Review Article

Hashimoto's Encephalopathy in a Pediatric Female: Time to Revisit This Diagnosis

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DOI: 10.21276/APALM.3258

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Submitted: 09-Mar-2024
Final Revision: 05-May-2024
Acceptance: 09-May-2024
Publication: 01-June-2024

Abstract

Hashimoto's encephalopathy (HE) is an infrequent encephalopathy of presumed autoimmune origin characterized by high titres of antithyroid antibodies. It is common in females, and although it is seen across all age groups, it is relatively uncommon among the paediatric population, with a prevalence of only about 1.2%. Hashimoto's encephalopathy is a rare complication of Hashimoto's thyroiditis and presents with a syndrome of persistent fluctuating neurologic and neuropsychologic deficits associated with elevated antithyroid antibodies, specifically thyroid peroxidase (TPO) antibodies. We present one such case of Hashimoto's encephalopathy, diagnosed in an 11-year-old female, which mimicked brain death, along with a review of the available literature.

Keywords:

Hashimoto Disease, Thyroiditis, Autoimmune, Cytology

Introduction

Hashimoto's encephalopathy (HE) is defined as an encephalopathy of presumed autoimmune origin characterized by high titers of antithyroid peroxidase antibodies [1]. It is described as a rare complication of Hashimoto's thyroiditis. It is known to affect around 2.1 people per 100,000 general population and is more common in women, with a male to female ratio of 1:5 [2]. The prevalence of Hashimoto's thyroiditis in the pediatric age group is noted to be around 1.2%. HE is characterized by a syndrome of persistent fluctuating neurologic and neuropsychiatric deficits such as seizures, cognitive decline, myoclonus, disorientation, frequent episodes of alternating hemiparesis, high protein levels in the cerebrospinal fluid (CSF), and electroencephalographic (EEG) abnormalities, associated with the presence of circulating anti-thyroid antibodies, mostly anti-thyroid peroxidase (TPO) antibodies [1, 3, 4]. It is a rare medical emergency and, if not diagnosed and treated in time, can lead to untoward consequences,

including brain function impairment in children. We present one such case of Hashimoto's encephalopathy in an 11-year-old female who presented with an acute onset of symptoms, which later mimicked brain death. With the right diagnosis at the right time, the patient was revived to normal life.

Case

An 11-year-old female presented to the emergency room of a secondary care hospital with chief complaints of vomiting of one-day duration, associated with rapidly progressive generalized weakness, abnormal stiffening of the body, and loss of consciousness since the morning of the same day. On further evaluation, it was found that she also had difficulty moving her limbs, with all four limbs being involved. The limb involvement was bilaterally symmetrical and rapidly progressive, resulting in limb stiffening and tonic posture. However, there was no urinary or stool incontinence. She had no history of any trauma, fever, headache, loose stools, rashes, insect or snake bite, or any drug or toxin ingestion. She did not have any similar complaints in the past. She was born out of a non-consanguineous marriage and had an uneventful birth and normal development.

On examination, her vitals were stable; however, CNS examination revealed generalized hypotonia associated with absent deep tendon reflexes, neutral plantar reflexes, and sluggishly reactive pupils, indicating likely encephalitis, with a differential diagnosis of Guillain-Barré Syndrome.

She was immediately shifted to the intensive care unit (ICU), where she rapidly desaturated with a sudden and swift drop in her SpO2 levels from 98% on initial evaluation to 82% with an oxygen face mask. An additional progressive deterioration was noted, with no recordable pulse and non-reactive pupils. She was immediately intubated, and cardiopulmonary resuscitation (CPR) was initiated. She was revived and placed on mechanical ventilation but presented with absent brainstem reflexes. She was started on intravenous immunoglobulins (IVIG) along with IV corticosteroids, and an IV antibiotic and antiviral cover.

CSF examination revealed elevated CSF proteins (400 mg/dL), with other biochemical and cytological parameters within normal limits (Table 1).

