Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful response to intravenous immunoglobulin as rescue therapy in a patient with Hashimoto's encephalopathy

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Summary

The authors describe the case of a 61-year-old woman who was admitted to our intensive care unit (ICU) due to impaired consciousness associated with generalised seizures. Her cerebrospinal fluid, electrolytes, acid-base analysis, and common laboratory and toxicology tests were normal. An MRI ruled out the presence of stroke or haemorrhage but showed severe leukoencephalopathy. Parkinson's disease, Creutzfeldt–Jacob disease, vascular alterations, cancer, and rheumatological and metabolic diseases were evaluated and excluded. In view of her history of hypothyroidism despite adequate hormonal replacement and clinical behaviour, Hashimoto's encephalopathy was considered. Anti-thyroperoxidase levels were above 3000 IU/ml. The patient received prednisolone followed by prednisone, but after a favourable initial response, returned to a comatose state. However, after intravenous immunoglobulin (IVIg) 2 g/kg, the patient recovered with resolution of neurological symptoms and was discharged.

hyperintensity related to Hashimoto

BACKGROUND

Hashimoto's encephalopathy is an uncommon disorder that is seldom diagnosed correctly. We describe when Hashimoto's encephalopathy should be suspected and how a timely diagnosis can change the patient's prognosis. Opportune treatment has a dramatic effect, transforming a severe neurological illness into curable neurological impairment. Although good response to corticosteroids is one of the main characteristics of Hashimoto's encephalopathy, some patients are non-responsive and require other therapies, as described here. Immunoglobulin has been successfully used as rescue therapy in Hashimoto's encephalopathy non-responsive or partially responsive to corticosteroids.

CASE PRESENTATION

A 61-year-old female patient with surgical hypothyroidism due to multinodular goitre and two stroke-like episodes without sequelae, presented with a 2-month history of malaise and bradypsychia. On 23 November 2009, after 12 h of sudden altered consciousness, she had a generalised seizure with sphincter relaxation. She was brought to the emergency department of the Clinical Hospital Universidad de Chile, where she had another seizure. In view of her altered state of consciousness (Glasgow Coma Scale 7), she was intubated, connected to mechanical ventilation and admitted to the intensive care unit (ICU).

An MRI ruled out the presence of stroke or haemorrhage, while showing noticeable hyperintensity of white matter in both hemispheres, especially in the frontal and temporal lobes, resembling vasogenic oedema (figure 1A,B,C). Basic

tests were within range and no toxic substances were detected. Her thyroid function was well substituted. A lumbar puncture was performed: cerebrospinal fluid was clear, with 60 red cells, no white cells, glucose 77 mg/dl and proteins 25 mg/dl. Gram stain was negative. The patient was started empirically on acyclovir, but as Chinese ink and PCR for herpes virus, varicella zoster virus, Epstein Barr virus, herpes 6 virus and enterovirus all turned out to be negative, the antiviral was suspended.

The patient was evaluated again using MRI with gadolinium (figure 1D), which showed severe leukoencephalopathy, perhaps due to a toxic, metabolic, infectious or inflammatory disorder, with ischaemic lesions possibly indicating secondary vasculitis according to the neuroradiologists.

There were no signs or symptoms of rheumatological disease in her background, and all antibodies were negative (ANA, ENA, ANCA, FR, anti-DNA, IgM and IgG β_2). Arylsulfatase A was normal, ruling out metachromatic leukodystrophy.

The patient was thoroughly evaluated with different radiological studies. A CT scan of the chest showed the presence of a mass in the anterior mediastinum. A paraneoplastic syndrome was suspected and a biopsy was carried out, but the sample did not show malignancy. During clinical evolution, the patient's neurological condition worsened to deep coma and decerebrating posture.

