BMJ Case Reports

Unusual association of diseases/symptoms

Seizures and postictal stupor in a patient with uncontrolled Graves' hyperthyroidism

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Summary

A 16-year-old girl with a history of Graves' disease presented with two episodes of generalised tonic-clonic seizures, necessitating intensive care admission. Laboratory examination demonstrated a suppressed thyroid-stimulating hormone level with dramatically elevated free triiodothyronine, free thyroxine and thyroid-stimulating immunoglobulins. Cerebrospinal fluid analysis showed oligoclonal banding in the absence of pleocytosis, thyroid peroxidase antibodies or infection. Neuroimaging revealed the presence of a congenital arachnoid cyst in the right temporal lobe. Despite restoration of euthyroidism and administration of antiepileptic and antiviral drugs, neurological features persisted. Subsequently, intravenous corticoids were administered to exclude the contribution of an underlying autoimmune encephalopathy. The patient gradually recovered and, in retrospect, elevated serum *N*-methyl-D-aspartic acid-receptor (NMDA-R) antibodies were detected. Although this patient presented with an intracerebral arachnoid cyst that can act epileptogenic per se, the combination of prolonged postictal encephalopathy with unresponsiveness to antiepileptic measures, absence of focal epileptiform activity on EEG, response to corticoids and serum NMDA-R antibody positivity favours the diagnosis of autoimmune NMDA-R encephalitis in this case.

BACKGROUND

Although little or no evidence exists for neuronal tropism of circulating thyroid autoantibodies, encephalopathy in patients with autoimmune thyroid disease has often been attributed to 'Hashimoto's encephalitis'. However, recently, evidence is accumulating for the existence of an entity called autoimmune encephalopathy, characterised by circulating neuron-specific autoantibodies and often associated with concomitant non-neuronal autoimmune or neoplastic disease. With the present case, we aim to emphasise the need to screen for *N*-methyl-D-aspartic acid-receptor (NMDA-R) and voltage-gated potassium channel-receptor (VGKC) autoantibodies in individuals with a history of autoimmunity or neoplasm, presenting with seizures and/or cognitive impairment in which evident causes of encephalopathy (eg, infectious, metabolic, neoplastic, vascular or toxic) have been excluded.

CASE PRESENTATION

A 16-year-old girl, with no history of ethanol or drug abuse, was transferred to the intensive care unit with important postictal stupor after experiencing a second episode of generalised tonic-clonic seizures.

Since 3 years, the patient had been diagnosed with autoimmune hyperthyroidism, but unfortunately was incompliant for the intake of antithyroid drugs (thiamazole) due to fear of significant weight gain.

Upon physical examination at the critical care department, a pale slender girl could be observed with tachycardia, tremor, important goitre and altered consciousness. The Glasgow Coma Scale evaluation at admission was 10/15. Owing to the suspicion of aspiration pneumonia on physical and x-ray examination, treatment with intravenous antibiotics was initiated. Since encephalopathy features persisted for several days, additional testing was performed.

INVESTIGATIONS

Biochemical evaluation revealed thyroid-stimulating hormone, free triiodothyronine, free thyroxine, antithyroid peroxidase (TPO) and thyroid stimulating immunoglobulin levels of <0.015 mIU/l (0.27–4.2), 7.7 ng/l (2.6–4.4), 25.5 ng/l (9.3–17.0), >600 kIU/l (<34) and >40 U/l (<1.75), respectively. Postictal lactate level was 14.1 mmol/l (ref <2.2 mmol/l). Blood glucose, electrolyte levels, calcium, phosphor, ammonia, pyruvate, liver and kidney function tests appeared normal. A mild hypomagnesaemia of 1.5 mg/dl (1.7–2.2 mg/dl) and a non-specific 1/320 titre of antinuclear antibodies were detected. Cerebrospinal fluid (CSF) analysis showed normal glucose and total protein levels without signs of infection by culture or PCR. Isoelectric focusing revealed oligo-clonal banding in CSF (figure 1) with at least one identical band in the patient's serum.

EEG demonstrated generalised slow waving (figure 2) and a brain CT/MRI scan revealed the presence of an arachnoid cyst at the medial side of the right temporal lobe with a pressure effect on the hippocampus, resulting in hypotrophy of its posterior part (figure 3). Echography of the thyroid finally revealed a highly vascularised multinodular goitre of 50 cc.

