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CASE REPORT

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Streaming through a case of SREAT

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Abstract

Background Hashimoto's encephalopathy, also known as steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is an autoimmune neuroendocrine disorder marked by impaired brain function. It is a diagnosis of exclusion with variable nature of presentation and no gold standard investigation of choice.

Case presentation Here, we report a case of SREAT in a 26-year-old female who presented to our Emergency Department with altered sensorium and generalised tonic clonic seizures. After thorough clinical examination and initial resuscitation, a provisional diagnosis of neuroglycopenic injury or possible encephalitis was made. Broad-spectrum antibiotics were initiated. Routine investigations and cerebrospinal fluid (CSF) study were inconclusive except for neutrophilic leucocytosis. Magnetic resonance imaging (MRI) depicted hyper-intense signal changes around bilateral hippocampus and thalamus. Serum anti-thyroid peroxidase (anti-TPO) was strongly positive while other serum and CSF autoantibodies were within normal limits. A diagnosis of SREAT was made and she responded brilliantly to systemic corticosteroids. Incidentally, anti-SSA (anti-Ro) and anti-SSB (anti-La) were positive and a possible association between Sjogren's syndrome and SREAT was insinuated.

Conclusion There is a long list of differentials for SREAT and a proper diagnostic criteria must be followed to reach at a conclusion. It can be easily missed and remain underreported due to its overlapping nature and ambiguous presentation. Hence, clinicians must have high index of suspicion for the disease and optimal therapy should be initiated early to improve the long term mortality.

Keywords SREAT, Diagnosis of exclusion, Anti-TPO, MRI, Corticosteroids

Background

Hashimoto's encephalopathy (HE) is a rare autoimmune neuroendocrine disorder marked by impaired brain function [1]. Nowadays, it is also known as steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT). It is characterised by altered mental status, cognitive impairment, sleep–wake cycle disorders, seizures or stroke-like episodes. The epidemiological distribution proves its sparse nature as it has a prevalence of 2.1 out of 100,000 and approximately it is four times more common in females than in males [2].

HE is a diagnosis of exclusion. There is no standardised gold standard test designed to conclude the presence of the disease. It can be identified early by recognition of the characteristic clinical symptoms, thorough clinical examination and performing appropriate laboratory investigations. However, due to overlap in the nature of symptoms, acute and emergent medical conditions like meningitis, encephalitis, poisoning and substance abuse first need to be ruled out. The presence of high proteins and anti-thyroid peroxidase antibodies (anti-TPO) in CSF and serum, as well as meningeal enhancement and white matter abnormalities in magnetic resonance

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imaging (MRI) hints at the diagnosis of the condition. The first-line treatment for the condition includes high-dose corticosteroid therapy. If patients do not respond to corticosteroids, alternative immunosuppressive drugs like cyclophosphamide, methotrexate, intravenous immunoglobulin or azathioprine are indicated.

Here, we report a case of Hashimoto's encephalopathy in a 26-year-old female who presented to our Emergency Department with altered sensorium.

Case presentation

A 26-year-old female presented to our Emergency Department with acute decline in sensorium for the past four hours associated with tonic and clonic movement of the body involving all four limbs. Detailed history taking revealed that she had consumed oral hypoglycemic agents in the form of metformin and gliclazide from a local pharmacy shop without the advice of a registered medical practitioner after which the episode precipitated. She was rushed to the nearby community hospital where her capillary blood glucose was noted as 34 mg/dl and 25% dextrose was infused immediately. Her abnormal movements were provisionally diagnosed as generalised tonic clonic seizure (GTCS). Despite the initial resuscitation efforts at the local hospital, her sensorium did not improve and she was finally referred to us in an unconscious state for further management. Her relatives did not give any history of recent trauma, ingestion of toxic substance, alcohol or drugs. She did not have any history of any significant medical condition like diabetes, hypertension, tuberculosis or typhoid or any event of surgical or medical hospitalisation in the recent past.

Clinical examination revealed a disoriented hypotensive patient with blood pressure of 80/60 mmHg, pulse of 78 beats/min with regular rhythm, severe disability and a Glasgow Coma Scale (GCS-P) score of $E_1V_1M_4P_0$ (6/15). There was mild pallor without any evidence of icterus, cyanosis, clubbing or oedema. Neurological examination revealed deep tendon reflexes (DTRs) of both upper and lower extremities were intact with positive Babinski sign. We noticed some jerky movements in the distal upper and lower extremities suggestive of myoclonus. Terminal neck rigidity, Kernig's or Brudzinski sign was negative. Sensory and cranial nerve examination could not be elicited due to the disoriented status of the patient. Rest of the physical and systemic examination did not have any abnormal findings.

