NEURO-PSYCHIATRIC MANIFESTATIONS OF HASHIMOTO THYROIDITIS; A CASE SERIES

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ABSTRACT

Hashimoto Encephalopathy (HE) or Steroid-Responsive Encephalopathy associated with Autoimmune Thyroiditis (SREAT) is a rare autoimmune disease characterized by encephalopathy and elevated anti-thyroid antibodies in the absence of a central nervous system (CNS) infection, tumour or stroke. Clinical presentation of HE includes amnestic syndrome, seizures including status epilepticus, ataxia, myoclonus and psychiatric manifestations like depression, mania, psychosis and hallucinations. A good clinical response can be achieved with corticosteroid therapy so early diagnosis and treatment is very beneficial for patients. Here we report four patients with Hashimoto encephalopathy who had neuro-psychiatric manifestations of the disease and had detectable thyroid specific antibodies in the serum (thyroperoxidase antibody formerly known as anti-microsomal antibody). All these patients showed an objectively significant response to methylprednisolone treatment.

Keywords: Autoimmune disease, Encephalitis, Hashimoto thyroiditis.

INTRODUCTION

Hashimoto thyroiditis is an organ-specific autoimmune thyroid disease characterized by diffuse goitre with lymphocytic infiltration and the presence of thyroid-specific autoantibodies. It was first described by Hakaru Hashimoto in 1912. Today, it is one of the most widespread thyroid disorders. The incidence is 0.3-1.5 cases per 1000 population per year[1]. In 1966, Brain and co-workers documented a patient with Hashimoto's disease and encephalopathy[2]. Hashimoto Encephalopathy (HE) is a rare, autoimmune disease characterized by encephalopathy and elevated anti-thyroid antibodies in the absence of a central nervous system (CNS) infection, tumour or stroke. The inflammatory findings in cerebrospinal fluid (CSF) and a very good response to treatment with steroids support the autoimmune aetiology of the disease. Overt or subclinical thyroid disease, usually hypothyroidism, occurs in most of the cases of HE. By definition, patients develop encephalopathy, which can be associated with seizures, myoclonus, hallucinations, and stroke-like episodes with normal or non-specific CSF and brain MRI abnormalities[3].

We report a series of cases of HE that were evaluated, diagnosed and managed at our hospital. The table summarizes the clinical, biochemical and radiological findings in suspected HE patients in this case series.

Case-1

A 55 year old lady gave a history of low mood, band like headaches and insomnia for the last three years. She was being managed with antidepressants in varying doses over the past two years without much relief. Psychiatric evaluation revealed impulsivity, poor coping, repressed anger and impaired perception. Neurological examination showed mild behavioral-cognitive abnormality. A small thyroid swelling was observed on systemic examination. Serum TSH was 6.56 mlU/l (ref range 0.4 - 4.0) and T4 was low. Anti-thyroperoxidase (TPO) antibodies were positive. Fine Needle Aspiration Cytology (FNAC) of the thyroid nodule showed adeno-

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matous colloid goiter. She was commenced on thyroxine replacement therapy and was reassessed after three months. At that time her Thyroid Function Tests (TFTs) were normal but symptoms persisted. She was continued on thyroxine with a plan to review after six months. Despite continued thyroxine replacement therapy and normal TFTs, her clinical condition did not improve. A possibility of HE was considered, keeping in mind the poor clinical response to the treatment. Magnetic Resonance Imaging (MRI) brain revealed diffuse increased signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the cerebral white matter. RA factor, Anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic auto anti-bodies (ANCA) and serum Venereal Diseases Research Laboratories (VDRL) were negative.

Case-2

A 32 year old man presented with right hemiparesis of sudden onset. He underwent CT scan brain which was normal but MRI brain performed later showed infarct in mid brain and pons. The patient was thoroughly investigated as a case of stroke in young. His thrombophilia screening was negative. Rheumatoid arthritis (RA) factor, antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), serum Venereal Diseases Research Laboratories (VDRL), anti-dsDNA and blood complete picture were also normal. Clinical examination revealed homogenous thyroid swelling which was confirmed on ultrasonography. Thyroid Function Tests (TFT's) were normal but anti-thyropero-xidase (TPO) antibodies were found to be present.

