

EVALUATION OF CLINICAL SYMPTOMATOLOGY IN PATIENTS WITH HASHIMOTO'S ENCEPHALOPATHY AND ASSOCIATION WITH UNDERLING THYROID DISEASE

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ABSTRACT

Objective: To determine the frequency of different neurological features in Hashimoto's encephalopathy and to evaluate association with underlying disease.

Study Design: Cross sectional study.

Place and Duration of Study: A Three-year study from Jul 2015 to Jul 2018. Conducted in Pak Emirates Military Hospital (PEMH) Rawalpindi.

Methodology: This study is comprised of diagnosed patients of Hashimoto's encephalopathy. These patients fulfilled the diagnostic criteria. Any case with metabolic, toxic, vascular or malignant etiology of encephalopathy was excluded. Data regarding clinical symptoms particularly neurological and neuropsychiatric features, of diagnosed cases with Hashimoto's encephalopathy was obtained from hospital record. Moreover, data about antithyroid antibody type, cerebrospinal fluid analysis, and MRI findings was gathered. Gender and age of the patients were also mentioned. Data was gathered on proforma by a resident doctor. The analysis was carried out using SPSS 20. Results were mentioned in the form of the mean for variables like age and percentage and frequencies for categorical variables.

Results: Out of 13 patients, 5 (38.5%) were male and 8 (61.5%) were females. Majority of the patients 8 (61.5%) were euthyroid. Neuropsychiatric symptoms were present in all 13 patients with depression present in 8 (61.5%) cases, while 5 (38.4%) had hallucinations. Most cases were cognitively normal 8 (61.5%), while rest had mild impairment. No neurological manifestation was found significantly more common in any of the thyroid disease. Migraine-like headaches was present in 4 (30.7%) cases while epileptic seizures were present in 8 (61.5%) patients with GTCS the most common seizures type in 3 (23%) patients. Only three patient had MRI changes including temporal and hippocampal T2WI hyperintensities.

Conclusion: If etiological factors for encephalopathy has been ruled out in the presence of underlying thyroid disease with a short history of symptoms, one should have a low threshold for treatment with the steroid to observe for the response.

Keywords: Hashimoto's encephalopathy, Non-vasculitic autoimmune inflammatory meningoencephalitis (NAIM), Steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT).

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INTRODUCTION

SREAT which stands for Steroid-Responsive Encephalopathy with autoimmune thyroiditis is the other name given to Hashimoto's encephalopathy (HE). Although all types of thyroid diseases can occur in the context of HE most importantly thyroiditis, particularly autoimmune type is considered to be associated with SREAT¹⁻⁴.

This specific encephalopathy is a less common complicated neurological syndrome with the wide variety of symptoms. It is often misdiagnosed due to poor knowledge and understanding of doctors of this condition. Description of the first case of HE was mentioned in 1966 by Lord Brain¹. However, initial criteria used for diagnosis of HE was proposed in 1999 by Peschen-Rosin and colleagues². This initial criterion for HE included recurrent experiences of seizures, neuropsychiatric syndrome, focal neurological deficit and at least three of the followings; elevated thyroid antibodies elevated CSF proteins

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and/or IgG Index, abnormal EEG, unremarkable MRI brain and response to steroids^{5,6}.

The HE in third world countries like Pakistan is still a diagnostic dilemma firstly because of its variable manifestations and secondly due to the absence of a specific diagnostic test. Recently the medical community is getting familiar with the diagnosis of HE due to its treatability. Although Autoantibodies against alpha-enolase particularly the amino terminal of enolase are considered important and vital diagnostic marker for encephalopathy associated with thyroid conditions³. The facilities for the detection of these specific anti-enolase autoantibodies are present in developed countries but often these tests are not carried out in poor countries like Pakistan due to limited resources and non-availability of these facilities. In such scenario, the clinical understanding of the condition is of utmost importance.

