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Learning Forum

A 50-Year-Old Woman with Recurrent Generalised Seizures

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DESCRIPTION OF CASE

A 50-year-old woman presented in May 2006 with recurrent generalised convulsions. She had a history of hypertension treated with indapamide, but was otherwise well. Her older sister and mother were known to have thyroid disease. She did not have any history of chronic alcohol use nor any recent history of head injury. The patient had never lived outside of Hong Kong. Prior to admission, she was taken to her general practitioner by her family for gradual onset of decreased alertness, cognitive decline, and reduced verbal communication, which worsened over the course of one week. She was found to have hypothyroidism with TSH (thyroid stimulating hormone) 52.3 mIU/l (normal range 0.47–4.68 mIU/l) and free T_4 4.2 pmol/l (normal range 10.0–28.2 pmol/l), and was started on thyroxine replacement. Four days later, she developed two generalised seizures within three days and was admitted into hospital. She was afebrile and had no focal neurological signs on examination. Baseline investigations, including electrolytes, liver function tests, calcium, and phosphate, were normal. Random plasma glucose was 5.7 mmol/l. Magnetic resonance imaging (MRI) of brain was unremarkable. She was subsequently transferred to our hospital for further management.

On admission, she was afebrile and had a series of seizures over a period of five hours without regaining full consciousness in between seizures. The patient was given intravenous diazepam and phenytoin, and was intubated and transferred to the intensive care unit.

What Was Our Differential Diagnosis at This Stage?

The patient presented with several days' history of decreased consciousness, followed by acute symptomatic seizures. The differential diagnosis of someone with a subacute encephalopathy is wide, and possible causes are listed in Box 1. These include metabolic derangements such as hyponatraemia, as well as infections, central nervous system (CNS) disorders, drugs and toxins, systemic conditions such as hepatic encephalopathy, and psychiatric conditions. The patient was at risk of hyponatraemia in view of her use of indapamide, but her serum electrolytes were normal. She was afebrile and had no neck stiffness, though CNS infection would still need to be excluded. There was no known history of neurological or psychiatric conditions, though this would not preclude her from suffering from such conditions. Although there was no easily identifiable drug or toxic cause, these remained distinct possibilities and a toxicology screen was indicated.

The Learning Forum discusses an important clinical problem of relevance to a general medical audience.

What Was the Most Likely Diagnosis?

Although the patient had been diagnosed with hypothyroidism shortly prior to her presentation, the abnormal thyroid function tests could not fully explain her neurological state. Repeat serum electrolytes, liver function tests, and calcium and magnesium levels were all normal. Repeat TSH was 11 mIU/l. Computed tomography (CT) of the brain on admission was normal. A lumbar puncture was performed, which showed raised cerebrospinal fluid (CSF) protein 1.5 g/l. The paired CSF–plasma glucose levels were 7.0 mmol/l and 7.1 mmol/l. The CSF cell count, microscopy, and Ziehl-Neelson stain were all normal. The opening pressure was 13 cmH_20. Polymerase chain reaction of the CSF was later found to be negative for herpes simplex, enterovirus, and varicella zoster virus DNA. Toxicology screen was negative. Her clinical seizures persisted, and intravenous infusion of propofol/thiopentone was commenced. Over the subsequent four days, upon withdrawal of propofol and thiopental, the patient still demonstrated altered mental state. The electroencephalogram (EEG) monitoring showed repetitive focal spikes or sharps of less than three per second, which may be abolished by combination anti-epileptic therapy with phenytoin and sodium valproate, pointing towards non-convulsive status epilepticus (Figures 1 and 2).

Some conditions associated with multiple seizures are listed in Box 2. Structural brain lesions were not likely in our case, given the initial normal MRI imaging. Nevertheless, repeat imaging was warranted if the patient's condition continued to deteriorate. Repeat CT brain performed three days after

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Abbreviations: CJD, Creutzfeldt-Jakob disease; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HE, Hashimoto encephalopathy; MRI, magnetic resonance imaging; TSH, thyroid stimulating hormone

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Box 1. Common Causes of Subacute Encephalopathy

