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Case Report

Levetiracetam-Resistant Self Limited Familial Infantile Epilepsy Mimicking Refractory Epilepsy - A Case Report

Ahmad HAMMOUD.[1], Duha L. TURJUMAN.[2], Abdulkareem ABUALI.[2], David AMAN EDDINE.[3]

1. Pediatric Neurology, American Wellness Center, Dubai, UAE

2. Medical Student, College of Medicine, University of Sharjah, Sharjah, UAE

3. Pediatrics, Head of Department, Department of Pediatric, Dr. Sulaiman Al Habib Hospital, Dubai, UAE

***Correspondence to:** Ahmad Hammoud, MD. Consultant Pediatric Neurology, American Wellness Center, Dubai, AE. Email: Dr.ahmadhammoud@outlook.com

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Abstract

This case report presents the clinical features and management outcomes of a 4-month-old female diagnosed with self-limited familial infantile epilepsy (SeLIE), formerly known as Benign Familial Infantile Epilepsy. The patient experienced abrupt onset seizures, with inconclusive results from routine seizure investigations. Initial treatment with Levetiracetam (LEV) proved ineffective, leading to the perception of refractory seizures. However, the addition of Oxcarbazepine (OXC) resulted in immediate seizure control. Genetic studies conducted during controlled seizure episodes confirmed the diagnosis of SeLIE, with the identification of a Proline-rich transmembrane protein 2 (PRRT2) mutation, the most prevalent causative mutation in SeLIE. This case underscores the significance of early suspicion of SeLIE and considering OXC as the initial treatment option to achieve earlier seizure control, mitigate aggressive management, and alleviate emotional stress for the patient and their family.

***Key words**: Self-limited familial infantile epilepsy (SeLIE), Levetiracetam (LEV), Oxcarbazepine (OXC), PRRT2 mutation, Case Report*

Introduction

Self-limited Familial Infantile Epilepsy (SeLIE)1, formerly known as Benign Familial Infantile Epilepsy,2 is a syndrome inherited in an autosomal dominant manner,3 with an unknown prevalence prevalence.4 This disorder is characterized by episodic seizures that are mostly focal with a usual age of onset between 3 and 8 months. Fortunately, as the name suggests, spontaneous resolution with a favorable outcome is predicted in patients with SeLIE, with the majority reaching a seizure-free state around the age of 2 years.5 Multiple mutations were identified to be the culprit behind this epileptic syndrome, including PRRT2, SCN2A, KCNQ2, KCNQ3 and GABRA6 mutations, with PRRT2 mutation being the most frequently reported cause of this condition.3,6 Throughout the past few years, off-label use of LEV has become the treatment of choice for pediatric epilepsies, including neonatal and infantile types. This has been mainly due to its broad coverage, and better tolerability compared to the older generation anti-seizure medications, for example the

sodium channel blocker carbamazepine. This case follows a 4-month-old female with was initially though as refractory epilepsy and her treatment journey.

Case Report

An emergency room visit to different hospital was required for a 4-month-old baby girl, daughter of a Lebanese mother and a Jordanian father, due to the complaint of sudden-onset seizures. Until her admission to the hospital, she had experienced 4 episodes of generalized tonic clonic convulsions in the same day. Her parents were non-consanguineous and her past medical and birth history were both unremarkable. The family history was considered insignificance at the beginning, but was later found more significant than they thought. The grandmother reported that the father had similar episodes when he was about his daughter's age, but they remitted spontaneously without the need for anti-seizure treatment.

The patient's physical and neurological examinations were normal and both her growth and development were appropriate for age.

The first EEG upon admission (24-hour EEG) showed mild right hemispheric slowing with no interictal discharges. Brain MRI epilepsy protocol was normal.

