

Hashimoto's Encephalopathy: Uncommon manifestation of a common disease

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ABSTRACT

Hashimoto's encephalopathy (HE) is a steroid-responsive encephalopathy usually seen in association with autoimmune thyroiditis independent of the thyroid status. However, its association with Graves' disease (GD) is rare. Here, we present a case of HE associated with GD. The patient presented with altered sensorium with varied psychiatric manifestations and went into rapid remission after steroid therapy. JMS: 2020; 23(2):43-46 DOI: <https://doi.org/10.33883/jms.v23i2.749>

INTRODUCTION

HE is a rare neurological condition characterized by highly variable neuropsychiatric manifestations, hightiters of anti-thyroid antibodies, and dramatic response to steroids. HE is a diagnosis of exclusion and can go unrecognized for a long time on account of highly varied nonspecific clinical manifestations. A high index of suspicion for HE, while evaluating a patient with a cognitive dysfunction of unexplained etiology and high titers of anti-thyroid antibodies is imperative for early recognition and appropriate management of the condition.

CASE REPORT

We present a case of a 27-year-old female patient, diagnosed as having GD previously but non-compliant to treatment, who was brought to our medical emergency with two-week complaints of altered behavior in the form of restlessness, agitated behavior, persistent desire to move around, irritability and irrelevant talking. Her family reported a one-month history of palpitations, heat intolerance associated with increased sweating and easy fatigability. There was no history of fever, abdominal pain, constipation, diarrhea,

headache, skin rashes, vomiting, blurring of vision, abnormal body movement, or sphincter incontinence. Her medical history revealed that she was on carbimazole for the last 3 years but had discontinued the medication of her own for the last four months.

On examination, she was conscious but disoriented with an anxious look, the pulse of 148 beats per minute with hyperdynamic circulation, respiratory rate of 14 per minute, the body temperature of 37.7 °C, blood pressure of 134/86 mm Hg, oxygen saturation of 98% on room air. The patient had a diffuse, non-tender goiter, and bilateral proptosis. Pemberton's sign was absent.

On admission, her Glasgow coma scale score fluctuated between E3V3M5 and E4V4M6. However, results from all motor and sensory examinations were normal except for brisk reflexes. Her neck was free with both Kernig's and

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Brudzenki's sign negative. Systemic examination was unremarkable. On Burch-wartofsky diagnostic point scale for thyroid storm, our patient scored 35. Clinical impression of thyrotoxicosis with impending thyroid storm with orbitopathy (Clinical activity score-CAS = 1) with acute psychosis was made.

Her baseline investigation including complete blood counts, renal and liver function tests, electrolytes, plasma glucose, and serum calcium levels was normal. The estimated serum osmolality was 280 milliosmoles per kilogram. ECG showed sinus tachycardia. Thyroid functions revealed raised T4- 23mcg/dl (4.87-11.72) and T3- 2.3ng/dl(0.6-1.6) levels with suppressed TSH- 0.001 μ IU/ml (0.35-4.90). TFT and anti-TPO were measured on the instrument Architect i2000SR (Abbott Diagnostics). Anti-thyroid peroxidase (anti-TPO) antibody and anti-thyroglobulin antibody (anti-TgAbs) titers were >972 IU/ml (0-9) and 37.5 IU/L (<1.75) respectively.

Considering the thyroid status of our patient, her clinical condition was assumed to be explained by a thyroid storm. The patient was initiated on propranolol 60 mg every 6 hours, propylthiouracil (PTU) 200mg 4hrly, and intravenous dexamethasone 2mg 6 hourly besides other supportive measures. The patient responded to treatment with clinical improvement in symptoms and signs including gradual improvement in mental status. However, the patient persisted with mild encephalopathy with occasional worsening in Glasgow Coma Score (GCS) score for which psychiatric and neurological opinion was sought, and investigations to rule out any organic cause were carried out. Blood culture and urine culture were negative at 48 h. Brain computed tomography (CT) and MRI was normal. Electroencephalogram (EEG) demonstrated nonspecific slow waves without spikes. Antinuclear antibody and anti-dsDNA were non-reactive. Cerebrospinal fluid (CSF) analysis was not done as patients and attendants didn't give consent for the same. As patients showed favorable clinical and biochemical response, attempts at the tapering of steroids resulted in worsening of encephalopathy which prompted us to look for an alternate diagnosis. The evidence of frank thyrotoxicosis with elevated anti-microsomal antibodies in the absence of any alternative neurological or infectious etiology that could account for her condition raised the suspicion of HE which was subsequently

established according to the criteria of Peschen-Rosin et al.⁽¹⁾

Steroid dose was hiked while the patient continued to receive PTU and beta-blockers. The patient responded to the treatment with improvement in encephalopathy. The patient was discharged on oral prednisolone 80mg in addition to anti-thyroid drugs. On subsequent OPD visit after 2 weeks, steroid dosage was tapered only to have a relapse of encephalopathy. The patient was again admitted and received pulse therapy with methylprednisolone 1gm for 3 successive days with a dramatic neuropsychiatric response. The patient was discharged on prednisolone 80 mg with gradual tapering on subsequent follow-up visits. At 4 months of follow up, her altered mental status has resolved completely without any long-term complications, and the patient continues to receive 40 mg prednisolone.