The understanding of the clinical spectrum of neurological features of HE will help in early diagnosis and management of this treatable condition in resource-constrained regions like Pakistan. Previously few case reports and little research^{4,5} has been published from Pakistan and perhaps this is the first study of its type demonstrating the various clinical aspect of HE in Pakistan over the period of three years.

METHODOLOGY

This was cross sectional study carried out in the department of Neurology, Pak Emirates Military Hospital Rawalpindi, Pakistan and comprised of patients, diagnosed with Hashimoto's Encephalopathy. After approval from the Institutional Ethics Committee, records of all patients who were diagnosed with HE over the period of three years from July 2015 to July 2018 were obtained. The sample size was calculated by using WHO calculator considering the prevalence of HE 2% as mentioned in the literature⁶. Non probability purposive sampling technique was used for data collection considering the rare nature of disease. A diagnosed case of HE was

defined according to the criteria mentioned below.

1: Encephalopathy which is demonstrated by altered consciousness, cognitive impairment, seizures or neuropsychiatric symptoms.

2: Raised levels of anti-thyroid antibodies in the serum.

3: Raised cerebrospinal fluid proteins and/or CSF IgG Index

4: Absence of alternative cause of encephalopathy including vascular, metabolic, toxic, infectious, and neoplastic as a reason for the neurological manifestations, either manifested in blood/serum, urine, cerebrospinal (CSF) fluid and neuroimaging.

5: Lastly response to the steroids.

Any patient with alternative etiology like metabolic, toxic, infectious, vascular or malignancies as a cause of encephalopathy was excluded from this study group. The cases were analyzed for clinical symptomatology regarding the type of neurological and neuropsychiatric symptoms, consciousness and cognitive impairment along with primary thyroid disease. Consciousness and cognitive impairment were assessed with Glasgow Coma Scale (GCS) and Mini-Mental State Examination (MMSE) respectively. Moreover, data such as antithyroid antibody titer, cerebrospinal fluid analysis, and magnetic resonance imaging findings. Demographic data, like age and gender of the patients, was also gathered from hospital records. Data was gathered on proforma that was completed by a resident doctor. The analysis was carried out using the statistical package for social sciences (SPSS) 20.

Results for the continuous variables like patients age were computed as the mean \pm standard deviation (SD). However categorical data such as the patient's gender, the pattern of neurological features and neuropsychiatric symptoms, types of seizures, MRI abnormalities, MMSE and GCS were expressed in the form of percentages and frequencies.

RESULTS

Out of 13 patients, 5 (38.5%) were male and 8 (61.5%) were females. The overall mean age was 44.3 ± 19.2 years. Majority of the patients 8 (61.5%) were euthyroid at time of diagnosis of Hashimoto's encephalopathy (table-I). Out of 13 patients, 4 (30.8%) were hypothyroid and 1 (7.7%) patient was diagnosed with hyperthyroidism (Graves' disease). Most of the patients 12 (92.3%) had multiple manifestations (either neurological, psychiatric or both), while only one patient had single manifestation.

Neuropsychiatric symptoms were present in all 13 patients but Overall 11 (84.6%) patients

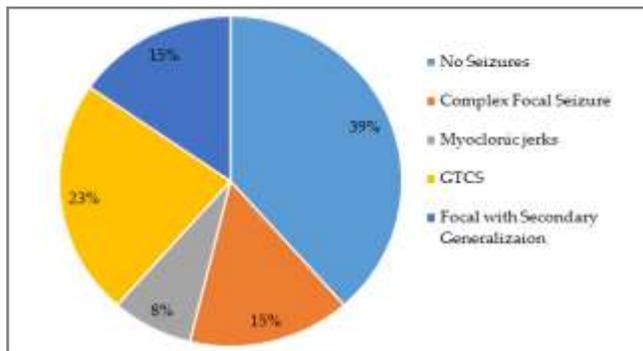


Figure: Pattern of different seizure types in Hashimoto's encephalopathy.

had only one neuropsychiatric symptom, while 2 (15.4%) patients had 2 neuropsychiatric symptoms. Depression was present in 8 (61.5%) cases, while 5 (38.4%) patients had visual hallucinations. One patient had bipolar affective disorder along with depression and another had hypersomnolence with hallucinations. Moreover, neuropsychiatric symptoms were more common in euthyroid and hypothyroid patients but this was not statistically significant.

