CASE REPORT

Altered mental status: what is the diagnosis?

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SUMMARY

We report a patient presenting with a 2-day history of altered mental status and lethargy. She had recently started taking prednisone for suspected 'autoimmune arthritis'. Clinical deterioration in hospital characterised by increasing confusion, alternating hyperarousal and somnolence, auditory hallucinations and eventual unresponsiveness led to an intensive care unit transfer. Initial laboratory and radiological testing did not reveal a cause for her symptoms. The only abnormality detected was antithyroid peroxidase antibody levels elevated to >900 IU/mL with patient demonstrating marked clinical improvement within 24 h of receiving high-dose steroids and plasmapheresis. Hashimoto's encephalitis is an underdiagnosed reversible neuropsychiatric disorder with unknown pathogenesis. Recent studies indicate that autoimmune encephalopathy and specifically Hashimoto's encephalitis is under-reported. Our case demonstrates the importance of maintaining a wide differential for altered mental status, especially after negative initial diagnostic work-up of more common aetiologies. Although steroids are an effective treatment for Hashimoto's encephalitis, the addition of early plasmapheresis may be indicated in patients with severe presentation and those who develop disease while taking steroids.

BACKGROUND

Hashimoto's encephalitis (HE) is a rare, underdiagnosed reversible neuropsychiatric disorder with unknown pathogenesis. Recent studies indicate that autoimmune encephalopathy and specifically HE is under-reported. Our case demonstrates the importance of maintaining a wide differential for altered mental status, especially after negative initial diagnostic work-up of more common aetiologies. Persons with a history of thyroid disease and other autoimmune disorders may be more at risk for HE.

CASE PRESENTATION

A 38-year-old African-American woman with a medical history of toxic multinodular goitre, treated with radioactive ablation 18 years ago, and hypertension presented with a 2-day history of confusion. History was obtained from patient's mother and the patient. Mother said the patient was 'staring off into space' with difficulty in understanding and processing speech, and appeared more tired. She reported that the patient had been subjectively more withdrawn and less interactive over past 3 weeks. There was no history of any trauma or toxic ingestions. The patient was seen at an outside hospital 7 days prior to presentation for joint pains and was initiated on oral steroid therapy for suspected autoimmune arthritis.

On presentation, patient was afebrile with temperature of 36.6 C, pulse rate 65 bpm, respiratory rate 20/min, blood pressure 105/51 mm Hg. She was oriented to person, place and time but slow to questioning. Physical examination revealed no focal neurological deficits. Initial imaging with non-contrast CT (NCCT) head was unremarkable. Empiric ceftriaxone vancomycin, acyclovir and fluconazole were started for possible meningitis. Over the course of her hospital stay, her mental status continued to deteriorate and she became increasingly somnolent and non-responsive to verbal and tactile stimulus with intermittent episodes of hyperexcitability and agitation. She also developed signs of facial muscle twitching and tongue biting without any significant tonic-clonic seizure like movements. She was transferred to the intensive care unit after due to concerns for airway compromise.

INVESTIGATIONS

Laboratory evaluation revealed electrolytes, renal and liver functions within normal limits. Thyroid function tests revealed mildly elevated free T4 and suppressed thyroid-stimulating hormone with normal free T3 (table 1). Blood and urine cultures, rapid plasma reagin and HIV tests were negative. Lumbar puncture (LP) was performed and cerebrospinal fluid (CSF) analysis was unremarkable with glucose levels of 68 mg/dL and protein of 13 mg/dL. MRI brain, with and without contrast, was unremarkable, showing no abnormal enhancement. An EEG performed was unremarkable for seizure, and displayed β waves consistent with pre-procedure benzodiazepine administration for her agitation. Serum prolactin level was within normal range.

Testing for autoantibodies revealed positive serum antinuclear antibody (ANA) at 1:640 dilution with a diffusely speckled pattern. Anti dsDNA and rheumatoid factor were negative. Ultrasound of the neck identified a symmetrically enlarged, heterogeneous appearing thyroid gland with multiple bilateral nodules. CSF studies for anti-NMDAr and antineuromyelitis optica antibodies were negative. PAVAL paraneoplastic serum and CSF studies were within normal limits. Thyroid antibodies were ordered.

Antithyroid peroxidase antibodies (anti-TPO) elevated to greater than 900 IU/mL, above the laboratory reference range (table 1). Thyroid-stimulating IgG level was elevated as well.

DIFFERENTIAL DIAGNOSIS

The patient's presentation in the setting of recent steroid resulted in a broad differential, with infectious and iatrogenic (steroid-induced) aetiology being most likely. Meningitis and encephalitis were initial concerns and empiric antimicrobial coverage

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Table 1 Pertinent laboratory tests

TSH	<0.01 µIU/mL
Free T4	2.3 ng/dL
Free T3	2.5 pg/mL
Thyroid peroxidase antibody	>900 IU/mL
TSI	3.5 TSI index

TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating IgG.

was initiated after LP was performed and NCCT head did not show any mass lesions. The patient's unremarkable CSF analysis and MRI, coupled with failure of patient to improve on antimicrobials, necessitated a change in therapy and broader differential.

