International Journal of Research in Medical Sciences
Isidoro MFF et al. Int J Res Med Sci. 2023 Aug;11(8):3030-3033
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20232441

Case Report

Levetiracetam-induced psychosis in a Filipino female diagnosed with anti-N-methyl-D-aspartate receptor encephalitis: a case report

Myrelle Frances F. Isidoro*, Marissa T. Ong, Renato S. Dejan Jr

Department of Neurosciences, Department of Health East Avenue Medical Center, Diliman, Quezon City, Philippines

Received: 29 May 2023
Accepted: 06 July 2023

***Correspondence:**
Dr. Myrelle Frances F. Isidoro,
E-mail: mfisidoro.sbcm@gmail.com

ABSTRACT

Levetiracetam (LEV), an SV2A inhibitor is a widely available anti-epileptic drug that is used to treat a range of partial and generalized seizure and juvenile myoclonic epilepsy. It is generally well tolerated and deemed safe due to the absence of drug-to-drug interaction. Despite its safety, there are adverse effects that can lead to the discontinuation of this anti-seizure medication. Some of the reported infrequent adverse effects are mood-related changes including agitation, depression, anxiety and suicidal ideations that can be observed after initiation or rapid up titration of the medication. The mechanism for this is still unknown but there are certain theories that attempted to determine the association. Risk factors reported were female sex, temporal lobe involvement and history of psychiatric disorder. In this case report, we present a 30-year-old female without history of psychiatric illness diagnosed with anti N-methyl-D-aspartate receptor (NMDAR) encephalitis who presented with seizure and was started on LEV for seizure control. She developed aggression and suicidal ideations secondary to initiation and up-titration of LEV. The symptoms resolved after discontinuation of the said medication.

Keywords: LEV, Psychosis, NMDAR encephalitis

INTRODUCTION

Levetiracetam (LEV) is a broad-spectrum and second-generation antiepileptic that exerts its effect by binding to and inhibiting synaptic vesicle protein SV2A which decreases the rate of presynaptic neurotransmitter release leading to neuronal inhibition.[1] It enhances GABA concentration by its interaction with GABA A receptor as well as decreasing glutaminergic excitation via modulation of the NMDA and the a-amino3-hydroxy-5 methyl-4-isozazolepropioni (AMPA) receptors including the upregulation of glial glutamate transporters.[2] It is widely available and is used to treat a range of partial and generalized seizures, and juvenile myoclonic epilepsy.[1] This medication demonstrates a number of pharmacokinetic advantages compared with other antiepileptics which includes absence of drug-drug interactions and reduced cytochrome P450 enzyme induction due to its partial extrahepatic metabolism.[1] It has a reported number of adverse effects that are associated with acute changes in dosage and initiation of treatment.[1] The most common reported adverse drug reactions (ADRs) in adults are the following: somnolence, weakness, and dizziness; while behavioral changes are more noticeable in children.[1] Psychiatric adverse effects including behavioral disturbance such as agitation, hostility, psychosis, mood symptoms and suicidality were also mentioned and when present can often lead to discontinuation of the medication.[2,3] It has been shown that about 13.3% or adults showed psychiatric effects with 0.7% presenting with severe symptoms like depression agitation, or hostility.[2] The mechanism by which LEV induces behavioral change is still unknown.[2]

Anti-NMDAR encephalitis (anti-NMDARE) involves a complex neuropsychiatric syndrome that can occur in both sexes ages <1 to 85 years old. It has a female

predominance with a ratio of 8:2 and the median age is at 21 years old.[4] Children presented with seizures, abnormal movements, irritability and insomnia while adults presented with memory impairment, hypoventilation and sometimes movement disorders such as paresis or ataxia. Agitation, behavioral changes can occur during the course of illness of Anti-NMDARE patients.[5] However, there is a report that LEV can increase behavioral changes and suicidal thoughts in patients with anti-LG1 encephalitis but no report has been made for patients with NMDAR encephalitis.[6]

CASE REPORT

This is a case of a 30-year-old, single, right-handed, college graduate female who presented with a chief complaint of seizure. She initially experienced undocumented fever and headache described as holocranial, with pain scale of 3-4/10, not associated with activities, without specific timing and spontaneously resolving. Patient was still able to do her clerical work and activities of daily living.

