Case report:

Hashimoto's Encephalopathy Presenting with Acute Behavioral Disturbances: A Case Report

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Abstract:

Hashimoto's encephalopathy (HE) is a rare and poorly understood neuropsychiatric illness of presumed autoimmune origin, with elevated titres of anti-thyroid antibodies. Its clinical presentation is highly variable that mimic a variety of neurologic and/or psychiatric disorders. Clinical presentation often suggests an infectious etiology which often leads to a mistaken diagnosis. We present the case of 35 year-old female who presented with acute onset behavioural disturbance of one day duration. On examination she was unkempt, emotionally labile, appeared withdrawn and unable to respond to questions. She had no focal neurological deficits. CNS infection was suspected and lumbar puncture was suggested, which the family members refused.She was empirically treated with intravenous acyclovir and ceftriaxone.Metabolic disorder, infectious and toxic issues were ruled out through laboratory testing.In view of her previous history of hyperthyroidism, suspicion of Hashimoto encephalopathy arose.The diagnosis was supported by the elevated level of anti-thyroglobulin (TG) antibody.We report this case to increase its awareness as it is one of the few treatable and easily reversible causes of acute encephalopathy. It should be considered in the differential diagnoses in any patient who presents with acute behavioural disturbance and has concurrent thyroid disorder.

Keywords: Hashimoto encephalopathy, autoimmune encephalopathy, anti-thyroid peroxidase antibody, steroids.

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Introduction:

Hashimoto encephalopathy (HE) is a rare condition characterized by encephalitis associated with elevated antithyroid antibodies,anti-thyroid-peroxidase antibodies (TPOAb) and anti-thyroglobulin antibody (TGAb).[1] It can affect any age group but is more common among females with a ratio of 5:1.[2,3] Its clinical presentation is frequently insidious but can be acute as stroke-like, seizures, or a behavioural disturbance as reported in our case.[4-9] It presents a diagnostic challenge since the clinical manifestations of the disease often suggests an infectious etiology. Its pathophysiology remains unclear, but the majority of evidence suggests it to be an autoimmune disorder because of its association with other autoimmune disorders and dramatic response to treatment with steroids.[1, 2] The role of thyroid antibodies in its pathogenesis is indecisive, as there is no correlation between the severity of symptoms and the antibody titre. Yet, normalization of these titres after clinical recovery has been reported by some authors.[8,9] We report this case due to her atypical presentation and to consider it among the differential diagnoses.

Case Presentation:

A 35 year-old lady was brought to our clinic by the family members due to acute behavioural disturbance of one day duration. She appeared withdrawn with no interest in her surroundings or performing her routine chores. She was unkempt, acting childishly and frequent a wakening during sleep. She had no known similar illness in the past nor did any family member have psychiatric disease. On examination, she was irritable, appeared withdrawn, and responded inappropriately to questions. She could not recall her spouse's or son's name and reported of having paranoid ideation in ward. She had no neurological deficit and other systemic examination was within

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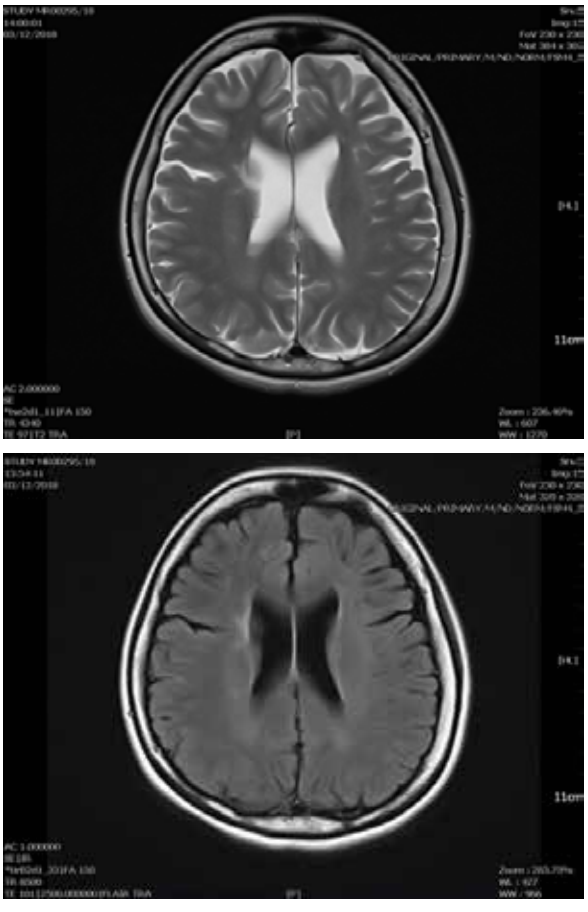
normal limits. She had two episodes of fever in the ward. Her chest radiograph, urine analysis, abdominal ultrasonography were unremarkable. Her white cells count was normal and C-reactive protein level was also normal. Lumbar puncture was suggested to which family members refused despite frequent medical explanations by the physicians. Magnetic Resonance Imaging (MRI) of the brain showed T2 hyper intensity at the periventricular white matter adjacent to the lateral wall of right lateral ventricle and at the lateral wall of third ventricle bilaterally. However, these were of indeterminate clinical significance and there was no evidence of abnormal enhancement pattern. Her electroencephalogram (EEG) demonstrated loss of posterior dominant rhythm with a background of predominantly beta waves. She was empirically treated for meningoencephalitis with ceftriaxone and acyclovir though the evidence did not point towards an infective cause. The other differential diagnosis considered at that time was autoimmune



encephalitis.

Figure 1: Brain MRI T2-weighted (above) and FLAIR (below) scans.