A. Metabolic derangements
- Electrolyte disturbances
  - Hyponatraemia or hypernatraemia
  - Hypocalcaemia or hypercalcaemia
  - Hypomagnesaemia or hypermagnesaemia
  - Hypophosphataemia or hyperphosphataemia
- Endocrine disturbances
  - Hypothyroidism (rarely thyrotoxicosis)
  - Hyperparathyroidism or hypoparathyroidism
  - Insulinoma
  - Pituitary insufficiency
  - Adrenal insufficiency or Cushing's syndrome
- Hypoxia
- Hyperglycaemia or hypoglycaemia
- Carbon dioxide
- Inborn errors of metabolism
  - Porphyria
  - Wilson disease
- Nutritional deficiencies
  - Vitamin B12 deficiency
  - Wernicke encephalopathy

B. Infections
- Sepsis
- Systemic infections
- CNS infections (see below)

C. Neurological
- CNS infections
  - Encephalitis
  - Meningitis
  - Brain abscess
- Epilepsy
  - Complex partial seizures
  - Non-convulsive status epilepticus
- Head injury
- Hypertensive encephalopathy
- Carcinomatous meningitis
- Paraneoplastic encephalitis
- Limbic encephalitis associated with anti–voltage gated potassium channel antibodies

D. Drugs
- Alcohol-related
  - Alcohol intoxication
  - Alcohol withdrawal
- Recreational drugs
  - Narcotics
  - Cocaine
  - Lysergic acid diethylamide (LSD)
  - 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
  - Phencyclidine
  - Ketamine
- Poisons
  - Methanol
  - Ethylene glycol
  - Insecticides
  - Carbon monoxide poisoning
- Prescription medications

E. Systemic conditions
- Hepatic encephalopathy
- Respiratory failure
- Renal failure
- Severe burns
- Hyperthermia or hypothermia

F. Psychiatric disease

admission was normal. Results of our investigations did not support metabolic or toxic causes. Sporadic Creutzfeldt-Jakob disease (CJD) can present with a similar clinical picture including dementia, myoclonus, ataxia, personality change, psychotic phenomenon, or even recurrent seizures [1,2] . However, the EEG of our patient did not reveal the periodic sharp wave complexes typical of CJD. Detection of the 14-3-3 protein in the CSF would also support a diagnosis of CJD, though this test was not available in our hospital. Once infectious causes were excluded, other causes of a subacute encephalopathy, such as an autoimmune or inflammatory process, including paraneoplastic encephalitis, need to be considered.

What Tests Would Now Be Helpful?

As there was no other organic pathology to explain her recurrent seizures and subacute encephalopathy, a diagnosis of Hashimoto encephalopathy was considered in view of the recent diagnosis of hypothyroidism. Anti-microsomal and anti-thyroglobulin antibodies titres were 1 in 25,600 and 1 in 400 respectively, supporting a diagnosis of autoimmune thyroid disease. Anti-nuclear antibodies, anti-DNA, anti-extractable nuclear antigen, and anti-cardiolipin antibodies were all negative. The patient's erythrocyte sedimentation rate and C-reactive protein were mildly elevated at 41 mm/h (normal <20 mm/h) and 39.5 mg/l (normal <9.9 mg/l), respectively, with complement C3 of 0.84 g/l (normal range 0.62–1.87 g/l) and C4 of 0.18 g/l (normal range 0.20–0.59 g/l).

What Was the Next Step in Her Management?

The patient was started on a trial of intravenous hydrocortisone 400 mg/day. Her neurological condition gradually stabilised, and a repeat EEG ten days after admission showed normal background with occasional interictal activities consisting of frontal predominant sharpish discharges. She was eventually taken off glucocorticoids after 18 days. The patient was fully orientated and able to walk unaided when discharged from hospital five weeks after admission, on maintenance phenytoin and valproate.

Progress

Six months after discharge, her anti-microsomal antibodies titre was reduced to 1 in 6,400, and anti-thyroglobulin antibodies were undetectable. She remained seizure-free six months after discharge, and the anti-convulsants were gradually tapered off. When last seen in January 2008, she was well and biochemically euthyroid on thyroxine 0.1 mg daily and had not had any further seizures. She gave written consent for this case to be published.