Cognition was normal in 8 (61.5%), mildly impaired in 4 (30.8%) and moderately impaired in 1 (7.7%) patient. Severe cognitive impairment was not observed in any patient. The commonest neurological symptom was epileptic seizures being present in 8 (61.5%) patients. GTCS were the most common seizure type present in 3 (23%) patients (fig-1). A migraine-like headache was

present in 4 (30.8%) cases while (table-II), tremors were present in 1 (7.7%) patient.

Anti-thyroid antibodies (anti-TPO and/or anti-TSI antibodies) were present in all 13 patients. Ten patients had anti-thyroid receptor antibodies (anti-TPO antibodies), while 3 patient had only anti-thyroid stimulating immuno-globulin antibodies (anti-TSI). CSF proteins were raised significantly ($>450\text{mg/dl}$) in all the 13 patients. In our study, only three patient had MRI changes

Table-I: Underlying thyroid status in HE.

Status of Thyroid	Patient No. (n=13)	Percentage (%)
Euthyroid	8	61.5
Hypothyroid	4	30.8
Hyperthyroid	1	7.7

Table-II: Pattern of different neurological symptoms in hashimoto's encephalopathy.

	Frequency	Percentage (%)
Seizure	8	61.5
Migraine-like headache	4	30.7
Tremors	2	15.4
Stroke-like symptoms	1	7.7
Ataxia	1	7.7

!Many patients had more than one neurological symptoms

including temporal and hippocampal T2WI hyperintensities while remaining patients had normal MRI at the of diagnosis.

DISCUSSION

Encephalopathy is one of the most common presentations in Neurology clinics. Although there is a wide spectrum of disorders including metabolic, toxic, vascular, ischemic and malignant tumors, which can cause encephalopathy but with the detailed history, clinical examination and radio-pathological evaluation, various reversible etiological factors can be identified. HE is considered to be a reversible autoimmune condition⁸⁻¹¹.

Only little has been known about its pathogenesis. Recently autoimmunity is postulated in the form of direct neuronal injury and immune complex deposition. This is supported by the

raised CSF proteins in these patients. Contrary to the immune complex deposition, Duffey *et al*, showed lymphocytic infiltration around vessel on the brain autopsy of HE patients^{7,12-14}. But what is initiating factor in autoimmunity is still to be recognized.

HE and nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM) are considered same disorders, suggesting that HE might be a subtype of NAIM⁸. Hashimoto's encephalopathy is almost always reversible with steroids, that's why sometimes it is also called SREAT which stands for Steroid-Responsive Encephalopathy associated with Autoimmune Thyroiditis.

HE like any other autoimmune disorder occurs predominantly in females and its mean age of onset is between 45 and 55 years. Similar facts have also been observed in our study with HE present in 8 female patients.

This steroid-responsive encephalopathy can have a long-term course. The disease pattern can be relapsing-remitting, self-limited and chronically progressive^{9,10}. There are two subtypes of HE, a vasculitis type with the stroke-like pattern. These patients present with focal neurological deficits with some cognitive impairment. The episodes of focal deficits can occur recurrently and multiple times over disease course, some time remitting without any treatment. Only 25% of the cases of HE have this type while remaining 75% cases manifest with insidious onset and progressive cognitive decline with some psychotic features¹¹. However, sometimes the two types can overlap and may not be possible to distinguish clinically.

Neuropsychiatric and neurological symptoms are the most common in our study, just as reported previously by Tang *at al*¹². We observed neuropsychiatric symptoms in all 13 patients with depression being the most common feature in our patients. Steroid responsive depression can occur in SREAT^{13,14}. Is this depression due to underlying autoimmune thyroid diseases¹⁵ or effect of encephalopathy is not clear. Frank

psychosis with hallucinations was also demonstrated in our patients.