Table 1: CSF analysis of the case

Parameter	Value
1. Protiens	400 mg/dl (15-45 mg/dl)
2. Glucose	118 mg/dl (>50mg/dl)
3. Cytology	Nil (<5 cells/cumm)
4. Viral and Bacterial PCR Panel	Negative
5. Autoimmune panel	Negative

She underwent magnetic resonance imaging (MRI) of the brain the following day, which revealed focal signal changes on FLAIR, pre-pontine cistern and right-sided CP angle enhancement with a possible subdural hematoma (SDH) and prominence of the optic nerve. An additional supportive ultrasonographic examination (USG) of the neck revealed features suggestive of thyroiditis.

Fine needle aspiration (FNA) examination of the thyroid gland was suggested in view of thyroiditis, and it yielded a blood-mixed aspirate. On microscopy, aspirate smears were cellular and revealed scattered thyroid follicles in a hemorrhagic background. These follicles presented with marked lymphocytic infiltration with lymphocytes impinging over them (Fig 1), confirming a diagnosis of lymphocytic thyroiditis.

Owing to the FNA report of lymphocytic thyroiditis, she underwent further serological investigations for thyroid function (Table

2), which exhibited raised TSH levels and high circulating titers of anti-TPO and anti-thyroglobulin antibodies, leading to a diagnosis of Hashimoto's thyroiditis.

Table 2: Serological investigations for assessment of thyroid function

Investigation parameter	Value
1. TSH	181 mIU/l (0.5-5 mIU/L)
2. T3	102 ng/dl (93-231 ng/dl)
3. T4	2.73 mcg/dl (5.99-13.8 mcg/dl)
4. Anti-TPO antibodies	>1000
5. Anti- thyroglobulin antibodies	>10000
6. ANA Panel	Negative
7. Autoimmune panel	Negative

She was immediately started on Tab. Eltroxin; however, she faced a challenging recovery, battling ventilator-associated pneumonia, tracheostomy, and deficient Vitamin D levels. She was finally weaned off mechanical ventilation on day 22 of her hospital admission. She was gradually tapered off steroids, administered an appropriate dosage of thyroxine, Vitamin D3, and calcium supplements, and advised on tracheostomy care. With the help of congruous physiotherapy, she began walking with support on day 38 of her admission. On day 44, she was decannulated with closure of her tracheostomy.

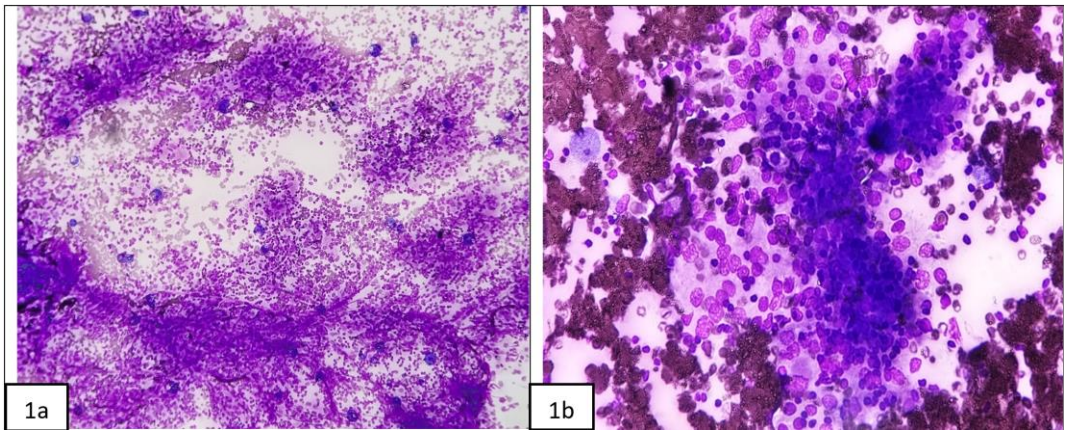

Figure 1: Fine needle aspiration smears from the thyroid reveal thyroid follicular cells with lymphocytes impinging upon them present within a background of abundant RBCs – suggestive of a diagnosis of Lymphocytic Thyroiditis (MGG stain (a, 100x; b, 400x)

She was finally discharged after an extensive and turbulent hospital stay of almost two months with a diagnosis of Hashimoto's encephalopathy, also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) secondary to Hashimoto's thyroiditis.

