Hashimoto’s Encephalopathy: A Rare Cause of Delirium in the Post Operative Period

**Introduction:** Hashimoto’s encephalopathy (HE) is a rare neuroendocrine disorder associated with autoimmune thyroiditis. It was first described by Lord Brain in 1966 and initially it was associated with controversy. (1-3) The cause of the disorder is thought to be autoimmune. The clinical findings are variable and non-specific. We present a case of a patient who developed acute confusional state/delirium in the post operative period who had circulating antithyroid antibodies, mild thyroid disorder & partial response to steroids.

**Case presentation:** A 78 years old, female patient was admitted with history of pain & deformity of the left sided hip joint for 1 day. On perusal of her records, it was found that she had been operated for inter-trochanteric fracture of the left femur, about 2 weeks ago with a cemented bipolar prosthesis. She was a known hypertensive on treatment with amlodipin, telmisartan, hydrochlorothiazide, aspirin, & atorvastatin. The general examination was normal. The patient was conscious & oriented. On examination the hip joint was in flexion, addition & internal rotation and the prosthetic femoral head was palpable posteriorly. Movements of the left hip joint were painful & restricted. Suture line was healthy. She was diagnosed to have a dislocated femoral hemiartroplasty of the left side. Her investigations sent on admission revealed a haemoglobin of 7.1, a WBC count of 15000/cumm with Neutrophils-81%, Lymphocytes-14%, Eosinophils-2%, Monocytes-2% and a platelet count of 674000/cumm. She was posted for closed hip reduction under general anaesthesia. Postoperatively she continued to be delirious. She had an episode of accelerated hypertension & had Ventricular Premature Complexes on the cardiac monitor which were treated with Oxygen by mask & intravenous Nitroglycerin. She was diagnosed to have Delirium-mixed etiology and investigations were sent to search for the cause. Serum ammonia was normal. Thyroid function was normal though T3 & T4 were near the lower side. She continued to be delirious with episodes of shouting and needed sedation. Antibiotics were changed according to culture reports of pus from operated wound site and the urine. CT brain showed lacunar infarcts in the bilateral thalamus & right lentiform nucleus; a small infarct in the right cerebellar hemisphere; ischaemic changes in the bilateral periventricular white matter with age related diffuse cerebral & cerebellar atrophy with disproportionate prominence of ventricular system. The Ultrasonography of the thyroid gland showed enlarged left lobe with a nodule & coarse echotexture in both the lobes. The microsomal (TPO) antibody was positive with a titre of 714.7 (Negative < 5.61 U/ml). The thyroglobulin antibody (ATA) was positive with a titre of 94.33 (Negative < 4.11 U/ml). The patient started having fluidic intervals interspersed with periods of irritable behaviour & irrelevant talk. She would obey verbal orders intermittently. Her delirium decreased gradually. She had an episode of nosocomial UTI which was treated with appropriate antibiotics according to the culture report.

After 10 days of intravenous hydrocortisone, oral prednisone (30mg/day or 0.8mg/kg/day) was started; which was further tapered to 20mg/day after another 10 days. The patient was discharged from the hospital.

The cause of the delirium was initially thought to be: i) Hyponatremia –but encephalopathy persisted even after correction of the hyponatremia and when the sodium level was normal. ii) Septic encephalopathy – but encephalopathy persisted even after the infection (UTI) was treated.

A diagnosis of Hashimoto’s encephalopathy was put forward as it fulfilled the criteria-positive antithyroid antibodies, neu-
ological illness presenting with neuropsychiatric manifesta-
tion, exclusion of other causes of encephalopathy.

Discussion:
The thyroid gland affects the Central Nervous System (CNS) in a variety of disease processes. Cognitive impairment & depression in hypothyroidism & tremors in hyperthyroidism are some of the manifestations of this interaction between the thyroid gland & the CNS. Encephalopathy associated with autoimmune thyroid disorders is rare. It is known as Hashimoto’s encephalopathy (HE) is a rare disorder in this complex interplay between the thyroid gland & the CNS.

Steroid Responsive Encephalopathy with Autoimmune Thyroiditis (SREAT), Encephalopathy Associated with Autoimmune Thyroid Disease (EAATD), Nonvasculitic autoimmune inflammatory meningoencephalitis, Autoimmune encephalopathy-nonparaneoplastic are the other terms used for HE. (5,6,7) None of the terms are fully validated. HE implies a pathogenic role for the thyroid antibodies which has not been demonstrated. SREAT may come to imply that response to steroids is needed for diagnosis. But the response to steroids varies. The very presence of this entity has been questioned & debated. (2,3)

Hashimoto’s encephalopathy is a rare disease with an estimated prevalence of 2.1/100000. (8) The average age of patients with Hashimoto’s encephalopathy is in the mid 40s. In Ferracci’s case review, patients were aged from 8 to 86 years, and in Chong’s series of patients, age varied from 9 to 78 years. (4,8) Females are predominantly affected, with a female: male ratio of 4:1. Hashimoto’s encephalopathy is associated with the euthyroid state or with hypothyroidism or after the correction of hypothyroid state. Some patients are hyperthyroid or have Graves’ disease. A review of 85 patients had shown that 38% had normal thyroid function at presentation, 35% had subclinical hypothyroidism, 20% had overt hypothyroidism & 7% had hyperthyroidism. (4)

Pathological evaluations of HE cases showed lymphocytic vasculitis of venules and veins in the brainstem, as well as diffuse gliosis involving the gray matter more than white matter. (9,10)

