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【 CASE REPORT 】

Seizure Deterioration with Increased Levetiracetam Blood Concentration during the Postpartum Period in Refractory Temporal Lobe Epilepsy

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Abstract:
We evaluated a 39-year-old pregnant woman with right temporal lobe epilepsy. During the second trimester, seizure deterioration was responsive to an increased daily dose of levetiracetam (LEV). However, immediately after delivery, new non-habitual seizures emerged along with a sharply increased LEV concentration. The frequency of habitual seizures also slightly increased. The non-habitual seizures completely disappeared, and the frequency of the habitual seizures improved to the baseline level after the LEV dosage was reduced. Thus, a paradoxical effect of an increased LEV blood concentration was assumed to be a potential cause of these events. Peripartum pharmacokinetic fluctuations in LEV levels should be monitored carefully.

Key words: focal impaired awareness seizure, levetiracetam, pregnancy

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Introduction

Levetiracetam (LEV) often exhibits dramatic pharmacokinetic fluctuations due to the glomerular filtration rate change during the peripartum period (1). Thus, patients with epilepsy require titration of the LEV dose during pregnancy because of the increased renal excretion.

We encountered a patient with epilepsy who continued to take high-dose LEV after delivery, resulting in postpartum seizure exacerbation. This event was considered to have been associated with elevated serum LEV concentrations after delivery. One of the potential underlying mechanisms included not only adverse effects but also a paradoxical effect (PE) caused by the elevation of the LEV concentration (2).

Continuing to take the high-dose LEV after delivery can lead to a postpartum increase in the serum concentration and may risk seizure exacerbation.

Case Report

A 39-year-old right-handed pregnant woman with medically refractory mesial temporal lobe epilepsy (MTLE) visited our hospital during the sixth week of gestation to manage her seizures. She had experienced natural childbirth once before the first visit. She had no history of any initial precipitating injury, such as febrile seizure. Her familial history of epilepsy was negative.

She had suffered from focal aware non-motor seizures (FNMS) characterized by fatigue lasting for less than a minute 8 times a month since she was 34 years old. There were no other forms of FNMS that were related to the temporal region, such as fear, auditory or olfactory hallucinations, or an epigastric rising sensation. Her FNMS was occasionally followed by loss of awareness, i.e. focal impaired awareness seizures (FIAS) accompanied by oral automatism, and lasted for less than a minute every week. She had never experi-

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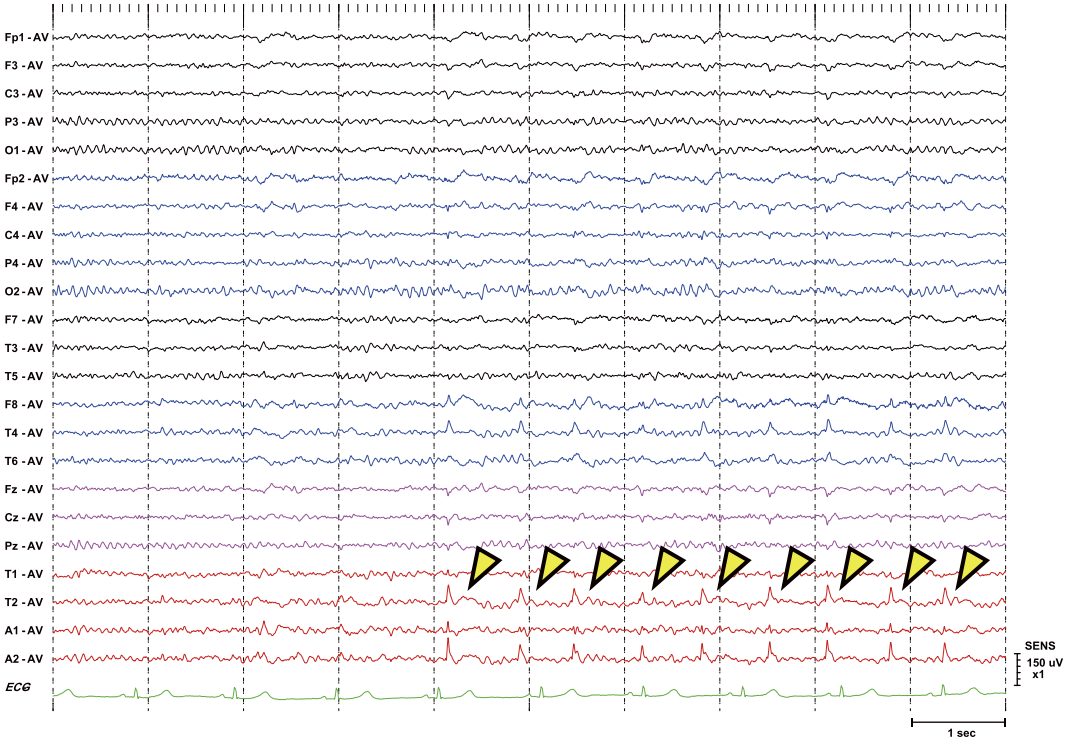

