Ophthalmoparesis Mimicking Myasthenia Gravis as Acute Manifestation of Hashimoto’s Encephalopathy

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Abstract
Hashimoto’s encephalopathy is a rare steroid-responsive disorder in which neuropsychological and neurological symptoms are associated with Hashimoto’s thyroiditis. Recently, it has gained attention in the differential diagnosis of encephalopathy of unknown origin, although its pathogenesis is poorly understood. The diagnosis of Hashimoto’s encephalopathy rests upon the association of autoimmune thyroiditis and neurological symptoms after excluding more common diseases, but is a serious challenge in atypical cases. We here present a patient with isolated ocular disorder as presenting and unique feature of Hashimoto’s encephalopathy that resolved with steroids therapy. Brain MRI showed non-specific white matter abnormalities; EEG and an extensive neurophysiological investigation were normal. The diagnosis in this euthyroid patient was supported by the presence of serum anti-thyroid antibodies and the identification in the CSF of anti-dimethylargininase-I and aldehyde reductase-I autoantibodies. The description of atypical cases of this rare but certainly underestimated condition is clinically important and adds relevant information for the clinical practice.

Keywords Hashimoto’s encephalopathy; Autoimmune thyroiditis; Diplopia; Ophthalmoparesis

Introduction
Hashimoto’s encephalopathy (HE), also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis [1] and nonvasculitic autoimmune inflammatory meningoencephalitis [2], is a rare disorder characterized by various neurological manifestations associated with anti-thyroid antibodies, which represent the major diagnostic clue for HE. The pathogenesis of HE is poorly understood and an autoimmune mechanism has been suggested, based on the response to steroids and the association with autoimmune disorders. The pathogenetic role of anti-thyroid antibodies is still a matter of debate, but it is supported by the demonstration of intra-thecal synthesis of anti-thyroid antibodies [3], probably cross-reacting with the neural antigens α-enolase, dimethylargininase-I (DDAIH) and/or aldehyde reductase-I (AKRIA1), with consequent vascular and neuronal damage [3, 4].

Case Report
We describe a 50 year-old man who was admitted for acute onset of diplopia in the right and upward gaze. His previous medical history was unremarkable. Neurological examination revealed ptosis on his left eye and ophthalmoparesis due to right troclear and left oculomotor nerve deficit. There were neither behavioural changes nor cognitive impairment. On admission, intramuscular administration of intrastigmine did not produce any clinical benefit on diplopia. Disimmune, infective and paraneoplastic screenings (along with anti-acetylcholine receptor, -Borrelia, -onconeuronal ganglioside autoantibodies) were normal. Cerebrospinal fluid (CSF) analysis showed elevated protein content (0.98 g/L, normal values <0.45) without oligoclonal bands. Brain MRI showed non-specific white matter hyperintensity on T2-weighted sequences. Single photon emission computed tomography (SPECT) demonstrated a global decrease of cerebral perfusion.

EEG was normal. Extensive neurophysiological investigation including repetitive nerve stimulation, single-fiber and needle EMG excluded neuro-muscular transmission failure or myopathy. The patient was euthyroid but displayed high levels of serum anti-thyroglobulin and anti-thyroidperoxidase antibodies (respectively 232 IU/ml, normal values <40 and 1376 IU/ml, normal values <60). Thyroid ultrasonography showed a non-homogeneous structure consistent with thyroiditis. In addition to the presence of serum anti-thyroid antibodies, the diagnosis of HE was supported by the identification in the CSF of anti-DDAH and anti-AKRIA1 autoantibodies. The patient was treated with oral corticosteroids (prednisone 75 mg per day with progressive tapering in two months) with complete clinical recovery and decrease of serum antithyroid antibodies’ titer within two weeks. At the last follow-up after one year, the patient is still asymptomatic.

Discussion
Since the first description of HE in 1966, different clinical pictures of this controversial disorder have been reported, including stroke-like episodes (presenting with focal deficits often with relapsing-remitting course), cognitive impairment, psychiatric manifestations, sleep disturbance, seizures and gait disorders [1,5]. Although anecdotal patients with visual defects have been reported [5], our patient represents the first case manifesting with acute ophthalmoparesis.

The pathogenesis of HE is largely debated: one possible mechanism of HE is an autoimmune cerebral vasculitis, supported by SPECT findings of focal or generalized cerebral hypoperfusion and the
presence of autoantibodies to neural antigens (i.e., α-enolase, DDAHI and AKRIA1) [3, 4]. In this regard, brain biopsies of HE patients showed mild perivascular lymphocytic infiltrates without vessel wall invasion typical of vasculitis or yielded negative results [2, 6]. Alternatively, HE may be caused by autoantibodies directed against shared brain-thyroid antigens [3, 4], although their pathogenetic role is still controversial. In fact, the titers of anti-thyroid antibodies do not correlate with the type or severity of neurological deficits nor to response to therapy [3].

Since HE can resemble toxic, metabolic, ischemic, inflammatory, degenerative or infectious encephalopathies, the diagnostic work-up should include rheumatologic and metabolic screening, CSF analysis, EEG and brain MRI to rule out any possible other causes. Unfortunately, EEG abnormalities and imaging findings are often not specific, as well as mild increase of CSF protein or lymphocytes. Key support features are an elevated titer of serum anti-thyroid autoantibodies and a positive response to immunosuppressive therapy; however, the elevation of anti-thyroid antibodies is present in 10-20% of the healthy population [1] and only some patients with HE are really steroids responsive [3].

In our patient, the identification of anti-DDAHI and -AKRIA1 antibodies in the CSF and the very prompt response to steroid supported the diagnosis of HE, although challenging for the atypical presentation of ophthalmoparesis mimicking acute onset of myasthenia gravis. The impaired cerebral perfusion in our patient could result from vasculitic changes of cerebral microvasculature [3], even if such finding has been detected also in patients with autoimmune thyroiditis but without any neurological complication [7].

**Conclusion**

In conclusion, the case reported suggests that, beyond the already known clinical features of encephalopathy, HE can manifest as isolated acute ocular nerve impairment. This case report underscores the importance of considering HE in the etiologies of isolated ocular disorders that can mimic myasthenia with ocular onset. The description of atypical cases of this rare but underestimated condition is clinically relevant in the medical practice and expand the clinical spectrum of this treatable disorder.

**References**