Case-3

A 24 year old man reported with brief history of catatonic posturing and cognitive decline. Psychiatric evaluation established some mania like features associated with disorientation in time and place. There was no history of any drugs or substance abuse. Antipsychotics worsened the condition and neurological evaluation was sought. Clinical examination revealed mini-mental state examination (MMSE) score was 17 which was consistent with moderate cognitive decline. Complete blood count, D-dimers, serum creatine kinase, liver function tests (LFTs), serum cerulo-plasmin level, ANA, ANCA, Human Immuno-deficiency virus (HIV) serology, anti-dsDNA, were all normal. Thyroid Function Tests (TFTs) showed raised T4 and low thyroid stimulating hormone (TSH) level (0.3 mIU/L). MRI brain showed some nonspecific deep white matter signals. CSF examination showed normal cell count and glucose level but mildly raised proteins. Anti-thyroglobulin antibodies were positive.

Case-4

A 35 year old male presented with two months history of uncontrolled seizures despite being on combined anti-epileptics. Neuro-psychiatric testing revealed impairment of visual retention and motor functioning and poor inhibitory control of frontal lobe. Bilateral clonus and brisk deep tendon reflexes warranted neuro-imaging. MRI Brain established multiple white matter hyper intensities in fronto-parietal area. Electroencephalography (EEG) was inconclusive. Cerebrospinal fluid (CSF) examination, Thyroid Function Tests (TFTs), Liver Function Tests (LFTs), RFTs, seum calcium, magnesium, phosphate, VDRL, lipid profile, folate and vitamin B12 levels were all normal. Anti-thyroid microsomal antibodies were found to be positive.

Management of Cases

All these cases were treated as indoor patients in Intensive Care Unit (ICU) of our hospital. The patient with cerebral infarct (case 2) was also managed with anti-platelets and other supportive care as required. The blood glucose level was tightly controlled. Once the diagnosis of Hashimoto Encephalopathy (HE) was suspected based on the positive antibody results, all these patients were also given methylprednisolone 1g/day for 5 days with a plan to taper off steroids gradually. The patients were given ulcer and bone prophylaxis as well. All these patients had a

dramatic response with the steroid therapy started showing signs of improvement. They were subsequently discharged with tapering regime of oral prednisolone and all have reported for follow up with good recovery.

DISCUSSION

Neurologists are often consulted to evaluate, diagnose and treat patients with acute or subacute encephalopathy. The differential diagnosis for encephalopathy is wide, but the clinical features and findings on blood, cerebrospinal fluid (CSF), electroencephalography (EEG), and neuroimaging studies often (but not always) lead to an accurate diagnosis. Once infectious causes are excluded, an autoimmune or inflammatory process may be suspected on the basis of inflammatory and autoimmune markers in the serum and CSF as well as meningeal and parenchymal abnormalities on magnetic resonance imaging (MRI) of the brain. Idiopathic autoimmune encephalopathy is also often defined on the basis of a clinical response to steroids[4].

HE is a rare disease and occurs predominantly in females, with a male to female ratio of approximately 1:5. The mean age of onset is between 45 and 55 years. Most patients with HE are usually suffering from Hashimotos thyroiditis, although a small number have Graves' disease[5]. The pathogenesis of HE is not clear. Some autopsy reports have observed that HE may be associated with lymphocytic infiltration and vasculitis in the brainstem or brain grey matter. Various etiological mechanisms such as autoimmune vasculitis, auto anti bodies directed against brain-thyroid antigens, encephalomyelitis-associated demyelination, global cerebral hypo perfusion, a direct toxic effect of thyrotropin-releasing hormone, and neuronal dysfunction due to brain edema have been presented as the underlying pathogenesis of HE[6]. Graus et al, have laid down a diagnostic criteria for HE. According to them use of the term HE should be used only when rigorous clinical assessment and comprehensive investigations exclude other potential causes of encephalopathy[7]. They described that diagnosis

Table: Clinical, biochemical and radiological finding in four cases of Hashimoto's Encephalopathy.

