Hashimoto Encephalopathy in Children

Sir,

Hashimoto encephalopathy (HE) is a rare but controversial entity encompassing a variety of neuropsychological presentations in the setting of autoimmune thyroid disease. The lack of clarity in the nomenclature and pathophysiology as well as absence of uniform diagnostic criteria make the diagnosis more challenging. We add a new case of HE in an adolescent girl and review pediatric HE.

A 14-year-old previously healthy girl was admitted with 1 day history of vomiting and encephalopathy. She had three episodes of non-projectile vomiting and received over-the-counter antiemetic. Subsequently, parents noticed involuntary urination, unresponsiveness to verbal commands, irritability, and then drowsiness. On admission to the hospital, her Glasgow Coma Scale score was 8. She was maintaining vitals and was hemodynamically stable. There were no meningeal signs or focal deficit. Eye examination, tone, and brainstem, superficial and deep tendon reflexes were normal. Child was admitted to the intensive care unit and was started on antimicrobials for presumed infectious etiology. She had one brief seizure. Initial blood work including blood counts, renal and liver function tests, C-reactive protein, erythrocyte sedimentation rate, serum ammonia, blood gas analysis, and vitamin B12 levels were normal, except high value of serum lactate (33.9 mg/dl, range: 4.5–14.4 mg/dl). Magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) examination were normal. Electroencephalography (EEG) showed generalized slowing of the background activity (delta range activity) without any epileptiform discharges. Patient had deterioration of sensorium on Day 2 of hospital stay and was electively intubated and ventilated. Further investigations including urine toxicology screen, CSF and serum profile for autoimmune encephalitis, antinuclear antibodies, and urine for porphobilinogen were normal. Thyroid profile was found abnormal with decreased thyroid-stimulating hormone (TSH) (0.025 micU/ml; range: 0.700–6.400 micU/ml), decreased free T3 (1.81 pg/ml; range: 2.90–5.10 pg/ml), and normal free T4 (2.27 ng/dl; range: 0.80–2.30 ng/dl). Patient was started on intravenous immunoglobulin (IVIG) (2 g/kg), levothyroxine, and injectable thiamine, with no improvement. Testing revealed high levels of anti-thyroperoxidase (TPO) antibodies (79.8 IU/ml, normal: <60 IU/ml) and anti-thyroglobulin (Tg) antibodies (74.7 IU/ml; normal: <60 IU/ml). A diagnosis of HE was made and pulse IV methylprednisolone (1 g/day) was started. There was a dramatic response to steroid therapy with return to normal sensorium within 3 days. Patient was discharged home after 7 days on oral steroids and levothyroxine. On 2.5 months of follow up, the patient is asymptomatic, off steroids, and her thyroid profile is normal.

We reviewed the literature for pediatric patients with HE. Forty-seven articles detailing 74 pediatric patients and the present patient were included. Average age of presentation is 13.1 years (range: 2 years 10 months–18 years) and a majority are female (F:M = 5:1). Duration of symptoms before diagnosis ranges from few days to 9 years. Around 20% present with acute onset. The most common clinical features are seizures (69%, status epilepticus: 25%, refractory epilepsy: 3%), alteration in sensorium (60%), psychosis (37%), behavioral alterations (33%), headache (25%), and cognitive decline (21%). Other presenting symptoms are academic issues, sleep disturbances, movement disorders, mood changes, and emotional liability. Recurrent strokes, myoclonus, ataxia, and tremors are less common compared to adults.[1]

A number of pathogenetic mechanisms have been suggested. Female prevalence, presence of autoantibodies, fluctuating course, and response to immunomodulatory therapy suggest the autoimmune nature of the disease. A shared target antigen between thyroid gland and central nervous system,[2] neurotoxic effects of thyroid hormones, and interference of neurotransmission by antibodies are suggested mechanisms.[3] Other autoantibodies have been found in a few patients.[4] However, antithyroid antibodies are also found in hypothyroid patients and normal adult population. It is conceivable that these antibodies are the markers for a specific neurologically targeted autoimmunity in these patients. Vasculitic process,[5] primary demyelination,[2] or an immune complex-mediated process have also been proposed. It is possible that some patients with presumed HE have a second autoimmune mechanism.[6]

The thyroid status in patients with HE is variable. Around 17% children were found to have pre-existing hypothyroidism. At the time of diagnosis, 47% children are euthyroid, 50% are hypothyroid, and 3% are hyperthyroid. Anti-TPO antibodies are elevated in 97% patients and anti-Tg antibodies are raised in 81% patients. Antithyroid antibody titers do not correlate with the severity and presentation of the disease[7] and may even be undetectable at disease onset.[3]

EEG is found to be abnormal in around 86% patients. The most common abnormality is generalized slowing of the background activity seen in around half the patients. Other abnormalities included focal slowing, focal or generalized epileptiform activity, and rarely electrical status epilepticus and burst suppression pattern. EEG acts as a marker of encephalopathy and serial EEGs may reflect clinical improvement.[8] CSF analysis is normal in nearly half the patients. Increased CSF protein levels are found in another 48% and pleocytosis in 4%. Increased cellular count is mild. CSF antibodies were found elevated in half the tested patients ($n = 6$); all these patients also had positive serum antibodies. Computerized tomography (CT) of the brain has poor yield. A higher proportion of pediatric MRIs are found to be normal (67%) as compared to adults.[9] The most common abnormality is non-specific white matter changes. Multiple other abnormalities have been reported.

Patients with HE, respond to immunotherapy. Some patients respond to levothyroxine alone. Around 30% patients received only steroids and 36% received a combination of steroids and levothyroxine. Since there are no controlled trials, the optimum duration and dose of steroid therapy is unclear. Many studies use high-dose IV methylprednisolone followed by tapering doses of prednisolone.[9]

There is incomplete response to steroids in around one-fourth patients who warrant second-line immunosuppression. Such patients have been described in case reports and small case series. IVIG has been used in 13 patients with no benefit in 8 and good response in 5 patients. Plasma exchange and rituximab have been reported to be beneficial. Methotrexate, cyclophosphamide, and azathioprine have been tried in varying combinations and duration. Response to flunarizine and risperidone has been reported.[1,8–11]

A total of 26 relapses were reported in 15 patients (time range: 14–518 days). Around 20% pediatric patients are likely to be left with sequelae. The likelihood of residual deficits did not correlate with the duration and severity of symptoms.

HE encompasses a huge array of neurological and psychiatric symptoms tied together by raised titers of antithyroid antibodies and response to immunotherapy. It is likely underdiagnosed in children. The availability of disease-modifying treatment makes the diagnosis imperative.

Consent

Written informed consent was obtained from the patient's guardians for publication of the case and any accompanying images. A copy is available for review by the editor of this journal.

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Conflicts of interest

There are no conflicts of interest.

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