CASE REPORT

Rare case of Hashimoto's encephalitis mimicking grief reaction

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SUMMARY

A 46-year-old woman was admitted with tonic-clonic seizures. She was noticed to be withdrawn and low in mood for few months. She had reduced level of consciousness with hyper-reflexia and myoclonus. Metabolic, vasculitic, autoimmune, paraneoplastic and septic screen were normal. Lumbar puncture showed raised protein in the cerebrospinal fluid but the cytology, bacterial and viral screens were negative. A CT of the head revealed global brain swelling consistent with encephalitis which was empirically treated with antibiotics and antiviral therapy. Despite this she continued to have altered sensorium. She had moderately raised titres of antithyroid peroxidase antibodies suggestive of an underlying diagnosis of Hashimoto's encephalitis. She displayed a significant improvement in her cognitive functions with high-dose steroids which was further in keeping with this rare diagnosis.

BACKGROUND

Hashimoto's encephalitis (HE) is an extremely rare but a potentially treatable condition which can present with clinical features of acute/subacute encephalitis. As the signs and symptoms at presentation are non-specific, it poses a diagnostic challenge. It remains a diagnosis of exclusion and patients need to be investigated for other possible causes of meningoencephalitis. Prompt recognition and early steroid therapy can help in reducing morbidity and improves long term outcome. HE can affect patients independent of their thyroid status with over half of the patients do not have any history of thyroid dysfunction.

Prior to hospital admission, our patient symptoms were attributed to grief reaction and anxiety from a recent family bereavement. She also did not have significant elevation of antithyroid peroxidase (anti-TPO) antibodies which is classically described in case reports. She showed dramatic clinical and radiological response to steroid therapy which was in keeping with an underlying diagnosis of HE.

CASE PRESENTATION

A 46-year-old woman was noticed by her family members to have progressive confusion over the last 5 months with steep decline in cognitive state a few days prior to admission. She was witnessed by paramedics to have tonic-clonic seizures en route to the hospital. Due to low Glasgow coma scale she was intubated and admitted to the intensive care unit.

Her medical history included Lyme's disease, fibromyalgia and previous spinal surgery. She was on citalopram, naproxen, cetirizine and lymecycline. There was no history of excess alcohol intake or use of recreational drugs.

Two weeks prior to hospital admission, she was reviewed in our medical assessment unit for symptoms of anxiety, cognitive decline and inability to sleep. Family members had noticed that she was not her normal self since bereavement in family about 5 months ago. She had reduced appetite, low mood and had been off work. Her general physical and systemic examination was unremarkable. Routine investigations including thyroid function tests, Vitamin B₁₂ and folate levels were normal. A CT of the head was reported as normal. In the absence of any obvious organic aetiology for her symptoms, a mental-health team review was sought who felt that she has developed reactive anxiety due to underlying grief reaction with a behavioural component. She was started on citalopram and referred to the bereavement service for support and discharged home.

On examination during current admission, she was noticed to have reduced level of consciousness, hyper-reflexia with myoclonus but no other focal neurological deficit. She underwent extensive investigations to ascertain the cause of her progressive decline in cognitive function and seizures. Metabolic, vasculitic, autoimmune (table 1), toxicology, septic and microbiology screen (table 2) were all normal. Lumbar puncture repeated twice showed raised protein in the cerebrospinal fluid but the cytology, bacterial and viral screens were negative (table 2). She had normal thyroid function tests (table 3).

A CT of the head revealed global brain swelling. MRI brain showed a diffused subcortical T2 signal change with global oedema in keeping with diffuse meningitis or encephalomyelitis (figure 1) and (figure 2). A CT cerebral venogram excluded possibility of venous sinus thrombosis. CT chest, abdomen and pelvis was unremarkable. Electroencephalogram (EEG) showed generalised slowing of waveforms but no other abnormalities.