Hence, after initial resuscitation efforts at the emergency in securing the airway and establishing peripheral intravenous access for fluid and drug infusion, neuroglycopenic injury or a possible encephalitis was suspected. Routine blood investigations, urine drug screening and cerebrospinal Fluid (CSF) examinations were ordered in view of the above scenario. Broad-spectrum antibiotics and antivirals like ceftriaxone, vancomycin and acyclovir were advised after the investigations were sent as shown in Table1. The blood reports depicted neutrophilic leucocytosis (14,000/[1]cu.mm; 75% neutrophils), but other blood investigations were in the reference range with negative urine toxicology screening report. CSF study revealed normal glucose, borderline protein and cell count of 4/cu.mm with 75% mononuclear cells and 25% polymorphonuclear leukocytes. The CSF adenosine deaminase (ADA) value was 1.84 IU/L. Her bedside EEG had showed generalised slowing of activity suggesting encephalopathy. Despite the ongoing management efforts, no satisfactory progress was noted in the patient's clinical status. On day 5 of the hospital admission, her scrub typhus IgM was positive and doxycycline was added to the existing medical regimen. Even after 48 h of starting doxycycline, the patient did not show any signs of clinical improvement. Radiological imaging studies with magnetic resonance imaging (MRI) was conducted that depicted T2/FLAIR hyper-intense signal changes around bilateral hippocampus and thalamus (Fig. 1). Intravenous acyclovir was continued for 2 weeks in view of suspicion of Herpes Simplex Virus (HSV) Encephalitis or Japanese Encephalitis (JE). However, CSF Japanese Encephalitis Immnoglobulin-M (JE-IgM) or Herpes Simplex Virus Polymerase Chain Reaction (HSV-PCR) and the respective serology were negative.

The next possibility in our list was limbic encephalitis. Her serum and CSF-autoantibodies like anti-NMDA-R, antiLGI1, anti-AMPAR and anti-CASPR2 were sent for examination in view of limbic encephalitis and it came out to be negative. However, the serum-anti-TPO came out to be strongly positive with a titre of more than 1:1300. Serum ANA was positive for the patient. Though, her thyroid profile and thyroid ultrasound did not reveal any abnormalities. Pulse IV methylprednisolone therapy was administered for five days and the patient responded brilliantly. She regained her consciousness with attainment of sensorium and had GCS score of $E_4V_5M_5P_0$ (14/15). A repeat MRI after one week of steroid treatment showed completely resolved lesions (Fig. 2) that were evident in the previous imaging. Thus, a diagnosis of SREAT was made and appropriate management plan was structured on discharge with oral prednisolone and close follow-up.

In view of SREAT, which is an autoimmune disorder, it is well known that there is high probability of it to be associated with other connective tissue disorders. Hence, we sent blood investigations for autoimmune

[1] Cu.mm: cubic millimetre.

Table 1 Summary of investigations done for the patient

Routine investigations

		Lab values	Reference ranges			Lab values	Reference ranges
Heamatology	Haemoglobin	13.4 g/dl	12–16 g/dl	Serum	Sodium	137 mEq/L	135–145 Meq/L
	Red blood cells (RBC)	4.6million/cu.mm	4.5–5.5 million/cu.mm		Potassium	4.2 mEq/L	3.5–5.5 mEq/L
	Total leukocyte count	14,000/cu.mm	4000–11,000/cu.mm		Urea	27 mg/dl	7–22 mg/dl
	Platelet count	2,60,000/cu.mm	1.5–4.5 lakhs/cu.mm		Creatinine	0.9 mg/dl	0.6–1.2 mg/dl
	ESR	11 mm	0-5 mm		Fasting blood sugar	168 mg/dl	< 200 mg/dl
	PCV	44%	45–55%		Glycosylated Haemoglobin	5.30%	< 5.7%

Specific investigations

		Lab values	Reference ranges			Lab values	Reference ranges
Urine	Drug screening	Negative		CSF	Glucose	55 mg/dl	(40-70mg/dl)
	Routine examination	no casts, glucose, protein, blood or bilirubin			Protein	45 mg/dl	(30-40mg/dl)
	Microscopic examination	No bacteria			ADA	1.84 IU/L	(< 5 IU/L)
	Culture and sensitivity	No growth of aerobic/anaerobic bacteria			Cytology	4 cells/cu.mm (3 PMNL, 1 leukocyte)	< 5 cells / cumm
					Auto immune encephalitis Panel	Negative	