The pathogenesis of Hashimoto’s encephalopathy is unknown. Several mechanisms, like cerebral autoimmune vasculitis with focal or global brain hypoperfusion, cerebral tissue-specific autoimmunity with or without demyelination, and neuronal dysfunction secondary to brain edema have been thought to be involved in the pathogenesis. (1,4,6-8,11,12) However, the pathogenesis is still not clear. Autoantibodies are thought to play a role in the pathogenesis. Ferracci’s case review, patients were aged from 8 to 86 years, and in Chong’s series of patients, age varied from 9 to 78 years. (4,8) Females are predominantly affected, with a female: male ratio of 4:1. Hashimoto’s encephalopathy is associated with the euthyroid state or with hypothyroidism or after the correction of hypothyroid state. Some patients are hyperthyroid or have Graves’ disease. A review of 85 patients had shown that 38% had normal thyroid function at presentation, 35% had subclinical hypothyroidism, 20% had overt hypothyroidism & 7% had hyperthyroidism. (4)

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The etiology of HE is believed to be autoimmune due to

i) its association with other autoimmune disorders (myasthenia gravis, glomerulonephritis, primary biliary cirrhosis, splenic atrophy, pernicious anemia, and rheumatoid arthritis), female predominance in the disease, and the presence of autoantibodies in the blood-brain barrier. (19)

ii) inflammatory findings in CSF, and

iii) typical response to treatment with steroids.

HE has been postulated to be an autoimmune cerebral vasculitis, (16-18) perhaps related to immune complex depositation, or it may be a recurrent form of acute disseminated encephalomyelitis (ADEM) with a presumed T-cell mediated lymphocytic vasculopathy accompanied by a breakdown of the blood-brain barrier. (19)

The first set of diagnostic criteria for HE was put forward by Peschen-Rosin and co-workers in 1999, consisting of unexplained episodes of relapsing myclon, generalized seizures, focal neurological deficits or psychiatric disorders, and at least 3 of the following: abnormal EEG, elevated thyroid antibodies, elevated CSF protein and/or oligoclonal bands, excellent response to steroids, unrevealing cerebral MRI. (20)

Our knowledge of almost all aspects of HE has evolved from those days; therefore, the following principles were included in the diagnostic criteria by majority of researchers: i) the elevated serum antithyroid antibodies;

ii) neurological illness mostly presented as clouding of consciousness, cognitive impairment, seizures, myoclonus, ataxia, psychiatric symptoms and focal neurological deficits;

iii) exclusion of infectious, toxic, metabolic, vascular or neoplastic etiologies. (4,5,21)

The clinical manifestations in a majority of patients of HE include cognitive impairment, transient aphasia, stroke-like episodes, tremor, myoclonus, ataxia, seizure, sleep disturbance and headache, with fluctuating symptoms. Up to 0.5 to 1% of patients show psychiatric features mostly resembling mood disorders or psychosis. Two subtypes are proposed: a vasculitic type with recurrent stroke-like episodes and a diffuse, progressive type with insidious onset but progressive deterioration of mental functions associated with cognitive & behavioural alterations. (4,5,16,21)

The cerebrospinal fluid shows an elevated concentration of protein and glucose concentration is usually normal. (19) Electroencephalogram shows nonspecific abnormalities with diffuse or generalized slowing of background activity; frontal intermittent rhythmic delta activity (FIRDA); focal spikes, sharp waves and transient epileptic activity. Photoparoxysmal and photomyogenic responses are also commonly seen. Most of these abnormalities resolve with treatment. (4) Magnetic resonance images are usually normal, but cerebral atrophy or nonspecific T2 signal abnormalities in subcortical white matter may be seen. (21,22) These findings may resolve with treatment. Single photon emission computed tomography (SPECT) studies show focal hypoperfusion in the majority of cases, global hypoperfusion in some, and normal findings in the rest of the patients. (4,12,23)

There are no clinical or investigative findings specific to Hashimoto encephalopathy. The diagnosis of Hashimoto’s encephalitis requires a high index of suspicion. Evidence of other autoimmune thyroiditis. The presence of goitre or a positive family history for thyroid dysfunction should prompt testing for thyroid function and antithyroid antibody titre. Additional studies such as EEG, MRI and lumbar puncture should be done for supporting evidence, but also to rule out other aetiologies of encephalopathy.

Treatment: Treatment of HE consists of

i) Steroids and/or

ii) Thyroid drugs (mostly levothyroxine), as well as

iii) Antiepileptic drugs for seizures.

In the treatment of initial or acute/subacute presentation of HE, prednisone in a high dose of 50–150 mg/day is given orally or methylprednisolone in a high dose of 1 g/day is given IV for 3–7 days. This usually results in marked improvement of neurological symptoms within 1 week (sometimes 4–6 weeks). Recurrences/relapses usually respond similarly. Prednisone is tapered over weeks to months, depending on the clinical response. Failure to respond or recurrences are treated with azathioprine, cyclophosphamide, plaqen...
methotrexate, intravenous immune globulin (IVIG), and plasma exchange either singly or in combinations. (20,24)

However, long-term treatment with steroids & immunosuppressive drugs is risky; it may result in serious side effects and requires frequent monitoring of clinical and laboratory parameters.

**Conclusion:**
Diagnosis of HE requires a high index of suspicion in cases which present with “investigation negative encephalopathy”/neuropsychiatric manifestation, especially in the presence of thyroid abnormalities. It is a very rare cause of delirium in the postoperative period and is potentially treatable. It should be kept in mind when evaluating a patient with neuropsychiatric abnormality in the postoperative period.

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