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Case Report

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Case of Adult Onset, Nocturnal, Refractory, Partial-Motor Epilepsy

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Abstract

This case report discusses the complex presentation and management of a 22-year-old female with medically refractory nocturnal focal epilepsy of unknown etiology. Initially misdiagnosed with a panic attack, the patient later exhibited tonic-clonic seizures and focal motor seizures predominantly during sleep, leading to a diagnosis of refractory epilepsy. Despite trials with multiple anti-epileptic drugs (AEDs), including Levetiracetam (Keppra), Lamotrigine (Lamictal), and Lacosamide (Vimpat), the patient continued to experience seizures, necessitating the placement of a responsive neurostimulation (RNS) device. This report highlights the challenges of diagnosing and managing epilepsy with an unclear etiology and emphasizes the potential benefits of surgical interventions in medically refractory cases.

Keywords: Medically Refractory Epilepsy; Nocturnal Focal Epilepsy; Anti-Epileptic Drugs (AEDs); Responsive Neurostimulation (RNS); Sleep-Related Hyper Motor Epilepsy (SHE); Seizure Generalization.

Teaching Points: Diagnostic Challenges in Epilepsy; Management of Medically Refractory Epilepsy; Importance of Genetic and Detailed Clinical Evaluation

Introduction

Epilepsy is an umbrella term describing a collection of debilitating seizure disorders, many of which exhibit significant heterogeneity in their etiology, age at onset, presentation, and response to treatment. Due to the wide variability across these domains, epilepsy can be challenging to recognize, diagnose, and manage effectively. While some forms of epilepsy have known causes (ex: genetic mutation, structural abnormalities), roughly 50% of all epilepsy cases are of unknown etiology [1]. Further, as many as 20-40% of individuals with epilepsy are deemed medically refractory. The International League Against Epilepsy's (ILAE) criteria for medically refractory epilepsy are failure of 2 or more adequate trials of anti-epileptic drugs (AEDs), each of which are required to be well tolerated, appropriately chosen, and appropriately administered to attempt seizure freedom [2].

Seizure types can also vary between patients with epilepsy. For example, a minority of epileptic patients (only about 1.8-1.9 per 100,000 cases of epilepsy) experience seizure onset exclusively or predominantly (>90%) during sleep [1]. These tend to be focal motor seizures that are brief, with abrupt onset, preserved awareness, and characterized by hyperkinetic movements. Patients exhibiting this pattern of seizure activity, known as sleep-related hyperkinetic epilepsy (SHE), often present within the first two decades of life, and most respond well to AEDs, such as carbamazepine [3]. The following case presentation explores the diagnosis and treatment of a young female with epilepsy of unknown etiology, occurring predominately during sleep, and being medically refractory.

Case Presentation

A 22-year-old female presented to the emergency room with her family following a reported tonic-clonic seizure. According to the patient, she awoke from sleep unable to breathe. She recalled

experiencing right-sided hemiparalysis and subsequently lost consciousness for about 4 minutes. Her family reported that the patient exhibited abduction and flexion of bilateral upper extremities with full body rigidity, shaking, salivating, and was cyanotic at this time. When the patient regained consciousness, she was confused and had no recollection of the event for about 30 minutes but complained of left shoulder pain.

At the time of her medical visit, head CT was unremarkable. X-ray showed left anterior shoulder dislocation, which was successfully reduced. Blood was notable only for a lactate of 3.0 mmol/L (normal <2.0 mmol/L). The patient was taking Zoloft (25 mg QD) at the time and symptoms were ultimately attributed to a panic attack, and she was subsequently discharged with a prescription for Lorazepam (Ativan) 0.5 mg as needed.

Within 48 hours, the patient developed episodes of intense involuntary contraction of her right-sided facial muscles, primarily above her cheek and mostly involving the area around her eye. These episodes lasted about 10 seconds each and persisted intermittently during sleep for 2 days. The patient also recalled feeling this sensation upon waking about once per week for the past two years but did not seek medical attention. She returned to the hospital for evaluation and was subsequently admitted. A head CT and standard 20 lead EEG were performed and showed no abnormality. The patient underwent monitoring for 2 nights. Based on the patient's history, she was diagnosed with focal epilepsy with generalization to tonic-clonic convulsions and discharged on a loading dose of 1g levetiracetam (Keppra) PO, followed by 750 mg BID and weekly increased doses (Table 1).

