Hashimoto's encephalopathy in a ten-year-old girl

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Hashimoto's encephalopathy is a steroid-responsive, relapsing or progressive encephalopathy associated with thyroid autoantibodies. Age at presentation varies from 10 to 78 years. In children, Hashimoto's encephalopathy is rare, and seizures, confusion and hallucinations are the most commonly described features. We report a 10-year-old girl with the diagnosis of Hashimoto's encephalopathy and review the literature.

Key words: Hashimoto's encephalopathy, thyroid autoantibodies, status epilepticus, acute encephalopathy, children.

Hashimoto's encephalopathy (HE) is a rare, steroid-responsive disease, characterized by the association of symptoms of acute or subacute encephalopathy with high levels of antithyroid antibodies independent of thyroid function tests, which usually have normal results[1].

The estimated prevalence of HE is 2.1/100,000 in adults[2]. Adequate information is not available about the frequency of HE in children[3]. The underlying pathology is not completely understood, but evidence of autoimmune mechanisms has been found[3]. The clinical picture in children, as with adults, is pleomorphic but frequently associated with seizures, confusion and hallucinations[4-6].

We report a 10-year-old girl with the diagnosis of HE and review the literature.

Case Report

A 10 4/12-year-old girl presented to the emergency department with generalized tonic-clonic seizures of more than 30 minutes' duration. She had a three-month history of weakness, fatigue and decline in school performance. The mother had been operated because of goiter, and was using L-thyroxin, 150 μg/day. The weight of the patient was 41.5 kg (75-90th percentile) and height 142 cm (75-90th percentile). On physical examination, she was agitated and lethargic. Neurologic examination revealed hyperreflexia, bilateral sustained ankle clonus and bilateral positive Babinski sign. Other system examinations were within normal limits. There was no palpable goiter. She required intubation and mechanical ventilation. Phenytoin, phenobarbital and midazolam infusion were administered to control status epilepticus, and phenytoin was continued for the chronic antiepileptic treatment. The etiology of status epilepticus and acute encephalopathy was not clear, but intravenous acyclovir was administered because the diagnosis of encephalitis could not be excluded. White blood cell (WBC) count was 6,000/mm^3, hemoglobin 11.1 g/dl, platelet count 280,000/mm^3, and C-reactive protein (CRP) 0.21 mg/dl. Routine biochemical analysis of serum, blood gases, blood ammonia and lactate were within normal limits. Tandem mass spectroscopy (MS-MS) and urine organic acids were uninformative. Serum free thyroxin (fT4) was 9.9 pmol/L and thyroid stimulating hormone (TSH) 4.42 mIU/L. Cerebrospinal fluid (CSF) analysis was normal, and CSF culture was sterile. Cranial magnetic resonance imaging (MRI) showed bilateral, symmetric thalamic high signal intensity on T2-weighted and FLAIR images. Electroencephalography (EEG) showed bilateral diffuse slow wave

activity. After five days she was extubated. On the 14th day, she was discharged to home. Three days later she was hospitalized again with right-sided tonic seizures. Phenytoin was first changed to oxcarbazepine, but because of the diffuse exanthematous lesions oxcarbazepine was stopped and valproic acid ordered. Seizures could not be controlled with valproic acid, and carbamazepine was added to therapy. She had no seizures with this combination for two months, at which time she reported to the emergency department because of frequent seizures and apathy. Her school performance had been declining gradually. She could not read or write, could not calculate simple math problems and had concentration deficit. Seizures were mainly characterized by staring and sometimes tonic convulsions of any of the extremities. Valproic acid was discontinued, and topiramate was added to carbamazepine. Seizures were controlled with this combination. EEG showed bifrontal sharp wave activity. Thyroid function tests were repeated. Serum fT4 was 10.8 pmol/L, TSH 4.91 mIU/L, anti-thyroid peroxidase 314 IU/ml (0-35), and anti-thyroglobulin 636 IU/ml (10-110). Anti-nuclear antibody was negative.

The results were compliant with autoimmune thyroiditis, and the diagnosis of HE was made. CSF antithyroid antibodies were negative. Second cranial MRI was normal without any specific therapy. After basal neuropsychologic evaluation, prednisolone was ordered at a dosage of 2 mg/kg/day by oral route. No seizures were observed during steroid treatment, and clinical findings returned to normal at the 4th week of therapy. She was able to read, write, and follow at school without concentration deficit.

