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Case Report
Navigating Drug-Resistant Epilepsy: A Case Report on Achieving Seizure Freedom for 5 Years with Perampanel Therapy in a Patient with Multiple Comorbidities

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Abstract

Background and Objective: Epilepsy is a common neurological condition that significantly impacts quality of life, particularly in cases of drug-resistant epilepsy (DRE). Perampanel, a third-generation antiseizure medication (ASM), has shown promise as a treatment option. This case report describes the successful long-term management of a patient with DRE using perampanel after deferring epilepsy surgery. **Materials and Methods:** A 49-year-old woman with a history of multiple medical comorbidities, including morbid obesity, experienced drug-resistant focal to bilateral tonic clonic seizures since age 40. She had failed trials of various ASMs. Intracranial Electroencephalogram (iEEG) monitoring confirmed a left temporal lobe epileptic focus but the surgical intervention was deferred due to her complex medical status. Perampanel was subsequently added to her treatment regimen and the patient achieved sustained seizure remission for over 5 years. **Results:** This case highlights the potential utility of perampanel in the management of DRE, particularly in patients unsuitable for or deferring epilepsy surgery. The long-term seizure freedom achieved with perampanel in this complex case suggests it may serve as a valuable alternative therapeutic option. **Conclusion:** Further research is warranted to elucidate the role of perampanel in the comprehensive care of individuals with DRE.

Key words: Perampanel, intracranial electroencephalogram, drug-resistant epilepsy, seizure

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Epilepsy affects about 70 million people worldwide and is considered by the World Health Organization (WHO) the most serious neurological condition leading to multiple medical comorbidities and premature mortality with adverse impact on the quality of life[1,2].

Antiseizure medications (ASMs) have been used to prevent seizure recurrence, however, it is reported that 30% of people with epilepsy (PWE) are considered to have Drug-Resistant Epilepsy (DRE)[3]. Perampanel is among the third-generation ASMs a selective, noncompetitive α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) receptor antagonist[4,5]. In the current study, a patient who failed multiple ASMs was described and eventually evaluated for epilepsy surgery using an Intracranial Electroencephalogram (iEEG). Although the patient had potentially resectable focal epilepsy in the left temporal lobe, she was not a candidate for surgical intervention due to the presence of multiple comorbidities. In the interim period before surgery, she was treated with perampanel and achieved seizure remission for more than five years.

Case report: In February 2012, 49-year-old right-handed woman who had been experiencing epileptic seizures since the age of 40 was admitted to the Department of Clinical Neurological Sciences at Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada. Her first seizure was a witnessed unknown onset tonic-clonic seizure without warning at the workplace. She bit her tongue during the seizure and had urinary incontinence. A few days later, she experienced another convulsive seizure with a similar semiology. One month later, she developed other types of seizures characterized by staring, behavioural arrest, impaired awareness, fumbling with her hands (mainly the right hand) and occasional oral automatisms. These seizures reportedly lasted from two to ten minutes and were followed by up to half an hour of difficulty in comprehension. They recurred three times per month up to twice per week and could be triggered by emotional stress and menstrual periods. She had no risk factors for epilepsy. She had multiple comorbidities including obstructive sleep apnea that was managed by Continuous Positive Airway Pressure (CPAP), asthma requiring inhalers, rheumatoid arthritis (RA), morbid obesity, Grave's disease, menorrhagia and cellulitis of the right leg requiring hospitalization for two weeks in her early thirties. She lived with her fiancé and parents and worked as a sales assistant. After her first seizure, she lost her driver's license. Upon her initial assessment by our team, she was on levetiracetam 3000 mg daily, lacosamide 400 mg daily and clobazam 5 mg daily. Multiple ASMs had been tried earlier, including carbamazepine, phenytoin, valproic acid and topiramate. Phenytoin induced hives and valproic acid caused weight gain, while topiramate caused speech difficulties and psychomotor slowing. Her general and neurological examination revealed only morbid obesity.

Magnetic Resonance Imaging (MRI) of the brain was normal. She was admitted to the epilepsy monitoring unit (EMU) for 9 days, from March 20 to 28, 2012, for the characterization of her seizure. The scalp EEG was conducted, revealing a normal background and bilateral temporal slowing, maximum over the left side. Two clinical seizures were recorded manifesting with speech arrest and staring followed by impaired awareness. In both seizures, the ictal discharges started from the left anterior temporal region. Serum and Cerebrospinal Fluid (CSF) autoimmune workup for late-onset epilepsy were normal. She had elevated C-reactive protein and rheumatoid factor was elevated as well (222 IU/mL, normal range 0-21) likely due to RA. The psychological evaluation demonstrated mild depression. Neuropsychological assessment showed left hemispheric dominance for language and moderate to high impairment of verbal fluency that put her at high risk of verbal memory decline following the removal of her dominant left mesial temporal structures. The patient underwent Intracranial Electroencephalogram (iEEG) recording to confirm a neocortical origin and possible sparing of left mesial temporal structures. Seven depth electrodes were implanted in the left hemisphere to cover the left amygdala, the anterior, middle and posterior left hippocampus, the left angular gyrus and the left posterior temporal neocortical area (Fig. 1).

