Reminder of important clinical lesson

Why the confusion in Hashimoto's encephalopathy?

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A 13-year-old girl presented with an afebrile seizure followed by prolonged confusion and visual hallucinations. Initial investigations in the form of blood tests, cerebrospinal fluid analysis and head imaging by CT, were normal. She represented with two further episodes within a period of 3 weeks. Further investigations considering infective, metabolic and some autoimmune causes of encephalopathy were negative. An MRI head scan was normal. Thyroid function testing disclosed primary hypothyroidism and elevated antithyroid antibodies. She responded well to glucocorticoid therapy for presumed Hashimoto's encephalopathy (HE). HE describes patients with various neurological manifestations with elevated titres of antithyroid antibodies. There are no clear criteria for diagnosis, with many cases labelled as HE. Responses to corticosteroid therapy are favourable. In patients with unexplained encephalopathy, HE should be considered given the favourable response to glucocorticoid therapy.

BACKGROUND

This case highlights the importance of considering Hashimoto's encephalopathy in children presenting with unexplained neurological symptoms including seizures and encephalopathy, given the favourable response seen in this ill-defined condition to glucocorticoid therapy.

CASE PRESENTATION

We describe a 13-year-old previously well girl who presented with an afebrile seizure followed by period of prolonged confusion lasting 18 h. During this period the patient was unable to communicate with restlessness and agitation, and urinary incontinence. She also experienced visual hallucinations. Initial investigations including a CT brain scan and cerebrospinal fluid (CSF) analysis were normal. She was discharged with a possible diagnosis of first epileptic seizure. Her neurological examination following her recovery from her seizure was essentially normal.

She had two further episodes which were similar within a 3 week period. These were preceded by myoclonic jerks. In between these episodes she suffered with constant headaches, associated with nausea and vomiting. Her clinical examination showed she was overweight but was otherwise normal.

INVESTIGATIONS

Initial investigations were unremarkable with the exception of a neutrophilic leukocytosis and raised alanine transaminase (ALT) of 73 IU/l (ref range 10 – 45 IU/l). Her erythrocyte sedimentation rate and C reactive protein (CRP) were not raised. Urea and electrolyte and remaining liver function tests were within normal limits. A lumbar puncture on the second day of admission, revealed a CSF with no white cells, four red cells and no organisms seen on Gram stain. CSF glucose was 3.4 mmol/l, protein 467 mg/l (raised) and

lactate 1.1 mmol/l with normal paired blood glucose of 4.0 mmol/l and plasma lactate 1.0 mmol/l.

A CT scan of her head was normal. During the second admission the following investigations were all within normal limits: full blood count, urea and electrolytes, magnesium and calcium, CRP, ammonia, lactate and venous blood gas. A second CT scan was reported as normal. Abdominal ultrasonography for her raised ALT demonstrated a fatty liver. An MRI scan under general anaesthesia was reported as normal.

Further investigations including immunoglobulin levels, autoantibody screen, convalescent viral titres (mycoplasma, borrelia, CMV, HSV, west nile virus) paired bloods and CSF for oligoclonal bands, glucose, lactate, protein, viral PCR's and routine microscopy and culture were all normal/negative. Urine for organic acids and toxicology were also normal/negative. Thyroid function tests were requested which demonstrated primary hypothyroidism (free T4 9.4 Pmol/l (11–19.5) thyroid-stimulating hormone 12.5 mU/l (0.8–7.5). Elevated titres of antithyroid peroxidase antibodies were noted (2313 IU/ml) IgG and IgA were slightly elevated at 15.2 g/l (4.9–13) and 2.7 g/l (0.4–2.0) respectively. Antinuclear antibody was detectable at 160 dilution (0–80) and oligoclonal bands were detected in CSF. N-Methyl-D-aspartic acid receptor antibody levels were negative.

DIFFERENTIAL DIAGNOSIS

- ▶ Epilepsy
- ▶ Acute confusional state (possible drug related)
- ▶ Encephalitis associated with antineuronal antibodies
- ▶ HE.

TREATMENT

While in the emergency department during her first admission she was treated with lorazepam, and given intravenous ceftriaxone, acyclovir and azithromycin. She continued to

have seizures and was treated with phenytoin, and then thiopentone (1 g in total) intubated and ventilated and started on a propofol infusion. She was transferred to our Paediatric intensive care unit the same day. She was extubated the following morning. On receipt of her CSF results her antibiotics and acyclovir were stopped and she was discharged home with buccal midazolam.

During her second admission, she was prescribed intravenous ceftriaxone, aciclovir and oral azithromycin.

On the third admission, following receipt of the thyroid function tests and thyroid peroxisomal antibody results, she was commenced on levothyroxine 50 mcg once daily and prednisolone 30 mg once daily for presumed Hashimoto's encephalopathy.

OUTCOME AND FOLLOW-UP

After commencing prednisolone she started to feel better and her headaches improved. She was later discharged and her steroids tapered over 10 weeks. The patient has experienced no further seizures or encephalopathic episodes, and apart from one self resolving episode of headache, has been well.

