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Case Report

Levetiracetam-induced rage and suicidality: Two case reports and review of literature

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ABSTRACT

Background: Levetiracetam-induced rage is a rare neurobehavioral adverse effect of levetiracetam that is characterized by seething rage, uncontrollable anger, fits of fury, depression, violence, and suicidal tendencies. It occurs more in patients with prior mood or psychotic disturbances. No such case has been reported in Nigeria.
Method: We report two cases of levetiracetam-induced rage. The first patient was a 29-year-old male with a 14-year history of intractable posttraumatic epilepsy. He was initially placed on sodium valproate and phenobarbitone and later had phenobarbitone replaced with levetiracetam. Within the first week of initiating levetiracetam, he became aggressive, bursted into fits of fury, and attacked his siblings. Levetiracetam was stopped, and the seething rage ceased only to reappear when it was reintroduced; hence, the complete withdrawal of levetiracetam. Naranjo probability score for adverse drug reaction was 8.
Results: The second patient was a 23-year-old lady who developed seething rage and made several attempts to kill herself with a knife following addition of levetiracetam to the clonazepam and carbamazepine that she was taking for treatment-resistant epilepsy. Withdrawal and reintroduction of levetiracetam by the relatives led to cessation and reemergence, respectively, of the rage and suicidal tendencies. Naranjo score was 8. Levetiracetam was discontinued.
Conclusion: Neuropsychiatric evaluation for prior mood or psychiatric disorders in those initiating levetiracetam therapy is suggested alongside monitoring for early features of levetiracetam-induced rage by both caregivers and physicians. This will help stem the morbidity and potential mortality associated with this life-threatening adverse drug reaction.

1. Introduction

Epilepsy is a chronic neurologic condition characterized by recurrent seizures [1]. It is estimated that about 70 million people worldwide are affected with epilepsy [2]. Approximately 70–80% of patients with epilepsy (PWE) achieve seizure control with one or more antiepileptic drugs (AEDs) [3]. Unfortunately, 20–30% of PWE will continue to have seizures despite active treatment and are considered candidates for epilepsy surgery [4]. Paucity of facilities for epilepsy surgery has made polytherapy using different AED combinations the only option for this group of patients in most parts of sub-Saharan Africa. Newer AEDs such as levetiracetam have become increasingly available in Nigeria and have helped in achieving seizure control in some of these drug-resistant epilepsies. Unfortunately, the association of levetiracetam and an untoward rare neurobehavioral adverse effect is increasingly being reported globally. It is characterized by seething rage, uncontrollable anger, fits of fury, depression, violence, and suicidal tendencies. Levetiracetam-induced rage and suicidality occur more in patients with prior psychiatric disturbance [5,6]; we report two cases of levetiracetam-induced rage in which one of the cases had several suicide attempts.

2. Case presentation

The first patient was a 29-year-old male who fell from a two-storey building at 2 months of age and subsequently developed intractable seizures and left hemiparesis. His body mass index was 28.4 kg/m^2 (weight: 86 kg, height: 1.74 m). Initially, he took sodium valproate (600 mg BD) and phenobarbitone (60 mg tds). His phenobarbitone was replaced with levetiracetam at a starting dose of 250 mg twice daily for one week and then escalated to 500 mg twice daily for the next four weeks.

Within the first week of taking levetiracetam, he became aggressive, bursted into fits of fury, and attacked his siblings. Levetiracetam was stopped, and the seething rage ceased only to reappear when it was reintroduced; hence, the complete withdrawal of levetiracetam. Naranjo score or adverse drug reaction probability was 8 (i.e., +1 for

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the presence of previous conclusive reports on this adverse reaction, +2 for appearance of the adverse event following initiation of the suspected drug, +1 for improvement of the adverse event following discontinuation of the suspected drug, +2 for reemergence of the reaction following readministration of the drug, and +2 for the absence of an alternative explanation for the adverse event).

The second patient was a 23-year-old lady who developed seething rage and made several attempts to kill herself with a knife after two weeks of initiating adjunctive levetiracetam at a starting dose of 250 mg twice daily for the first week and then 500 mg twice daily subsequently. She had been on clonazepam and carbamazepine for treatment-resistant epilepsy. Her body mass index was 20.31 kg/m^2 (weight: 52 kg, height: 1.60 m). Withdrawal and reintroduction of levetiracetam by the relatives led to cessation and reemergence, respectively, of the rage and suicidal tendencies. Naranjo score was 8 as in the first patient. Levetiracetam was discontinued, and the levetiracetam-induced rage ceased.

