Introduction

Hashimoto’s encephalopathy (HE) is a rare syndrome associated with Hashimoto’s thyroiditis, and was first described by Lord Brain in 1966. The prevalence of HE is estimated to be 2.1/100,000 subjects, with an approximately 4-times higher frequency in women than in men.

The HE patients mostly present with a subacute onset of confusion with altered level of consciousness, seizures, and myoclonus. The clinical symptoms are non-specific and variable ranging from seizure and behavioral change to coma. The disease is characterized by increased titers of anti-thyroid antibodies such as anti-thyroperoxidase (TPO) and anti-thyroglobulin (TG). An elevated anti-TPO antibody level is detected in most patients with HE, while an elevated anti-TG antibody level is detectable in some patients.

It is considered that pediatric HE is frequently associated with seizure and confusion. And several pediatric cases report long-term sequelae, further indicating the importance of early recognition and proper diagnosis in children.

In this report, we present two pediatric HE patients to illustrate the common clinical features and disease courses.
Case reports

1. Case 1

An 11-year-old girl presented to the emergency room with altered mentality. She had an 11-day history of a headache and a 2-day history of vomiting. At the time of admission, she was unable to answer questions and was stuporous. She had visited an endocrinologist for a thyroid goiter seven months prior to the admission, and a thyroiditis evaluation at the time had revealed elevated titers of anti-thyroid antibodies and normal levels of thyroid hormones. She was diagnosed with Hashimoto’s thyroiditis with euthyroidism and was regularly followed-up without any medication. Her mother also had thyroid goiter. Her physical examinations at the time of admission were normal, and her neurological examination revealed no focal neurologic abnormalities except for drowsiness and inappropriate responsiveness. Routine laboratory tests for complete blood count and chemistry were normal, and the inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were not elevated. An examination of the cerebrospinal fluid (CSF) showed increased intracranial pressure (opening pressure >20 mmHg); however, the white blood cell (WBC) count and the level of protein and glucose in the CSF were within normal limits. The serum titers for anti-TPO (695 U/mL, normal value 0–60 U/mL) and anti-TG antibodies (237 U/mL, normal value 0–60 U/mL) were both still elevated. Other serum markers associated with autoimmune encephalopathy such as anti-nuclear antibodies, anti-dsDNA, rheumatic factor, anti-neutrophil cytoplasmic antibodies, immunoglobulin G/A/M and complements were all negative. Brain magnetic resonance imaging (MRI) revealed multifocal T2-weighted fluid attenuated inversion recovery (T2/FLAIR) hyperintensities in the left basal ganglia and subcortical areas (Fig. 1). Electroencephalography (EEG) showed frequent bilateral high amplitude delta slowing. Intravenous immunoglobulin (1 g/kg/day) was initiated on hospital day 2 and was continued for two days; however, her confused mental state persisted. High-dose methylprednisolone (1 g/day) treatment was initiated on hospital day 5, after confirming the negative blood and CSF cultures. Her mentality recovered completely after the methylprednisolone treatment, and she was discharged on hospital day 10. Her brain MRI was reevaluated two weeks after discharge and revealed significantly decreased hyperintensity compared to the initial scan (Fig. 1). At the last follow-up in the outpatient clinic, she still had an elevated level of anti-thyroid antibodies (anti-TPO antibody: 1,073 U/mL; anti-TG antibody: 231 U/mL) but did not exhibit any neurological sequelae.

2. Case 2

A 15-year-old girl was admitted via the emergency room with sudden onset confusion. She was previously healthy, and there were no unusual events until the day of admission. On the day of her admission, she woke up from a nap and started speaking incoherently, and could not recognize her family. Her physical examination findings at the time of admission were normal except for an intermittent hand tremor, disorientation, and agitation. Extensive laboratory examinations for encephalopathy, including work up for infectious and autoimmune causes, were performed. The results showed high levels of anti-TPO (136 U/mL, normal value 0–60 U/mL) and anti-TG antibodies (192 U/mL, normal value 0–60 U/mL) in serum and CSF studies were unremarkable. Her thyroid function tests were normal. Brain MRI and EEG scans were also normal. We made a provisional diagnosis of HE, and as her mental status recovered fully after a day of hospitalization, she was discharged without medication. However, two days after discharge, she complained of a headache at school and lost her way home. She was readmitted to the hospital. Brain MRI and EEG were repeated, and subtle high signal intensities in the bilateral posterior hippocampi were noted at this time on the MRI (Fig. 2) along with occasional posterior slowing on the EEG. She was treated with intravenous methylprednisolone (1 g/day) for 3 days. She showed remarkable improvements with no residual cognitive deficits and was discharged on hospital day 4. However, she exhibited poor compliance with...
the oral steroids and was reported to have intermittent mild disorientation at the outpatient clinic after three weeks of symptom onset.

Discussion

We present here two cases of HE that showed acute cognitive deteriorations with high titers of anti-TPO and anti-TG antibodies. HE is occasionally misdiagnosed as it manifests with nonspecific and heterogeneous symptoms. Furthermore, extensive laboratory examinations to detect other causes such as infections usually take precedence over the diagnosis of HE. Routine laboratory blood tests are usually normal and hypothyroidism is observed in approximately half of the reported pediatric cases.

