CASE REPORT

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Super Refractory Status Epilepticus in Hashimoto's Encephalopathy

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ABSTRACT

We present a case of a 38-year-old woman who was at eight weeks of gestation and was admitted to Sultan Qaboos University Hospital with refractory status epilepticus (SE). She presented with a two-day history of fever and a depressed level of consciousness that was followed with generalized tonic-clonic seizures. She progressed to refractory SE that required intubation and mechanical ventilation. Autoimmune workup was suggestive of Hashimoto's encephalopathy (HE) as suggested by the high levels of thyroid antibodies. Her magnetic resonance imaging showed bilateral hippocampal and basal ganglia hyperintensities, and electroencephalogram showed bilateral frontal epileptiform discharges. Other autoimmune workup was negative. Intravenous anesthetics were started including propofol, midazolam, ketamine, and thiopentone. She was started on multiple immunosuppressive therapies. Multiple antiepileptics were used including phenytoin, lamotrigine, levetiracetam, sodium valproate, clobazam, phenobarbital, and lacosamide. The outcome was unusual in terms of refractoriness to immunotherapy treatment despite a confirmed diagnosis. We did a literature review of all cases with HE presenting with SE with their clinical characteristics and outcome.

The clinical manifestations of Hashimoto's encephalopathy (HE) include an altered level of consciousness, tremor, myoclonus, stroke-like episodes, and seizures. Seizures have been documented in 66% of patients with HE.[1] Treatment consists of corticosteroids, which results in remarkable recovery thus giving this syndrome the term "steroid-responsive encephalopathy".[1]

CASE REPORT

A 38-year-old woman was transferred to Sultan Qaboos University Hospital with a diagnosis of refractory status epilepticus (SE). At the time of presentation, she was eight weeks pregnant. She presented with a two-day history of fever and abdominal pain followed by a one-day history of depressed level of consciousness and generalized tonic-clonic seizures. There was no family history of seizure disorder, thyroid, or autoimmune disease. She progressed to generalized SE, which required intubation and mechanical ventilation.

She was started on intravenous (IV) anesthetics and phenytoin. Her temperature at initial examination was 38 °C. There were no signs of meningeal irritation, and her pupils were mid-position and reactive. An obstetrical examination revealed an empty sac consistent with an abortion.

Her investigations revealed normal complete blood count, serum electrolytes, and calcium profile. Cerebrospinal fluid showed three white blood cells, elevated proteins (0.96 g/L), normal glucose, and negative cultures. Computed tomography (CT) of the brain was normal while CT venography excluded venous sinus cerebral thrombosis. Magnetic resonance imaging (MRI) showed hyperintensities in the hippocampal region as well as bilateral basal ganglia [Figure 1]. An electroencephalogram (EEG) on admission showed continuous generalized frontally dominant rhythmic epileptiform discharges consistent with SE [Figure 2]. This pattern was resistant to sensory stimuli and would occasionally, and transiently, responds to IV midazolam. Thyroid peroxidase antibodies were positive (222 IU/mL). Another autoimmune workup was negative (including anti-Hu, anti-NMDA, anti-GAD65, ANA, and antiphospholipid). Viral screen was also negative including herpes simplex virus, polymerase chain reaction, and West Nile virus.

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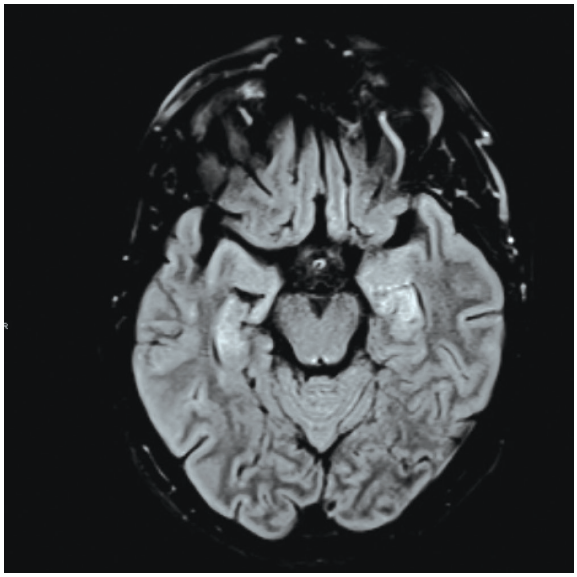

Figure 1: Magnetic resonance imaging showing pattern of bilateral symmetric increased signal hyperintensity of the hippocampal formation. There is increased signal intensity within the caudate nuclei and lentiform nuclei, which is associated with diffusion restriction.

