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A confused patient with raised anti-thyroid antibodies – an unusual case

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Case presentation

A 69-year-old Caucasian female was admitted with a four-day history of acute confusion, behavioural change and reduced responsiveness. Her past medical history was only of mild osteoarthritis and she was not on any regular medications. She was a lifelong non-smoker, drank no alcohol and there was no known psychiatric history of note.

General examination was normal except for alopecia. There was no visible or palpable thyroid swelling. She was afebrile with normal vital signs. Glasgow Coma Scale (GCS) was 9/15 (eyes, 2; verbal response, 3; motor response, 4) with intermittent jerking movements of upper and lower limbs. Neurological examination revealed mild generalised hypertonia with symmetrically brisk reflexes. Corneal and gag reflexes were intact. Plantars were flexor bilaterally. The rest of her systemic examination was unremarkable.

Initial blood tests on admission including full blood count, urea and electrolytes, liver function tests, calcium, magnesium, arterial blood gas, blood glucose, creatine kinase and ammonia were normal except for a mildly raised erythrocyte sedimentation rate (ESR) of 34 mm/hr. Chest X-ray (CXR) and computed tomography (CT) of the head on the day of admission were normal. Lumbar puncture showed an opening pressure of 16 cm H_2O. Cerebral spinal fluid (CSF) microscopy revealed a white cell count of 0/mm^3 and red cell count of 78/mm^3. CSF biochemistry showed protein = 0.65 g/l (0.15–0.45 g/l) and glucose = 2.4 mmol/l (serum glucose = 5.2 mmol/l). Thyroid function tests (TFTs) were abnormal with a thyroid stimulating hormone (TSH) of 8.82 mu/l (0.35–5.50 mu/l) but normal free thyroxine (FT4) of 12 pmol/l (10–22 pmol/l). Blood, urine and CSF cultures did not grow any organisms. CSF viral polymerase chain reaction (PCR) was negative for varicella zoster (VZ), herpes simplex virus (HSV) and cytomegalovirus (CMV).

Differential diagnosis and further investigations

There are innumerable causes of encephalopathy that can present with a similar constellation of signs and symptoms. Likely differential diagnoses in this case included disseminated meningitis/encephalitis, cerebral vascular disease, primary brain tumour or a paraneoplatic manifestation of an occult malignancy, hypoxic brain injury, non-convulsive status epilepticus as well as rare metabolic causes of encephalopathy. Further investigations were conducted in an attempt to exclude these pathologies and obtain a definitive diagnosis.

An electroencephalogram (EEG) showed diffuse slow waves with no features to suggest an epileptic focus or encephalitis. CT chest, abdomen and pelvis were done to exclude an underlying malignancy and were normal. Magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) of the brain revealed small vessel disease only with normal flow in cerebral vessels. Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), auto-antibody screen, rheumatoid factor, antineuronal/purkinje cell antibodies and human immunodeficiency virus (HIV) test were all normal. Antithyroid peroxidase antibody (TPO) titres were grossly elevated at >1,300 (normal value <60 U/ml) with a marginally low complement 3 (C3) = 0.69 (0.75–1.65) and normal C4. The mildly raised CSF protein count could be consistent with viral meningitis; however this does not explain the full neurological findings in this patient. In the absence of any definitive results, a working diagnosis of presumed encephalitis was made on admission and intravenous (iv) ceftriaxone and acyclovir were started empirically.

Case progression

The patient deteriorated clinically on day three of admission with marked unresponsiveness (GCS = 5/15, E1V1M3) and obvious generalised seizure activity which did not respond to iv lorazepam and phenytoin. The patient was intubated and subsequently transferred to the intensive care unit (ICU). There was no change in her conscious level in the following days despite weaning off all sedatives/anaesthetics and she continued to need intensive care support. Acute renal failure developed on day five of admission and the dose of acyclovir was reduced to renal dose.

