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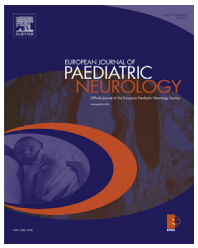

Case study

Anti-NMDAR encephalitis misdiagnosed as Hashimoto's encephalopathy

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ABSTRACT

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a well-defined autoimmune disorder. Hashimoto's encephalopathy (HE) is a still controversial entity, lacking definite diagnostic criteria.

We described a 14-year-old-girl presenting with a clinical picture consistent with the diagnosis of anti-NMDAR encephalitis, confirmed by NMDAR antibody testing. Four years earlier, she had presented a similar episode of acute encephalopathy diagnosed as HE.

Anti-NMDAR encephalitis and HE share similar clinical features so that the differential diagnosis can be difficult if specific antibodies are not tested. The correct diagnosis of anti-NMDAR encephalitis is crucial to plan the appropriate management and follow-up, namely in term of oncological screening, since it can be paraneoplastic in origin. We suggest to re-evaluate the clinical history of all subjects with previous HE diagnosis in order to evaluate the possible diagnosis of anti-NMDAR encephalitis and plan the appropriate management of these patients.

1. Introduction

Hashimoto's encephalopathy (HE) is a clinically heterogeneous condition characterized by acute or subacute onset of neurological and/or psychiatric symptoms, associated to high titres of anti-thyroid antibodies (Abs).[1] However, this entity is controversial since definite diagnostic criteria are still lacking and the aetio-pathogenesis is unclear.

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, firstly described in 2007 by Dalmau and colleagues, may be either paraneoplastic or non-paraneoplastic in origin and it is characterized by an acute onset of psychiatric symptoms,

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decreased levels of consciousness, seizures, episodes of autonomic instability, orofacial-limb dyskinesias and cognitive impairment.[2]

Here we describe a patient who, four years after a diagnosis of HE, presented with a second episode of acute encephalopathy recognized as anti-NMDAR encephalitis.

2. Case study

The proband is a 14-year-old-girl who was healthy until the age of 10 years when, because of hypothyroidism symptoms, she received a diagnosis of Hashimoto thyroiditis and started L-thyroxin therapy.

After nine months she was admitted to a local Hospital for headache and complex partial and generalized seizures followed by dizziness, behaviour disturbances, impaired consciousness, orofacial dyskinesis and flushing over a few days. Brain MRI was normal. EEG showed slowing of the background activity. Anti-TPO Abs were 74 UI/ml (normal values <55) and anti-TG Abs 366 UI/ml (n.v. <40). She was treated with high dose of intravenous steroid (methylprednisolone, 1 g/day for 5 days) with partial response followed by the addition of intravenous immunoglobulins (IVIG) (2 g/Kg in five days) with excellent response and complete rapid recovery. Diagnosis of HE was posed. In the following four years she didn't receive any treatment nor neurological follow-up.

Four years later she was admitted to our Hospital with subacute onset of headache and partial seizures followed by behavioural disorder (frequent cries, aggressiveness, anxiety). A presumptive diagnosis of relapsing HE was made and treatment with high-dose of intravenous steroid (methylprednisolone, 1 g/day for 5 days) was started. However, her clinical picture worsened with gait and speech loss, unresponsiveness, orofacial dyskinesias, flushing, rigidity with opistotonic posture. Brain MRI was normal. The EEG showed slowing of background activity and focal seizures originating from the right temporo-occipital areas were recorded. Serum anti-TPO Abs were 56.7 UI/m and anti-TG Abs 213 UI/ml. Cerebrospinal Fluid (CSF) analysis revealed normal cytochemical composition and absent oligoclonal IgG bands. Extensive microbiological tests in serum and CSF were negative. Despite the previous diagnosis of HE, the lack of steroid response and the clinical presentation led to test NMDAR Abs in the serum that were positive (serum 1:100; CSF 1:2). Under IVIG (2 g/Kg in 4 days) we observed a rapid progressive clinical improvement with disappearance of symptoms in the reverse order of their appearance. Two weeks after IVIG administration the patient appeared conscious, able to walk and speak, showing only residual clumsiness and paratonia that disappeared during the following month. Screening for an occult tumour (pelvis and abdomen ultrasonogram, chest X-ray, serum tumour markers) was negative. A detailed medical history revealed that identical signs and symptoms had been observed in the first episode.

She underwent further IVIG cycles for six months and then therapy withdrawal was attempted but focal seizures reappeared, rapidly resolved by IVIG administration. At the present time, one year after her last seizure, she is undergoing monthly IVIG, with neither further relapse nor residual symptoms.

3. Discussion

Anti-NMDAR encephalitis and HE share similar clinical features so that the differential diagnosis can be difficult if specific antibodies are not tested. Misdiagnosis has negative implications for both treatment and management of patients. Indeed, HE is typically steroid-responsive with favourable outcomes in the majority of cases,[1] whereas IVIG, plasma exchange and corticosteroids are the first-line treatments recommended for anti-NMDAR encephalitis, although additional treatments (rituximab and/or cyclophosphamide) may be required and the relapses occur in 20–25% of patients.[2,5] Furthermore, anti-NMDAR encephalitis can be paraneoplastic in origin, mainly associated to ovarian teratoma, thus a comprehensive work-up to screen for possible neoplasms (including serum markers and pelvis imaging, preferably MRI) is mandatory. In paraneoplastic cases, removal of the tumour increases the effectiveness of immunotherapy.[2] However, the tumour can appear after the encephalitis onset and it can remain silent for many years.[3] So, in all cases of anti-NMDAR encephalitis the periodic screening for neoplasms for at least 2 years is recommended.[2,5]

In the present patient, the initial diagnosis of HE was based on the association of anti-thyroid Abs and encephalopathy with neurological and psychiatric symptoms and a good response to treatment. However, a complete recovery was not obtained by steroids only, as it should be expected in HE, and anti-thyroid Abs are necessary but not sufficient for HE diagnosis since they can be found in association with other autoimmune diseases including limbic encephalitis, anti-GAD or anti-NMDAR encephalitis. This observation suggests that neuronal and thyroid autoimmunities might represent a continuum of "immunological dysfunction".[4] Moreover the pathogenic role of neuronal surface Abs such as anti-NMDAR Abs has been demonstrated in vivo and in vitro studies,[2] whereas the anti-thyroid Abs pathogenicity in HE is uncertain.[1] It is increasingly apparent that the presence of one autoimmune disorder makes another autoimmune disorder more likely. Indeed the presence of other autoimmune disorder has been proposed as supportive feature in flow-chart for approach to suspected neuronal surface antibodies syndromes in adults[6] as well as to suspected autoimmune epilepsy in children.[7]

Before the identification of anti-NMDAR Abs in 2007, patients presenting with clinical symptoms resembling anti-NMDAR encephalitis were often diagnosed with encephalitis of other causes or unknown origin.[3] It is likely that some cases diagnosed as HE are in fact related to other autoantibodies-mediated encephalopathies, such as anti-NMDAR encephalitis, that can be easily diagnosed by serum analysis.

In conclusion, since HE is a controversial entity and the diagnosis should be made only after exclusion of known autoimmune forms, we suggest to re-evaluate all subjects with previous HE diagnosis in order to obtain the correct diagnosis and to plan the appropriate management and follow-up, also in term of oncological screening.

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