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Case Report

Refractory status epilepticus in a pediatric patient: Exploring the association with thyroid dysfunction

Alaa Hmeedan [1], Hadi Adnan Rabee [2], Mahmoud Doudein [3] and Abdalhakim R. M. Shubietah [4,5,*]

[1]Internal Medicine Department, An-Najah National University, Nablus, Palestine
[2]Internal Medicine Specialist, Al-Watani Hospital, Nablus, Palestine
[3]Internal Medicine Department, Specialized Arab Hospital, Nablus, Palestine
[4]Medical Surgical Department, Jaffa Specialized Surgical Hospital, Ramallah, Palestine
[5]Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestine
*Correspondence address. Faculty of Medicine and Health Sciences, An-Najah National University, 00970, PO Box 7, Nablus, Palestine.
Tel: +970594421750; E-mail: hakeemraqi@gmail.com

Abstract

Hashimoto's thyroiditis is an autoimmune thyroid disease characterized by lymphocytic infiltration and thyroid-specific autoantibodies. Hashimoto's encephalopathy, a rare entity associated with these antibodies, presents as a relapsing encephalopathy with neuropsychiatric manifestations and seizures. A 15-year-old girl, initially healthy, experienced a tonic-clonic seizure. Despite unremarkable initial assessments, she returned with generalized convulsive status epilepticus. Hashimoto's thyroiditis was suggested by elevated thyroid-stimulating hormone levels, low thyroxine levels, and high anti-thyroid antibodies, and was confirmed by ultrasound. Steroids were not used initially due to seizure cessation with anesthesia. Post-treatment with levothyroxine and antiepileptics, she was seizure-free at follow-up and eventually maintained solely on levothyroxine. Hashimoto's encephalopathy, characterized by diverse symptoms, often necessitates corticosteroids, immunoglobulins, and plasmapheresis, as traditional anti-seizure medications fail. Further research into its etiology and pathophysiology is essential. Consider Hashimoto's encephalopathy in unexplained seizures, especially with ineffective standard treatments. Pediatric diagnostic criteria need to be revisited.

INTRODUCTION

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is an autoimmune thyroid disease in which the gland is attacked by lymphocytes and thyroid-specific autoantibodies directed towards thyroid peroxidase (TPOAb) and/or thyroglobulin (TgAb). HT is the leading cause of primary hypothyroidism, with an incidence rate of 0.3–1.5 cases per 1000 people per year. While histopathologic examination of thyroid tissue remains the gold standard for diagnosing HT, a diagnosis can be made clinically and confirmed with a thyroid ultrasound [1].

Hashimoto's encephalopathy (HE), also described as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), is a rare, chronic, relapsing, and remitting encephalopathy associated with autoantibodies against the thyroid antigens, thyroid peroxidase, and thyroglobulin [2]. In contrast to HT, HE is a controversial and poorly understood disease entity. The first description was in 1966 when Lord Brain and colleagues described a case of neurological illness associated with elevated titers of thyroid autoantibodies in a 63-year-old male who was known to have HT confirmed with thyroid biopsy [3]. Since then, many cases of unexplained encephalopathy with positive anti-thyroid antibodies have been reported [4]. 'Hashimoto's encephalopathy' describes a condition with encephalopathy-like symptoms not caused by infectious, metabolic, toxic, or neoplastic factors, but associated with elevated thyroid autoantibodies, such as TPOAb and TgAb. Patients typically have normal or slightly low thyroid function, non-specific neuroimaging, and show positive clinical response to steroids. This condition can manifest through cognitive or psychiatric symptoms, focal neurological deficits, and seizures, including status epilepticus [5].

Status epilepticus (SE) is now defined as five or more minutes of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness [6]. Occurring in about 12% of HE, SE shows characteristic resistance to anti-epileptic drugs but demonstrates good clinical responsiveness to steroids and other immunomodulatory agents, suggesting an autoimmune pathophysiology. This is made clear in one review study, which identified 31 patients with HE and SE and 104 controls with symptoms other than SE [5].

Herein we present the case of a 15-year-old girl who presented with generalized convulsive status epilepticus, whose condition was ultimately controlled with general anesthesia due to failure to respond to anti-epileptic agents and was then diagnosed with Hashimoto's disease.

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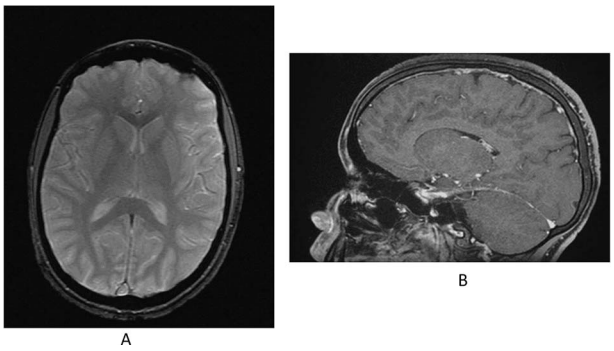

Figure 1. Normal Brain MRI: Axial (**A**) and Sagittal (**B**) Views with IV Gadolinium.

