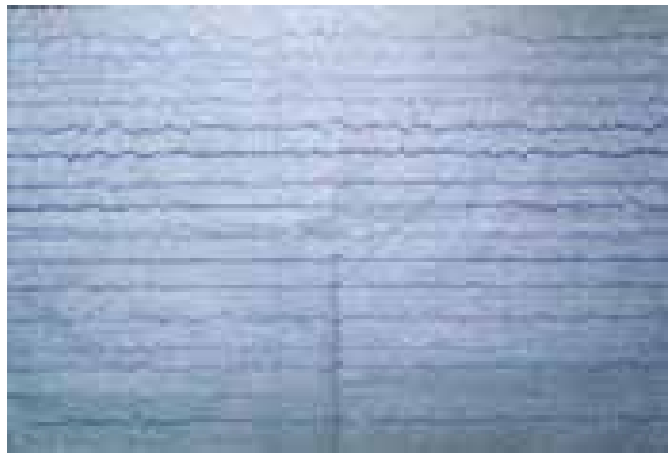


Fig. 1 : EEG showing diffuse slow wave pattern.

eightht day the motor function improved to withdrawal on pain stimulus and over-all GCS score improved to 10/15. Verbal response improved at the end and she became communicating at the end of fourth week. Because of worsening hyperglycemia we reduced the dose of steroid gradually and azathioprine 50 mg/ day was added. Patient was discharged with oral prednisolone 30 mg/ day and azathioprine 50 mg/day.

### Discussion

HE was first described by Brain et al in 1966.<sup>1</sup> Other names for the disorder include steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and nonvasculitic autoimmune meningoencephalitis (NAIM). Average age of onset for HE is 47 years (range 14 to 78 years) and majority of patients are women. Presence of goiter or a positive family history for thyroid dysfunction may be present. Two types of clinical presentation are commonly observed. First type is acute stroke-like presentation with transient focal neurologic deficits. It may be associated with speech problems (transient aphasia), focal or generalized seizures and status epilepticus. Second form is of insidious onset, progressing to dementia, psychosis and coma over several weeks without any focal neurologic deficits. Associated features include lack of concentration, sleep abnormalities, headaches, tremors, myoclonus and ataxia.

Differential diagnosis for the disorder includes Alzheimer’s disease, cerebrovascular accidents (CVA), Creutzfeldt-Jakob disease, HIV and other viral encephalitis.

Exact pathogenesis of HE is unknown. It is considered to be an autoimmune encephalopathy because of its higher prevalence in females, fluctuating course, association with other autoimmune disorders and improvement with corticosteroid therapy. It is associated with anti-TPO and anti-thyroglobulin (anti-Tg) antibodies. But the precise role of antithyroid antibodies is unclear. No shared antigen has been identified between thyroid gland and brain.<sup>2</sup> Antithyroid antibody titers also do not correlate with disease severity. Thyroiditis and encephalopathy may represent two concurrent autoimmune diseases. Presence of other autoantibodies, such as anti-parietal cell antibody or anti-intrinsic factor antibody, has also been reported in patients with HE. Alpha-enolase (isoenzyme of enolase, a glycolytic enzyme) has been identified as an auto-antigen for the disease.<sup>3</sup> Though it is considered as nonvasculitic disorder; lymphocytic vasculitis of cerebral venules has been documented. Table 1 shows some autoimmune encephalopathies including HE.

