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Hashimoto's Encephalopathy: A rare Cause of Delirium in the Post Operative Period

KEYWORDS: Hashimoto's encephalopathy, delirium, postoperative-period.

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ABSTRACT *Introduction: Hashimoto's Encephalopathy is a rare, neuroendocrine disease, probably autoimmune in nature. It is seen in patients with high titre of antithyroid antibodies. Clinical manifestations include encephalopathic features like seizures, neuropsychiatric manifestations (like cognitive impairment, transient aphasia, ataxia, hallucinations & delusions), movement disorders (like myoclonus, tremors), sleep disturbances, headache, & coma.*
Case presentation: We present a case of a 78 years old, female, who presented with acute confusional state/ delirium in the postoperative period who had circulating antithyroid antibodies with a mild thyroid disorder and a partial response to steroids.
Conclusion: Hashimoto's Encephalopathy is a diagnosis of exclusion requiring a high index of suspicion. It is a potentially treatable cause of delirium.

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 amlodepin, telmisartan, hydrochlorozide, aspirin, & atorvastatin. The general examination was unremarkable except for her poor build. The systemic exam was normal. The patient was conscious & oriented. On examination the hip joint was in flexion, adduction & 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 hemiarthroplasty 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 reduction under general anaesthesia. Postoperatively she was given two units of packed cells and started on antibiotics and analgesics. Patient had irrelevant talk occasionally in the postoperative period and hence was referred to the psychiatrist and physician. She was found to be grossly oriented by the psychiatrist on first postoperative day. Mild hyponatremia was found which was corrected. Her RFT's/LFT's were normal. Her urine culture report showed growth of Klebsiella pneumonia which was sensitive to nitrofurantoin, which was started in the dose of 100mg bid. Her records of the previous admission were sought and they revealed that the patient had surgery for intertrochanteric fractureof the femur on the left side, about 2 weeks ago and the patient had delirium on the seventh postoperative day which had responded partially to olanzepine. The patient had been discharged after her orthopaedic problem was tackled.

On the fifth day after the present surgery, the patient had irrelevant talk, was disoriented and was not obeying verbal commands. The oral intake had reduced. Vital signs were normal except for mild fever and the general and systemic examination was normal. There was no focal neurodeficit. Hemoglobin had improved to 8.4mg% and the WBC count had decreased to 12300/cumm. The patient was shifted to the surgical ICU. The patient continued to be irritable, though conscious & oriented for the next 3-4 days. On the 9th postoperative day, she became drowsy. There was irrelevant talk and she was found spitting all the time & hallucinating. By the next day she became 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 thalami & right lentiform nucleus; a small infarct in the right cerebellar hemisphere; ischemic 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 < 4.11U/ml). The patient was started on steroids (Inj. Hydrocortisone 100 mg i.v.8H). The patient started having lucid 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 20 mg/ 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-

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rological illness presenting with neuropsychiatric manifestation, 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 auto- immune thyroiditis responsive to steroids, known as Hashimoto' 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 of HE. Anti-thyroid peroxidise antibody (TPO-Ab) are present in almost all HE cases. (13) But a direct causal relationship between thyroid antibodies and HE seems unlikely. Another auto antigen alpha- enolase (found in the thyroid & brain; concentrated in the endothelium) was found in some patients with HE, suggesting a pathogenic role.(14) A 36 kDa protein present in a soluble fraction in the cerebral cortex have been implied in the pathogenesis but has not been documented enough. Antineuronal autoantibodies have been found in the serum of patients with HE. (15) However, whether the presence of these autoantibodies is just an epiphenomenon or whether they are pathogenic is not yet definitely known.

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,
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 deposition; 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 myocloni, 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 a third 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 encephalopathy should be thought of when there is a neuropsychiatric condition that is not responding to conventional treatment, especially in the setting of probable or known 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, plaquenil,

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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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