CASE PRESENTATION

A 15-year-old female with a nonsignificant past medical history and no previous hospital admissions was initially brought to the emergency department in a post-ictal state following her first-ever tonic–clonic seizure, which lasted approximately three minutes. The seizure was associated with tongue biting, frothy oral secretions, and urinary incontinence. On physical examination, she appeared drowsy but was otherwise unremarkable. Initial laboratory workup, including a CBC, showed no abnormalities except for microcytic anemia. A head CT scan revealed no abnormalities. A plan was made for admission to observe and conduct further investigations, including MRI and an EEG. However, she was discharged the same day against medical advice, and follow-up was lost.

Two months later, she was brought back to the emergency department after experiencing generalized convulsive status epilepticus (GCSE). Upon arrival, her parents reported a 20-minute episode of tonic-clonic activity with loss of consciousness. The patient had no recent history of infection, head trauma, drug use, travel, tick bites, academic decline, childhood febrile seizures, or a family history of thyroid disease or epilepsy/seizure activity. In infancy, there were no reports of seizures or febrile seizures. She appeared to be of appropriate weight and height for her age, with good nutritional status and normal cognitive development.

During the initial resuscitation, the patient received two doses of intravenous diazepam at 0.15 mg/kg each, followed by a loading dose of phenytoin at 20 mg/kg over 30 min with no response. Due to continuous seizure activity after 20 min, a rapid sequence intubation using general anesthesia was performed, and the patient was transferred to the medical ICU.

A thorough investigation was conducted to identify the cause of the status epilepticus. This included CBC, comprehensive metabolic profile, random blood glucose, infectious workup, urine toxicology screen, CSF analysis and cultures, ECG, and cardiac echocardiography, all of which yielded normal results. Head CT and brain MRI with IV contrast (Fig. 1 A and B) also showed no abnormalities, and the EEG was unremarkable. An abdominal ultrasound was done and found no abnormalities.

The only laboratory abnormality was a high thyroid stimulating hormone (TSH) level of 55 mIU/ml, along with a low total thyroxine (T4) level of 2.80 ug/dl. Both TgAb and TPOAb antibodies were significantly elevated, exceeding 1000 IU/ml (Table 1). A thyroid ultrasound revealed a mildly enlarged thyroid gland with lobulated margins, heterogeneous nodular parenchymal echotexture, and prominent echogenic fibrous septa, all consistent with Hashimoto's thyroiditis. Consequently, the patient was initiated on thyroxine replacement therapy. Despite the autoimmune profile suggesting HE, steroids were not considered in her management plan due to the cessation of seizure activity with general anesthesia and the delayed results of her autoantibodies.

Table 1. Laboratory Findings

Laboratory Findings	Results	Normal Range
TSH	55 mIU/ml	0.4–4.0 mIU/ml
TgAb	>1000 IU/ml	<40 IU/ml
TPOAb	>1000 IU/ml	<35 IU/ml
Total Thyroxine (T4)	2.80 ug/dl	4.5–11.2 ug/dl

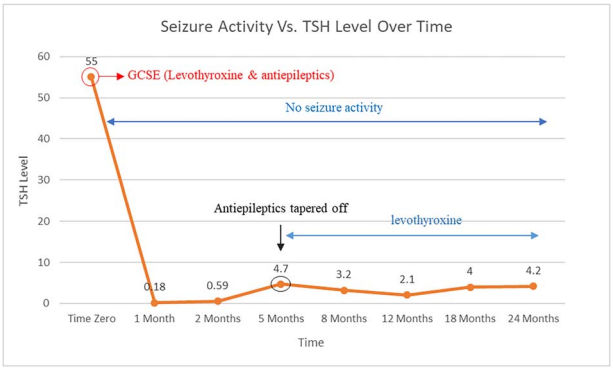

Figure 2. Correlation of TSH levels with seizure activity over a 24-month period. (This figure is copyright-free as it was created by the authors. Colors should be used in print).

Her eight-day hospital stay proceeded without any further seizure activity. She was maintained on levothyroxine and antiepileptic medication, sedation was discontinued, and she was successfully extubated. Physical exam upon extubation was normal. A workup for additional autoimmune diseases was conducted, including tests for ANA, anti-dsDNA, anti-tissue transglutaminase IgG and IgA, anti-proteinase 3, anti-myeloperoxidase, rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), anti-topoisomerase I, anti-centromere antibodies, and anti-SSB/La antibodies. All results were negative.

At her one- and two-month follow-up visits, the patient reported no further seizures and had returned to her baseline physical function. Three months later, she was successfully tapered off antiepileptics and maintained on levothyroxine. A follow-up brain MRI with IV contrast was also performed at that time and showed no abnormalities. Review of the records revealed the family's refusal to use steroids, citing concerns about side effects and potential impacts on puberty.

Extended follow-up of the patient after discharge and a review of her medical records revealed a downward trend in both TSH, TgAb, and TPOAb levels, as depicted in the line graphs of Figures 2 and 3**.** While the diagnostic criteria do not depend on TSH levels or the trend of anti-thyroid antibodies, we believe these graphs could offer fresh insights into the disease, suggesting the potential for reevaluating its understanding and management.