Early on the treatment, the patient responded well to Levetiracetam of a dose of 20 mg/kg/day divided twice daily (BID) and did not have seizures for a few days. 1 week later, patient is still seizure free, they sought our hospital for a second opinion. A 45 minute awake and asleep EEG was done, and was normal. The patient was kept on the same medication and advised to follow up every 3 months.1 week later, she relapsed and began having daily seizures, accordingly LEV was increased gradually but with no effect. She was having daily multiple seizures that were more focal on the right side, necessitating a readmission where LEV dose was increased to a maximum of 60 mg/kg/day BID but her seizures were not yet controlled. A 3 hour EEG was done and showed very few multifocal, nonspecific epileptiform discharges. The dose was then divided into 3 times a day (TID) and the patient became seizure free for 2 weeks. 2 weeks later she was brought back to the hospital with uncontrolled seizures, after her parents decided to switch her back to BID. Switching the dose back to TID was not helpful this time and did not show any signs of improvement.

At this point, Oxcarbazepine 25 mg/kg/day was added to her regimen and the patient showed immediate seizure control. At the same time, blood was sent for genetic testing. 2 months later, a diagnosis of Self-limited familial infantile epilepsy was confirmed by Whole Exome Sequencing test that revealed a

heterozygous pathogenic variant of the PRRT2 gene.

LEV was tapered and stopped as the patient responded well to OXC and was seizure free. The plan is for her to continue on OXC until she reaches the age of 2 years.

Discussion

The diagnosis of SeLIE is established based on the nature and onset of the seizures, which are usually clusters of sudden focal seizures that start during the first year of life, a positive family history of similar episodes from at least one of the parents, as well as genetic testing that has reported several mutations causing this type of infantile epilepsy thus far.7 This condition has been vastly explored in the west and far east countries, but is yet to be addressed and focused on in the Arab world. Diagnostic modalities like EEG and brain MRI are often done in infantile seizures, however, they more often than not come back normal or inconclusive in SeLIE.7 Throughout the past years, LEV has had its fair share of use in treating SeLIE, aside from its favorable safety profile, it is tolerable and does not interact with other drugs.8 Although other anti-seizure drugs like OXC can also be used in focal epilepsies in pediatric population, LEV is still being considered first. Fortunately, SeLIE has an excellent prognosis, as infants are most likely to achieve seizure freedom by the age of 1-2 years with no cognitive or developmental delays.8

PRRT2 mutation is considered the most common genetic variant for SeLIE patients.5 Multiple articles suggest that the best treatment option for patients with this mutation are antiepileptic drugs that are sodium channel blockers. Zhao et al.5 compared the treatment of two female siblings with PRRT2 mutation, each receiving different medication to control their seizures. One of the sisters received OXC as her initial treatment and was immediately seizure-free. The treatment was stopped when she turned 3 years old, and OXC dose was fixed throughout the treatment period. On the other hand, her sister was started on LEV 20 mg/kg/day which was not effective. The dose was increased gradually every month until it reached the maximum recommended dose. Yet, the patient's condition did not improve. The same patient responded quickly to the first dose of OXC and did not experience seizure episodes anymore. During her 1-year follow-up, her OXC dose was decreased and it is to be further tapered until it is stopped at the age of 2 years.

20 SeLIE patients with PRRT2 mutation were included in another study that compared their response to different antiepileptic medications.6 9 of these patients were subjected to low dose OXC and showed 100%

response to the treatment. 8 of these patients were given LEV, and the remaining 3 received Valproate(VAL) as their initial treatment. Nevertheless, seizures could not be controlled in these patients despite increasing the doses of LEV and VAL. Remission was only attained after switching the patients to OXC.

Mutations in the voltage-gated sodium channel α2 subunit (SCN2A) gene on chromosome 2 were also identified in families affected by self-limiting infantile seizures.9 Striano et al.10 presented 3 family members over 3 subsequent generations with this mutation. The 3 individuals suffered clusters of focal seizures with an age of onset between 4 and 12 months. All members were treated with Phenobarbital, with a favorable response and outcome. The same mutation was found to be related to a variety of neurological phenotypes, with benign neonatal and infantile epilepsy accommodating 20% of the phenotypic spectrum.11 Seizures in these patients are easily controlled by AEDs or even without treatment. However, it has been reported that some patients with this mutation had drug resistance to AEDs in the early course of the disease. Sodium channel blockers like OXC had to be used in those AED-resistant patients in order to reach seizure freedom.

