CASE REPORT

Steroid-responsive encephalopathy: an under recognised aspect of Hashimoto's thyroiditis

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Accepted 19 February 2015

SUMMARY

We present a case of a patient who was diagnosed with Hashimoto's encephalopathy based on the presence of subacute behavioural changes, negative work up for infection and immunological serology except for high serum titres of thyroid autoantibodies. Thyroid function tests (TFTs) and MRI of the brain were normal. EEG showed low amplitude, slow waves and θ waves at both frontal areas. His condition improved dramatically after treated with high-dose glucocorticoid. After 2 years of a relapsing–remitting course, a new episode occurred. There was an abrupt change of TFTs within 5 days: free thyroxine (fT4) from 1.52 to 1.53 ng/mL, free triiodothyronine (fT3) from 3.25 to >30 pg/mL and thyroid-stimulating hormone (TSH) from 5.08 to 0.78 mIU/L. On the following day found fT4 2.58, fT3 14.67 and TSH 0.042. The patient was diagnosed with Hashitoxicosis. High-dose glucocorticoid and β -blockers were initiated. The symptoms gradually improved and TFTs normalised within 2 weeks.

BACKGROUND

Hashimoto's encephalopathy (HE), also termed as steroid responsive encephalopathy associated with autoimmune thyroiditis, is used to describe cases with unexplained neurocognitive symptoms such as encephalopathy, cognitive impairment, intractable seizure and coma; these cases show elevated thyroid autoantibody levels and improve significantly with glucocorticoid therapy. Diagnosis of HE needs to be excluded by other aetiologies such as infectious, vascular, metabolic, toxic, neoplastic and paraneoplastic causes. Previously, there was controversy over whether HE is a clinical syndrome or a coincidence. However, Chong *et al*¹ reviewed these common findings among articles, which led to the conclusion that it was unlikely to occur by chance. Nonetheless, the definite pathogenesis has not been clearly identified.

HE is a rare syndrome with an estimated prevalence of 2.1 per 100 000 subjects.² The mean age of onset is between 45 and 55 years. In the adult population, the female-to-male ratio is approximately 4:1.¹ There is association with other autoimmune disorders that are similar to Hashimoto thyroiditis.³ A majority of the patients are in a euthyroid or hypothyroid state,^{1 4} although some patients with thyrotoxicosis from either Graves' disease or subacute thyroiditis have also been reported.⁵ There is no correlation between thyroid function status or degree of elevation of thyroid autoantibodies and the severity and clinical manifestations of neurological deficits.³ Moreover, thyroxine replacement

or antithyroid drug therapy without steroid did not improve the patient's neurological symptoms in several cases of HE with thyroid dysfunction.^{6–8} However, levels of thyroid autoantibody mostly decrease in conjunction with clinical improvement.⁹

We report a case of HE that showed the temporal association of Hashitoxicosis with a relapse of neurological symptoms suggesting the relation between the exacerbation of thyroid autoimmunity and putative neurological immune phenomena.

CASE PRESENTATION

A 26-year-old previously healthy man presented with a 7-day history of behavioural changes, including psychomotor retardation, aggression and confabulation. He had resigned from his previous job three months earlier due to occupational stress. There was no history of trauma, smoking, drinking alcohol, illicit drug use or medical problems including autoimmune diseases in patient or family members. On examination, the patient was alert and oriented. His vital signs were normal except body temperature, which was 37.8°C. He was partially responsive to commands and showed apathy. Deep tendon reflexes were 3+ all jerks and frontal lobe signs; palmomental and glabellar signs were positive. Complete blood count, serum electrolyte, blood urea nitrogen, creatinine, liver function test and thyroid function tests (TFTs) were all normal. Infectious disease work ups of serum and cerebrospinal fluid (CSF) were negative, including haemoculture, CSF and stool aerobic culture, *Burkholderia pseudomallei*, syphilis, *Mycobacterium*, fungus, enterovirus, cytomegalovirus, herpes, hepatitis B, dengue, Japanese encephalitis and Epstein-Barr virus. Immunological work ups including erythrocyte sedimentation rate, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-Ro, anti-La and anti-N-methyl-D-aspartate, were all negative, except for high titres of antithyroglobulin 1822 IU/mL (reference range 0–115) and antithyroperoxidase 520 IU/mL (reference range 0–34). CT and MRI of the brain revealed normal studies. Lumbar puncture was performed with open pressure 16.5 cm of water. The CSF contained 50 red blood cells, which could have been caused by traumatic tapping, and no white cell count. CSF total protein was 29 mg/dL. CSF glucose was 50 mg/dL (concurrent plasma glucose was 92 mg/dL). EEG showed low amplitude, intermittent slow waves and θ waves at both frontal areas, compatible with an encephalic pattern. The patient was initially treated with acyclovir for 5 days but showed no improvement. After all the investigation results were reported,

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To cite: Riangwiwat T, Sangtian J, Sriphrapadang C. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208969

diagnosis of HE was established. The patient was started with intravenous methylprednisolone 1 g daily for 3 days and then switched to oral prednisolone 60 mg/day and risperidone 2 mg at bedtime. After 1 month of treatment, he returned to normal and regained the ability to perform instrumental activities of daily living. On physical examination, antithyroglobulin, antithyroperoxidase levels and EEG returned to normal within 6 months. TFTs were within normal limits.