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Figure 1. Electroencephalogram Showing Repetitive Focal Spikes or Sharps Less Than Three per Second

Box 2. Causes of Acute Symptomatic Seizures with Multiple Seizures upon Presentation

A. Withdrawal of benzodiazepines, barbiturates, alcohol

B. Acute structural injury
- a. Tumour or cerebral metastases
- b. Encephalitis/meningitis
- c. Brain abscess
- d. Stroke
- e. Head injury
- f. Subarachnoid haemorrhage/intra-cerebral haemorrhage/subdural haematoma
- g. Cerebral hypoxia
- h. Cerebral arteriovenous malformations
- i. Posterior reversible encephalopathy syndrome
- j. Systemic lupus erythematosus
- k. Sagittal sinus thrombosis

C. Metabolic disturbances
- a. Hypoglycaemia
- b. Hyponatraemia
- c. Hypocalcaemia
- d. Hypomagnesaemia
- e. Hepatic encephalopathy
- f. Uraemia
- g. Hashimoto encephalopathy

D. Drugs (particularly overdose) and other toxins
- a. Theophylline
- b. Ciprofloxacin
- c. Tricyclic antidepressants
- d. Lithium
- e. Flumazenil
- f. Cyclosporine
- g. Lidocaine
- h. Metronidazole

DISCUSSION

Hashimoto Encephalopathy

The association of Hashimoto disease with an encephalopathy was first described by Lord Brain in 1966 [3]. Hashimoto encephalopathy (HE) is characterised by an encephalopathy with acute or subacute onset, accompanied by seizures, tremor, myoclonus, ataxia, psychosis, or stroke-like episodes, with a relapsing/remitting or progressive course. The prevalence is estimated to be 2.1 per 100,000 [4], although the condition is often under-recognised. Women are more commonly affected than men. In a recent series, the mean age at onset was 56 years, with the most