At follow-up 7 days later, the patient's seizure activity had decreased, but had not been eliminated. It was recommended to continue increasing the Keppra dosage until either complete seizure elimination, or the maximum dose of 3,000mg daily had been reached. Clonazepam (1 mg, BID) was added for agitation, likely the result of Keppra.

Over the next month, the patient experienced difficulty adapting to Keppra and clonazepam, although her seizure activity seemed to be under control. She had gradually increased Keppra to the target dose of 3,000 mg. Pyridoxine (Vitamin B6) 50mg BID was added to decrease irritability and clonazepam was replaced with 1 mg Ativan nightly.

40 days after her initial episode, the patient once again awoke suddenly with right sided hemiparalysis and inability to breathe which progressed to bilateral upper extremity abduction and flexion, full body rigidity, shaking, cyanosis and loss of consciousness. She was evaluated at the ER and it was determined the patient failed Keppra. It was recommended she switch to Lamotrigine (Lamictal) with a target dose of 300 mg. Clonazepam 1 mg BID was resumed while the patient transitioned medications (Table 2).

By week 6, the patient developed a full body rash. The patient once again presented to the ER. Lamictal was immediately discontinued, and the patient instead continued a full dose of Keppra (3,000mg). At follow up, the patient was advised to continue Keppra 1,500 mg BID and Clonazepam 1 mg BID. A trial of Lacosamide (Vimpat) was begun at 50 mg daily for 3 days, followed by an increase to 100 mg BID in 1 week, all while continuing Keppra and Clonazepam.

At follow-up three months later, the patient was taking Vimpat 400 mg and Clonazepam 1 mg BID. She reported no seizure activity over the past two weeks. It was recommended the dose of Vimpat be increased to 500 mg daily for one week, then 600 mg daily. After a week at 600 mg Vimpat daily, the patient was to off Clonazepam. However, the patient was unable to eliminate seizure activity on Vimpat alone. It was determined the patient met all criteria for refractory epilepsy. Vimpat and Clonazepam were continued but an epilepsy monitoring unit admission was recommended.

Six weeks later, the patient was admitted into an epilepsy-monitoring unit including 8 days of continuous EEG/CCTV monitoring and standard international 10-20 system electrode placement with additional bilateral anterior temporal electrodes. All medication was titrated until the patient began showing signs of seizure activity at 0 mg Vimpat and 0.5mg Clonazepam QD on day 6 (Table 3).

Imaging during the admission was normal, including contrast CT PET Brain, Abdomen/Pelvis, Chest, and NM Skull Base to Mid Thighs. Labs were all within normal limits including CBC with differential, CMP, electrolytes, PT-INR, PTT, and encephalopathy autoimmune panel. A lumbar punction was performed; CSF was evaluated for total protein, glucose, autoimmune encephalopathy panel, cell count/differential that were all normal. A CSF culture/smear showed no organisms.

Overnight between day 6 and 7, the patient experienced the first electroclinical generalized tonic-clonic seizure awaking her from sleep, beginning with right hemiparalysis and progressing to full body tonic-clonic movement with loss of consciousness. This was then followed by 6 focal motor seizures throughout the rest of the night starting at the left frontal EEG derivations. After analysing the EEG data, it was determined that the seizures originated near the left motor cortex (leads Fp2>Fp1) and spread posteriorly before attenuating (no involvement of leads O1/O2). The patient began Clobazam (Onfi) 30 mg qHS as monotherapy with good effect initially. The patient was subsequently diagnosed with refractory nocturnal focal motor onset epilepsy with secondary generalization to tonic clonic.

Approximately 5 months later, the patient experienced her first focal motor seizure while taking Clobazam. Clonazepam 0.5mg QD was added with subsequent seizure control until 2 days later when she experienced another focal motor seizure. It was decided

to increase Clobazam to 35 mg QD and discontinue Clonazepam. Six months later, the patient experienced another breakthrough on Clobazam, the dose was increased to 40 mg QD. An additional breakthrough occurred 5 months later, Clobazam was no longer able to be increased so a surgical consult for SEEG monitoring and possible resection/RNS placement was recommended.

Week	Medication	Dose (am-pm)
1	Keppra	750-1,125 mg
2	Keppra	1,125 mg BID
3	Keppra	1,125-1,500 mg
4	Keppra	1,500 mg BID

Table 1: Titration schedule for Keppra dosage increase.