Discussion

Hashimoto's encephalopathy, also known as Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT) or Non-vasculitic Autoimmune Meningoencephalitis, is an uncommon syndrome associated with Hashimoto's thyroiditis [5]. It is a clinically heterogeneous condition characterized by corticosteroid-responsive encephalopathy associated with high titers of serum antithyroid antibodies, which may or may not accompany any associated thyroid hormone abnormalities. It is characterized by the presence of neuropsychiatric symptoms with serological evidence of autoimmune thyroid disease. If

present, thyroid dysfunction is variable and may range from hypothyroidism to euthyroid and even hyperthyroidism in some cases. Literature mentions the presence of high circulating titers of anti-TPO antibodies in 100% of cases, while around 73% of cases present with significant circulating anti-thyroglobulin (anti-TG) antibodies. Additionally, most of the published reports in the literature do not have any significant association between the severity of the disease and its clinical presentation [1, 4].

Hashimoto's encephalopathy was first described by Brain et al. in 1966, who reported it in a 49-year-old man presenting with seizures, fluctuating consciousness, hallucinations, disorientation, frequent episodes of alternating hemiparesis involving different vascular territories, high protein levels in the CSF, EEG abnormalities, and biopsy-confirmed Hashimoto thyroiditis. He also presented with significant titers of antithyroid microsomal antibodies as well as anti-TG antibodies [6]. In 1991, Shaw et al. used this term for the first time to describe five cases who exhibited similar symptoms. These patients also had hypothyroidism and presented with high circulating anti-thyroid antibody titers [7].

HE is an infrequent syndrome, and determining its exact incidence and prevalence is arduous. However, various studies on this topic have inferred its overall prevalence to be approximately 2.1%. This condition has been reported across all age groups throughout the world; however, literature mentions the mean age of onset to be in the 4th-5th decade of life, with the age of the affected individuals ranging from 9 years to 86 years. The disease is more prevalent among adult females, with a male to female ratio of 1:5, while in children, it has an equal incidence among both genders [1]. According to separate studies conducted by Gayatri et al. [8] and Byrne et al. [9], about one-fifth of HE cases are presumed to be prevalent in the population under 18 years of age. Watemberg et al. found 22 case reports of HE in the pediatric literature. Eighteen of those cases were girls between 8 and 17 years of age, and two cases were diagnosed in patients under 10 years of age [10]. This concurs with our case, where the patient is an 11-year-old female child.

HE may co-exist with other autoimmune diseases. A study of 20 patients with HE found that 30% of them had a co-morbid autoimmune disorder like diabetes mellitus type 1, systemic lupus erythematosus (SLE), and Sjogren's syndrome [11].

Several pathogenetic mechanisms have been proposed regarding this entity; however, the role of the autoimmune mechanism in the development of this condition has been generally accepted. This theory has been supported by the various clinical aspects of this entity, such as female preponderance, fluctuating course of the illness, and its association with other autoimmune diseases [3].

Considering the heterogeneity of the presenting symptoms, the likely mechanisms responsible for the development of HE include disseminated encephalomyelitis and/or autoimmune general cerebral vasculitis [3]. However, there is no significant evidence confirming these mechanisms at a pathological level. In vivo pathological features have been obtained from very few cases, and they are diverse; the most common being mild lymphocytic infiltration of the small vessels. However, whether these features are enough for the phenomenon to be labeled as vasculitis remains controversial as there is little evidence of vessel wall destruction and transmural infiltration that characterizes vasculitis in the CNS and other organs [1]. Additionally, the same has not been completely ascertained through post-mortem studies, as scarce literature is available regarding autopsy features of HE. Few available studies, however, describe a vasculopathic picture composed of mild perivascular lymphocytic infiltration with gliosis being present in the cortex, basal ganglia, thalamus, or hippocampus, or a predominant brainstem process with T-cell infiltration of the leptomeningeal venules only [12, 13].