She was empirically treated with broad spectrum antibiotics and antiviral therapy. Antiepileptics were also initiated to prevent further seizures. Post extubation, she remained confused and had minimal verbal communication. She was also noticed to have hyper-reflexia with myoclonic movements affecting upper limbs. In view of the absence of any obvious infectious, metabolic, vasculitic aetiology a diagnosis

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Table 1 Autoimmune/paraneoplastic antibodies

Anti-AMPA1 antibody	Negative
Anti-AMPA2 antibody	Negative
Anti-GABAb receptor antibody	Negative
Anti-VGKC antibody	Negative
Anti-NMDA receptor Antibody	Negative
Anti-Yo antibodies	Negative
Anti-Hu antibodies	Negative
Anti-Ri antibodies	Negative
Other neuronal antibodies	Negative
Anti-nuclear Ab screen	Negative
ANCA screen	Negative
Antithyroid peroxidase antibodies	358.1 U/mL (<34.0)

AMPA-1, anti-glutamate receptor-1; AMPA-2, anti-glutamate receptor-2; ANCA, Anti-neutrophil cytoplasmic antibody; GABAb, gamma aminobutyric acid; NMDA, N-methyl-D-aspartate; VGKC, voltage gated potassium channel.

of HE was considered. A modestly elevated anti-TPO antibody titres were supportive of this diagnosis. She was commenced on high-dose steroid therapy (prednisolone 60 mg daily) which resulted in a dramatic clinical response. There was marked improvement in her speech, memory and behaviour. She had no further abnormal myoclonic movements or seizures. A significant improvement in her cognitive state with steroid therapy was in keeping with an underlying diagnosis of HE. Repeat MRI after steroid therapy was commenced showed complete resolution of diffuse cerebral swelling (figure 3) and (figure 4). She is currently undergoing rehabilitation and remains on a tapering dose of steroids.

DIFFERENTIAL DIAGNOSIS

Viral encephalitis/meningitis.
Status epilepticus.
Hypoxic brain injury post seizures.
Toxic/metabolic encephalopathies.
Autoimmune encephalitis.
Paraneoplastic syndromes.
Central nervous system vasculitis.
Space occupying lesions.

Outcome and follow-up

A significant and dramatic improvement in her cognitive status was noticed within few days of initiation of high-dose steroid

Table 2 Microbiology and Cerebrospinal fluid (CSF) investigation results

Cerebrospinal fluid protein:	1.46 g/L (0.15–0.45)
Cerebrospinal fluid glucose:	6.3 mmol/L (2.2–3.9)
Red blood cells count	6×10^6 /L
White blood cell count	1×10^6 /L
Gram stain:	No organisms seen
Herpes simplex type 1 PCR	DNA not detected
Herpes simplex type 2 PCR	DNA not detected
Meningococcal PCR	DNA not detected
Pneumococcal PCR	DNA not detected
Enterovirus PCR	RNA not detected
B.burgdorferi DNA	Negative
MTB Complex PCR	DNA not detected
Mycobacterium spp.PCR	DNA not detected

Table 3 Thyroid function test

Free T4	15.7 pmol/L	(11.0–25.0)
Thyroid stimulating hormone	1.72 mU/L	(0.27–4.20)

therapy. A repeat MRI brain showed normalisation of previously noticed subcortical signal and global oedema related changes. She is currently undergoing rehabilitation and being gradually weaned off her steroid therapy.

DISCUSSION

Hashimoto's encephalitis is an extremely rare condition with a prevalence of 2.1 cases per 100 000 persons.¹ It was first described by Brain *et al* in 1966² with around 200 reported cases in literature so far. There is a clear woman preponderance with woman to man ratio of 4:1 and it can affect all age groups.³

The clinical presentation of Hashimoto's encephalitis remains variable with patients presenting with seizures, psychosis, stroke like episodes, impairment of cognitive function, disturbance of consciousness, behavioural and mood disturbance, focal neurological deficits, ataxia, coma and presenile dementia.⁴ On a retrospective review, the onset of symptoms in our patient was insidious. The initial symptoms were non-specific and included low mood, lack of sleep and restlessness. Over a period of 5 months she was noticed to have anxiety, progressive confusion and altered behaviour.

Our patient underwent preliminary investigations in our medical assessment unit 2 weeks prior to her admission with worsening confusion and seizure. Interestingly, basic biochemical and radiological investigations were normal. In absence of any obvious organic cause for her symptoms it was felt by the mental health team that she has a grief reaction due to recent bereavement in family. This raises an important point regarding consideration of rarer aetiologies which can present insidiously with altered personality and/or psychosomatic symptoms. A possible differential diagnosis for such patients includes HE, viral

Figure 1 MRI brain showing diffuse cerebral swelling before steroid treatment.