3. Discussion

An adverse drug reaction (ADR) describes any noxious and unintended response to a drug that occurs at doses normally used in man for prophylaxis, diagnosis, therapy, or modification of a physiological function [7]. Clinically significant ADRs following emergent AEDs can cause serious morbidity and mortality if unrecognized [8]. Levetiracetam is one of the emergent antiepileptic drugs that has become available to patients with epilepsy in sub-Saharan Africa, especially Nigeria. Levetiracetam-induced rage is a rare neuropsychiatric ADR characterized by seething rage, uncontrollable anger, fits of fury, depression, violence, and suicidal tendencies. Levetiracetam-induced rage occurs more in patients with prior mood or psychiatric disturbance [5,6].

Our multiple cases were patients who were being managed for drug-resistant epilepsy using multiple medications. Levetiracetam was used to replace phenobarbitone in the first patient who was also taking carbamazepine; levetiracetam was added to carbamazepine and clonazepam in the second patient. In both of these patients, there was reduction in seizure frequency despite the seething rage, fits of fury, aggressiveness, and suicidal tendencies (the second patient). In addition, the first patient had no prior mood or psychiatric disturbance though he was overweight and had a history of traumatic brain injury; the second patient was initially managed for depression and had a normal weight. In both of these patients, the neuropsychiatric features started in the first week of commencing levetiracetam and became well established by the second week of therapy. The first patient had the neuropsychiatric adverse effect while on 250 mg twice daily of levetiracetam; the second patient was commenced on 250 mg of levetiracetam twice daily for the first week and subsequently escalated to 500 mg twice daily.

Causality assessment describes the evaluation of the likelihood that a particular treatment is responsible for an observed adverse event [9]. The objective causal assessments are predicated on four basic principles—temporal eligibility, dechallenge and outcome, rechallenge and outcome, and confounding factors [10]. The Naranjo algorithm assesses the probability that an adverse event is related to a particular drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, and previous patient experience with the medication [11]. Both of these patients had a Naranjo score of 8 meaning that it is probable that the neuropsychiatric manifestations seen in these patients are secondary to levetiracetam intake.

In a cohort of 71 Korean subjects with drug-resistant epilepsy (DRE) receiving adjunctive levetiracetam, 3 of them (4.2%) had suicidal tendencies which led to the discontinuation of the drug [6]. The investigators had argued that forced normalization, a phenomenon whereby depressive or psychotic episodes develop in patients who become seizure-free after having suffered from DRE would not explain their finding as only 1 of their patients who developed suicidal tendency had seizure control [12]. In another study, 4 out of 517 Caucasian patients (0.7%) taking levetiracetam reported suicidal ideation [13].

It is worthy of note that while previous literature associates levetiracetam-induced rage and suicidal tendencies in patients with prior history of mood or psychiatric disorder [5,6,13,14], newer studies and case reports have described de novo presentation of levetiracetam-associated rage and suicidality in the absence of prior history of mood or psychiatric disorder [15,16]. The first patient presented here did not have any prior psychiatric disorder and, thus, supports de novo presentation of levetiracetam-associated rage.

Our second patient demonstrated an apparent dose-dependent rage, aggressiveness, and suicidal tendencies similar to what has been previously documented [15]. The first patient, on the other hand, had the associated rage and aggressiveness in a dose-independent manner which would suggest that patient-related factors may be related to the development of this adverse effect.

Our patients' seizures, though reduced in frequency, were not yet controlled with the adjunctive levetiracetam. This implies that forced normalization would also not explain their neuropsychiatric ADR.

From the foregoing, levetiracetam-associated rage, aggressiveness, and suicidal tendencies appear to occur rarely in PWE. Both sexes may be affected, the adverse effect could be dose-dependent or dose-independent, and it may occur de novo or on a background of prior psychiatric disorder and is not readily explainable by the theory of forced normalization.

The strength of these findings though germane and worthy of consideration pales in significance considering the fact that they are predicated on results from only two PWE taking levetiracetam. Nevertheless, a well designed prospective study to determine the prevalence and predictors of levetiracetam-induced rage and suicidality in a large cohort of Nigerian PWE taking levetiracetam is suggested.

4. Conclusion

Neuropsychiatric evaluation for prior mood or psychiatric disorders in those initiating levetiracetam treatment is suggested alongside continual monitoring for early features of levetiracetam-induced rage and suicidality by both caregivers and physicians. This will help in stemming the adverse morbidity and potential mortality associated with this adverse effect.

Conflicting interest

The authors have no conflict of interest to disclose.

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