DISCUSSION

Hashimoto's encephalopathy is characterised by concomitant encephalopathy and high titres of antithyroid antibodies. The first description of such an association was by Brain and co-workers in 1966.¹ Brain describes a 49-year-old man, who suffered from a progressive impairment of conscious level, intervening episodes of confusion and coma and multiple stroke like episodes within different vascular territories. This was associated with elevated titres of antithyroid antibodies and histologically confirmed Hashimoto's thyroiditis. The neurological and psychiatric manifestations of reported cases of Hashimoto's encephalopathy vary greatly, including stroke like episodes, psychosis, hallucinations, seizures, coma, headaches, tremor and subacute cognitive decline.² In the review by Chong *et al*,³ out of 85 patients all were encephalopathic during some course of their illness. Stroke like episodes were seen in 27%, whereas seizures including focal, motor, tonic, generalised tonic clonic and myoclonic were seen in 66%. Psychosis was seen in 36%. The variety of presentations makes defining illness on the basis of clinical presentation difficult. Diagnosis has therefore been based on demonstrating elevated antithyroid titre autoantibodies and steroid responsiveness, though Brains original case was not steroid responsive. Without clear criteria for diagnosis, cases with varied neurological and psychiatric manifestations in the context of elevated thyroid autoantibodies have been classed as Hashimoto's encephalopathy.

Other terms have been introduced in order to clarify clinical syndromes. The term steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) highlights the high proportion of patients who are steroid responsive. Other acronyms such as NAIM (non-vasculitic autoimmune meningoencephalitis) include other

autoimmune conditions such as Sjogren's syndrome and systemic lupus erythematosus associated meningoencephalitis, which share the feature of steroid responsiveness. Broader terms such as the latter allude to the non-specific nature of elevated thyroid autoantibodies. Thyroid autoantibodies are elevated in myriad autoimmune conditions, as well as being elevated in 10% of healthy adults.⁴ By classifying patients solely on the basis of variable neuropsychiatric manifestations, associated with elevated thyroid autoantibodies one risks falsely unifying quite distinct clinicopathological entities under the same term and thereby obscuring true differences. This is the principle controversy in labelling patients as suffering from Hashimoto's encephalopathy.

Abnormalities in other laboratory investigations and imaging studies are recognised though are not pathognomic. However, they are helpful in excluding other diagnoses. Elevated CSF protein levels are often seen, though are not ubiquitous. In their study of 20 patients with SREAT, 19 patients had abnormal EEG's characterised by generalised slowing.⁵ Other changes included focal slowing, triphasic waves, epileptiform abnormalities and photomyogenic responses. In 17 patients steroid therapy was associated with improvements in EEG appearances. Changes seen on MRI scans of the head vary from normal appearances to dural enhancement, cerebral subcortical (focal and diffuse) and focal cortical signal changes and cerebral atrophy.⁶ Single photon emission photographic studies in the literature were reported by Chong *et al*³ as two cases with normal cerebral perfusion, global hypoperfusion in one case and focally decreased perfusion in eight cases.

The aetiopathogenetic basis of Hashimoto's encephalopathy is unknown. The significance of elevated titres of thyroid autoantibodies is also unclear. Do thyroid autoantibodies lead to encephalopathy, or are they an immune epiphenomenon of different disease entities with distinct aetiopathogenetic basis? Proposed pathogenetic mechanisms include cross reactivity of thyroid and CNS epitopes by thyroid autoantibodies, an autoimmune vasculitis and effects of elevated cerebral thyrotrophin releasing hormone levels.⁷

As highlighted by Schiess *et al*⁷ in their review, the variety of clinical and laboratory presentations of Hashimoto's encephalopathy likely reflects a variety of pathological entities which await identification as distinct disease entities. However, as reported in the review by Chong *et al*,³ a large proportion of patients diagnosed with Hashimoto's encephalitis are steroid responsive. Of the 85 patients included in their review, 45 patients were treated with glucocorticoids, of which 44 (98%) demonstrated a clinical improvement. No features clinical or laboratory are currently capable of predicting glucocorticoid responders from non-responders. Therefore in those patients in whom another diagnosis is not suspected and who present with neuropsychiatric episodes associated with elevated thyroid peroxidase antibodies, we recommend a trial of glucocorticoid therapy.

Learning points

- ▶ In unexplained encephalopathy we recommend screening for antithyroid antibodies.
- ▶ Hashimoto's encephalopathy is an ill-defined clinical entity.
- ▶ Of those patients defined as having Hashimoto's encephalopathy, a high proportion respond to treatment with glucocorticoids.
- ▶ When alternative diagnoses are exhausted, in those patients who have neuropsychiatric episodes associated with elevated thyroid autoantibodies a trial of glucocorticoids should be considered.

Competing interests None.

Patient consent Obtained.

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