DISCUSSION

Hashimoto's encephalopathy is an extremely rare diagnosis first described by the brain et al. in 1966. It was initially thought to occur in association with Hashimoto's thyroiditis only, however; association with GD though rare has been described in the literature.⁽²⁾ It is also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) on account of the dramatic response to steroids and is characterized by relapsing encephalopathy in association with thyroid autoimmunity, with high titers of anti-thyroid antibodies.

Several other conditions grouped together as steroid-responsive encephalopathies, characterized by diffuse brain injury and responsiveness to corticosteroids and or immunosuppressants include limbic encephalitis, systemic lupus erythematosus encephalopathy, ANCA-related vasculitis encephalopathy, viral encephalitis and primary central nervous system lymphoma. However, the absence of autoimmune thyroiditis distinguishes these disorders from HE.

The criteria for the diagnosis of HE, as described by Peschen-Rosin et al⁽¹⁾ include unexplained episodes of relapsing neurologic symptoms and at least 3 of the following: abnormal EEG; positive anti-TPO antibody; elevated CSF protein; excellent response to steroids; and normal head MRI findings. Our patient fulfilled all the criteria for HE except for the absence of CSF analysis. Anti-NH2-terminal of α -enolase (NAE) antibody has been found

to have utility as a biomarker of HE, with a sensitivity and specificity of 50% and 91%, respectively.⁽³⁾

HE is relatively a rare condition with an estimated prevalence of 2.1/100,000, affecting females more than males in the ratio of 4:1.⁽⁴⁾ The mean age of onset is 44 years with 20% of cases presenting before the age of 18 years.

Clinical presentation of HE is quite heterogeneous and has been divided broadly into two subtypes including vasculitic subtype which presents as a stroke-like pattern of recurrent episodes of focal neurologic deficits with variable degrees of cognitive dysfunction and more common subtype, a diffuse, progressive pattern presenting as slowly progressive cognitive impairment with dementia, hallucinations, somnolence, or confusion⁽⁵⁾. Seizures, involuntary movements (tremors and myoclonus), pyramidal tract signs and spectrum of broad psychiatric manifestations including psychosis and depression (hallucinations, paranoid delusions) have also been found to be associated with diffuse subtype. However; the two types may overlap; particularly in the long-term course without treatment. The onset of symptoms is gradual and tends to occur over 1-12 months. Onset may go unnoticed by close associates of the patient. Sometimes the symptoms resolve themselves within days to weeks. Most of the time, HE may confuse clinicians due to the diffuse nature of symptoms. These manifestations of HE described in GD mirrors that occurring in Hashimoto's thyroiditis patients.

The pathogenesis of HE is not yet fully understood. Cerebral autoimmune vasculitis with focal or global brain hypoperfusion resulting from distorted microvasculature caused by immune-complex deposits, cerebral tissue-specific autoimmunity with or without demyelination, and neuronal dysfunction secondary to brain edema have been thought to be involved in the pathogenesis of HE.^(6,8) Role of other biochemical molecules including anti-thyroid antibodies and thyroid-stimulating hormone, in the pathogenesis of HE has been explored but no conclusive evidence of their involvement has been established so far. Elevated levels of antithyroid antibodies including anti-TPO and anti-Tg antibodies, a characteristic marker of HE, do not correlate with the severity of the disease and their possible role in the pathogenesis is not yet clear.⁽⁹⁾ Similarly, thyroid hormone abnormalities are common in HE however; the condition seems to be unrelated to thyroid

function.^(8,9) Despite the number of mechanisms forwarded to explain the pathogenesis of HE, the most frequently mentioned pathogenesis is the autoimmune mechanism, based on the elevated antibody background.

Treatment of HE ranges from monotherapy with glucocorticoids to various combinations of glucocorticoids with levothyroxine or immunosuppression. Excellent response to glucocorticoid therapy makes steroids the first-line of treatment⁽¹⁰⁾ with a 96% response rate.⁽⁴⁾ At present, there is no definite consensus on the recommended duration of steroid therapy in HE. The doses and schedules are extremely variable. In general initial treatment is usually with oral prednisone (50-150 mg/day) or high-dose IV methyl prednisolone (1 g/day) for 3-7 days. Immunosuppressant drugs i.e. azathioprine, cyclophosphamide, periodic intravenous immunoglobulin (IVIg) and plasma exchange are other modalities of management in case of non-responsiveness to first line treatment. However, use of IVIg as the first-line treatment in the presence of contra-indications to steroids has been described in the literature.⁽¹¹⁾ Similarly, thyroidectomy after a relapse of HE led to the improvement of the symptoms without any concomitant corticosteroid administration.⁽¹²⁾ Symptomatic treatment of seizures and of underlying thyroid disorder besides supportive measures help in the proper management of the disease. Our case highlights the importance of considering HE as a significant differential diagnosis in cases of unexplained neuropsychiatric manifestation especially in the patients of underlying thyroid disorders to avoid unnecessary delay in diagnosis and subsequent unwarranted complications.

CONCLUSION

HE is a reversible form of encephalopathy with varied non-specific clinical manifestations resulting in delayed diagnosis and thus inappropriate management. Association with GD though rare has been described in the literature as was demonstrated in our case. A high index of suspicion in unexplained cases of encephalopathy and determination of antithyroid antibodies along with anti- α enolase in such patients may help in early diagnosis and prompt management.

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