Approximately two-thirds of the patient can have seizures either focal or generalized with status epilepticus being documented in only 12% of the cases¹⁶. Focal or multifocal myoclonus is documented previously in 38% of the patients compared to the 1 (7.7%) patients in the present study. Interestingly in our study GTCS were present in 23% of the patients while focal seizures with secondary generalization and complex focal seizures were observed in 15% cases each. Interestingly around 40% of the cases had no seizures during the course of illness.

Previously stroke-like symptoms were present in 23 out of 85 HE patients according to Chon *et al*¹⁶. but we found stroke-like symptoms in only one patient (7.7%) however, migraine-like headache was commonest manifestation among neurological symptoms in our study, being present in 4 (30.8%) patients.

Since HE has a very variable spectrum of presentations, it may rarely present with different central and peripheral neurological manifestations like myelopathy, cerebellopathy, different movement disorders, behavioral disorders and various types of polyneuropathy as published in different case reports previously¹⁷⁻¹⁹. Most of the time there are no systemic features like fever in HE²⁰. Two patients in our study were observed to have tremors while single patient had ataxia (table-II).

An increased level of antithyroid autoantibodies in serum is an important feature of HE and they were present in all our patients, with 10 (76.9%) patients having anti-TPO antibodies and remaining 3 (23%) cases had anti-TGI/TSI antibodies. Findings of this study analysis were consistent with previous studies. The nervous system involvement has been reported previously with elevated levels of these antibodies. The role of these antibodies in the pathophysiology of this disorder is largely unknown^{16,20-23}. These antibodies are often not measured in CSF due to undetermined sensitivity and specificity. CSF analysis

is found to be abnormal in almost 80% of the patients¹¹, with raised protein concentration is the most common finding along with varying range of lymphocytic pleocytosis in such patients.

HE can occur many years earlier than the onset of underlying thyroid disease². In HE, patients have variable thyroid status with euthyroidism being the most common condition diagnosed in cases of HE^{16,24}. In our study, as per the breakdown of underlying thyroid status at the time of presentation, euthyroidism was present in 8 (61.5%) cases, while hypothyroidism was present in 4 (30.8%) and hyperthyroidism was observed in 1 (7.7%) cases. The association of Hashimoto's encephalopathy with hyperthyroidism is less common²⁵. However, previously sub-clinical hypothyroidism has been reported in various studies which are contrary to our study^{16,24}.

Steroids are the mainstay of treatment for HE. Either high dose of prednisolone orally or methylprednisolone intravenously have been used in the initial management of the disease. Our all patients responded well to high dose steroids. Alternatively, intravenous immunoglobulins and plasma exchange can be used, either as primary treatment options or in patients not responding to high dose of steroids. Both modalities have shown a good response in various cases^{20,25}. Other steroid-sparing agents can be used in patients with limited response to steroid or other modalities, or in relapsing disease. Most commonly used agents are cyclophosphamide, azathioprine, and methotrexate. In our study all patient responded to intravenous methylprednisolone while only 2 patients required steroid-sparing agents to maintain remission in long term.

The main limitation of this study is that it is carried out at only a single center, that's why the results cannot be generalized. To make results more generalized and true representative of population multi-centric study may be required. Although our study span extends over three years, we could diagnose only 13 patients with

Hashimoto's encephalopathy fulfilling diagnostic criteria, perhaps this is because of either the rare nature of the disease or poor understanding of doctors.

CONCLUSION

The understanding of symptomatology of Hashimoto's encephalopathy is of utmost importance due to reversible nature of disease with steroids. If other etiological factors for encephalopathy has been ruled out in the presence of underlying thyroid disease with the short history of symptoms, one should have the low threshold for treatment with the steroid to observe for the response.

CONFLICT OF INTEREST

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

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