The patient was initiated on IV acyclovir empirically (until the exclusion of herpes encephalitis) with multiple sequential anticonvulsants including phenytoin, lamotrigine, levetiracetam, sodium valproate, clobazam, phenobarbital, and lacosamide. However, they failed to completely suppress the seizures. After 48 hours of admission, she continued to have breakthrough uncontrollable seizures. Multiple IV anesthetics were used, including midazolam, propofol, ketamine, and thiopentone. Burst suppression was initially achieved, but seizures recurred during IV anesthetics withdrawal.

On day two after admission, IV methylprednisolone 1 g was initiated for five days. There was no notable response. IV immunoglobulin was also given for five days. Five sessions of plasmapheresis were started. There was still failure of seizure control with episodes of two to three tonic-clonic seizures per hour. Eventually, the course was complicated with pseudomonal sepsis with multiple organ failure. She died on day 18 after admission.

DISCUSSION

The above case highlights a fatal outcome of SE secondary to HE. We reviewed the literature for cases of SE secondary to HE with their findings and outcome [Table 1]. HE is considered a steroid-responsive disease with the overall outcome good even in the setting of SE.[10,11] Chaigne et al,[11] reported six cases of patients with SE admitted to intensive care, and all had an overall good outcome. However, there were two reported cases that showed severe refractoriness demonstrating that the disease course can have a resistant form that does not respond to immunotherapy.[7,12]

SE occurs in 12% of patients with HE.[13] The diagnosis in these cases is challenging as SE has a variety of causes.[14] Immunological causes are the most challenging to diagnose and treat.[14] The most common immunological disorders are paraneoplastic syndromes, HE, and anti-NMDA receptor encephalitis.[14]

The hallmark of diagnosing HE is the presence of antithyroid antibodies.[1,15] The most common antibody identified is antithyroperoxidase (anti-TPO) formerly known as antimicrosomal antibodies.[15] It is found in most patients with HE. The second antibody commonly found in HE is antithyroglobulin (anti-TG),[15] which is found to a lesser extent. Anti-alpha anolase is another antibody that can be diagnostic of HE.[16] In one study, five out of six patients with HE were positive compared with 25 control patients with encephalopathy.[16] In our patient, the diagnosis of HE was based on the

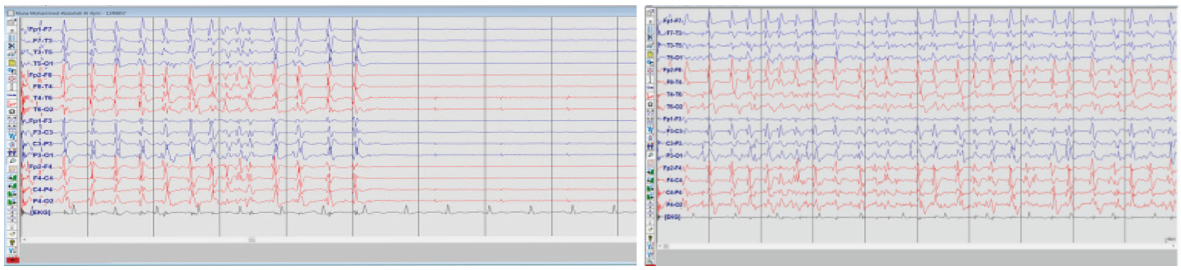

Figure 2: Electroencephalogram of status epilepticus showing continuous generalized, fairly rhythmic epileptiform discharges. The discharges were not responsive to any sensory stimulation.

Table 1: Summary of reported cases of Hashimoto's encephalitis presenting with status epilepticus, investigations, and treatments.