Some studies have revealed the presence of demyelination on MRI as well as histopathology occurring in HE and frequently seen along with perivascular lymphocytic cuffing without any significant loss to axonal integrity. Reports of this finding have led some

investigators to postulate that recurrent Acute Disseminated Encephalomyelitis (ADEM) could be responsible for demyelination in HE [14].

ADEM is characterized by perivenular demyelination and injury to the cerebral capillary endothelial cells. It usually follows a viral infection or a monophasic vaccination and is responsive to corticosteroids, similar to HE. However, it has also been argued that disruption of the capillary endothelial cells results in localized demyelination in Hashimoto's encephalopathy. This loss of endothelial integrity in the capillary beds can explain increased CSF protein and occasional CSF pleocytosis seen in HE. In addition, as Hashimoto's encephalopathy may present a relapsing and remitting course, and a more progressive form, it could be possible that both recurrent ADEM and a progressive vasculopathy are involved. The precise autoimmune or metabolic mechanisms remain largely unknown [1, 14, 15].

Pathogenetically, the presence of Hashimoto's thyroiditis is also associated with the development of HE. Thyrotropin-releasing hormone (TRH), which is said to be raised in secondary and tertiary hypothyroidism, may play a role in the development of HE by exerting toxic effects on the nerve cells and medulla. This may be directly or indirectly responsible for the demyelination of HE. This theory was proposed after Ishi et al., in their study, noted that a patient developed myoclonus after administration of intravenous TRH infusion [16].

Additionally, immune complex formation of Hashimoto's thyroiditis may also be responsible for a generalized decrease in cerebral perfusion seen in HE. This can be attributed to the microcirculatory abnormalities occurring secondary to the deposition of immune complexes in the cerebral blood vessels as demonstrated by the hypoperfusion on SPECT (Single-Photon Emission Computed Tomography) described in a few case reports in the literature [17, 18]. This proposed theory of immune complex deposition also justifies the response to corticosteroids seen in HE. Chong et al., in their review, have concluded that "the combination of encephalopathy, high serum antithyroid antibody concentrations, and responsiveness to glucocorticoid therapy seems unlikely to be due to chance," which further backs up the above-mentioned theory of immune complex deposition [19]. Moreover, Ferracci et al. were able to detect antithyroid antibodies along with circulating immune complexes in the CSF of a small group of patients with HE in their study, which supports the role of Hashimoto's thyroiditis in the pathogenesis of HE [20].

Being a relatively rare condition, HE has a broad range of clinical presentations and, hence, often has a high risk of being misdiagnosed and mistreated. A high index of suspicion is necessary for the diagnosis of HE among the pediatric population. Doherty proposed a diagnostic criterion for HE in adults, which includes cognitive impairment with or without neuropsychological symptoms; presence of seizures and stroke-like events with focal neurologic deficits associated with elevated anti-thyroid antibody levels, especially TPO, with the patient being hypothyroid or euthyroid. Additionally, CSF should have elevated protein levels but no pleocytosis, and the patient should respond well to corticosteroid therapy. The EEG abnormality could show mild-to-moderate generalized slowing, and MRI may be normal or show nonspecific changes [21]. However, since children may or may not present with all of the above said criteria, Watemberg et al. presented a diagnostic triad among the pediatric population composed of neuropsychiatric symptoms, often affecting more than one area of the central nervous system; the detection of antimicrosomal or antithyroglobulin antibodies in serum; and the elimination of other potential etiologies. They also put forth that elevated CSF proteins were suggestive while a response to corticosteroids was supportive of the diagnosis [10]. Our case fulfilled all of the above proposed criteria for diagnosis.

HE may clinically mimic Creutzfeldt-Jakob disease, rapidly progressive dementias, and paraneoplastic and non-paraneoplastic limbic encephalitis along with GBS [1]. Table 3 indicates the differentiating features of these entities.

