CASE REPORT

Lacosamide as an Adjunctive Therapy in Drug-Resistant Absence Epilepsy: Successful Treatment of Four Patients

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ABSTRACT

Absence epilepsy is one of the most common epileptic syndromes in children, and despite its benign nature, a percentage of these children are drug-resistant. This study presents four cases of drug-resistant absence epilepsy in children who were unresponsive to traditional antiepileptic drugs. The study reports the successful use of Lacosamide as an adjunctive therapy to completely control symptoms and electroencephalogram (EEG) abnormalities. The patients, aged four to ten years, had previously failed treatment with Ethosuximide, Sodium Valproate, Levetiracetam, and Topiramate in various combinations. Lacosamide was initiated at a dose of 10 mg/kg per day in combination with Sodium valproate, resulting in rapid and sustained improvement. The patients remained symptom-free and showed no EEG abnormalities for one to two years. These findings suggest that Lacosamide can be considered a safe add-on drug for refractory absence epilepsy. However, it may be contended that additional confirmatory trials are necessary to investigate the effects of Lacosamide in a larger patient population.

Introduction

Childhood absence epilepsy accounts for approximately 10% to 15% of childhood epilepsies. Around 80% to 90% of cases respond well to traditional medications, particularly monotherapy with drugs such as Sodium Valproate or Ethosuximide, or in some cases, combination therapy with Lamotrigine, Topiramate, and Benzodiazepines. However, 10% to 20% of patients are resistant to treatment, specifically those that onset at a young age or where a significant delay is found in starting medication (1, 2).

In such cases, different modalities, including steroids, Ethosuximide, 00, and the ketogenic diet, may demonstrate some degree of effectiveness. However, the existing studies are limited, and the clinical trial results indicate that these methods have yet to be extensively embraced (2).

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In this small series, we share our experience with Lacosamide as a suitable medication in childhood absence epilepsy, with high efficacy and safety.

Case Presentation

All four cases of absence epilepsy met the clinical and electroencephalographic criteria and were referred to the pediatric neurology clinic in Tehran, Iran, between July 2020 and July 2021. They were resistant to at least two medications, including Valproate and Ethosuximide, and sometimes received combination therapies such as Lamotrigine, Levetiracetam, and Topiramate for at least 2-4 months. The levels of the medications were within the therapeutic range in all cases. Lacosamide was initiated at a dose of five mg/kg/day and gradually increased over 15 days to a maintenance dose of ten mg/kg/day, administered every 12 hours, in addition to Valproate. All cases underwent an electroencephalogram (EEG) evaluation with provocative testing one month after initiation. After confirming normalization, they underwent clinical and EEG follow-up, monitoring the adverse effects.

The four cases consisted of three boys and one girl, ranging in age from four to ten years at the start of the medication. All cases had normal development at the time of examination, without a history of hospitalization prior to starting the medication. One case had onset at the age of two years, accompanied by staring and blinking, suggestive of Jeavons syndrome, and the other cases had multiple episodes of staring, more than 20 times per day, with a history of 1-2 generalized seizures during this period. All cases were on polytherapy, and their EEGs showed generalized 3-cycle-per-second spike-wave discharges.

Following the initiation of Lacosamide, all cases became seizure-free after one week on the final dose, and gradually, medications such as Levetiracetam and Ethosuximide were tapered and discontinued, while Sodium Valproate and Lacosamide were continued.

Case 1:

A 4-year-old boy with normal development had blinking seizures since the age of two, and he had been controlling the blinking with a combination of Levetiracetam, Sodium Valproate, and Topiramate. However, starting from one year ago, he experienced momentary pauses in blinking and closing his eyes while speaking. The EEG findings are shown in Figure 1A. An event-related paroxysmal generalized wave pattern was observed on his EEG during video EEG monitoring 2-3 cycles per second. With suspicion of Jeavons syndrome, Lacozamide was started for him, resulting in complete cessation of all seizure activities within a week of reaching the therapeutic dose. Subsequent EEGs over two years remained normal, and gradually, Levetiracetam (keppra) was discontinued, while Sodium Valproate, Lacozamide, and Topiramate were continued.

Case 2:

A 9-year-old boy with normal development had brief absence seizures in the form of blinking and deviation of the head for about 30 seconds, accompanied by a decrease in consciousness with normal tone from one week ago. The seizures were repeated up to 50 times a day. The EEG findings are shown in Figure 1B. EEG showed paroxysmal generalized 3 Hz spike-and-wave discharges. It resisted to Sodium Valproate, Ethosuximide, and Levetiracetam at the therapeutic dose for three months. Fasting CSF glucose level was normal. Lacosamide was added to previous drugs, resulting in the normalization of the EEG

and complete cessation of seizures. After two weeks, Ethosuximide and Levetiracetam were discontinued. The patient has been followed up for at least one year after taking Lacosamide added to Sodium Valproate, and he is entirely seizure-free.