Considering her background and clinical presentation, Hashimoto's encephalopathy was considered a likely diagnosis. Anti-thyroperoxidase (TPO) levels were measured and were above 3000 IU/ml. The patient was treated with

Figure 1 Axial fluid attenuation inversion recovery images (A,B,C) show diffuse white matter hyperintensity related to Hashimoto's encephalopathy, extending into the gyri but sparing the immediate juxtacortical white matter. It mainly affects the frontal lobes, but also involves insular, temporal and parietal regions with moderate mass effect. Axial T1 gadolinium image (D) shows no pathological enhancement.

intravenous methylprednisolone (5 g on each of 5 consecutive days) followed by prednisone (2 mg/kg/day). Although she initially responded and spontaneously opened her eyes, she returned to a comatose and hypotonic state with palsy of the left VI nerve. Considering her extremely serious condition, we decided not to wait for a corticosteroid response as it can be delayed, and administered intravenous immunoglobulin (IVIG) at a dose of 2 g/kg body weight on each of 5 days, while tapering off prednisone. The patient recovered completely with resolution of her neurological symptoms. She was transferred from the ICU on 12 December 2008 and finally discharged from hospital on 8 January 2009, after successful treatment of pneumonia and physical rehabilitation. At discharge, the patient was lucid and in good general condition.

DIFFERENTIAL DIAGNOSIS

Hashimoto's encephalopathy is, by definition, a diagnosis of exclusion and therefore more frequent pathologies must first be ruled out. The clinical features of Hashimoto's encephalopathy may mimic stroke or other vascular complications. Progressive encephalopathy, another common presentation, can also be confused with Alzheimer's disease. On the other hand, when encephalopathy presents less acutely, Creutzfeldt-Jacob disease (CJD) is another possible diagnosis, especially since protein 14-3-3 has been observed in the spinal fluid of Hashimoto's encephalopathy patients and anti-TPO antibodies have been isolated in CJD patients.¹ In our patient's case, other possible causes for leukoencephalopathy were also rejected. Her clinical presentation did not suggest vascular alteration (as in CADASIL or

Moya Moya disease). Arylsulfatase A was normal, ruling out metachromatic leukodystrophy. The patient had not been exposed to radiation or chemotherapy, and had no evidence of neoplastic disease.

TREATMENT

The patient received conventional treatment with corticosteroids. We administered high-dose methylprednisolone, followed by prednisone (2 mg/kg/day). However, while on high-dose oral prednisone, her clinical condition worsened and she regressed to a comatose state. We therefore decided to add IVIG at a dose of 2 g/kg body weight for 5 days, while tapering off prednisone. The patient recovered with resolution of her neurological symptoms and was discharged from the ICU 4 days after finishing IVIG treatment.

OUTCOME AND FOLLOW-UP

Since her discharge on 8 January 2009, the patient has been in good general condition. However, she has experienced three relapses when corticosteroids were suspended or significantly tapered off. In each case, she responded to a temporary increase in corticosteroid dose. One of the relapses required hospitalisation. Anti-TPO and anti-thyroglobulin levels measured after discharge were in the normal range.

DISCUSSION

Hashimoto's encephalopathy is a clinically heterogeneous condition consisting of encephalopathy including seizures and variable neurological and psychiatric manifestations accompanied by a high titre of serum anti-thyroid antibodies. It has been defined by three characteristics: anti-TPO antibodies in plasma, good response to corticosteroids and the absence of another possible diagnosis.¹ It is an infrequent disease, with an estimated prevalence of 2.1/100 000.² In Ferracci's case review,³ patients were aged from 8 to 86 years, and in Chong's, from 9 to 78 years.⁴ In both series, the average age of patients with Hashimoto's encephalopathy was in the mid 40s. It is predominantly a female disease, with a female:male ratio of 4:1.³ It has been linked to autoimmune conditions such as systemic lupus erythematosus, type 1 diabetes and Sjogren's syndrome.⁵ More than a third of Hashimoto's encephalopathy patients are euthyroid, with or without exogenous supplementary thyroxine.^{3,4} A small percentage present with hyperthyroidism.^{3,4} Hashimoto's encephalopathy has also been diagnosed in a patient with Graves' disease.^{6,7}

Hashimoto's encephalopathy was first described in 1966.⁸ Findings on histopathology are rare, since patients are rapidly started on corticosteroids once the diagnosis is suspected and response is quick. Lymphocytic infiltration has been found in small vessels from the central nervous system (CNS) in a few Hashimoto's encephalopathy patients,^{4,9,10} but panencephalitis with intact blood vessels has also been reported. In fact, Hashimoto's encephalopathy has been suggested to be a variant of non-vasculitic autoimmune meningoencephalitis.^{5,11} The histological elements of vasculitis are unclear.⁹ Demyelination or spongiform changes detected on biopsy, resembling CJD alterations, have also been reported.⁵ The role of anti-TPO antibodies is also poorly understood. The mechanism through which they may cause damage is unknown. Thy-

roid function is usually preserved, even if antibody titres (eg, anti-TPO) are high.