She had a history of hyperthyroidism with the initial presentation as thyroid storm in 2011; when her anti-microsomal antibody titre was 1:1600. She was treated with propylthiouracil which was later changed to carbimazole. Her medication was stopped in 2013 as she was clinically and biochemically euthyroid. A year later, she presented with altered behaviour of one-day duration,two days after delivering her first child. Her thyroid-stimulating hormone (TSH) and thyroxine (T4) levels were 0.882 mIU/L and 16.47 µg/dL respectively (Reference range:TSH 0.38-5.33 mIU/L, T4 4.6-12 µg/dL).In August 2016, she presented again to the outpatient clinic with hyperthyroid symptoms. Her TSH level was suppressed with a T4 level of 100 µg/dL. Carbimazole treatment was reinitiated and the dose was tapered down slowly till 5mg every other day. Her latest thyroid function test in March 2018 was TSH 1.37 and T4 19.46.

Suspicion of Hashimoto encephalopathy arose in view of her previous history of hyperthyroidism and positive anti-microsomal antibody (1:1600). Serology for N-methyl-D-aspartate Receptor (NMDAR) antibody was negative. Her anti-thyroglobulin antibody (TGAb) level came back as high at 392 IU/mL while thyroid peroxidase (TPOAb) and thyrotropin receptor antibodies levels were normal; 58.50 IU/mL and 1.0 IU/mL respectively.These findings further supported the diagnosis of Hashimoto encephalopathy.

Our patient had spikes of temperature during her hospital admission. We decided not to initiate any steroid therapy as the possibility of infective cause of encephalitis could not be completely ruled out.We took 'wait and watch' caution prior to the initiation of steroid therapy. After 10 days of close monitoring and diagnostic work up, she showed clinical improvement. She was able to engage in a simple conversation though briefly with more frequent ambulation in the ward. She was then discharged on her usual medication of carbimazole 5mg every other day with the plan of starting her on corticosteroid therapy during the next follow up visit. We reviewed her again in the neurology clinic after three months. She had marked clinical improvement of being back to her usual self,despite not being on steroid therapy.

Discussion:

Hashimoto encephalopathy is an uncommon neurological syndrome, associated with autoimmune thyroiditis, which was first described in 1966.[10]As per a hospital-based epidemiologic study its prevalence is estimated to be 2.1 per 100 000 and it is more common among females[3,5] There are many uncertainties still remain about this condition. It has been proposed that it might be caused by immune complex deposition, vasculitis, or other inflammatory condition.[9,11] As per post-mortem studies of some individuals, lymphocytic infiltration in the brain grey matter or brainstem

was reported.[12,13]An auto antibody against the amino terminal end of the enzyme α-enolase, an antigen of the thyroid and the brain, has also been identified which may be diagnostic.[9,14] There is much evidence to suggest that elevated serum levels of antithyroid antibodies are important in its diagnosis. However, thyroid status in these patients varies greatly; as 18% to 45% of them are euthyroid.[9] The relationship between HE and Hashimoto thyroiditis is controversial. It is possible that some of these patients develop HE without a concomitant clinical thyroid disease because asymptomatic thyroid autoimmunity is frequent in these patients.[11,16]

The diagnosis of HE should be considered among patients presenting acute onset neuro-behavioural manifestations, particularly together with the presence of high thyroid antibody levels.[15] High titres of anti-TPO-Ab are found in nearly 80-100% of cases and it is considered to be the hallmark of this disease.[17-20] The presence of thyroid antibodies in the cerebrospinal fluid (CSF) have also been reported with unclear sensitivity and specificity.[15] CSF analysis is abnormal in about 80% of patients mostly demonstrating elevated total protein (75%), a lymphocytic pleocytosis with normal sugar concentration.[21] Nonspecific abnormalities in EEG have been reported in 90% to 98% of the patients.[9] Clinical assessment, blood and cerebrospinal fluid (CSF) examination, neuroimaging studies, and electroencephalography (EEG) are essential to establish a diagnosis and exclude other causes of encephalopathy. The clinical manifestations are variable and can be non-specific.[9] Since its first described in 1966,[10] various presentations have been recognized; 25% of patients present acute-onset stroke-like episodes, seizures or psychosis, while about 75% of patients present a slow, diffuse, and progressive decline of cognitive function.[9] Here in, we present a rare case of acute behavioural disturbance with high level of anti-thyroglobulin (TG) antibody. The final diagnosis of HE was established after excluding other causes of encephalopathy.

Neuroimaging findings:MRI brain findings of HE vary from normal, diffuse cortical atrophy or localised increased T2 signal, including ischemic lesions, white matter demyelination, and focal vasogenic oedema.[22-24] Although the findings may be normal or nonspecific, MRI is important to exclude other possible diagnostic possibilities.

The course of HE ranges from self-limiting, relapsing-remitting to progressive disease.[2,25]About 25% of patients have residual cognitive impairment secondary to the long-standing, untreated disease.[15] There are no accepted guidelines for its treatment. Most patients respond to corticosteroids, but the optimal dose and duration of steroid therapy have not been defined.[26,27] Many patients recover spontaneously. Many of treated patients who were followed up to several years remained disease free despite discontinuation of steroid therapy.[21]

The clinical presentation of our patient with acute encephalopathy, elevated serumanti-TG antibody and normal findings on MRI of the brain concluded the diagnosis of HE. She had a spontaneous, progressive clinical recovery without steroids.

Conclusion:

HE also known as steroid-responsive encephalopathy is believed to be autoimmune in origin with myriad of clinical presentations. It should be considered in all patients who present acute or sub-acute unexplained encephalopathy, particularly with current or previous thyroid dysfunction.

Conflict of interest:

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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