DIFFERENTIAL DIAGNOSIS

Encephalopathy with(-out) concomitant epileptic seizures can be either cryptogenic or symptomatic. While the cause for cryptogenic encephalopathy/seizures remains unknown, symptomatic encephalopathy/seizures are provoked by either acute or remote disorders, including (among others) metabolic (eg, hypoglycaemia), neoplastic,

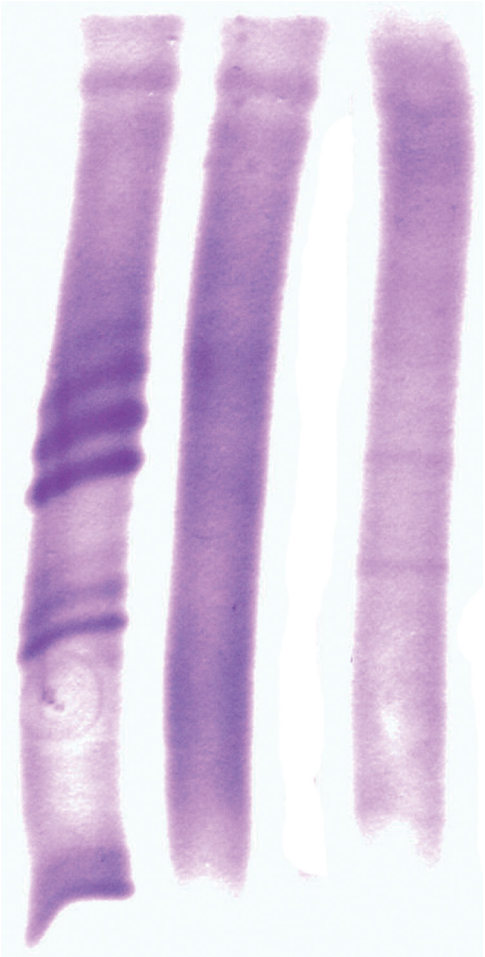

Figure 1 Isoelectric focusing illustrating oligo-clonal banding in the cerebrospinal fluid (CSF) of our patient (right lane) together with CSF-positive (left lane) and serum-negative (middle lane) control.

toxic, infectious, vascular ischaemic or haemorrhagic, traumatic and alcohol or drug withdrawal. When standard laboratory, toxicology, CSF and neuroimaging findings do not reveal a clear aetiology, autoimmune encephalopathy should be considered, especially in patients with a (family) history of autoimmunity or cancer and with subacute or rapidly progressive neurological presentation.

TREATMENT

At admission to the intensive care department, a nasogastric tube was placed and prompt treatment with antithyroid (thiamazole) and antiepileptic (levetiracetam) drugs was initiated. Since consciousness remained altered, an extra antiepileptic drug (phenytoin) and acyclovir were added, thereby anticipating a potential viral cause. Unfortunately, mental state did not improve and intravenous corticoids, at a starting dose of 500 mg methylprednisolone daily, were administered.

OUTCOME AND FOLLOW-UP

After 3 days of intravenous corticoid administration, consciousness spectacularly recovered and corticoid treatment could gradually be tapered off without neurological relapse. Serological screening confirmed the presence of circulating NMDA-R antibodies and supported our hypothesis of autoimmune encephalopathy. The patient was dismissed from the hospital 16 days after initial admission. Abdominal ultrasound did not reveal signs of ovarian teratoma and thyroidectomy was performed taking into account the important non-compliance of our patient for the intake of antithyroid drugs.

DISCUSSION

We present a case of repetitive seizures and concomitant encephalopathy in a young patient with Graves' disease who initially did not respond to antithyroid, antiviral, or antiepileptic measures, but gradually recovered consciousness and cognition after the introduction of corticoid treatment.

Although neurological hyperexcitability can theoretically be a cause of seizure development, the prevalence of thyrotoxicosis-related seizures appears to be very low with only 17 papers reported in the literature over the past 40 years.[1 2] On the other hand, encephalopathy has been associated since several decades with thyroid dysfunction and was first described by Lord Brain in 1966.[3] Consequently, the diagnosis of Hashimoto's encephalopathy (HE) has been applied to patients with encephalopathy features, coinciding with elevated titres of plasma antithyroid antibodies and with non-specific neuroimaging/CSF findings when other evident causes of encephalopathy have been excluded. At present, more than 200 cases of HE have been reported in the literature.[4] Although an autoimmune reaction to antigens shared by the thyroid gland and the central nervous system has been implicated in the pathogenesis of HE, only one report showed specific binding of anti-TPO antibodies to cerebellar astrocytes in HE patients, but not in Hashimoto's thyroiditis patients without concomitant encephalopathy.[5] Nevertheless, it remains highly debated and controversial whether circulating thyroid antibodies