Other investigations

		Lab values	Reference ranges			Lab values	Reference ranges
LFT	Total bilirubin	1 mg/dl		Miscellaneous	TSH	1.9 IU/L	
	SGPT	48 IU/L			CRP	3.6	
	SGOT	34 IU/L			HBsAg, anti-HCV, HIV-I,II	Negative	
	INR	1.1			Anti-TPO	Strongly positive (1:1300 titres)	
	aPTT	25.8			Blood C/S	No growth of aerobic/anaerobic bacteria	

Radiological investigations

USG whole abdomen	Normal impression: no organomegaly, no visible lymph node abnormality
MRI brain	T2/FLAIR hyper-intense signal changes around bilateral medial temporal lobe and thalamus

All laboratory values and reference ranges are reported in their standard units of measurement

mEq/L: milliequivalent per litre; Mg/dl: milligram per deciliter; ADA: adenosine deaminase antibody; TSH: thyroxine stimulating hormone; SGPT: serum glutamic pyruvic transaminase; CRP: C-reactive protein; SGOT: serum glutamic oxaloacetic transaminase; INR: international normalised ratio; Anti-TPO: anti-thyroid peroxidase antibody; APTT: activated partial thromboplastin time; C/S: culture sensitivity; [I]MRI: magnetic resonance imaging

panel that incidentally came out to be positive for anti-SSA (anti-Ro) and anti-SSB (anti-La). The patient did not have any symptoms of dry mouth, decreased oral secretions or dental caries. However, some degree of dry eyes were reported on detailed history taking but Schrimer's test was negative. Hence, some degree of association of Sjogren's syndrome can be hinted in light of the existing scenario. It needs further evaluation for definite conclusion and thus the patient was kept on close follow-up and further investigations were scheduled in this regard with appropriate opinions.

HE or SREAT has been a matter of discussion in the recent medical literature since 1966 due to its ambiguous and indistinguishable nature of presentation [3]. As discussed earlier, HE can have variety of overlapping clinical features with other central nervous system

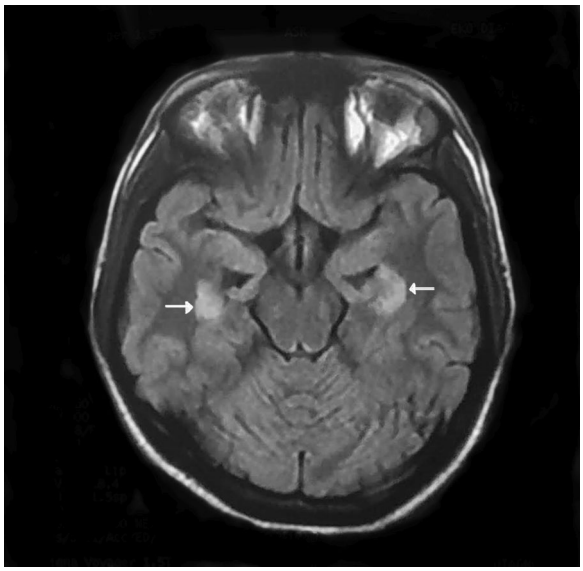

Fig. 1 Hyperintensities in bilateral medial temporal lobe in FLAIR imaging of MRI brain

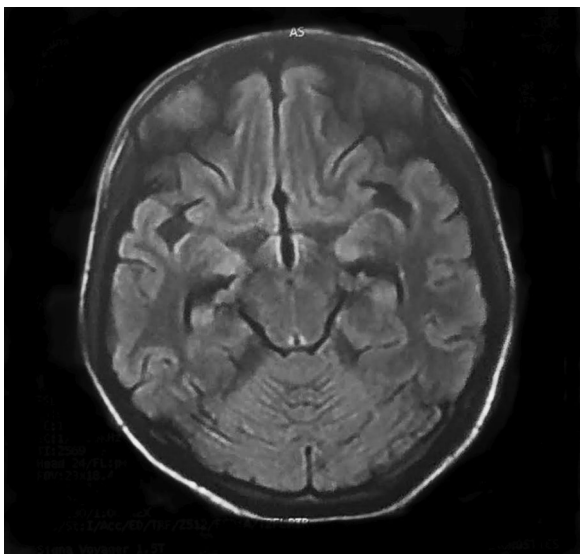

Fig. 2 Follow-up imaging after therapy showing resolved medial temporal lobe lesions in FLAIR imaging of MRI brain

(CNS) disorders. They manifest in a different way for every individual, which can range from loss of consciousness, seizure episodes such as GTCS or focal seizure with impaired consciousness, cognitive impairment, myoclonus to memory loss, psychiatric manifestations and hallucinations [4]. Patients may also present with cranial nerve palsies, opsoclonus, bulbar/pseudo bulbar palsy, vertigo or headache.