Feature	Case 1	Case 2	Case 3	Case 4
Clinical features	Depressive symptoms	Stroke like episode	Catatonia and mania	Seizures
Antimicrosomal Antibodies	Positive	Positive	Positive	Positive
ANA	Negative	Negative	Negative	Negative
RA factor	Negative	Negative	Negative	Negative
LFT's	Normal	Normal	Normal	Normal
T4	Low	Normal	Raised	Normal
TSH (mIU/L)	6.56	Normal	0.3	Normal
CSF Findings	Normal	Normal	Normal	Mildly elevated proteins with normal cell count
EEG (Electroencephalography)	Not done	Not done	Moderate diffuse cortical dysfunction	Inconclusive
MRI Brain	Increased signal intensity on T2 and FLAIR	Infarct in mid brain and pons	Nonspecific white matter signals	Multiple white matter hyper intensities in fronto-parietal area

of HE can be made when all six of the following criteria have been met:

- Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes.
- Subclinical or mild overt thyroid disease (usually hypothyroidism).
- Brain MRI normal or with non-specific abnormalities.
- Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies (There is no disease-specific cut-off value for these antibodies).
- Absence of well characterized neuronal antibodies in serum and CSF.
- Reasonable exclusion of alternative causes.

The clinical presentations of HE include encephalopathy, stroke like episodes, seizures, status epilepticus, myoclonus, visual hallucinations and paranoid ideations. In our case series patients had varied presentations including the clinical features mentioned above. But we also describe one patient (case 2) who had findings of infarct in midbrain and pons on neuroimaging but also had positive thyroid anti-microsomal antibodies and he showed a good response to the steroid therapy in terms of improvement in the muscle power. The thyroid function of patients with HE may manifest as subclinical hypothyroidism, euthyroidism, overt hypothyroidism, or less frequently, hyper-thyroidism[8]. Various neuro imaging features have been reported in HE. MRI may show normal, diffuse cortical atrophy or localized increased T2 signal. MRI is also used to differentiate HE from acute disseminated encephalomyelitis (ADEM). In this study, most patients had normal MRI or nonspecific abnormalities. Instead of providing direct evidence for diagnosis, neuroimaging studies in HE patients are more important for exclusion of other possible neurological disorders[9]. Steroid therapy has been shown to be very effective for the treatment of HE in many studies[4,6,10]. Consequently the disorder is deemed immune mediated due to excellent response to the steroid therapy despite the unclear physiopathology. Different regimens of corticosteroid treatment have been used in various studies. According to the literature, methylprednisolone 1000 mg as an intravenous infusion for 3-5 days is mostly recommended. For patients with a recurrence of the disease, corticosteroids are still effective. Oral prednisone (1 mg/kg/day) after initial high-dose intra-venous corticosteroid, can be considered for patients showing frequent recurrence, followed by progressive tapering until the drug is withdrawn after 6-12 months, depending on clinical improvement and responsiveness However, several cases have been reported where the patients have not responded to steroids and alternative drugs have been tried. Some studies have suggested the role of intravenous immunoglobulins in the management of this condition. Drugs like aspirin, azathioprine, mycophenolate mofetil have also been tried in this setting and found to be variously successful. No long-term data exists on the effectiveness of these drugs in maintaining remission in these patients[11]. Spiegel et al used azathioprine after induction of remission with intravenous methylprednisolone and reported a remission period that lasted 5 months[12].

Many case reports, small series, and literature reviews have characterized this entity further. Nevertheless, many uncertainties regarding this disease persist, including the spectrum of clinical findings, associated laboratory and radiologic findings, the diagnostic significance of the quantitative level of TPO antibody, the criteria required for diagnosis, the appropriate terms for the condition, and the outcome of steroid treatment[4]. Thyroid antibodies are not specific for HE because they are present in up to 13% of healthy individuals and patients with other autoimmune disorders. There is no causal relationship between level of anti-thyroid antibodies and development of encephalopathy[13]. But encephalopathy in the presence of thyroid antibodies in patients with neuro-psychiatric symptoms and subsequent excellent response to steroids therapy is unlikely to be due to chance only. Further studies and case reports may help

ascertaining the existence, exact nature and pathogenesis of the syndrome. However, an important point to remember is that this disease is very often misdiagnosed and labelled as viral encephalitis (25%), degenerative dementia (20%) and crentzfeldt Jacob disease (15%)[14].

CONCLUSION

In conclusion, HE has a wide range of clinical, laboratory, and radiologic findings. All patients with an unexplained acute/subacute/ chronic encephalo-pathy should be screened for HE as the therapeutic response is excellent. The incidence is probably underestimated because of the low overall awareness about the disease. Hashimoto thyroiditis is not as uncommon in our setup as is presumed on the basis of western research and literature. In our geographic settings, it, usually, afflicts young age group from both genders. The common presentation seen in this case series, is with neuro-psychiatric symptoms. It is therefore recommended that young people with neuro-psychiatric presentations should be evaluated for Hashimoto thyroiditis.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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