Week	Medication	Dose (am-pm)	Medication	Dose (am-pm)
1	Lamictal	25 mg QD	Keppra	1,500-1,500 mg
2	Lamictal	25-25 mg	Keppra	1,500-1,500 mg
3	Lamictal	25-50 mg	Keppra	1,500-1,500 mg
4	Lamictal	50-50 mg	Keppra	1,500-1,500 mg
5	Lamictal	75-75 mg	Keppra	1,500-1,500 mg
6*	Lamictal	100-100 mg	Keppra	1,000-500 mg
7	Lamictal	100-150 mg	Keppra	1,000-1,000 mg
8	Lamictal	150-150 mg	Keppra	500-1,000 mg
9	Lamictal	150-150 mg	Keppra	500-500 mg
10	Lamictal	150-150 mg	Keppra	0-500 mg
11	Lamictal	150-150 mg	Keppra	0-0 mg
*Lamictal discontinued a week 6 due to a rash, Keppra was continued at 1,500-1,500mg				

Table 2: Titration schedule for Lamictal dosage increase and Keppra dosage decrease.

Day	Medication	Dose (am-pm)	Medication	Dose (am-pm)		
0 (home dose)	Vimpat	300-300 mg	Clonazepam	0.5-1.0 mg		
1	Vimpat	300-150 mg	Clonazepam	0.5-1.0 mg		
2	Vimpat	100-100 mg	Clonazepam	0.5-1.0 mg		
3	Vimpat	0-0 mg	Clonazepam	0.5-1.0 mg		
4	Vimpat	0-0 mg	Clonazepam	0-0.5 mg		
5	Vimpat	0-0 mg	Clonazepam	0-0.5 mg		
6*	Vimpat	0-0 mg	Clonazepam	0-0.5 mg	Medication	Dose (am-pm)
7	Vimpat	0-0 mg	Clonazepam	0-0.75 mg	Onfi	10-15 mg
8	Vimpat	0-0 mg	Clonazepam	0-0 mg	Onfi	30 mg qHS
*Dose at which seizure activity began						

Table 3: Titration schedule for Vimpat and Clonazepam dosage decreases and Onfi increase.

Discussion

Ultimately, this patient was diagnosed with simple partial motor seizures with secondary generalization to tonic-clonic that are nocturnal in nature and refractory to medication. Medication targeting multiple mechanisms of action were chosen for therapy trials. These included drugs affecting synaptic vesicle proteins, voltage-dependent sodium channels, and neurotransmitters such as GABA, glutamate, and aspartate. All the trialed medications were approved as first line therapy or adjunct therapy for focal seizures [4]. Keppra, Lamictal and Vimpat were each discontinued due to break through seizure activity and side effects. It is notable that Keppra caused the patient significant neuropsychiatric effects, which is among the most common reasons for discontinuation [4]. Reports suggest Pyridoxine can help neuropsychiatric effects associated with Keppra, but most studies are retrospective and further investigation is needed. Trial of adjunct Pyridoxine was unsuccessful in managing neuropsychiatric effects in this patient. The patient also experienced a full body rash on Lamictal, which is seen in 10% of individuals. The risk of development of Steven-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or angioedema is 1/1000 and any rash while taking Lamictal necessitates immediate discontinuation [4].

The patient's original misdiagnosis needs to be emphasized here. Despite extensive workup strongly suggestive of a tonic-clonic seizure, the patient was diagnosed with a panic attack and sent home from the ER. Thus, the patient was not seen by a hospital neurologist, and had to seek care at another institution before receiving an adequate diagnosis.

Based on the definition of sleep-related hypermotor epilepsy (SHE), the patient meets most criteria and further genetic work up could be explored to determine if she is positive for genes associated with SHE. It is unknown if a diagnosis of SHE would change the outcome for this patient, however, there have been management recommendations based on specific associated genes [3]. Research suggests most patients with SHE respond to AEDs, particularly carbamazepine [5]. Although this medication was not tried, the patient still failed >2 AED's deeming her medically resistant. However, she does experience a majority of seizures during sleep, epileptiform abnormalities located in the frontal areas on EEG, and no brain lesions, all accurately describing aspects of SHE [3]. Overall, this patient's presentation is distinguished from other epilepsy presentations due to her age of onset without any notable brain lesions or history of trauma, lack of family history, medically refractory and nocturnal at presentation.

Outcome/Follow-up

This patient was taken to surgery to obtain an SEEG and place an RNS device. Post-operation, she was continued on a lower dose of Clobazam (30mg QD) with adequate seizure control in adjunct to the RNS device. Any breakthrough partial seizures have been detected by the RNS device. Side effects of Clobazam include fatigue, but otherwise the patient has tolerated surgery and current medical treatment well. She reports a better quality of life since her original diagnosis with the RNS and Clobazam therapy.

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