Author	Case	Thyroid antibodies	CSF findings	MRI findings	EEG	Treatment	Outcome
Tsai et al[2]	16-year-old girl presents with confusion	Anti-TPO, Anti-TG titers: 1:1 600	Normal	Right hyperintense lesions right medial temporal	High amplitude delta (Right parietal-temporal)	Methylprednisolone	Recovered
Monti et al[3]	51-year-old with Hashimoto thyroiditis present with convulsive seizures	Anti-TPO: 349.4 IU/mL Anti-TG: > 500 IU/mL	Normal	Normal	Bilateral frontal spikes and waves	Methylprednisolone 1 g × 2 days, 500 mg × 3 days.	Recovered
Monti et al[3]	66-year-old admitted with non-convulsive status	Anti-TPO: 643.9 IU/mL Anti-TG: 126.9 IU/mL	Normal	Normal	Bilateral frontal spikes and waves	Methylprednisolone 1 g × 2 days, 500 mg × 3 days.	Recovered
McGinley et al[4]	42-year-old admitted with convulsive status	Anti-TPO titre: 1:25 600 Anti-TG: negative	Normal	Normal	Bilateral slow waves	Dexamethasone	Recovered
Bektas et al[5]	12-year-old presents with behavioral changes and convulsive status	Anti-TPO: 725 IU/mL Anti-TG: 100 IU/mL	Normal	Unavailable	Bilateral frontal spikes	IVIG followed by plasmapheresis and steroids	Recovered
McKeon et al[6]	61-year-old with absence status epilepticus	Anti-TPO titer: 1:6 400 Anti-TG: unavailable	Normal	Normal	Bilateral slow spikes and waves	Steroids × 6 days	Recovered
Striano et al[7]	27-year-old woman presents with myoclonus then status epilepticus	Anti-TPO: 1 781 IU/mL Anti-TG: 127.5 IU/mL	Raised protein 55 mg/dL, two oligoclonal bands	Unavailable	Bifrontal theta stimulus-induced myoclonus	Methylprednisolone	Died, uncontrolled seizures
Ferlazzo et al[8]	41-year-old male with convulsive status epilepticus	Anti-TPO: 3 107 IU/mL Anti-TG: 36 569 IU/mL	Increased proteins	Normal	Generalized epileptic discharges	IV methylprednisolone	Recovered
Canton et al[9]	17-year-old female with generalized tonic-clonic seizures	Anti-TG: 638 IU/ml	High protein 85 g/dL	Normal	Frontal sharp waves	Methylprednisolone	Recovered
Canton et al[9]	21-year-old female generalized tonic-clonic seizures	Anti-TG: 6 020 IU/mL Anti-microsomal: 15.684 IU/mL	High protein 71 g/dL	Normal	Generalized slowing	Methylprednisolone	Recovered

CSF: cerebrospinal fluid; EEG: electroencephalogram; MRI: magnetic resonance imaging; Anti-TPO: antithyroperoxidase; Anti-GT: antithyroglobulin; IV: intravenous; IVIG: intravenous immunoglobulin.

exclusion of all other causes and the presence of anti-TPO with a level of 222 IU/mL. It is not clear in the literature what level is considered abnormal or diagnostic, as there is variability in the sensitivity and reference range.[17] The reference range in our laboratory is 0–50 IU/mL. Other paraneoplastic and autoimmune antibodies were negative.

The cerebrospinal fluid findings in most cases with SE secondary to HE is normal as evident by Table 1. Few cases showed high protein level with

no leukocytes.[8,9] Most patients had normal MRI finding.[3-6]

EEG findings in our patient consisted of bifrontal spikes and waves, the most commonly identified pattern in reported cases.[18] In a study that looked at EEG findings in HE in general, there were several findings including generalized abnormalities like slowing, triphasic waves, and periodic sharp waves.[18] Focal temporal slowing was also demonstrated in some patients. Those EEG findings also varied within patients.[18]

The mainstay of treatment of HE is corticosteroids. The majority of cases show remarkable response with good outcome after treatment with pulse methylprednisolone.[13,15] Other modalities of immunotherapy used in HE are plasmapheresis and IV immunoglobulin.[5,19] However, although there are cases where those modalities were used, the long-term outcome is uncertain.[19] In our case, there was progression of SE despite the use of IV immunoglobulin and plasmapheresis. This was most likely a state of SE refractoriness rather than a failure of a treatment targeting HE.

CONCLUSION

HE should be considered in patients admitted with SE. Thyroid antibodies should be among the panel of investigation. While the overall prognosis is good, this case report demonstrates that severe progressive encephalopathy, particularly with refractory SE in such patients, may have a fatal outcome. However, prompt treatment with corticosteroids should be initiated before the period of super-refractoriness sets in.

Disclosure

The authors declared no conflicts of interest.

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