A novel assessment and treatment approach to patients with Hashimoto's encephalopathy

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Summary

Hashimoto's encephalopathy (HE) is rarely reported with only a few hundred cases published. Diagnosis is made in patients with an appropriate clinical picture and high antithyroperoxidase (anti-TPO) antibodies after infectious, toxic and metabolic causes of encephalopathy have been excluded. There is little objective data on the neurocognitive impairment in patients with HE and their improvement with treatment. We present the case of a 28-year-old woman with HE. Approach to management was novel as objective neuropsychological assessment was used to assess her clinical condition and response to treatment. Intravenous immunoglobulin (IVIg) as the first-line treatment instead of steroids. She responded well. The case illustrates that a different approach is required for the diagnosis and treatment of HE. A new diagnostic criteria is proposed that includes neurocognitive assessment, serum and CSF antibodies, an abnormal EEG and exclusion of other causes of encephalopathy. Furthermore, treatment should be tailored to the patient.

Learning points:

- Neurocognitive assessment should be carried out to assess the extent of brain involvement in suspected Hashimoto's encephalopathy pre- and post- treatment.
- Treatment of Hashimoto's encephalopathy should be tailored to the patient.
- Unifying diagnostic criteria for Hashimoto's encephalopathy must be established.

Background

Hashimoto's encephalopathy (HE) is characterised by a subacute, steroid-responsive encephalopathy in patients with positive antithyroid antibodies (1). The clinical presentation is highly variable; common clinical features include confusion, altered consciousness, tremor, transient aphasia, gait ataxia, seizures and sleep abnormalities. The natural history of the disease is relapsing-remitting (2). There have been just a few hundred cases reported in the literature. The average age of onset is 42 years, and it has an estimated prevalence of 2.1/100 000 people (3). The heterogeneity of the clinical presentation, the high prevalence of antithyroid antibodies in the general population and the lack of a clear underlying pathophysiological process has led many to question whether HE is a true syndrome. Diagnosis is made in patients with an appropriate clinical picture and high antithyroperoxidase (anti-TPO) antibodies after infectious, toxic and metabolic causes of encephalopathy have been excluded (4). However, objective data on the neurocognitive impairment in patients with HE and their improvement with treatment is limited. We present the case of a 28-year-old woman, illustrating a different approach to diagnosis and treatment of HE.

Case presentation

A 28-year-old woman was initially referred to the chronic fatigue clinic. She was a special needs teacher. During her teenage years she suffered from relapsing lethargy that coincided with menarche. She developed hypothyroidism secondary to autoimmune thyroiditis aged 20 years.

At the age of 26 years, she had been housebound for a year with fatigue. Her symptoms were dominated by lethargy, cognitive decline, poor concentration, generalised muscle aches and migraines. She was unable to sustain employment. On examination, her body mass index (BMI) was $35.7\,kg/m^2$, and she had no features of endocrinopathy.

Investigation

Blood results showed that she was adequately replaced with thyroxine, TSH: 1.78 mU/L (0.35–5.5 mU/L) and T4: 15.1 pmol/L (10–19.8 pmol/L). Routine bloods including full blood count, urea and electrolytes, liver function, erythrocyte sedimentation rate and C-reactive protein were within normal range. An autoantibody screen revealed high anti-TPO antibody titre 1214 IU/L (0–50 U/L). Antibodies for autoimmune and paraneoplastic encephalitis were negative.

Cerebrospinal fluid (CSF) examination showed normal protein, glucose and white cells. She had positive oligoclonal bands restricted to the CSF compatible with a central nervous system-specific autoimmune disorder. Anti-TPO antibody CSF titre was high at 771 IU/mL.

Random glucose readings ranged between 4.3 mmol and 4.8 mmol, and she had no symptoms of Whipple's triad. Thus, the possibility of hyperinsulinaemia or hypoglycaemia contributing to the clinical picture was not formally investigated.

Sleep apnoea studies were normal. MRI brain was unremarkable and an ultrasound of her thyroid revealed signs of chronic thyroiditis with multiple sub-centimetre nodules.

Electroencephalogram (EEG) showed no epileptiform discharges but a slower than expected background rhythm with intermittent sharper waveforms. The positive CSF TPO antibody in conjunction with her symptoms, normal imaging and nonspecific changes on the EEG were consistent with HE.

We organised comprehensive neuropsychological evaluation before and after treatment. The results are illustrated in Table 1 and show an average or below average intellectual performance at presentation.

Methods

TSH was measured by a two-site sandwich immunoassay method using direct chemiluminometric technology with two antibodies on the ADVIA Centaur analyser by Seimens.

MRI of the brain was done on Siemens Avanto MRI scanner using the following sequences: T2W axial and coronal, axial flair, sagittal T1W, diffusion-weighted images (DWI) and ADC maps. The scans were done using MRI brain protocol, and no contrast was given.

TPO antibody titres were measured by Fluorescence Enzyme ImmunoAssay (FEIA) method (Immunocap solid phase, PHADIA 250, manufacturer PHADIA AB, Uppsala, Sweden).

Treatment

High-dose steroids are the first-line treatment for HE and indeed encephalopathy of unknown cause. However, in the patient's case, concerns were raised about the metabolic side effects given her BMI. Following discussion between the endocrinologists, neurologists and the patient, the decision was taken to start pulsed IVIg. To our knowledge, this is the first case in the literature where IVIg has been used as the initial treatment of HE.