Figure 2 MRI brain showing diffuse cerebral swelling before steroid treatment.

encephalitis, Creutzfeldt-Jakob disease, central nervous system vasculitis and paraneoplastic autoimmune encephalopathies.⁵

The exact mechanism which leads to HE remains unknown although there is indirect evidence which supports a possible autoimmune pathogenesis for example, female preponderance, association with other autoimmune disorders, relapsing-remitting clinical course and good response to immunosuppression.⁶ Based on autopsy findings of perivascular lymphocytic infiltration, a vasculitic aetiology for HE has been proposed although

Figure 3 MRI brain showing resolution of cerebral swelling after steroid treatment.

Figure 4 MRI brain showing resolution of cerebral swelling after steroid treatment.

the sample size analysed was relatively small.⁷ On the other hand, an alternative hypothesis for development of HE is based on interaction of thyroid autoantibodies present in CSF with intracranial antigens and localised immune complex formation.⁵

Our patient had no history of thyroid dysfunction. She was clinically as well as biochemically euthyroid. Based on the existing published case reports, HE may be associated with Hashimoto's thyroiditis although a few patients with pre-existing Graves' disease have been reported.⁸ Thyroid dysfunction is believed to have no bearing on development and prognosis of HE. Patients can have subclinical hypothyroidism (35%), euthyroidism (30%), overt hypothyroidism (20%), or less frequently, hyperthyroidism (7%).⁸

Our patient had a modest elevation of anti-TPO antibody titre ($\times 10$ times the upper limit of normal) as compared with significantly high titres reported in literature. It is important to keep in mind the high prevalence (up to 20%) of anti-TPO antibodies titres in normal population. Therefore positive anti-TPO antibody in a patient with encephalitis needs to be interpreted cautiously.

Patients with HE may show EEG abnormalities (mainly slowing pattern), normal or non-specific findings on neuroimaging and elevated proteins in CSF⁸ as was seen in our patient. HE remains a diagnosis of exclusion, although raised antithyroid antibody titres, (predominantly anti-TPO and/or antithyroglobulin antibodies), is deemed to be an essential feature for diagnosis. Serum autoantibodies against the NH2-terminal of alpha-enolase are useful biomarker for the diagnosis of HE but these are not widely available. These are usually not detected in normal individuals and have a specificity and sensitivity of 91% and 50%, respectively, for HE.⁹

Patients with HE typically respond well to steroid therapy and this is considered an essential prerequisite for diagnosis. There are different regimens for initiation of steroid. A few previous reports recommended high dose of methylprednisolone (1000 mg/day for 3–5 days) but our patient responded well to

oral prednisolone (60 mg/day). There are case reports of patients requiring plasmapheresis¹⁰ and intravenous immunoglobulins¹¹ as an alternative to steroid therapy.

To sum up, the absence of an alternative infective, autoimmune, vasculitic aetiology, a modest elevation in anti-TPO antibodies and dramatic clinical response to steroid therapy was supportive of underlying diagnosis of HE in our patient. HE remains an important differential diagnosis for patients presenting with acute/subacute encephalitic features. Early recognition and prompt therapeutic intervention of this condition can reduce long term morbidity and significantly improve patient outcomes.

Learning points

- ▶ Hashimoto's encephalitis is an extremely rare but potentially a treatable condition. It should be considered as a differential diagnosis in patients presenting with acute/subacute encephalitis of unknown aetiology.
- ▶ It remains a diagnosis of exclusion and hence it is imperative to rule out other contenders in the differential diagnosis.
- ▶ A non-vasculitic autoimmune meningoencephalitic process is believed to play a key role in its pathogenesis.
- ▶ Raised antithyroid peroxidase antibody titres and dramatic response to steroids are essential criteria for diagnosis.
- ▶ Early recognition and steroid therapy can help to significantly reduce morbidity and improves long term outcome in such patients.

Contributors AG: wrote case report and searched literature for discussion with references. SA: helped in writing and editing case report and discussion. Provided

MRI images and took patient's consent. CS: consultant physician responsible for this patient care and approved the final version. AK: critical analysis of the case and made necessary changes to the text and approved the final version.

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