A week after, she had stiffening of the jaw and left facial asymmetry which lasted for 1 minute. In the interim, she was observed to have anxiety attacks repeatedly mentioning the incident. Few days after, she had another seizure episode with a different semiology, presenting as upward rolling of eyeballs and stiffening of all extremities for 30 seconds with spontaneous resolution followed by post-ictal drowsiness. There were no associated incontinence, head versions or cyanosis. She was never diagnosed with psychiatric illness nor any of her family members presented with the same condition. She was subsequently admitted at a tertiary hospital and neurologic examination findings included anxiety episodes manifested as excessive and repeated questions about her current condition and desire to leave the hospital, poor insight about her condition, poor concentration with inability to do serial 7's, an error in the clock-drawing test and impairment in recent memory (inability to recall 3 words after 5 minutes). Upon admission, she had repeated seizure episodes of the same semiology and LEV 900 mg/IV diluted in saline was given as loading dose for 30 minutes followed by a maintenance of 500 mg/IV every 12 hours to control the seizure. However shortly after initiation of therapy, she was noted to have child-like demeanor and crying spells. Patient was referred to the psychiatry service and was started on Escitalopram and Clonazepam, however, patient still had labile mood associated with insomnia. Patient had recurrence of the seizure with the same semiology and LEV was shifted to oral form and increased to 500 mg/tablet-1 and ½ tablet twice a day. After which, patient was observed to have aggressive behavior necessitating restraints and with suicidal ideations. Patient was given olanzapine by psychiatry service which did not reduce the symptoms. Due to the persistence of the seizure episodes, LEV was increased to 1g/tablet-1 tablet every 12 hours. The patient became disoriented with disorganized speech and thoughts. Due to the persistence of the psychotic symptoms despite medication, LEV was then shifted to carbamazepine 200 mg/tablet-1 tablet thrice a day which controlled the seizure, and the suicidal ideations and combative behavior were no longer observed after discontinuation of LEV.

Cranial MRI with contrast and 21-channel EEG were done which revealed normal results. Anti-NMDAR antibodies were detected in the CSF analysis. Transvaginal ultrasound to rule out the presence of an ovarian teratoma was performed with normal results. Patient underwent a course of pulse therapy for 5 days with notable improvement in the behavioral symptoms. Despite improvement in the psychosis, the patient still had 1-2 episodes of seizure with decrease in frequency and decrease in duration. Patient was eventually discharged with anti-seizure medications: Carbamazepine, and lacosamide and escitalopram. At present, patient was able to secure an employment and do activities of daily living.

DISCUSSION

The introduction of new anticonvulsant drugs renewed the attention to treatment-emergent effects specifically the behavioral syndromes.[7] Anticonvulsant-induced psychiatric disorders was recognized as contributory to the development of psychiatric disorders as reported by Krishnamoorthy et al.[8] It was associated with both induction, abrupt increase in dosage, and withdrawal of medication.[9,10] The following should be specified: specific AED, details of the AED therapy, change in AED treatment if any, AED institution, and AED withdrawal. In 2003, Cramer et al conducted a review that reported the behavioral adverse events occurring among adults receiving LEV.[11]

LEV has a broad range of pharmacological effect which makes it difficult to determine the certain cause for aggressive behavior.[12] The high rate of this adverse effect may not be related to SV2A since bivaracetam, a derivative of LEV, was reported to have a 15-30x higher affinity with SV2A but has a lower incidence of behavioral changes.[12] It also appears that Bivaracetam does not modulate NMDA, AMPA or kainite receptors. These findings suggests that the negative modulating effect on AMPA receptors by LEV contributes to aggressive behavior.[12] The possible link of the increase in psychotic symptoms in the patient can be related to the action of LEV on the glutamatergic receptors since NMDAR encephalitis also alters the physiology of glutamine transmission and receptors but further studies are needed to be done to prove this theory. The following were reported risk factors associated with developing psychosis with the use of anti-epileptic medication: female sex, LEV use, and epilepsy involving the temporal lobe.[13,14] In the study of Chen et al it was reported that female sex and temporal lobe involvement were