Outcome and follow-up

In the neuropsychological evaluation, following IVIg therapy, the patient showed improvement on measures of general intellectual functioning. She also demonstrated greater efficiency across all other cognitive domains post treatment with performance falling within the low average to average range (Table 1).

Discussion

Currently, there is no consensus over the diagnosis or pathogenesis of HE. HE is characterised by a subacute, steroid-responsive encephalopathy in patients with positive antithyroid antibodies[1]. It is likely that it is an autoimmune condition given the association with other autoimmune diseases, female preponderance, the fluctuating course of the disease and its response to steroids (2, 4, 5). Thyroid status does not seem to be a factor in the development of HE and indeed many patients are euthyroid at presentation (6).

Most patients have anti-thyroperoxidase antibodies, and these have been shown to fluctuate with disease

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Table 1 Neuropsychological test results.

	Pre-treatment		Post-treatment	
	Value	Percentile	Value	Percentile
General intellectual function				
Short-Form WAIS-IV+				
Verbal comprehension index (VCI)	105	63	114	82
Perceptual reasoning index (PRI)	109	73	123	94
Attention and working memory				
WAIS-IV Digit Span Scaled Score++	6	9	8	25
Longest digit forward span	6		7	
Longest digit backward span	4		4	
Processing speed and attention				
WAIS-IV Digit Symbol Scaled Score	5	5	8	25
Memory				
Camden Memory Test				
Words	19/25	<5	23/25	5–10
Faces	23/25	50	24/25	75
RBANS Story				
Immediate	16	16–21	15	13–16
Delayed	8	16	9	32
CVLT-II Standard Form				
Trials 1–5			41	16–21
Long delay free recall			−0.5	32
Language				
Graded Naming Test	15/30	10	19/30	25–30
Visual perceptual function				
VOSP				
Incomplete letters	20/20		20/20	
Position discrimination	20/20		20/20	
Executive function				
Animals/boys names, 2 min	32	9	35	16
Letter C, 1 min	8	9	10	16
TMT trials A, seconds	37	10–20	28	20–30
TMT trials B, seconds	90	<10	64	10–20

WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition (11); Graded Naming Test (12); Camden Memory Tests (13); RBANS, Repeatable Battery for the Assessment of Neuropsychological Status (14); CVLT-II, California Verbal Learning Test-Second Edition (15); VOSP, The Visual Object and Space Perception Battery (16); TMT, Trial Making Test (17); + index score of 100 represents an average performance; ++ scaled score of 10 represents an average performance.

activity and in response to treatment. Their role in the pathogenesis, however, is unclear (3). The high prevalence (up to 20%) (7) of anti-TPO antibodies in the general population and the lack of scientific data showing a causal link suggest that they are probably a marker of disease rather than the root of the problem (1, 4).

Autoimmunity and vasculitis directed against common brain-thyroid antigens represent the most probable aetiologic pathway in HE (15). Antibodies against the amino terminal of alpha-enolase have been found in patients with HE with relatively high specificity for the condition (8). Several other anti-neuronal antibodies have been found in patients with HE (8). These include IgG found in the CSF of patients that bind the enzymes dimethylargininase-I and two isoforms of aldehyde reductase-I potentially leading to endothelial and vascular damage (8).

Conclusion and recommendations

Neurocognitive assessment should be carried out to assess the extent of brain involvement in suspected HE pre- and post-treatment. An alternative modality such as functional brain imaging could have been deployed, but this carries the risk of irradiation and does not measure an individual's functional performance. Most evidence of improvement in HE with treatment is subjective. This case illustrates the superior insight neurocognitive assessment can have in evaluating the impact of treatment on a patient's wellbeing.

Treatment of HE should be tailored to the patient. Steroids are accepted as the first-line treatment for patients with HE, and there are a number of cases where IVIg and plasmapheresis have been used as second-line treatment (9, 10). There are only however some 200 cases in the literature to draw upon.

The patient described is currently the only case where IVIg has been used as a first-line treatment. When deciding on the most effective modality of treatment the patient should be involved in the decision making process.

Unifying diagnostic criteria for HE must be established. The presentation of HE is heterogeneous. An unspecified number of patients on thyroid replacement therapy report euthyroid dysphoria. Given that the current diagnostic criteria for HE are not robust it may be that HE is a continuum of disease with some cases of euthyroid dysphoria being mild HE. We propose a new set of diagnostic criteria need to be put forward for HE and suggest:

- Positive serum anti-TPO antibodies with positive CSF anti-TPO antibodies in high titres (>500).
- CSF oligoclonal bands.
- Neurocognitive impairment pre-treatment with response to immunosuppressant therapy.
- Exclusion of others causes of encephalopathy.
- Exclusion of other possible differential diagnosis, such as sleep apnoea syndrome.
- Abnormal EEG.

While these diagnostic criteria reflect our experience and literature review, the list should not be regarded as comprehensive. Further research into this condition is required to clarify the pathogenesis and reach the consensus on establishing the diagnosis of HE. Without agreed diagnostic criteria for encephalopathy patients with HE may go undiagnosed with a treatable and reversible cause of encephalopathy.

Author contribution statement
Kate Laycock: lead author, Abhijit Chaudhuri: direct care, Charlotte Fuller: direct care, Zahra Khatami: direct care, Frederik Nkonge: direct care and Nemanja Stojanovic: direct care and author.

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