Discussion

In 1966, Brain et al.[7] reported the first case of encephalopathy in association with Hashimoto's disease. It is still debatable whether this is a specific syndrome seen in patients with autoimmune thyroiditis or the coincidence of a rare neurologic condition with a common endocrinologic disease[4,8]. Chong et al.[9] systemically reviewed all reported cases and they concluded that the combination of encephalopathy, high serum anti-thyroid antibodies, and responsiveness to steroids was unlikely to be due to chance, therefore constituting a new syndrome. However, the association of neurologic symptoms and increased titers of serum anti-thyroid antibodies is not a sufficient requisite to the diagnosis of HE and may yield a false-positive diagnosis, because the role of thyroid antibodies in the pathogenesis of encephalopathy has not been defined[2]. Furthermore, antithyroid antibodies are present in 10% of the normal population[10]. Some authors have used the terms "autoimmune encephalopathy associated with Hashimoto's thyroiditis", "corticosteroid-responsive encephalopathy associated with Hashimoto's thyroiditis" or "encephalopathy associated with autoimmune thyroid disease" instead of HE[8]. Although it is not an accurate description, the term "Hashimoto encephalopathy" was used in this report because of the uncertainty surrounding the new suggested terms.

Hashimoto's encephalopathy is an under-recognized cause of acute encephalopathy in children[3]. Teenage girls with progressive cognitive decline warrant special attention[4]. More common causes of encephalopathy such as infection, electrolyte imbalance, metabolic disease, toxins, neoplasms or CNS involvement of vasculitic syndromes should be excluded[4]. Measurement of antithyroid antibodies is essential to make the diagnosis and should be undertaken in any such patient even when standard thyroid function tests are normal[6]. HE is usually diagnosed based on a combination of neurological findings, the presence of anti-thyroid autoantibodies, and steroid responsiveness[11]. Our patient had all three of these criteria.

The presenting clinical features of HE vary widely[3]. Two distinct forms of presentation are described in adults, a vasculitic type with seizures, acute deterioration of consciousness and stroke-like episodes, and a diffuse progressive type with insidious deterioration in cognitive function leading to dementia, confusion, agitation, restlessness, and hallucinations or inactivity, apathy and social isolation[6]. Both forms may be associated with tremor, seizures, stupor and myoclonus[8]. Children tend to present with seizures, confusion, or hallucinations[4]. Generalized tonic-clonic seizures followed by complex partial seizures, with or without secondary generalization, is the most common type of seizure pattern[12]. Progressive cognitive decline manifested by decline in school performance

may be evident[9]. Focal neurologic signs are less common in children than in adults[4]. This patient had acute encephalopathy, status epilepticus history and poor school performance for the last year, and then was followed-up with the diagnosis of resistant partial epilepsia.

The CSF protein concentration may be high and mild pleocytosis may be present[8].

Ferracci et al.[1] found antithyroid antibodies and circulating immune complexes in the CSF, although the titer does not reflect clinical status. Diffuse slowing of the background is the most common EEG abnormality in children and adults[5]. Neuroimaging is usually normal; however, MRI may occasionally demonstrate bilateral subcortical high signal lesions on T2-weighted images. Computed tomography and angiography are typically normal[4]. The cranial MRI of the patient showed bilateral thalamic high signal intensity on T2-weighted and FLAIR images when the diagnosis of acute encephalopathy was made. Thalamic involvement in HE was not reported by the other studies, and this finding disappeared after four months without any treatment. SPECT may show global hypoperfusion[4]. Fujii et al.[11] reported that HE autoantibodies specifically recognize the amino terminal of α-enolase and are a useful marker for the diagnosis of HE. Thyroid autoantibodies are elevated in all patients and are required for diagnosis. Free thyroxin is normal in the majority of children[5].

Most patients respond dramatically to steroid therapy[5,6]. Both high doses of oral prednisone and short courses of intravenous methylprednisolone have been shown effective, but pulse intravenous therapy is the preferred choice for acute encephalopathy of HE. Rapid improvement may be seen in a few days, and the average time to significant clinical improvement is 3-4 weeks. Vasconcellos et al.[5] suggested continuing the steroid treatment for at least six months, but normalization or improvement in the EEG and neuropsychologic testing are considered better tools for monitoring the response and the length of the therapy. Other forms of immunomodulatory treatment have been used in some cases with some clinical benefit[8]. The prognosis of HE in adults when treated is good, with 90% of patients in remission after 10 years, but children tend to have more residual sequelae than adults[4,5]. Oral prednisone treatment was used for this patient, because there were no clinical findings of acute encephalopathy when the diagnosis of HE was made. She responded well to therapy within seven days, and at the end of the first month she recovered dramatically.

In conclusion, HE is a rare, but probably underdiagnosed disease in children. Because of the presence of effective treatment strategies and high morbidity and mortality rates in HE, early diagnosis is critical. HE should be considered in any patient, especially girls above nine years of age with unexplained acute encephalopathy, recurrent status epilepticus, and acute psychosis in the emergency department, or with progressive cognitive-behavioral decline and movement disorders such as myoclonus and tremor in the outpatient clinic.

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