significant risk factors in AED-induced psychotic disorder-both of which were seen in our patient: she had a female sex and was diagnosed with NMDAR encephalitis which affects various areas particularly the temporal lobe.[14] A retrospective cohort study by Josephson et al in 1173 patients taking LEV showed 4 risk factors for adverse reactions: female sex, depression, anxiety and use of recreational drug.[15,16] Other probable additional risk factors for the development of behavioral abnormalities include history of febrile convulsions, history of status epilepticus, previous psychiatric illness, and lamotrigine co-therapy.[17] The study of Campbell et al indicated that 1% of people exposed to LEV develop ADRs hence, they utilized a variety of approaches to assess the role of genetic variation in psychiatric and behavioral ADRs associated with LEV.[18] In their case-control study, they compared cases of LEV-associated behavioral disorder or psychotic reaction to LEV-exposed people without history of psychiatric ADRs and they showed that polygenic burden for schizophrenia is a risk factor for LEV-induced psychotic reaction. Their recommendation included the possibility of screening individuals with epilepsy to identify those at risk of developing ADRs and clinical knowledge on clinical risk factor such as history of depression and use of recreational drug.[18] Though it was commonly associated with a history of psychiatric disorder, the study by Molokwu et al deduced that there can be de novo presentation of this drug reaction.[19] Some studies showed that the higher risk for developing psychiatric symptoms from LEV can be attributed to a genetic predisposition.[20] In one case series by Ruiz et al they determined the plasma LEV level in their patients and all of the results were within therapeutic range thus it is safe to say that the psychotic symptoms probably do not correlate with the LEV plasma level. They also utilized the Naranjo scale for estimating the probability that LEV caused the clinical event and the 3 cases scored 8/13 thereby pointing to the probable association between treatment with LEV and symptoms.[16]

Since there is no definite cause for its association, Sarangi et al proposed to investigate the neuroendocrine relationship of oxidative stress biomarkers with psychiatric symptoms associated with anti-seizure medications since this can possibly help in understanding the correlation of the symptoms. They mentioned the following biomarkers: brain-derived neurotrophic factor, dopamine and serotonin-like neurotransmitters, plasma homovanillic acid, 5-hydroxyindoleacetic acid, and total antioxidant capacity.[20] Loss of hippocampal neurons and disruptive excitatory synaptic reorganization in the mesolimbic pathway are also thought to play a role but this warrants further investigation.[16]

As for the treatment of seizures in patients with NMDAR encephalitis, carbamazepine and valproic were two of the most frequently used anti-epileptics. Carbamazepine was deemed to have the best effect to reduce seizure frequency while Valproic acid was preferred for its mood-stabilizing property. Jones et al reported that carbamazepine was noted to reduce aggression but not LEV.[21] In a report by Marienke et al LEV was generally preferred to treat the seizure in autoimmune encephalitis, however patients were often reported to have serious behavioral changes, and suicidal thoughts were seen in patients with anti-LGI1 encephalitis.[6] As mentioned, the patient was given LEV during her hospital stay and after which, she was observed to have suicidal thoughts and aggressive behavior. Though the course of anti-NMDAR encephalitis can include suicidal ideations and aggression, it is usually seen during 1st to 3rd week of illness and thus, it is still possible that her behavioral manifestations were due to her current condition. However, the symptoms were observed right after the initiation and up titration of LEV and there was significant improvement after the discontinuation of the said medication. Ideally, the patient should have been placed on continuous EEG monitoring in order to rule out if the aggressive behavior were seizure episodes.

CONCLUSION

LEV induced acute aggression is a known adverse effect but is rarely reported in the literature. This case report documents a patient who had sudden suicidal ideations and combative behavior after initiation of LEV and was noted to disappear after discontinuation of the medication. Future studies are still needed to ascertain the cause of this adverse event but this observation should not dissuade clinicians from using LEV since not all patients can develop this side effect and this medication is a safe and effective anti-seizure medication. However, they should be wary of the possible adverse effects and patients should be monitored closely with careful dose titration especially those cases who present with psychiatric symptoms like patients with encephalitis and those known to have psychiatric disorders.