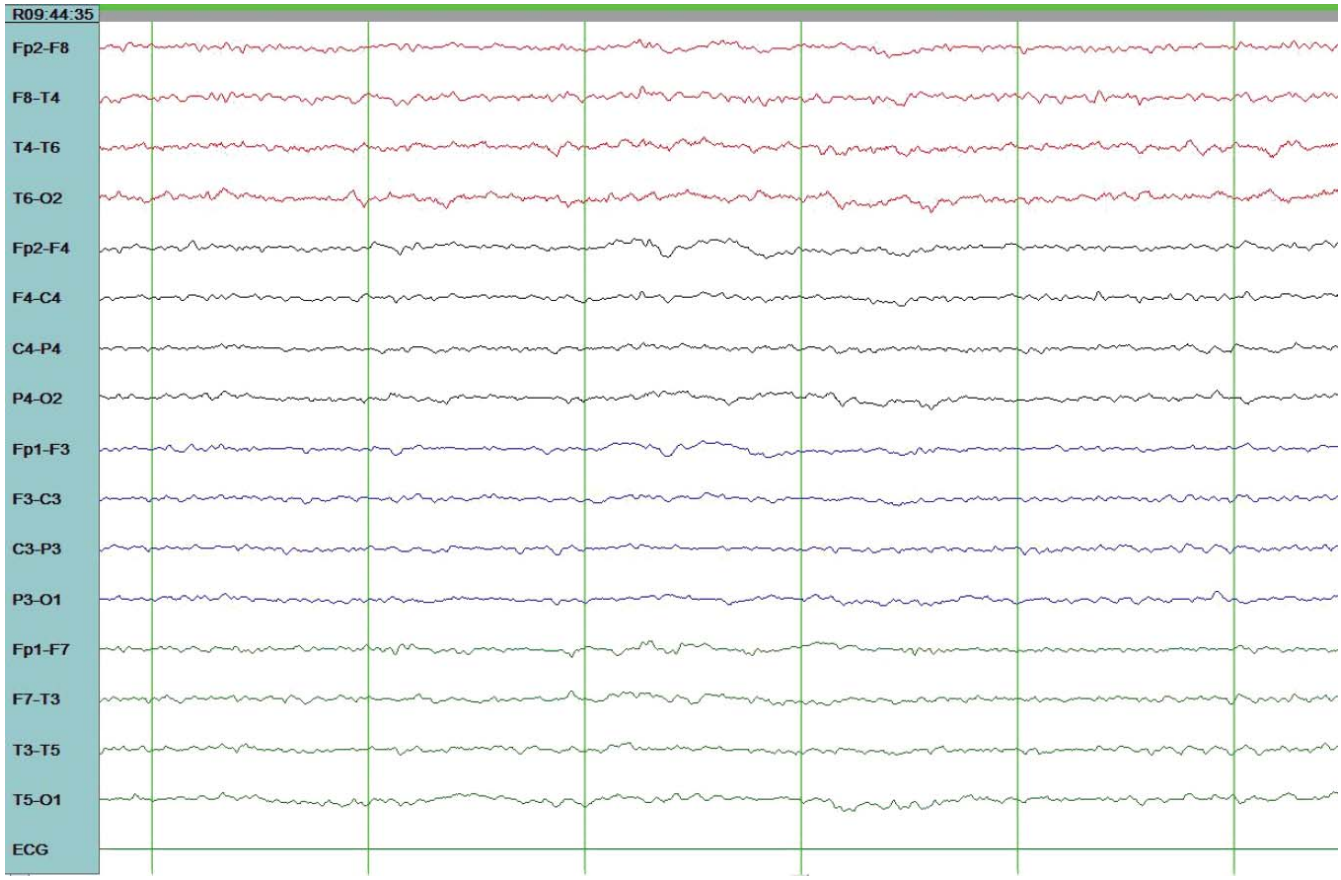

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Figure 2. Electroencephalogram after Combination Anti-Epileptic Therapy with the Focal Spikes Abolished
Ten days after successful treatment, occasional interictal discharges within a normal background were observed.

frequent presenting features being tremor, transient aphasia, myoclonus, gait ataxia, cognitive impairment, seizures, and sleep abnormalities. Misdiagnosis at presentation was common, with most cases misdiagnosed as viral encephalitis, Creutzfeldt-Jakob disease, dementia, or psychiatric disorders [5]. Recurrent seizures are a recognised presentation of this condition [6]. Other causes of acute symptomatic seizures with multiple seizures upon presentation are listed in Box 2.

Making the Correct Diagnosis

The diagnosis of HE is based on presence of elevated anti-thyroid antibodies in patients with a compatible clinical presentation and exclusion of other causes of encephalopathy or acute confusional state (Box 1). Diagnosis requires presence of high titres of anti-thyroid peroxidase and/or anti-thyroglobulin antibodies, although this is not specific and there is no clear correlation between antibody titres and the severity of neurological symptoms [7]. The presence of anti-thyroid antibodies can sometimes be detected in normal individuals, though usually at lower titres. In some cases, presence of anti-neuronal antibodies has been noted [8]. Most patients have overt or subclinical hypothyroidism at the time of presentation, but can also be euthyroid at the time of diagnosis. Erythrocyte sedimentation rate and C-reactive protein are elevated in some patients [5]. In some aspects, Hashimoto encephalopathy resembles a heterogenous group of conditions, including Sjögren syndrome and systemic lupus erythematosus-associated meningoencephalitis, which are characterised by the association with underlying autoimmune conditions as well as the unifying feature of steroid responsiveness [5,9].

CSF analysis is abnormal in around 80% of cases of HE, often with elevated protein concentrations, and less often, a lymphocytic pleocytosis [7]. MRI is usually normal. Non-specific EEG abnormalities are often seen in the absence of seizures, with slowing of background activity that correlates with the clinical severity of the underlying encephalopathy. Other EEG findings reported include triphasic waves, epileptiform abnormalities, photomyogenic response, and photoparoxysmal response. The EEG abnormalities often paralleled the clinical course, showing improvement with the clinical condition. In one series, myoclonic jerks were recorded during the EEG study of about half the patients [10]. Patients with sporadic CJD may have clinical features identical to that of Hashimoto encephalopathy, when steroid responsiveness may be the only differentiating feature [1,9]. In addition, diffusion-weighted MRI imaging may also help differentiate between the two conditions, with hyper-intense abnormalities involving cortex and deep gray matter being highly sensitive and specific for sporadic CJD.

Treatment Approach

In addition to supportive measures, use of high-dose glucocorticoids is usually associated with marked clinical

improvement, as well as improvement in EEG findings. In a review of 85 cases, the majority of patients who received glucocorticoids improved with treatment [11]. In some cases, additional short courses of glucocorticoids or other immunomodulatory therapy may be required to treat relapses [5]. In more severe cases, intravenous immunoglobulins and plasmapheresis may also be helpful [12]. Treatment of seizures with anti-convulsant medications may be necessary as a temporary measure, though in some cases seizures do not respond to anti-epileptic drugs but may respond to steroid therapy. Thus, considering HE in the differential diagnosis is of paramount importance. Whilst thyroid hormone replacement is indicated in patients with biochemical evidence of overt hypothyroidism, there is no correlation between neurological improvement and thyroxine replacement. The treatment of subclinical hypothyroidism, on the other hand, remains controversial [13].

