Case Report

A Rare Cause of Autistic Regression in a Boy with Down Syndrome: Hashimoto Encephalopathy

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Background: Hashimoto encephalopathy (HE) is a rare condition associated with autoimmune thyroid disease. We aimed to report the youngest patient with Down syndrome and HE with an unusual presentation. Case Report: Six years and six months old boy with Down syndrome admitted due to loss of speech. His physical development was appropriate for his age and had no goiter. Neurological examination revealed the absence of eye contact and stereotypic movements. Autism spectrum disorder was considered based on his result on Gilliam autism evaluation scale. He had subclinical hypothyroidism with markedly elevated anti-thyroid peroxidase antibody level, rare spikes in the frontocentral area were found in electroencephalography, and cranial magnetic resonance imaging was normal. Neurologic improvement was observed to a treatment with glucocorticoid and thyroid hormone. Conclusion: HE might be considered in patients with Down syndrome along with progressive cognitive decline and autistic regression.

Keywords: Autistic regression, autoimmune encephalopathy, autoimmune thyroiditis, Down syndrome, steroid-responsive encephalopathy

INTRODUCTION

Hashimoto encephalopathy (HE) is a rare condition associated with autoimmune thyroid disease and might be presented as cognitive decline or behavioral changes, myoclonus, seizures, and psychological changes.¹,² The incidence of HE is 2.1/100 000.³ Females are five times more likely to be affected by HE, and the age at presentation is usually between 45 and 55 years.³ A few pediatric cases have been reported so far.⁴⁻⁶ An elevation in the titers of anti-thyroid peroxidase and anti-thyroglobulin antibodies is essential for diagnosis, but thyroid function tests might be completely normal.⁷

Patients with Down syndrome have higher rates of hypothyroidism, both congenital and acquired.⁸ Chronic autoimmune thyroiditis (Hashimoto’s) is the major cause of acquired hypothyroidism with increasing incidence after puberty.⁹ Although the incidence of HE is higher among patients with Down syndrome, it is often underrecognized. In these patients, the changes in mood and behavior might be misdiagnosed as juvenile Alzheimer’s disease, a condition that is more often than HE.² The proper diagnosis is important since many patients can benefit from therapy. The treatment of HE consists of high-dose steroids and plasmapheresis.

Our aim was to report the clinical course and response to treatment of a pediatric case with Down syndrome and HE who has an unusual presentation. To the best of our knowledge, our patient is the youngest in literature with Down syndrome and HE.

CASE REPORT

Six years and six months old boy with Down syndrome admitted to our pediatric neurology clinic due to loss of speech. He was born to a 32-year-old mother after

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an uncomplicated pregnancy by Cesarean section. His birth weight was 3000 g, and he was hospitalized in the first 5 days of life due to breathing problems. He had no known heart disease nor thyroid problems. He started walking at the age of 2 years and the family declared that he was able to speak in sentences. He started to lose eye contact and a regression in his speech was realized 10 months ago which progressed slowly until he lost his speaking ability completely.

On physical examination, his weight was 17.2 kg (50–75 p), height was 111.7 cm (75 p), he had no goiter, and puberty was Tanner stage 1. Neurological examination revealed that he had no eye contact, no response when calling his name, stereotypic movements like putting hands together in midline, and shaking forwards and backward. A diagnosis of autism-spectrum disorder was considered based on his result on Gilliam autism evaluation scale (GARS-cut off 85 points).

Laboratory measurements revealed subclinical hypothyroidism with an elevated thyrotropin (TSH) and normal free thyroxine level (fT4), markedly elevated anti-thyroid peroxidase antibodies, and normal anti-thyroglobulin antibodies [Table 1]. Other biochemical and hormonal measurements were found within normal ranges, except elevated cholesterol levels. His brain magnetic resonance imaging was normal, and electroencephalography (EEG) revealed rare spikes in the frontocentral area. Ultrasound of the thyroid was compatible with chronic thyroiditis. Hashimoto encephalitis was considered based on the findings and a treatment with glucocorticoid (deflazacort 1 mg/kg/day) and thyroid hormone (l-thyroxine 25 µg/day) was started.

He was re-evaluated after 3 months of treatment. There was an increase in the duration time of eye contact, and the GARS score was 80. He started to express a few words, his ability to mimic and common attention reappeared. There was also a decrease in anti-TPO titers along with a normalization of TSH levels [Table 1]. Steroid treatment was continued as 1 mg/kg for a further 3 months, and then tapered and discontinued after 12 months. At the end of the sixth-month treatment, we observed an incline in anti-TPO levels due to tapering of steroid treatment. No adverse effects have been noted during treatment.

**DISCUSSION**

Hashimoto encephalitis, also known as glucocorticoid-responsible encephalitis, might be fatal with a rapid decline in cognitive function, myoclonus, and alterations in consciousness. The symptoms of HE are often nonspecific and comprise a relatively broad spectrum of neurologic deficits. The diagnosis may be delayed in pediatric patients since many physicians are not familiar with this rare condition. In patients with unexplained neurologic or psychiatric symptoms and elevated anti-thyroid antibodies, HE should be considered after exclusion of all toxic, metabolic, and infectious causes of encephalopathy.