During her admission to the EMU, abundant spikes were captured from the left anterior, middle and posterior hippocampus. Four seizures were captured, three of which originated from the left temporal neocortex and spread after five to six seconds to the left anterior hippocampus, while one seizure was a purely left hippocampal onset seizure without a spread. On the fourth day of her iEEG recordings, she developed coughing, breathing difficulties and oxygen desaturation and the chest X-ray revealed bilateral consolidations. She was treated for pneumonia with antibiotics. Moreover, pulmonary embolus was suspected but could not be confirmed. Given the respiratory complications, depth EEG electrodes were removed and her respiratory symptoms gradually improved.

On a follow-up visit to her epileptologist and neurosurgeon, there was an extensive discussion about the risks and benefits of dominant left temporal lobe resection. There were several concerns about a proposed left anterior temporal lobectomy surgery because of the ictal involvement

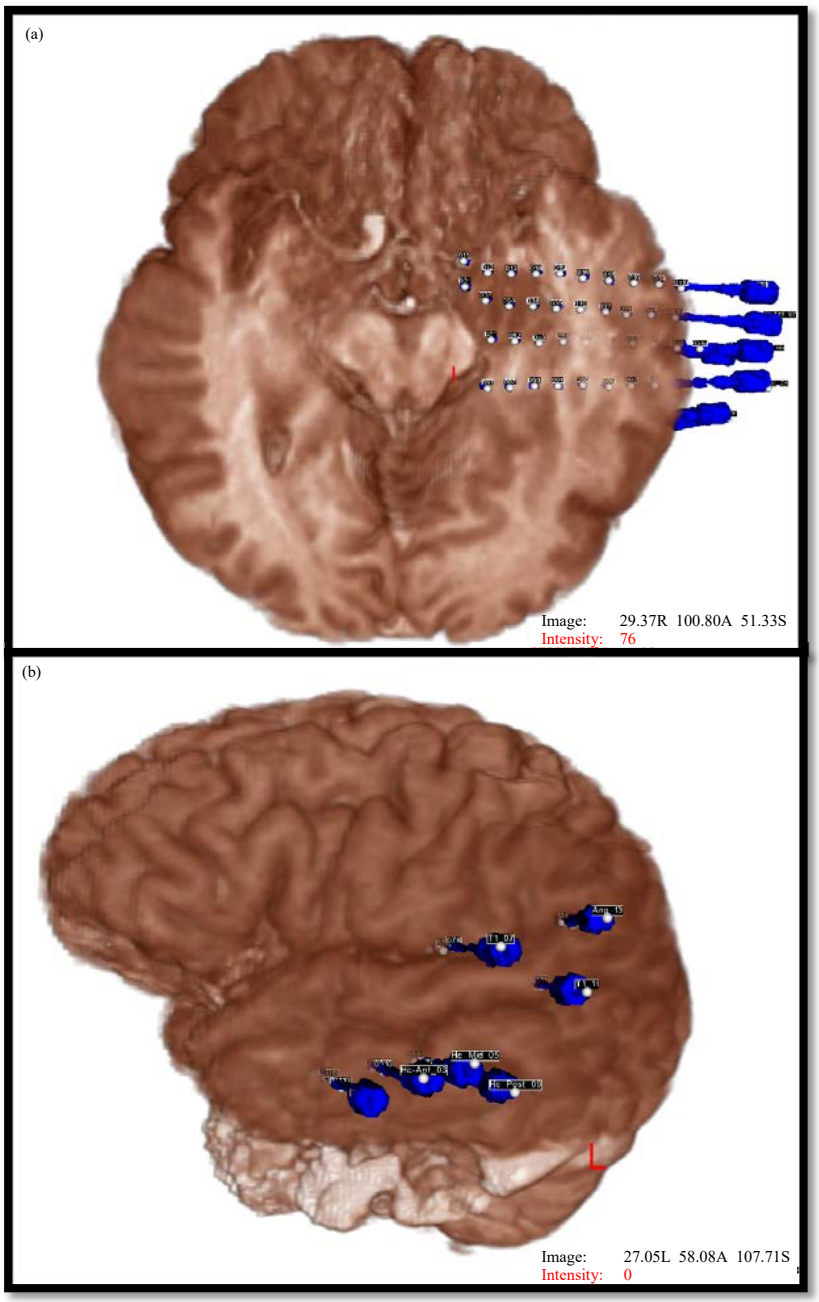

Fig. 1(a-b): The placement of electrodes for the current patient (above): Axial view and (below): lateral view. The blue color is related to the bolts securing the electrodes, while the small white letters are of clinical insignificance (used for labelling in the capturing process)