Identifying the elevated titers of anti-thyroid antibodies, including anti-TPO and anti-TG antibodies, is essential for the diagnosis of the HE; however, the pathogenic role of anti-thyroid antibodies remains unclear. Several studies have suggested that these auto-antibodies could cross the blood brain barrier and cause encephalopathy. However, anti-thyroid antibodies can also be detected in patients with autoimmune thyroiditis without encephalopathy, and even in healthy individuals. Thus their role as markers of an autoimmune disorder, rather than a pathogenic component of the disorder, is a more plausible and persuasive concept. The term SREAT, or steroid-responsive encephalopathy associated with autoimmune thyroiditis, has been recently proposed due to the uncertain autoimmune basis of HE.

In our study, the elevated serum levels of anti-thyroid antibodies were not normalized. Our report provided the evidence for the role of antibody as diagnostic marker although correlation between antibody titer and clinical course remained controversial.

There have been limited reports of HE in pediatric patients. The low number of pediatric cases is probably attributable to an actual low incidence rate, although the possibility of under-diagnosis cannot be excluded. Alink et al. reviewed 25 published pediatric cases of HE and reported that half of the patients were euthyroid, while all patients exhibited elevated anti-TPO antibody titers. Steroid therapy was effective in 55% of the patients, who subsequently made a complete recovery.

In our study, both patients had normal thyroid function and elevated anti-TPO and anti-TG antibody titers. Both patients were treated with high dose of steroids and made a complete recovery.

Corticosteroids are the first line therapy for HE and levothyroxine may also be considered when a patient has hypothyroidism. Most cases of HE are responsive to steroids: a low dose of oral steroids, a 1–2 mg/kg dose of prednisone, and a high dose of methylprednisolone (1 g/d for 3–5 days) are also considered efficacious. In our study, methylprednisolone at a dose of 1 g/d was administered for 3 days to both patients and subsequently tapered off over a two-week period. In case two, the patient showed a recurrence of symptoms after discontinuation of the steroid therapy, highlighting the efficacy of steroids on the encephalopathic symptoms of HE.

For patients refractory to steroid treatment, intravenous immunoglobulin or plasmapheresis may be considered. A few previous studies have demonstrated their effectiveness in HE patients with poor response to steroids. In our study, for the first patient, intravenous immunoglobulin was administered prior to steroid due to the possibility of infection but it was not effective. Further, Yu et al. reported a pediatric HE case that responded poorly to steroid and intravenous immunoglobulin but recovered completely after plasmapheresis.

According to the previous reports, pediatric HE is frequently associated with seizure and confusion, unlike adults who usually exhibit clinical features ranging from vasculitis to diffuse progressive presentations. These two cases presented with subacute and nonspecific symptoms suggesting the possibility of variable spectrum of encephalitis. At initial evaluation, extensive laboratory studies including autoimmune antibodies screening were done and the identification of elevated anti-TPO and anti-TG antibodies made the diagnosis of HE.

Although HE is a rare autoimmune encephalopathy in pediatric patients, it is a treatable condition with good responsiveness.

Fig. 2. Magnetic resonance imaging (MRI) performed on case 2. High signal intensities in the bilateral posterior hippocampi are observed in the T2-weighted fluid attenuated inversion recovery (T2/FLAIR) images (A–D).
to steroids. Therefore, HE should be considered when diagnosing patients with unexplained encephalopathy, and confirmed with the anti-thyroid antibody tests.

Acknowledgements

The authors are thankful to the patients who participated in this study.

요약

하시모토 뇌병증은 항갑상선과산화효소 항체, 항사이로글로불린 항체와 같은 갑상선 자가면역 항체의 상승과 관련된 뇌병증으로 나타나는 드문 질환이다. 이에 저자들은 급성 인지 장애를 보인 소아에서의 하시모토 뇌병증 2례를 보고하는 바이다. 첫번째 환자는 11세 여아로 하시모토 갑상선염의 과거력이 있고 갑상선 호르몬은 정상수치로 유지되고 있었던 환자이며 두번째 환자는 15세 여아로 특별한 과거력은 없었다. 두 환자는 모두 급격히 발생한 의식혼탁을 주소로 내원하였고 혈청에서 항갑성선과산화효소 항체와 항사이로글로불린 항체의 증가가 관찰되었다. 다른 감염이나 자가면역질환을 시사하는 검사 소견은 확인되지 않았다. 두 환자는 모두 급격히 발생한 의식혼탁을 주소로 내원하였고 항갑상선과산화효소 항체와 항사이로글로불린 항체의 증가가 관찰되었다. 다른 감염이나 자가면역질환을 시사하는 검사 소견은 확인되지 않았다. 두 환자는 스테로이드 치료 후에 신경학적 증상의 호전을 보였으나, 하시모토 뇌병증은 비특이적인 증상으로 진단하기 어려움이 있을 수 있으나 진단되고 치료 후에는 대부분 가역적인 경과를 가져오므로 알려져 있다. 그러므로 소아에서 설명되지 않은 뇌병증을 보일 때 하시모토 뇌병증의 가능성을 고려하는 것이 중요하다.

References