Table 3: Mimickers of Hashimoto Encephalopathy

Feature	Hashimoto Encephalopathy	Creutzfeldt-Jakob Disease	Guillian Barre Syndrome	Paraneoplastic limbic encephalopathy (PLE)	Wernicke Encephalopathy	Subacute Sclerosing Panecephalitis (SSPE)
Origin/ Cause [1, 22–27]	Autoimmune origin Associated with high titres of circulating antithyroid antibodies	Prion disorder	Autoimmune disease, secondary to a few bacterial and viral infections – likely Campylobacter jejuni, Zika virus and Covid19	Onconeural antibody to cancer that cross-reacts with self-antigen in the neurons and muscles. Most commonly seen in lung cancer	Thiamine deficiency	Complication of measles
Incidence and Prevalence [1, 22, 25, 26, 28–30]	Overall estimated prevalence of 2/100,000 Paediatric prevalence of 1.2%a	1-2 cases/million population in the world	Annual incidence of 1.55/ 100,000 incidence increases from 0.8/100,000 in patients younger than 35 to 4.67/100,000 in patients older than 75 years.	<1/10000	1-3%	1/2792 measles cases in children >1 year, and 1/158 measles cases in children <1 year of age.
Age group affected [22, 31–35]	45-55 years	45-75 years. Symptoms begin to appear by 60-65 years	39.1±20 years	15-45 years	30-70 years	<20 years. Highest risk is to those who develop measles <02 years
Gender [23, 31, 36–39]	M:F = 1:5	M:F = 1:1	M:F = 1.5:1	M:F = 7:1	M:F = 1.7:1	M:F = 2.8:1
Patho-physiology [3, 39–43]	Disseminated encephalomyelitis and/or also autoimmune general cerebral vasculitis	Transformation of the normal cellular prion protein PrP into an abnormal, structurally changed, disease-causing form called the prion PrP scrapie, which then self-propagates and accumulates throughout the brain.	Molecular mimicry, antiganglioside antibodies and, likely, complement activation	Antibodies are produced mostly against onconeural antigens located intracellularly	Thiamine deficiency causes dysfunction of the Krebs cycle (tricarboxylic acid, TCA cycle) and the pentose phosphate pathway with consequent development of brain cytotoxic edema and vasogenic edema	Hypermutated Measles virus combined with an inadequate cellular response
Clinical features [3, 24, 36, 38, 39, 43]	Neuro-psychiatric manifestations	-Confusion and disorientation. -Behavior and personality changes. -Hallucinations or delusions. -Ataxia -Dystonia -Seizures. -Paralysis. -Wasting of muscles and atrophy.	Weakness and tingling numbness in the extremities which rapidly spreads resulting in paralysis	Personality changes, irritability, depression, seizures, memory loss and sometimes dementia	Abnormal mental state, ataxia, and ophthalmoplegia	Irritability, personality changes, difficulty in school, lethargy and/or speech impairment leading to behavioral changes leading to movement disorders leading to paralysis
Pathology [44–47]	Lymphocytic thyroiditis with Lymphocytic vasculitis	Spongiform encephalopathy: small vacuoles throughout the neuropil (spongiform change) associated with neuronal loss, diffuse astrogliosis, and microglial proliferation	Lymphocytic infiltration of spinal roots and peripheral nerves (cranial nerves may be involved as well), followed by macrophage-mediated, multifocal stripping of myelin.	Non-specific encephalitis.	Vascular changes followed by reactive gliosis	Large areas of myelin loss, Neuronal degeneration in infected grey matter, Chromatin margination in neurons and oligodendrocytes, and Intranuclear eosinophilic viral inclusions
Serology [38, 48–51]	Anti TPO antibodies Anti thyroglobulin antibodies	14-3-3 protein assay in CSF T tau proteins (post mortem)	Anti GQ1b ganglioside antibodies	Onconeural antibodies directed against intracellular antigens, including	No specific serological tests available	Measles specific antibodies