At 1-year follow-up, risperidone was discontinued and prednisolone was reduced to a maintenance dose of 5 mg/orally on alternate days. This regimen successfully stabilised the patient for 8 months before the second episode occurred. The patient showed a 10-day history of behavioural changes, including insomnia, psychomotor retardation, aggressive moods and impairment of cognitive functions. He had good drug compliance and no recent stress. His vital signs were stable except for heart rate, which was 108 bpm. Deep tendon reflexes were 3+ at all jerks and glabellar sign was positive. Complete blood count, electrolytes including inorganic phosphate, magnesium,

blood urea nitrogen, creatinine and liver function tests revealed normal results. There was an abrupt change in thyroid function within 5 days (figure 1): free triiodothyronine (fT3) from 3.25 to >30 pg/mL (reference range 1.71–3.71), free thyroxine (fT4) from 1.52 to 1.53 ng/mL (reference range 0.70–1.48) and thyroid-stimulating hormone (TSH) from 5.08 to 0.78 μ IU/mL (reference range 0.35–4.94). High titres of thyroid autoantibodies were noted: antithyroglobulin 1700 IU/mL (reference range 0–115), antithyroperoxidase 421 IU/mL (reference range 0–34) and antibody to TSH receptor 0.3 IU/L (reference range 0.3–1.75). Thyroid scintigraphy showed decrease in thyroid uptake activity. The findings suggested a thyroiditis pattern. The possible aetiologies included infection, autoimmune-related inflammation, structural abnormalities and paraneoplastic syndrome, which were investigated and returned negative, except as mentioned earlier. Therefore, the diagnosis of HE with Hashitoxicosis was established. Intravenous methylprednisolone 1 g daily for 5 days was given and then switched to oral prednisolone 60 mg/day with taper, but no antithyroid medication was

Figure 1 Longitudinal follow-up of the thyroid function tests and thyroid autoantibodies of the patient (Anti-TG, antibody to thyroglobulin; Anti-TPO, antibody to thyroperoxidase; fT3, free triiodothyronine; fT4, free thyroxine; IV, intravenous; TSH, thyroid-stimulating hormone).

administered. The TFTs returned to normal within 3 days. It took 3 months to realise significant clinical improvement. At the latest visit, on November 2014, the patient remained stabilised on oral prednisolone 10 mg/day.

DISCUSSION

Since HE is a treatable disorder, it should be considered in cases of unexplained encephalopathy. The search should include evaluation of TFTs and thyroid autoantibodies. Our patient showed thyrotoxicosis with a rapid change in TFTs at the time of active disease, which could be easily missed without close follow-up. However, previous studies revealed a mainstream of cases presenting with hypothyroidism or euthyroidism.^{1–8} Some patients with thyrotoxicosis, such as Graves' disease, subacute thyroiditis or radiation thyroiditis, have been reported as well.^{10–12}

The pathogenesis of HE is unknown but the most accepted hypothesis is of an autoimmune aetiology that causes cerebral vasculitis and directed injury against common brain–thyroid antigens. This hypothesis is supported by some common circumstances such as the preponderance of female patients, the fluctuating clinical course and the association with other autoimmune diseases. In addition, brain biopsy shows mild lymphocytic infiltration of small vessels, but only a few samples have been provided for studies.¹³ Our patient showed various characteristics that support this hypothesis. First, the level of serum thyroid autoantibodies that decreased in parallel with the clinical improvement of the patient. Second, the presence of Hashitoxicosis in this patient might determine the interconnection between HE and Hashimoto's thyroiditis since there was a case series showing that thyrotoxicosis may develop later in patients with euthyroid Hashimoto's disease.¹⁴ According to TFTs during Hashitoxicosis, dominantly elevated fT3 was a similar characteristic with Graves' disease, which also showed the possibility of an autoimmune aetiology. Unfortunately, the limitation in the presented case was that antithyroperoxidase and antithyroglobulin levels in CSF were not obtained. However, there is no evidence of a pathogenic role for thyroid autoanti-

bodies and levels of CSF thyroid autoantibodies are not correlated with clinical manifestations of HE.¹⁵ Thyroid autoantibodies might probably be markers of some other autoimmune disorder affecting the brain.⁴ The presence of antithyroperoxidase can be found in nearly 9% of the general Thai population,¹⁶ therefore, presence of high titres are necessary for the diagnosis of HE, but not specific. A recent report showed that serum autoantibodies against the N-terminal of α -enolase are a useful diagnostic biomarker for HE.¹⁷

CONCLUSIONS

Physicians should be familiar with HE because of an increasing incidence of this syndrome. However, thyroid dysfunction should be managed in the same way as in patients without encephalopathy. Measurement of TFTs during the active phase of HE may be helpful for management of thyroid dysfunction.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Hashimoto's encephalopathy is a diagnosis by exclusion of cases presenting with unexplained neurocognitive symptoms together with elevated thyroid autoantibody levels that improve significantly with glucocorticoid therapy.
- ▶ The presence of thyroid autoantibodies can be found in the normal general population, therefore, presence of high titres are necessary for the diagnosis of Hashimoto's encephalopathy, but not specific.
- ▶ A majority of patients with Hashimoto's encephalopathy are in a euthyroid and hypothyroid state, but some patients with thyrotoxicosis or thyroiditis have also been reported. Hence, physicians should check patients' thyroid function and manage patients according to the result.

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