Systemic causes of encephalopathy such as hepatic or renal failure or sepsis might be excluded on clinical grounds and routine investigations. Symptoms of acute disseminated encephalomyelitis which is characterized by demyelination of the central nervous system might be similar to those of HE. Other disorders in the differential diagnosis of HE include Alzheimer’s disease, vasculitis, paraneoplastic syndromes, and Creutzfeldt–Jakob disease. Structural or functional neuroimaging might help to exclude vascular and neoplastic disorders, while seizure

| Table 1: Laboratory measurements of the patient |
|-----------------------------------------------|
| On admission | Three months after treatment | Six months after treatment | Nine months after treatment | Twelve months after treatment |
| TSH (N: 0.37–6.0 µIU/mL) | 7.89 | 1.93 | 1.70 | 2.33 | 1.71 |
| Free T4 (N: 11.60–21.50 pmol/L) | 14.66 | 20.58 | 15.50 | 15.04 | 12.36 |
| Anti-thyroid peroxidase antibody (N < 34 IU/mL) | 587.52 | 108.4 | 70.6 | 242.98 | 156.62 |
| Anti-thyroglobulin antibody (N < 115 IU/mL) | 13.64 | 19.81 | 2.4 | 4.76 | 4.75 |
| Total cholesterol (N < 200 mg/dL) | 214 | | | 193 |
| LDL-cholesterol (<100 mg/dL) | 127 | | | 120 |
| HDL-cholesterol (N: 35–55 mg/dL) | 62 | | | 66 |
| Aspartate aminotransferase (N < 40 U/L) | 25 | | | 30 |
| Alanin aminotransferase (N < 41 U/L) | 14 | | | 22 |
disorders can be excluded by EEG monitoring.\cite{10} Typical EEG and cerebrospinal fluid findings along with the rapidly declining course and the lack of responsiveness to corticosteroid treatment might help to differentiate Creutzfeld–Jakob disease from HE. Our patient had no toxic, metabolic, and infectious cause of encephalopathy. The otherwise unexplained autistic regression and the presence of high anti-TPO antibodies in our patient led us to the diagnosis.

The majority of pediatric patients with HE has been reported as having normal thyroid hormone levels.\cite{10} Our patient had subclinical hypothyroidism. The typical EEG findings of HE are as follows: slowing of background activity, focal spikes, and temporary epileptic activities. The EEG of our patient revealed rare spikes in frontocentral region. The other supportive criteria for the diagnosis were the thyroid ultrasound findings compatible with chronic thyroiditis and the good response to glucocorticoid treatment.

High-dose steroid (iv methylprednisolone 500–1000 mg/day for 3–5 days or oral 1–2 mg/kg prednisolone), followed by gradual reduction, is the first line of treatment of HE, and corticosteroid responsiveness is considered as a part of defining criteria.\cite{10} The rare patients in whom corticosteroid therapy remains ineffective, intravenous immune globulin (IVIG) and plasma exchange might be considered.\cite{11,12} Other treatment options in patients who are refractory to glucocorticoid treatment include immunosuppressants such as azathioprine or cyclophosphamide.\cite{10} Our patient had an uncommon presentation and slow progression of symptoms, hence we decided to treat with oral high-dose glucocorticoid with close monitorization of the clinic response. Glucocorticoid treatment was tapered gradually.

The clinical response to glucocorticoid treatment has been observed within 10 days in children and within 4-to-6 weeks in adults.\cite{2} Our patient responded after 4 weeks of treatment. Rapid tapering of treatment might lead to a relapse;\cite{3} therefore, maintaining the treatment for longer periods and tapering the dose slowly are recommended. We continued our treatment for 12 months due to good clinical response.

Long-term outcomes are favorable in HE. In a series of 11 cases, complete remission after steroid therapy was reported in 80% of patients.\cite{13} A systemic review of 130 cases with HE revealed complete remission of symptoms after treatment in 114 patients (87.6%), no improvement in eight patients (6.2%), partial improvement in four patients (3.1%), and no information on outcome after steroid therapy in four cases (3.1%).\cite{14} Follow-up data of 82 patients with a duration ranging from 6 to 24 months showed no recurrence of disease during follow-up in 48 cases (58.5%), relapse was associated with the withdrawal of corticosteroid in 22 cases (26.8%), relapse requiring further treatment in 12 patients (14.7%), and death in four patients (4.8%).\cite{14}

Although the association of Down syndrome and HE has been merely reported before, it is estimated that the true incidence might be higher, since in individuals with Down syndrome, thyroid antibodies are detected four times more likely than the general population.\cite{4} The autistic regression in our patient with Down syndrome is of interest. A study reported a 15-year-old female patient with Down syndrome and HE presented with cognitive decline, withdrawing into herself and involuntary movements similar to our patient.\cite{3} The autistic regression seen in our patient responded to the steroid treatment as demonstrated by GARS.

In conclusion, HE might be considered in patients with Down syndrome along with progressive cognitive decline and autistic regression and in adults with rapidly advanced dementia, as all symptoms might be reversed with an early and proper treatment.

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Conflicts of interest
There are no conflicts of interest.

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