				anti-Hu2, anti-Ma23, anti-amphiphysin, and anti-CRMP5		
Treatment [24, 26, 52–54]	Corticosteroids	Some potential treatments include Quinacrine, Pentosan Polysulphate, and Flupirtine	Intravenous immunoglobulin (IVIg), plasma exchange (PE), and supportive care	Tumour removal Immunotherapy Anti-cancer therapy Supportive care	IV/IM Thiamine	Ribavarin Interferon - alpha
Survival rates [38, 40, 51, 55–57]	90% cases respond positively to treatment	Highly fatal disease with average survival being 4-8 months	The 12-month mortality rate is 3.9%, with 20% of deaths occurring during the acute phase, 13% during the plateau phase, and 67% during the recovery phase.	64% at 3 months, 40% at 1 year, and 22% at 3 years.	If left untreated, Wernicke's encephalopathy (WE) has a mortality rate of 10–20%	95% mortality rate

Almost all the reported cases of HE, including our case, have responded well to high doses of corticosteroids. In fact, some reports in the literature mention response to corticosteroids as a defining criterion for HE. Patients who fail to respond are often atypical cases and may also present with other features and are frequently proven to have other diagnoses. Amongst corticosteroids, the mainstay of management remains 1-2 mg/kg of prednisolone per day. Although a short course of this therapy is effective, early drug tapering may result in relapse of symptoms, resulting in prolonged requirement of therapy, in some cases, as long as a year. Clinical improvement is noted within 4-6 weeks of treatment, after which the corticosteroid dose may be gradually weaned off. Literature has little evidence mentioning the exact duration of treatment. Kothbauer-Margreiter et al., in their survey of HE patients, noted that complete remission was achieved with a treatment duration range of 4 months to 10 years [1, 15].

An important adverse effect of long-term corticosteroid therapy is osteoporosis. Hence, appropriate preventive measures must be undertaken for those patients requiring prolonged corticosteroid therapy in the form of calcium and vitamin D [1].

A safer alternative to prednisolone is high pulse methylprednisolone, which is administered in the dose of 1 gm/day over 3-5 days. It is known to avoid the long-term side effects of conventional prednisolone. Lower doses of oral corticosteroids may also be used in conjunction with pulsed methylprednisolone, and relapses can be managed with further pulses [1].

In spite of prolonged corticosteroid therapy, some patients only partially respond or are refractory to this management. In such patients, azathioprine is known to be helpful, especially when combined with corticosteroids [1, 7].

Intravenous immunoglobulins and plasma exchange can be effective as initial treatment or when corticosteroids are not efficacious. Other treatments trialed include cyclophosphamide and methotrexate with a variable degree of success [1].

Other supportive measures which play an important role in the management of HE include the provision of adequate fluids, analgesia, monitoring for co-morbid infectious diseases, and comprehensive nursing care. Seizures need to be controlled with appropriate anti-epileptics while neuropsychiatric symptoms may require antipsychotic therapy in addition to corticosteroids [1].

Conclusion

Hashimoto’s encephalopathy is a rare, complex disorder characterized by a heterogeneous clinical clustering of symptoms and behavioral changes. Consequently, it may present to clinicians from different backgrounds and training. It should be considered in the differential diagnosis of patients with acute or subacute features of encephalopathy, cerebellar and extrapyramidal features,

autonomic failure, status epilepticus, NCSE, as well as rapidly progressive cognitive impairment and psychiatric symptoms of unclear etiology. Taking into account the possibility of the coexistence of various autoantibodies, HE should, in some cases, be differentiated from other autoimmune encephalopathies and paraneoplastic syndromes. If elevated titers of antibodies to thyroid antigens are demonstrated, corticosteroid treatment should be considered as soon as possible. This case was presented for its unusual clinical presentation, as well as to increase the number of reported cases to add to the knowledge of this condition and to promote research on its pathophysiology and appropriate management. Future research should also seek a more specific marker for Hashimoto's encephalopathy.

Funding: None

Competing Interests: None declared

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