A diagnosis of Hashimoto's encephalopathy (HE) was suspected by the neurologist because of strongly positive antithyroid antibodies, extensive negative work-up, and lack of response to empirical treatment. The patient was treated with iv methylprednisolone 1 g daily for four days with dramatic improvement in her conscious level. She was successfully weaned off the ventilator and started on tapering doses of high dose oral prednisolone 60 mg daily. Acute renal failure resolved completely with rehydration and discontinuing acyclovir.

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She made a complete neurological recovery, started mobilising independently by day 15 and subsequently was discharged home without any additional help. She was put on a gradual tapering course of prednisolone on discharge. She was reviewed in the neurology outpatient clinic eight weeks later and continues to do well without any neurological or psychiatric sequelae. Follow-up EEG carried out four weeks after discharge was completely normal.

Discussion

Hashimoto's encephalopathy is a rare clinical entity with acute or subacute onset that was first described in 1966.[1] Around 85 cases have been reported so far and it usually presents with a combination of various neuropsychiatric manifestations.[1] The diagnostic criteria are the presence of encephalopathy and elevated antithyroid antibodies in the absence of central nervous system infection, tumour or stroke. HE has also been reported as steroid responsive encephalopathy associated with thyroid autoimmunity, which may describe this condition better.[1]

The estimated prevalence of HE is around 2/100,000,[2] however it is probably under diagnosed. Like most of the other autoimmune diseases, HE is more common in middle-aged females (4:1 female/male ratio) with mean age at onset of 44 years.[3] The clinical presentation may involve a relapsing and remitting course and include seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms, myoclonus, stupor or coma.

The aetiology of HE is presumed to be autoimmune due to its association with other autoimmune disorders, female preponderance and typical response to treatment with steroids.[1,4] The exact underlying pathogenesis is not very well understood, however two likely mechanisms have been postulated. The first is that HE is an autoimmune cerebral vasculitis related to immune complex deposition but there is limited pathological data available to confirm this theory.[4–6] A more recent review suggested that HE is a form of recurrent acute disseminated encephalomyelitis (ADEM) with presumed underlying vasculopathy as opposed to vasculitis.[7]

Laboratory evaluation[3,8,9] shows that all patients have elevated antithyroid peroxidase antibodies (anti-TPO) which are essential for diagnosis and the majority of cases have either subclinical hypothyroidism or are biochemically euthyroid. The majority of cases with HE have elevated CSF protein without any nucleated cells. EEG is abnormal in approximately 90–95% of cases with nonspecific diffuse slow waves. Imaging abnormalities (CT/MRI) are seen in nearly 50% of cases but are again non-specific in nature with focal and diffuse subcortical white matter abnormalities. Raised thyroid peroxidise antibodies are usually associated with Hashimoto's thryoiditis but extent of thyroid dysfunction is variable in patients who are diagnosed to have HE. In a recent review of the literature, 35% of cases had subclinical hypothyroidism; 22% were euthyroid; 20% had overt hypothyroidism; 7% had hyperthyroidism; 6% had unknown thyroid status; and 1% did not have thyroid disease.[1]

Treatment of HE usually consists of immunomodulatory agents (mostly steroids), initially given as iv methyprednisolone for the first three days followed by a slow tapering course of prednisolone over several months.[1] Some of the patients with subclinical or overt hypothyroidism have been successfully treated with levothyroxine alone but the majority have been treated with steroids. The exact underlying pathogenesis of HE needs to be further explored to help understand this disease spectrum better.

Key learning points

- This case highlights the importance of considering rare cases of encephalopathy such as Hashimoto's encephalitis (HE) in the list of differential diagnosis, especially once the common ones have been excluded. This will be possible only with an increased awareness of this condition.
- HE is a diagnosis not to be missed as it has a favourable prognosis once treated and with a possibility of even a full neurological recovery. It would, however, be interesting to follow-up these patients to look for any long-term consequences such as relapses and dementia.
- The importance of a multidisciplinary team approach involving physicians, neurologists and anaesthetists, as well as physiotherapists, cannot be over emphasised in this case and was key in the management of this patient.

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