As illustrated by our case, recognition of this form of autoimmune encephalopathy and its varied presentation is important, as it is readily treatable. Presence of a personal or family history of thyroid disorder should alert clinicians to the possibility of Hashimoto encephalopathy in patients with an otherwise unexplained subacute encephalopathy. Measurements of thyroid function and thyroid antibodies will be helpful in this setting.

Key Learning Points

Autoimmune thyroid disease may be associated with an encephalopathy (HE) with acute or subacute onset, accompanied by seizures, tremor, myoclonus, ataxia, psychosis, or stroke-like episodes, with a relapsing/remitting or progressive course.

A diagnosis of HE should be considered in patients with unexplained delirium, encephalopathy, or seizures. The diagnosis is based on exclusion of other causes of delirium, and is supported by the finding of elevated titres of anti-thyroid antibodies.

Other autoimmune conditions such as Sjögren syndrome and systemic lupus erythematosus may also be associated with a steroid-responsive meningoencephalitis and a similar clinical presentation to HE.

Treatment is supportive, though use of intravenous glucocorticoids is associated with improvement in neurological features as well as EEG abnormalities.

Thyroid hormone replacement is indicated in patients with biochemical evidence of overt hypothyroidism, though there is no correlation between neurological improvement and thyroxine replacement. ■

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References

1. Seipelt M, Zerr I, Nau R, Mollenhauer B, Kropp S, et al. (1999) Hashimoto's encephalitis as a differential diagnosis of Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 66: 172-176.
2. Rees JH, Smith SJ, Kullmann DM, Hirsch NP, Howard RS (1999) Creutzfeldt-Jakob disease presenting as complex partial status epilepticus: A report of two cases. J Neurol Neurosurg Psychiatry 66: 406-407.
3. Brain L, Jellinek EH, Ball K (1966) Hashimoto's disease and encephalopathy. Lancet 2: 512-514.
4. Ferracci F, Bertiato G, Moretto G (2004) Hashimoto's encephalopathy: Epidemiologic data and pathogenetic considerations. J Neurol Sci 217: 165-168.
5. Castillo P, Woodruff B, Caselli R, Vernino S, Lucchinetti C, et al. (2006) Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 63: 197-202.
6. Ferlazzo E, Raffaele M, Mazzu I, Pisani F (2006) Recurrent status epilepticus as the main feature of Hashimoto's encephalopathy. Epilepsy Behav 8: 328-330.
7. Kothbauer-Margreiter I, Sturzenegger M, Komor J, Baumgartner R, Hess CW (1996) Encephalopathy associated with Hashimoto thyroiditis: Diagnosis and treatment. J Neurol 243: 585-593.
8. Oide T, Tokuda T, Yazaki M, Watarai M, Mitsuhashi S, et al. (2004) Anti-neuronal autoantibody in Hashimoto's encephalopathy: Neuropathological, immunohistochemical, and biochemical analysis of two patients. J Neurol Sci 217: 7-12.
9. Chong JY, Rowland LP (2006) What's in a NAIM? Hashimoto encephalopathy, steroid-responsive encephalopathy associated with autoimmune thyroiditis, or nonvasculitic autoimmune meningoencephalitis? Arch Neurol 63: 175-176.
10. Schauble B, Castillo PR, Boeve BF, Westmoreland BF (2003) EEG findings in steroid-responsive encephalopathy associated with autoimmune thyroiditis. Clin Neurophysiol 114: 32-37.
11. Chong JY, Rowland LP, Utiger RD (2003) Hashimoto encephalopathy: Syndrome or myth? Arch Neurol 60: 164-171.
12. Mocellin R, Walterfang M, Velakoulis D (2007) Hashimoto's encephalopathy : Epidemiology, pathogenesis and management. CNS Drugs 21: 799-811.
13. Gharib H (2008) Review: Available evidence does not support a benefit for thyroid hormone replacement in adults with subclinical hypothyroidism. Evid Based Med 13: 22.