Case 3:

A 10-year-old boy with normal development experienced two generalized seizures starting from one year ago. He was initially treated with levetiracetam at a dose of 40 mg per kg and gradually developed recurrent benign attacks with epileptic 3 Hz spike-and-wave discharges on EEG.

The EEG findings are shown in Figure 1C. Sodium Valproate was prescribed at a dose of 40 mg per kg. However, due to a shortage of Ethosuximide, the combination therapy of Sodium Valproate and Ethosuximide could not be provided. Consequently, the patient's condition remained resistant to treatment. Lacozamide was added to his regimen alongside Sodium Valproate, and Levetiracetam was discontinued. Within a week, the seizures ceased utterly, and the EEG returned to normal. The patient has been followed up for at least 18 months, and no abnormalities were found.

Case 4:

A 4-year-old girl with generalized seizures and normal EEG in the last year ago, controlled with Primidone and Levetiracetam, developed secondarily staring seizures 5-10 times a day for

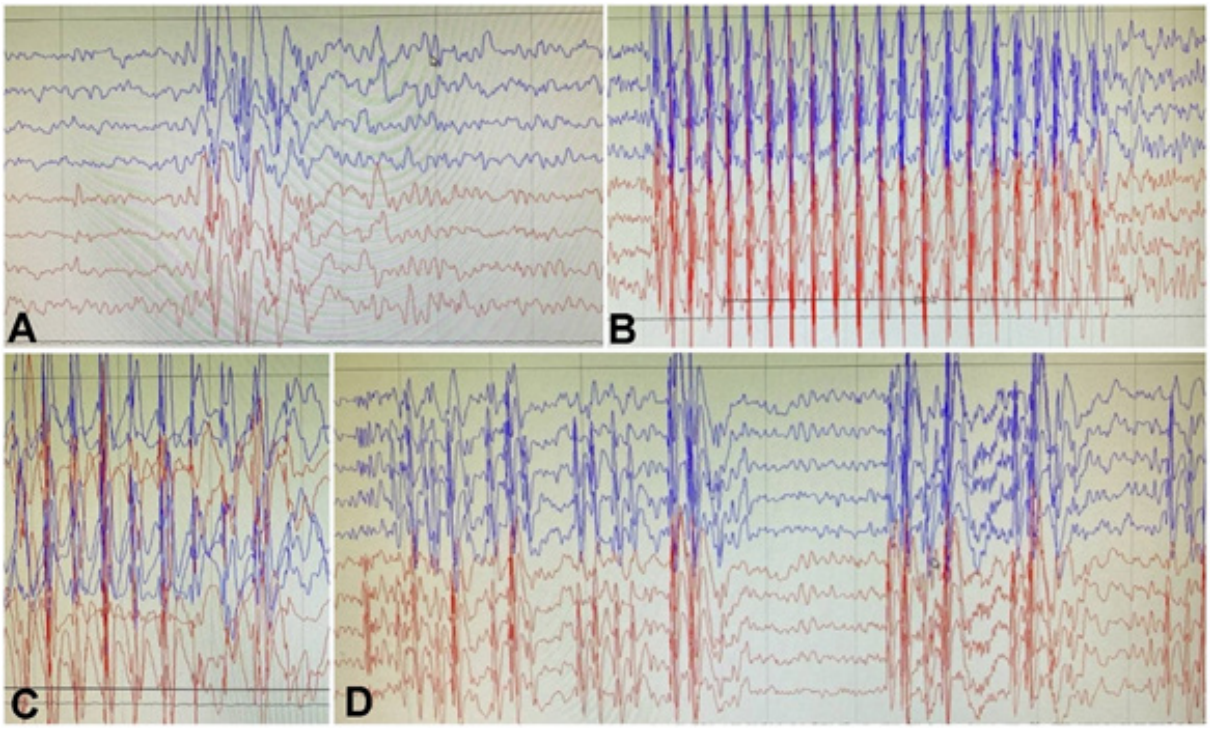

Figure 1. EEG findings in the patients with absence epilepsy.

A. Patient 1: Paroxysmal abrupt onset of spike wave discharges while closing his eyes for a few seconds and interrrupting his speech (ictal phase).

B. Patient 2: Abrupt onset of spike wave discharges as three cycles per second during her event.

C. Patient 3: Paroxysmal spike wave discharges in interical period without stimulation of hyperventilation.

D: Patient 4: Frequent generalized spike wave discharges as 3 cycles per second in interictal event in a 4 years old girl with frequent stairing

the past six months. The EEG showed 3 Hz spike-and-wave discharges.

The EEG findings are shown in Figure 1D. Sodium Valproate was added to the medications, and Primidone was gradually discontinued. The frequency of absence seizures was reduced to 2-3 times a day, but the EEG remained abnormal with suspicion of resistant absence seizures. The dose of Lacosamide was titrated to ten mg per kg, and after one month, the seizures wholly normalized, and the EEG became normal. Sodium Valproate and Lacozamide have been continued, and it has been about a year now without any seizure symptoms for the patient.