DISCUSSION

We report a unique case of refractory status epilepticus in a pediatric patient, ultimately diagnosed as HE, which required rapid sequence intubation for management.

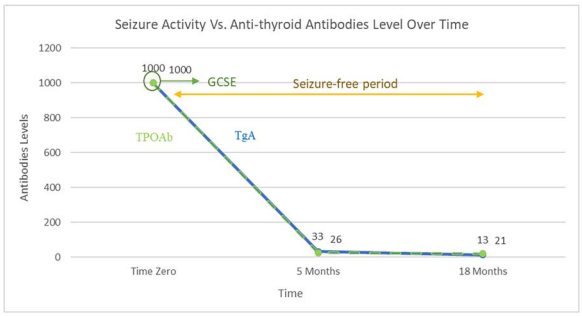

Figure 3. Correlation of TgAb and TPOAb levels with seizure activity over a 24-month period. (This figure is copyright-free as it was created by the authors. Colors should be used in print).

Table 2. Current diagnostic criteria for HE proposed by Graus and colleagues [8]

1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or nonspecific abnormalities
4. Presence of serum thyroid (TPOAb, TgAb) antibodies (no disease-specific cutoff)
5. Absence of well-characterized neuronal antibodies in the serum or CSF
6. Reasonable exclusion of alternative cause

HE remains an enigmatic disorder with an as-yet unestablished pathophysiology despite autoimmune theories supported by consistent elevations in autoantibodies in reported cases [5]. It exhibits a predilection for women, with approximately three-quarters of cases affecting females. Onset has been documented across all age groups [7]. Graus and colleagues' HE diagnostic criteria requires the presence of encephalopathy marked by seizures, hallucinations, stroke-resembling episodes, or myoclonus, alongside raised thyroid antibodies and either subclinical or mild thyroid disease. It also requires an MRI showing either normality or non-specific abnormalities, no specific neuronal antibodies in serum or CSF, and effectively ruling out other potential causes for the patient's symptoms. Table 2 summarizes the diagnostic criteria used by Graus and colleagues [8]. Our patient met the criteria HE but did not show symptoms of hypothyroidism. This situation could be attributed to subclinical thyroid dysfunction or it is indeed true that the diagnostic criteria for HE varies between children and adults.

Clinical presentations of HE are remarkably variable, spanning altered mental status and stroke-like symptoms to seizures and coma. Remarkably, nearly 80% of pediatric cases present with new-onset seizures unaccompanied by other neurological abnormalities, although status epilepticus is a rare occurrence [7]. Diagnosing HE in children is challenging, as many do not show thyroid disease signs. Adams et al. proposed a new pediatric HE diagnostic criteria focusing on sudden cognitive decline and neuropsychiatric issues with antithyroid antibodies, without needing evidence of thyroid disease [9].

The wide-ranging clinical presentations, coupled with the absence of clearly defined diagnostic criteria and the requisite extensive workup to effectively exclude more common etiologies, render the early recognition and diagnosis of HE challenging, often necessitating a process of exclusion [4] and resulting in delays in commencing appropriate treatments. First-line treatments encompass high-dose corticosteroids, intravenous immunoglobulins, and plasmapheresis [5]. Unfortunately, conventional anti-seizure medications prove ineffective in the majority of cases [7]. Our patient, for instance, did not respond to first- and second-line anti-epileptic drugs, ultimately necessitating the management of her refractory status epilepticus with general anesthetics and antiepileptic agents. Steroids were not initially given due to the delayed diagnosis of HE, highlighting the condition's diagnostic challenges. The family later opted against steroid treatment. Literature review shows that 67% of HE patients improved with levothyroxine alone, excluding steroids [10]. This emphasizes the disease's complexity and underscores the necessity for more research. Although the existing diagnostic criteria for HE doesn't rely on TSH levels or trends in anti-thyroid antibodies, we propose that analyzing these graphs could illuminate new aspects of the disease (Figs 2 and 3). This approach might pave the way for rethinking its diagnosis and treatment strategies.

CONCLUSION

Hashimoto's encephalopathy should be considered in the differential diagnosis for patients presenting with seizures of unknown etiology and no prior history of epilepsy, particularly when conventional anti-seizure medications fail to control their seizures. Further research is imperative to shed light on this complex disorder and its underlying mechanisms. Different diagnostic criteria for children can be suggested.

AUTHOR CONTRIBUTION STATEMENT

Study concept and design: A.H, H.A.R. Literature search: M.D, A.H. Literature analysis and interpretation: A.R.M.S, A.H. Writing the paper: H.A.R, A.H, M.D, A.R.M.S. Writing—Review & Editing: A.R.M.S, A.H. Figures Design: A.R.M.S.

CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Ethical approval is exempt/waived at our institution.

CONSENT

The assent of the child was obtained for the publication of this case report and accompanying images, along with written informed consent from the patient's parents. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

GUARANTOR

Abdalhakim Shubietah.

PROVENANCE AND PEER REVIEW

Not commissioned, externally peer-reviewed.

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