ACKNOWLEDGEMENTS

The researchers would like to extend their gratitude to the patient and her family for allowing us to document her case. It is part of a physician's fulfillment to see their patients restore their baseline functional capacity and achieve full recovery.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Zhang JF, Piryani R, Swayampakula AK, Farooq O. Levetiracetam-induced aggression and acute behavioral changes: A case report and literature review. Clin Case Rep. 2022;10.
2. Ogunsakin O, Tumenta T, Louis-Jean S. Levetiracetam Induced Behavioral Abnormalities in a Patient with Seizure Disorder: A Diagnostic

Challenge. Case Rep Psychiatr. 2020;2020:1-4.
3. Tao K, Chen H, Chen Y, Gu Y, Wang X. Levetiracetam induces severe psychiatric symptoms in people with epilepsy. Seizure. 2022;S1059131122002783.
4. Dalmau J, Armangué T, Planagumà J. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18:1045-57.
5. Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Schizophr Res. 2016;176:36-40.
6. De Bruijn MAAM, Van Sonderen A, Van Coevorden-Hameete MH. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABA B R encephalitis. Neurology. 2019;92:e2185-2196.
7. Trimble MR. Anticonvulsant-Induced Psychiatric Disorders. Drug Saf. 1996;15:159-66.
8. Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: A proposal by the ILAE Commission on Psychobiology of Epilepsy. Epilepsy Behav. 2007;10:349-53.
9. Trimble M. New Antiepileptic Drugs and Psychopathology. Neuropsychobiology. 1998;38:149-51.
10. Ketter TA, Malow BA, Flamini R, White SR, Post RM, Theodore WH. Anticonvulsant withdrawal-emergent psychopathology. Neurology. 1994;44:55.
11. Cramer J. A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. Epilepsy Behav. 2003;4:124-32.
12. Hansen CC, Ljung H, Brodtkorb E, Reimers A. Mechanisms Underlying Aggressive Behavior Induced by Antiepileptic Drugs: Focus on Topiramate, Levetiracetam, and Perampanel. Behav Neurol. 2018;2018:1-18.
13. Lynch DR, Rattelle A, Dong YN, Roslin K, Gleichman AJ, Panzer JA. Anti-NMDA Receptor Encephalitis. Clin Features Basic Mechanisms. 2018;235-60.
14. Chen Z, Lusicic A, O'Brien TJ, Velakoulis D, Adams SJ, Kwan P. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. Brain. 2016;139:2668-78.
15. Josephson CB, Engbers JDT, Jette N. Prediction Tools for Psychiatric Adverse Effects After Levetiracetam Prescription. JAMA Neurol. 2019;76:440.
16. León Ruiz M, Rodríguez Sarasa ML, Sanjuán Rodríguez L. Levetiracetam-induced de novo psychosis: is there a type of patient with epilepsy who is neurostructurally and/or biologically more vulnerable to developing it? Neurol. 2020;35:684-7.
17. De Smedt T, Raedt R, Vonck K, Boon P. Levetiracetam: Part II, the Clinical Profile of a Novel Anticonvulsant Drug. CNS Drug Rev. 2007;13:57-78.
18. Campbell C, McCormack M, Patel S. A pharmacogenomic assessment of psychiatric adverse drug reactions to levetiracetam. Epilepsia. 2022;63:1563-70.
19. Molokwu OA, Ezeala-Adikaibe BA, Onwuekwe IO. Levetiracetam-induced rage and suicidality: Two case reports and review of literature. Epilepsy Behav Case Rep. 2015;4:79-81.
20. Sarangi SC, Kaur N, Tripathi M. Assessment of psychiatric and behavioral adverse effects of antiepileptic drugs monotherapy: Could they have a neuroendocrine correlation in persons with epilepsy? Epilepsy Behav. 2019;100:106439.
21. Jones RM, Arlidge J, Gillham R, Reagu S, Van den Bree M, Taylor PJ. Efficacy of mood stabilisers in the treatment of impulsive or repetitive aggression: systematic review and meta-analysis. Br J Psychiatr. 2011;198:93-8.

Cite this article as: Isidoro MFF, Ong MT, Dejan Jr RS. Levetiracetam-induced psychosis in a Filipino female diagnosed with anti-N-methyl-D-aspartate receptor encephalitis: a case report. Int J Res Med Sci 2023;11:3030-3.