The pathophysiology of the condition is not very clear. Several theories have been proposed and an autopsy report by Nolte et al. have demonstrated vasculitis and lymphocytic infiltration in the brain stem and the grey matter in a patient who died with HE [5]. Several mechanisms have been proposed behind the progression of the disease such as global cerebral hypo-perfusion, autoantibody mediated cerebral vasculitis, direct toxic effect of thyrotropin releasing hormone (TRH),and autoimmune cerebral demyelination [6].

The anti-TPO antibodies are also present in Hashimoto's thyroiditis (HT) and studies have demonstrated some degree of association between HT and HE but the causal relationship has not been established yet [7]. There are several associations of HE that justifies its autoimmune nature; some of them are higher frequency in females, middle-aged predominance, increased cerebrospinal fluid (CSF) inflammatory markers, presence of serological autoantibodies and excellent response to steroid therapy. Although, there is established association between HE and anti-TPO antibodies but it is not specific for the disease or its severity [8]. Hence, a multidimensional approach with exclusion of other autoantibodies in CSF like anti-NMDAR, M anti-AMPAR is essential before arriving at conclusion. The long list of differentials for HE are along with their possible points of identifications and relevant investigations are summarised in Table 2.

Due to such a long list of differentials, it is very essential to set appropriate diagnostic criteria for the disease, which was proposed and modified by Graus et al. in 2016 [9]. The diagnostic criteria are summarised in Table 3.

It has always been a common norm in the medical literature that an autoimmune disease raises suspicion for the presence of another autoimmune disease. In view of that comprehensive serum autoantibody profile was sent for laboratory analysis that was positive for anti-SSA and anti-SSB. In a cross-sectional study conducted by Biro et al., they observed that out of 170 patients with Hashimoto's thyroiditis nearly 17% had SS [10]. In 2012, Baszis et al. have observed that Sjogren's syndrome (SS) was ten times more common in patients having anti-TPO positive thyroid disease and patients having Sjogren's syndrome developed autoimmune thyroid disease (AITD) more frequently than controls [11]. In another set of retrospective study by Zeher et al. in a large group of Hungarian patients having primary SS, the frequency of AITD was three to six times higher than the general population [12]. Al-Salahat et al. in their case series showed brilliant steroid responsiveness of three patients with anti-TPO positive encephalopathy of which only one case had overt thyroid abnormalities (hypothyroidism) [13]. Although our study did not report the presence of any AITD, the presence of anti-TPO antibodies raises suspicion for a

Table 2 Differential diagnosis of Hashimoto's encephalopathy (along with relevant clinical features and lab investigation)