Table 1 : Causes of autoimmune encephalopathies

Diseases	Auto-antibodies	Clinical and laboratory features	Associated diseases
Hashimoto’s encephalopathy	Anti-TPO, anti-Tg, anti-alpha enolase	Dementia, coma, stroke like episode, myoclonus, seizure, slow wave activity in EEG, raised CSF protein	Hashimoto’s thyroiditis
Paraneoplastic limbic encephalitis (PLE)	Anti-Hu, anti-Ta, anti-Ma, anti-LGL1	Short-term memory impairment, complex partial seizures, psychiatric symptoms, temporal lobe abnormalities in MRI, epileptic activity in temporal lobes in EEG.	Small cell carcinoma (CA) of lung,, thymoma, breast or testicular CA, Hodgkin’s lymphoma
Non-paraneoplastic limbic encephalitis (NPLE)	Anti-voltage-gated potassium channels (VGKC), anti-onconeural antigen, anti-glutamate receptor, anti-novel cell membrane antigen (nCMAg)	Like PLE	Auto-immune thyroiditis, type 1 diabetes mellitus
Para-neoplastic cerebeller degeneration	Anti-Yo, anti-Ri, anti-Hu, anti-Tr antibodies	Vertigo, nystagmus, ataxia, tremor, dysarthria, sometime brainstem involvement with bulbar palsy	Ovarian CA, breast CA, small cell CA of lung, Hodgkin’s lymphoma
Morvan’s syndrome	Anti-VGKC	Behavioral changes, severe insomnia, confusion, amnesia, delusions, hallucinations, autonomic hyperactivity, neuromyotonia.	Myasthenia gravis, thymoma, small cell CA of lung, autoimmune thyroiditis
Stiff man syndrome	Anti-GAD, anti-pancreatic islet cell, anti-amphiphysin antibodies	Stiffness of axial and proximal limb muscles, sleep disturbance, depression	Diabetes, thyroiditis, breast CA, small cell CA of lung

Patients of HE may have subclinical or overt hypothyroidism, or patients may be euthyroid.<sup>4</sup> Hyperthyroidism may occasionally be seen. Liver enzymes and ESR may be elevated. Serum ammonia level may be elevated especially in presence of hypothyroidism.<sup>5</sup> Our patient had mild elevation of ammonia but thyroid function and liver function tests were normal.

CSF usually reveals elevated protein level with occasional mononuclear pleocytosis.<sup>6</sup> Oligoclonal bands are detected in some cases. Glucose level is normal. Normal CSF examination may be present in up to 25% of cases. EEG shows diffuse or generalised slowing or frontal intermittent rhythmic delta activity. Prominent triphasic waves, focal slowing, epileptiform abnormalities, photoparoxysmal and photomyogenic responses may be seen. EEG features usually revert to normal after steroid therapy. Anticonvulsant therapy does not improve epileptiform abnormalities and even worsen EEG features. MRI may be normal or reveal nonspecific findings, such as diffuse cerebral atrophy, focal mesiotemporal, basal ganglia or white matter abnormalities. Cerebral angiograms and Doppler ultrasound of cerebral vessels are usually normal. In single photon emission computed tomography (SPECT) focal and global hypoperfusion are common.

Patients with HE respond dramatically to steroid therapy. Initial dose varies between 50 mg and 150 mg of oral prednisolone daily, slowly tapered over weeks to months, depending on clinical course of the disease. High dose intravenous methylprednisolone (1 gm / day) may also be given for initial three to seven days, followed by oral prednisolone therapy. Rapid improvement can be observed within three days but significant clinical improvement may take average four to six weeks. Most patients stay in remission even after discontinuation of treatment. But treatment may be required lifelong. Azathioprine, cyclophosphamide, chloroquine, methotrexate may be used as steroid sparing agent. Periodic intravenous immune globulin and plasma exchange are other therapeutic options.<sup>7</sup>

Our patient had sudden onset unconsciousness with initial examination revealing focal neuro-deficit. CT scan of brain did not reveal any features of CVA. Infective causes were ruled out (malaria, enteric fever and meningo-encephalitis). Hyponatremia and hypokalemia (probably due to vomiting/hydrochlorothiazide) were corrected. MRI of brain excluded central pontine myelinolysis. During hospital stay she developed infection (high leucocyte count) which was also controlled with higher antibiotics. All the measures failed to improve consciousness of the patient. Presence of anti-TPO antibody in high titer with EEG finding clinched the diagnosis of HE.

Presence of high ESR also corroborated with the diagnosis. Dramatic response to steroid also suggested the autoimmune pathology.

## Conclusion

HE is probably under reported as a cause of coma. Very high level of awareness is needed to diagnose HE because of its rarity, variety of presentations and high chance of misdiagnosis. It is important to recognize HE as it is potentially reversible and treatment is cheaper. It should be suspected in any cause of coma or cognitive dysfunction which remains undetected despite through investigation or when any neuropsychiatric condition is not responding to conventional therapy especially in the setting of probable or known autoimmune thyroiditis. The disease is highly responsive to steroid. However, more common causes of encephalopathy, such as infections, electrolyte imbalance, toxins and neoplasms must be excluded before steroid therapy is initiated.

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