Maljevic et al.12 reported data on family members carrying a missense mutation in the KCNQ3 gene, which is a less common cause of this syndrome. Patients with this mutation generally presented with earlier onset of seizures, mainly during their first week of life. Response to Antiepileptics in general and to LEV specifically was fluctuating. Moreover, patients that responded to LEV and were seizure free only responded to very high doses of the drug, reaching above the maximum recommended dose for treatment, whereas patients that were switched to OXC, attained seizure-free status at a reasonable dose.

Conclusion

Over the past decade, the off-label use of LEV has become the norm in treating pediatric epilepsies. It is still used as a first option worldwide, mainly due to its broad-spectrum coverage (focal & generalized), tolerability, and not facing a case of SeLIE yet. Although this treatment option can be effective in most pediatric seizures, our case along with previously reported cases show that SeLIE patients can be resistant to LEV. Missing the diagnosis of SeLIE and the use of LEV subjects the patients to longer hospital stays, unnecessary investigations, and increased medical bills. Hence, pediatricians, pediatric neurologists, and

neurologists should be more aware of this entity, and their management should be to use of sodium channel blockers (like OXC) in idiopathic infantile epilepsies as a first-line option and not LEV.

Conflicts of Interest Disclosure

All authors declare that there are no conflicts of interest.

Informed Consent

The patient has consented to the submission of this case to the journal.

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References

1.Zuberi, S., Wirrell, E., Yozawitz, E., et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia, 63, 1349-1397, 2022

2.Berg, A., Berkovic, S., Brodie, M., et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia, 51, 676-685, 2010

3.Heron, S., Grinton, B., Kivity, S., et al. PRRT2 Mutations Cause Benign Familial Infantile Epilepsy and Infantile Convulsions with Choreoathetosis Syndrome. The American Journal Of Human Genetics, 90, 152-160, 2012

4.National Institutes of Health. Rare Diseases: National Institute of Health. https://rarediseases.info.nih.gov/diseases/1518/benign-familial-neonatal-infantile-seizures (Retrieved August 23, 2022)

5.Zhao, Q., Liu, Z., Hu, Y., et al. Different experiences of two PRRT2-associated self-limited familial infantile epilepsy. Acta Neurologica Belgica, 120, 1025–1028, 2020

6.Zhao, Q., Hu, Y., Liu, Z., et al. PRRT2 variants and effectiveness of various antiepileptic drugs in self-limited familial infantile epilepsy. Seizure, 91, 360–368, 2021

7.Yang, X., Zhang, Y., Xu, X., et al. Phenotypes and PRRT2 mutations in Chinese families with benign familial infantile epilepsy and infantile convulsions with paroxysmal choreoathetosis. BMC Neurology, 13, 2013

8.Benbadis, S. Benign (self-limited) focal epilepsies of childhood. UpToDate. https://www.uptodate.com/contents/benign-self-limited-focal-epilepsies-of-childhood#H17 (Retrieved 23 August 2022)

9.Zeng, Q., Yang, Y., Duan, J., et al. SCN2A-Related Epilepsy: The Phenotypic Spectrum, Treatment and Prognosis. Frontiers in Molecular Neuroscience, 15, 2022

10.Striano, P., Bordo, L., Lispi, M. L., et al. A Novel SCN2A Mutation in Family with Benign Familial Infantile Seizures. Epilepsia, 47, 218–220, 2006

11.Wolff, M., Brunklaus, A., & Zuberi, S. M. Phenotypic spectrum and genetics of SCN 2A -related disorders, treatment options, and outcomes in epilepsy and beyond. Epilepsia, 60, 2019

12.Maljevic, S., Vejzovic, S., Bernhard, M. K., et al. Novel KCNQ3 Mutation in a Large Family with Benign Familial Neonatal Epilepsy: A Rare Cause of Neonatal Seizures. Molecular Syndromology, 7, 189–196, 2016