She did not improve even 4 days after discontinuing oral steroids; delirium usually resolves in the first few days after discontinuing steroid therapy, and steroid-induced psychosis shifted lower on the differential. Her presentation was uncharacteristic for a thyrotoxicosis-related altered mental status given her lack of signs and symptoms consistent with thyrotoxicosis and normal free T3 levels.

History of staring spells with unresponsiveness was concerning for seizures. EEG obtained showed no evidence of seizure activity. There was no history of convulsions, jerking movements, muscle rigidity or loss of muscle tone, and none of these typical features were observed during the hospitalisation. Furthermore, serum prolactin levels were within normal limits.

Her history of recent treatment for autoimmune arthritis and hypertension raised concern for stroke caused by vasculitis or haemorrhage, but both CT and MRI did not demonstrate lesions.

Finally, based on her markedly elevated anti-TPO antibody titre, normal brain imaging studies and negative CSF studies for anti-NMDA antibodies, a diagnosis of HE was considered and patient was initiated on treatment for the same.

TREATMENT

High-dose steroid therapy and plasmapheresis were initiated with a marked and rapid improvement in mental status within 24 h. Therapy was continued inpatient for 5 days with 100 mg prednisone and daily plasmapheresis. The patient was discharged on a 4-week prednisone taper 80 mg×1 week→60 mg×1 week→40 mg×1 week→20 mg×1 week with close follow-up.

OUTCOME AND FOLLOW-UP

At discharge, the patient was ambulating and able to complete activities of daily living independently. At last follow-up 6 months after presentation, she remained asymptomatic with no residual neurological changes.

DISCUSSION

HE, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) and autoimmune encephalopathy associated with thyroid autoantibodies, is a rare autoimmune disease. It manifests in a wide variety of neurological and psychiatric characteristics and ranges from fulminant to subacute to chronic. Patients are typically middle-aged women, although children can be affected as well.¹

Postulated mechanisms of HE include antibody-mediated damage due to shared antigens in the central nervous system and thyroid, or immune complex deposition resulting in

autoimmune vasculitis or autoimmune encephalitis. The relationship between Hashimoto's thyroiditis and HE is unclear and could be completely artificial. Thyroid dysfunction is not considered the primary aetiology of HE, as most patients are euthyroid or subclinical hypothyroid at presentation.² Anti-TPO or antithyroglobulin antibody titre does not correlate with the severity of presentation.³ No definitive evidence links antithyroid antibodies in the direct pathogenesis of HE, although anti-TPO antibodies have been found to bind to cerebellar cells and alter their function.⁴ Non-specific immune activation may be present as evidenced by positive ANA titre in our patient.

The diagnosis of HE is one of exclusion, involving the presence of encephalopathy and elevated antithyroid antibodies, after excluding other causes. Elevated CSF protein levels are common in HE, with 85% of patients in a study by Castillo *et al*³ demonstrating increased CSF protein levels. Normal CSF studies, as in our patient, do not rule out the diagnosis of HE. Imaging is typically normal, although non-specific, in white matter changes and meningeal enhancement has been reported.^{3 5}

As the name 'SREAT' suggests, the current standard of care for acute HE is the initiation of high-dose steroids.⁶ Underlying thyroid disease should also be treated if present. The response rate to steroids is >90%. Response times may vary with patients improving over a few days to even months. Patients who do not respond to steroids, or in whom they are contraindicated, or who relapse, can be managed with the addition of other immunosuppressive therapies.^{3 7} Both intravenous immunoglobulin (IVIg) and plasmapheresis have been used to manage HE,⁸⁻¹² although these patients required rescue therapy with IVIg or plasmapheresis due to steroid failure or relapse. Our patient had already been taking steroids when she presented, and a decision to add plasmapheresis was undertaken. Most patients with HE respond to therapy within 5–6 weeks.¹³ Our patient had a severe clinical presentation and the possibly delayed response to steroids further strengthened our decision to add plasmapheresis to her treatment regimen. The prompt response to plasmapheresis does advocate humoral activity as a possible primary pathogenic mechanism for HE, although this is not proven. Long-term control remains a challenge with 77% of patients with autoimmune encephalopathy having a clinical relapse within 1 year after discontinuing treatment in a case series.⁵ Recurrent HE is managed with reintroduction of steroids and addition of other immunosuppressive drugs.¹⁴

Learning points

- ▶ History of thyroid disease, elevated antithyroid antibody titres and the exclusion of other causes of encephalopathy support the diagnosis of Hashimoto's encephalopathy.
- ▶ Hashimoto's encephalopathy is a reversible aetiology of life-threatening and debilitating encephalopathy.
- ▶ High-dose steroids are effective in the management of Hashimoto's encephalopathy, although early plasmapheresis may be indicated in patients who develop Hashimoto's encephalopathy while on steroids and those with a severe clinical presentation in who delay in response may not be tolerated.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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