Discussion

Absence epilepsy is a neurological disorder characterized by recurrent, brief episodes of impaired consciousness and absence of seizure. While many individuals with absence epilepsy find relief with appropriate treatment, a subset of patients exists who experience resistant absence epilepsy. Resistant absence epilepsy refers to cases where seizures persist despite standard treatment approaches. One commonly used antiepileptic drug for absence seizures is Valproate Sodium. However, instances exist where Valproate Sodium fails to provide the desired control over seizures. The reasons for Valproate Sodium non-responsiveness can vary and may include factors such as genetic predisposition, individual variations in drug metabolism, or the presence of specific seizure types that are less responsive to this medication. In such cases, it is crucial to explore alternative treatment options to provide better seizure control and improve the individual's life (1, 2). Switching to Ethosuximide or combination therapy with two or several antiepileptic drugs may be beneficial in cases where Valproate Sodium proves ineffective. Adding medications such as lamotrigine, Levetiracetam, or Topiramate to the existing treatment regimen may be considered in resistant cases (2). However, some patients do not respond to any of the recommended treatments, and despite the use of one or multiple medications, the symptoms of the disease continue to be present. In the current study, four patients with absence epilepsy who did not respond to traditional treatment with Sodium Valproate in combination with other drugs showed a complete response to the combination of Lacosamide and Sodium Valproate. In addition to clinical symptoms, the existing abnormalities in the EEG wholly improved. The patients were monitored for at least one year, and throughout the entire follow-up period until now, they have been free of disease manifestations. Lacosamide is a relatively newer antiepileptic drug that has gained recognition for its efficacy and tolerability in treating epilepsy. However, no information is available regarding the effectiveness of this medication in patients with resistant absence epilepsy. Lacosamide exerts its antiepileptic effects through a unique mechanism of action. It selectively enhances the slow inactivation of voltage-gated sodium channels, thereby stabilizing the hyperexcitable neuronal membranes. By modulating sodium channels, Lacosamide reduces excessive neuronal firing and seizure activity in the brain (7, 8).

Lacosamide has demonstrated efficacy in treating focal-onset seizures, the most common type of seizures in epilepsy. Clinical trials have shown that Lacosamide when used as adjunctive therapy, can significantly reduce seizure frequency and improve seizure control in patients with refractory focal-onset seizures. Furthermore, Lacosamide has shown efficacy across different age groups,

including adults, elderly patients, and children, making it a versatile treatment option in epilepsy management (5, 6, 7).

In 2015, Savvas et al. reported two cases of focal seizures evolving into status epilepticus in adults treated with Lacosamide monotherapy (6), and in 2013, Julia et al. introduced this drug as a novel and effective treatment for status epilepticus (3). A double-blind study investigated the efficacy of Lacosamide as an adjunctive therapy in drug-resistant absence seizures. The study included patients with idiopathic generalized epilepsies and found positive outcomes in terms of seizure control and tolerability (9).

Ifra et al. presented a case of a 15-year-old female with medically refractory jeavonse syndrome with seizure resolution in response to Lacosamide monotherapy at standard daily dose (5)

Overall, Lacosamide is well-tolerated, and there have been a few cases of intolerance and status epilepticus associated with Lacosamide (10). The most commonly reported side effects include dizziness, headache, nausea, and diplopia. These side effects are generally transient and dose-dependent. Lacosamide has a favorable pharmacokinetic profile, with minimal drug interactions and a low potential for interactions with hepatic enzymes. However, as with any antiepileptic drug, careful consideration should be given to individual patient characteristics, including comorbidities and concomitant medications (11).

Besides its antiepileptic properties, Lacosamide has shown potential benefits in other aspects of epilepsy management. Lacosamide has demonstrated a favorable cognitive profile compared to some other antiepileptic drugs. Studies suggest that it may have a neutral or even positive impact on cognitive function, making it an attractive choice for patients who prioritize cognitive well-being (12).

Lacosamide has a minimal effect on cardiac conduction, making it a safer option for patients with cardiovascular comorbidities or those who are at risk of cardiac arrhythmias. Nevertheless, caution should still be exercised, specifically in patients with pre-existing cardiac conditions (11).

While Lacosamide is primarily used as an adjunctive therapy, emerging evidence supports its potential as a monotherapy option. Several studies have shown promising results in terms of seizure control and tolerability when Lacosamide is used as the initial treatment in newly diagnosed epilepsy patients, specifically in myoclonic absence seizures (jeavonse syndrome)(9).

In Conclusion

In conclusion, this case series provides evidence of the effectiveness of combining Sodium Valproate and Lacosamide as a treatment option for patients with resistant absence epilepsy. The positive response observed in these patients suggests the potential for improved seizure control and symptom management in this challenging patient population.

Further research, including more extensive clinical trials, is needed to substantiate these findings and elucidate the underlying mechanisms of this combination therapy.

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Not applicable.

Authors' Contribution

T. Moosavian supervised the entire conduct of the study, conducted data collection, and reviewed the manuscript, and Hr. Moosavian assisted in the data collection and wrote the main manuscript

text . All authors reviewed the final manuscript.

Conflict of Interest

The authors declare no competing interests.

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