The neurological features of Hashimoto's encephalopathy are very different from case to case. There are two major presentations: progressive encephalopathy and symptoms resembling stroke,¹² with almost a third of patients having stroke-like symptoms. Encephalopathy is usually accompanied by cognitive and behavioural alterations. Up to a third of patients show psychiatric features, mostly resembling mood disorders or even psychosis. Seizures are the most common sign, being observed in more than 60% of cases. Motor deficit,^{3,4} malaise, myalgias and fever have been occasionally reported.⁵ Relapses and remissions occur throughout the patient's life,³⁻⁵ and symptoms can change or remain unmodified during relapses.³

The pathophysiology of Hashimoto's encephalopathy remains unknown. Vasogenic oedema has been mentioned as a possible mechanism, as put forward by Brain *et al.*⁸ According to this suggestion, Hashimoto's encephalopathy may be a relapsing form of acute disseminated encephalomyelitis;¹³ however, there is no direct relationship between infection or other triggering events and relapses. Vasculitis has frequently been considered a probable cause, but histological evidence has not conclusively supported this idea. The responsiveness of Hashimoto's encephalopathy to steroids or other therapies such as plasmapheresis, supports the hypothesis that this disorder involves immune pathogenic mechanisms. The relationship between anti-TPO antibodies in the blood or spinal fluid and the neurological symptoms is not known. There is sufficient evidence for the involvement of immunological mechanisms, but antibodies could be an epiphenomenon rather than a cause. Antibodies can in fact be present in patients with or without autoimmune thyroiditis, who never present with Hashimoto's encephalopathy. A gap of many years between the identification of anti-TPO antibodies and Hashimoto's encephalopathy has also been reported.¹⁴ It has been suggested that Hashimoto's encephalopathy should be considered a "corticoid-responded encephalopathy associated with Hashimoto's thyroiditis".^{1,15}

An autoantigen, α enolase, has recently been identified as a possible injury mechanism.¹⁶ Autoantibodies against the NH₂-terminal of α enolase have been found in 83.3% of Hashimoto's encephalopathy patients, compared to 11.8% of Hashimoto's thyroiditis patients.¹⁷ However, it is unclear whether α enolase actually plays a role in pathogenesis, especially since it is a ubiquitous enzyme. Other findings point towards more specific endothelial and CNS antigens.¹⁸ These various suggestions do not explain the mechanism of Hashimoto's encephalopathy, but may lead us towards possible answers.

Regarding treatment for Hashimoto's encephalopathy, clinical improvement with corticosteroid therapy is usually observed in the first 4–6 weeks.⁵ This positive response has been considered to be part of the definition of Hashimoto's encephalopathy, but does not occur in all patients.^{3,4,19} Other therapies such as plasmapheresis and immunosuppressant medications have been successfully used in patients non-responsive to corticosteroids. According to our knowledge, only a few Hashimoto's encephalopathy patients have been treated with IVIG.^{20,21} The precise mechanism by which IVIG suppresses harmful

inflammation has not been definitively established but is believed to involve the inhibitory Fc receptor. In our patient, IVIG treatment resulted in significant improvement. This is unusual, and suggests that IVIG, which has been previously recommended and described a few times, could be considered as rescue therapy in those patients resistant or partially-responsive to corticosteroids.

Learning points

- ▶ In a patient with acute or subacute neurological deterioration, all reversible causes must be considered, no matter how uncommon.
- ▶ Hashimoto's encephalopathy should be suspected in patients regardless of thyroid function.
- ▶ A lack of response to corticosteroids does not exclude Hashimoto's encephalopathy when all other components are present and no alternative diagnosis is likely.
- ▶ Hashimoto's encephalopathy resistant to corticosteroids should be treated with other therapies, such as immunosuppressive therapy (azathioprine or cyclophosphamide), plasmapheresis or intravenous immunoglobulin.
- ▶ The pathophysiology and clinical presentation of Hashimoto's encephalopathy are poorly understood, but it is very important that clinicians are aware of it as correct diagnosis and treatment can avoid severe neurological sequelae or death.

Competing interests None.

Patient consent Obtained.

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