Sl no.	Category	Disease	Differentiating clinical features (signs and symptoms)	Relevant laboratory investigation
1	Infective	Meningitis	Fever, neck stiffness, positive Kernig's and Brudzinski sign	CSF showing increased WBCs with neutrophilic or lymphocytic predominance; variable protein and glucose levels depending on the micro-organism involved
		Encephalitis	Seizure episode and focal neurologic findings are characteristic; other features may be common	Neuroimaging is required to localise any specific area of inflammation or lesion
2	Vascular	Cerebral vasculitis	Widespread systemic involvement along with CNS involvement. Present with skin rash, joint pains or fatigue	Cerebral angiography showing inflamed vessels
		Cerebrovascular accidents (CVA)/ transient ischaemic ATTACK	Focal neurologic finding, unilateral or bilateral limb weakness sings of lobar involvement or cranial nerve palsy, bulbar signs, Babinski sign positive	CT scan/MRI showing haemorrhagic or ischaemic lesion in the cerebral area or brainstem
3	Neoplastic	Tumours of the brain or spinal cord/Metastasis to the brain	Present with focal symptoms, weight loss, anorexia, early morning headache or signs of increased intracranial pressure. Mass effects	Neuroimaging is required to localise the lesion. PET scan to diagnose any metastasis. Other relevant imaging to find the source
4	Traumatic	Any road traffic accident involving Brain/spinal cord	Variable depending on area of lesion. Obvious signs and history of injury. Cushing's triad may be present. Basilar skull fracture, ecchymosis of eyes and CSF leak	Comprehensive imaging and screening,
5	Metabolic	Toxin induced (can be from substance abuse, prescription drugs or poison)	Variable symptoms depending on the nature of substance	Clinical; urine drug screening
		Hepatic or Uremic Encephalopathy	Asterixis, focal seizures, low urine output, altered sleep wake cycle	Clinical, urea and ammonia levels,
		Hypertensive encephalopathy	Variable symptoms (gait disturbance; headache; vomiting)	Serial BP measurements, electroencephalogram (EEG), ECG
		Nutritional Encephalopathy (glycopenic, Wernicke's)	Drowsiness, autonomic hyperactivity, sweating, confusion, ataxia, nystagmus	Blood glucose levels or vitamin B1 levels. In neuroglycopenia MRI brain may show T2 hyper intensity in basal ganglia, thalamus, cortex and splenium involvement may show 'boomerang sign'
6	Autoimmune	Anti-NMDAR Encephalopathy	Flu-like illness, along with encephalopathic symptoms and then progression to psychosis, paranoia or agitation	anti-NMDAR antibody + in CSF and/or serum, EEG
		Paraneoplastic limbic encephalitis	Associated with an underlying malignancy of lung or breast, amnesia, complex seizures and temporal lobe involvement	Anti-Hu+, anti-Ma+ in CSF and/or serum, EEG showing epileptic activity
		Paraneoplastic cerebellar degeneration	Associated with an underlying malignancy of lung, ovary or breast; bulbar palsy along with vertigo or tremor	Anti-Yo, anti-Hu, anti-Ri antibodies in csf and/or serum
		Hashimoto's encephalopathy	Altered sensorium, stroke-like episode, myoclonus, seizures, vertigo, headache	Anti-TPO antibodies in CSF and/or serum, MRI enhancement in basilar regions
7	Degenerative	Creutzfeldt–Jakob disease	Behavioural change, psychosis, dementia, involuntary movements and coma	EEG showing periodic sharp wave pattern, CSF having 14–3–3 protein

Table 3 Diagnostic criteria for Hashimoto's encephalopathy

Diagnostic criteria for Hashimoto's encephalopathy (HE)[9]		
Sl no.	**Criteria**	**Points**
1	Encephalopathy with clinical features of seizure episodes, myoclonus, or stroke episode	1
2	Thyroid disease (any state of thyroid illness that is not able to justify the current symptoms)	1
3	MRI with non-specific changes	1
4	Presence of serum anti-TPO or anti-thyroglobulin antibodies	1
5	Absence of other autoantibodies in serum and/or CSF	1
6	Justified exclusion of all other causes	1

Score ≥ 5 is required for the diagnosis of HE

Score < 5 requires comprehensive evaluation for an alternate diagnosis

subclinical AITD state. The presence of anti-SSA and anti-SSB antibodies in this patient without any clinical evidence of Sjogren syndrome strengthens the already existing evidence of association between the two. Hence, further research is warranted in this field to establish the temporal relationship or any other significant evidence that can add value to the already existing medical literature [14, 15].

Conclusion

Hashimoto's encephalopathy may be often misdiagnosed and it remains underreported due to the ambiguous nature of presentation and overlapping symptoms with other CNS disorders. This might contribute to the documented low incidence of the disease. Hence, clinicians must have high index of suspicion for HE in patients with unexplained encephalopathy or neuropsychiatric manifestation. Due to its rapid response to glucocorticoids and excellent prognosis if treated earlier, clinicians should emphasise on early detection of the condition to improve the mortality. Thus, diagnosis is the key and proper awareness of the condition with systematic approach required to achieve better life expectancy rate.

Abbreviations

Cu.mm	Cubic millimetre
mEq/L	Milliequivalent per litre
Mg/dl	Milligram per deciliter
ADA	Adenosine deaminidase antibody
TSH	Thyroxine stimulating hormone
SGPT	Serum glutamic pyruvic transaminase
CRP	C-reactive protein
SGOT	Serum glutamic oxaloacetic transaminase
INR	International normalised ratio
Anti-TPO	Anti-thyroid peroxidase antibody
Aptt	Activated partial thromboplastin time
C/S	Culture sensitivity
MRI	Magnetic resonance imaging

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Author contributions

DD worked up the case and managed as well as prepared manuscript. RS has prepared the manuscript. KJ, KB and AS were actively involved in supervision of case management and manuscript preparation. JG has been involved in patient care. All authors read and approved the final manuscript.

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Declarations

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Consent for publication

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Competing interests

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