of the dominant neocortical and mesial temporal structures, which could lead to a moderate to severe risk of verbal memory decline after surgery. Moreover, the lack of an identifiable lesion in the anatomical MRI decreases the chance of seizure freedom. Furthermore, her morbid obesity, other active medical conditions and respiratory difficulties were added risks to the surgery. Due to blurred vision, her lacosamide dose was decreased one month later, although this did not improve the vision, it led to an increase in seizure frequency to once per week. Therefore, the lacosamide dose was raised back to 400 mg daily. A few months later, she was started on perampanel 2 mg per day along with her other medications of levetiracetam 3000 mg per day and lacosamide 400 mg daily.

At her next follow-up visit eight weeks later, she reported experiencing only two seizures in the first few weeks after the introduction of perampanel. At that visit, perampanel was increased gradually to 6 mg daily and lacosamide was reduced to 200 mg per day. In follow-up visits, she reported seizure freedom. She returned to work and obtained her driver's license. At her later follow-ups, she remained seizure-free for nearly five years. She remains employed and drives to her appointments. Perampanel dose was maintained at 6 mg daily, levetiracetam was reduced to 2000 mg per day and lacosamide was discontinued. Levetiracetam was discontinued later, as well.

DISCUSSION

The current study reports an excellent response to the addition of perampanel in a late-onset focal epilepsy patient who had failed seven ASMs. Although DRE has multiple definitions depending on the number of ASMs used, appropriateness of treatment and follow-up duration, our patient met all of those criteria[3]. Her epilepsy severely impacted her quality of life, resulting in unemployment and the loss of her driver's license. After a comprehensive presurgical evaluation for her epilepsy, she was deemed a potential surgical candidate for epilepsy surgery only after addressing her morbid obesity. High morbidity and the potential for high cognitive deficits after a resective epilepsy surgery were discussed. It is to be noted that responsive neurostimulation (RNS) was not available in Canada, where the patient lived.

Perampanel is a selective, noncompetitive AMPA receptor antagonist indicated for focal seizure as adjunctive and monotherapy and as adjunctive therapy for primary generalized tonic-clonic epilepsy[5]. In the current case, it was started after more than four years from seizure onset following seven appropriately chosen ASMs. Seizure frequency decreased significantly at 4 mg per day and stopped completely at 6 mg per day. She remained seizure-free for five years without reporting any side effects.

Accumulating evidence for newer ASMs with remarkable seizure control is growing and this is an example of excellent seizure control that was accomplished with the addition of perampanel. It's unclear why this patient responded so well to the addition of perampanel after the failure of seven ASMs, this improvement is likely due to perampanel's different mechanism of action or its complementary, additive or synergistic effects with other ASMs.

The efficacy of perampanel was recently investigated in several clinical studies. A pooled analysis of phase III clinical trial data was conducted to evaluate the medication's efficacy. The results demonstrated that perampanel administration led to decreases in the frequencies of both focal seizures and secondary generalized seizures across different dosage levels. Specifically, patients treated with perampanel experienced greater than 50% reductions in seizure frequency compared to those receiving placebo[6-8].

However, studies of the combined effects of ASM combinations including perampanel suggested a less favourable response when perampanel is used alongside sodium-channel blockers or strong enzyme-inducing ASMs such as carbamazepine[9].

While promising results regarding the efficacy of perampanel in seizure elimination are demonstrated in the current case, additional research is warranted to comprehensively evaluate this medication. Future studies with larger, more diverse patient populations will be important to confirm and expand upon these initial findings. Moreover, comparative clinical trials assessing the relative efficacy and safety of perampanel versus other established ASMs would provide valuable insights. Furthermore, investigating potential synergistic effects between perampanel and other ASMs could uncover opportunities for optimizing combination therapy approaches. Expanding the evidence base through rigorous, well-designed studies with adequate statistical power will be crucial for fully elucidating the role of perampanel in the management of epilepsy and informing broader treatment guidelines.

CONCLUSION

A 49 years old woman who had failed multiple ASMs and was waiting for epilepsy surgery due to her medical comorbidities, despite having a well-defined left temporal lobe epilepsy, remained seizure-free for the last five years after starting perampanel, which allowed discontinuation of lacosamide and levetiracetam. This illustrative case highlights the role of third-generation ASMs in the management of DRE.

SIGNIFICANCE STATEMENT

This case report underscores the efficacy of perampanel in managing drug-resistant epilepsy, particularly in patients who are unsuitable for or deferring epilepsy surgery. The patient's sustained seizure remission over five years highlights perampanel as a viable therapeutic alternative, meriting further research into its long-term benefits and applications in complex DRE cases.

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