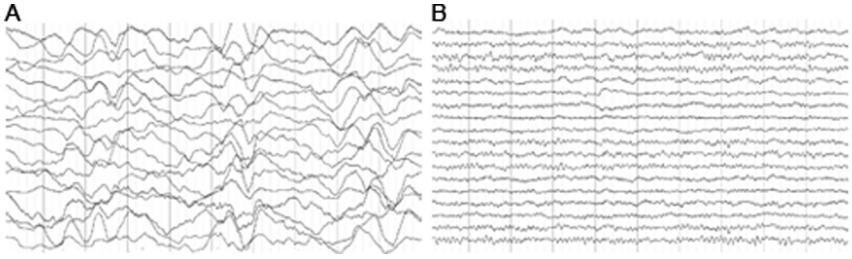

Figure 2 EEG showing generalised slow waving (A) with normalisation after corticoid treatment (B).

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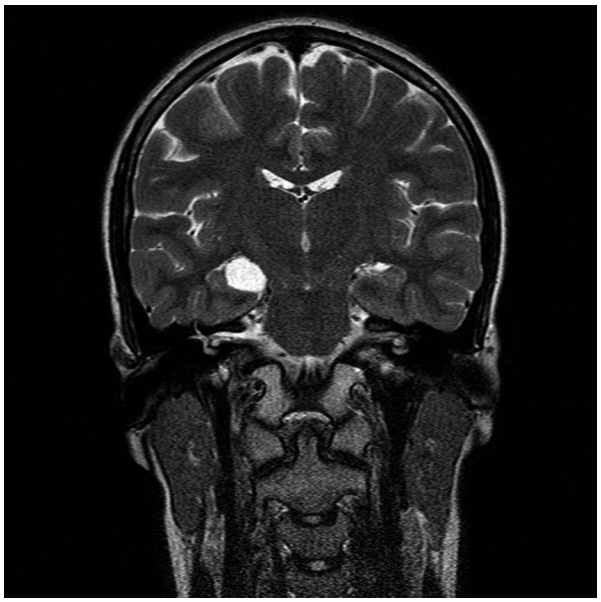

Figure 3 T2-weighted MRI image revealing the presence of an arachnoid cyst at the medial side of the right temporal lobe with a pressure effect on the hippocampus.

are genuine aetio-pathogenic triggers or simply constitute an autoimmune epiphenomenon in patients with coexisting autoimmune encephalitis and thyroid disease. We therefore favour the approach to screen for circulating neuron-specific antibodies in patients with documented autoimmune or neoplastic disease in which evident causes of encephalopathy have been excluded and propose to restrict, as suggested by Castillo *et al*,[6] HE as a diagnosis of exclusion to NMDA-R and VGKC sero-negative patients. Since NMDA-R autoantibody positivity has been predominantly described in teratoma-bearing children or in young females with a plethora of neurological symptoms including seizures, dystonic movements, autonomic dysfunction, hypoventilation and reduction of consciousness with necessity of intensive care admission, we screened for circulating NMDA-R antibodies and ovarian teratoma in our patient.[7 8] While echography revealed no evidence of ovarian abnormalities, NMDA-R antibody titres appeared to be elevated. Although brain MRI showed an arachnoid cyst, absence of local epileptiform activity on EEG, NMDA-R antibody positivity and neurological improvement after corticoid administration supports the diagnosis of autoimmune encephalopathy in our case. Of note, response to corticoid treatment in autoimmune encephalitis is variable and likely depends on the concomitant disease state. Paraneoplastic autoimmune encephalopathy reacts poorly to corticoid treatment and often necessitates complete tumour removal. Non-paraneoplastic forms with associated central nervous system vasculitis also respond weakly to corticoid administration and often require additional immune-modulatory regimens such as cyclophosphamide, azathioprine, methotrexate, rituximab, intravenous immune-globulins or, ultimately, plasmapheresis.[7 9 10] Since recent work from Finke *et al*[11] illustrated that cognitive deficits constitute a major long-term morbidity of antiNMDA-R encephalitis and cognitive outcome likely depends on early and aggressive treatment, we encourage initiation of an immunotherapy trial with intravenous methylprednisolone or immune-globulins when most evident causes of encephalopathy have been excluded, even when the result of neural antibody screening is pending.

Learning points

- Consider autoimmune encephalopathy when evident causes of encephalopathy have been excluded.
- Only employ Hashimoto's encephalopathy as a diagnosis of exclusion in *N*-methyl-D-aspartic acid-receptor, and voltage-gated potassium channel-receptor sero-negative patients with circulating antithyroid antibodies in which other causes of encephalopathy have been ruled out.
- Start an immunotherapy trial with intravenous methylprednisolone or immune-globulins when autoimmune encephalopathy is suspected even when neural antibody screening is pending.

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Competing interests None.

Patient consent Obtained.

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