Figure 1. An interictal electroencephalogram (EEG) recorded before the pregnancy. Continuous repetitive spikes are visible in the right anterior to basal temporal regions every second during the drowsy state (yellow arrowheads).

enced any generalized seizures.

Neurological abnormalities were negative except for her left emotional facial paresis (3). Blood examinations, which included autoimmune-related parameters (anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, anti-SS-A/B antibody, and antithyroid antibody, or anti-GAD antibody), were negative. An interictal electroencephalogram (EEG) revealed repetitive temporal spikes on the right (T2 and A2 max in the amplitude) (Fig. 1). There was no induction of a paroxysmal photic response, and magnetic resonance imaging (MRI) did not reveal any hippocampal sclerosis. A subsequent ictal EEG showed that her habitual seizures arose from the right temporal region. Thus, she was diagnosed with right MTLE.

The patient was able to avoid any seizure deterioration during the first trimester by continuing her LEV (2,500 mg/day) and lacosamide (LCM; 200 mg/day) treatments that had been administered prior to her pregnancy (Fig. 2). However, the FIAS frequency gradually increased from 4 times a month to 7 times a month during the second trimester (20th week of pregnancy). Given her body weight, the number of weeks of gestation, and the potential decrease in the LEV blood concentration, we increased the LEV dosage to 3,000 mg/day. This titration subsequently decreased the seizure frequency to the same level as before the second trimester, with the LEV blood concentration reaching 39.5 μg/mL at 3 weeks after the titration.

She gave birth to her child through normal labor at term (36 weeks) in a different hospital. The child was healthy with a normal condition. The patient continued to take her anti-epilepsy drugs (AEDs) at the same dose level even after delivery.

However, within a few days after delivery, a new non-habitual seizure characterized by a sense of rotation lasting for ten seconds appeared. The frequency of FIAS also slightly increased to more than four times a month. Conversely, as this was her second childbirth, she exhibited no marked fatigue, depression, or stress during the postpartum period. Thus, she revisited our hospital.

At the time of this visit (36 days after delivery), the serum LEV concentration had reached 61.7 μg/mL. The non-habitual seizure completely disappeared after reducing the LEV daily dosage (Fig. 2). Follow-up EEG showed no epileptic discharges. The LCM concentration remained stable during the pregnancy.

Discussion

The present case with MRI-negative medically refractory right MTLE showed the emergence of new non-habitual seizures after delivery under the high-dose administration of LEV. The non-habitual seizures immediately disappeared after decreasing the dose. Given the clinical course of seizure and LEV blood concentration, this event was likely to be associated with a postpartum elevation of the LEV blood concentration that was attributed to the continuation of the high-dose LEV even after delivery. Thus, PE related to the elevated LEV concentration can be a potential factor causing

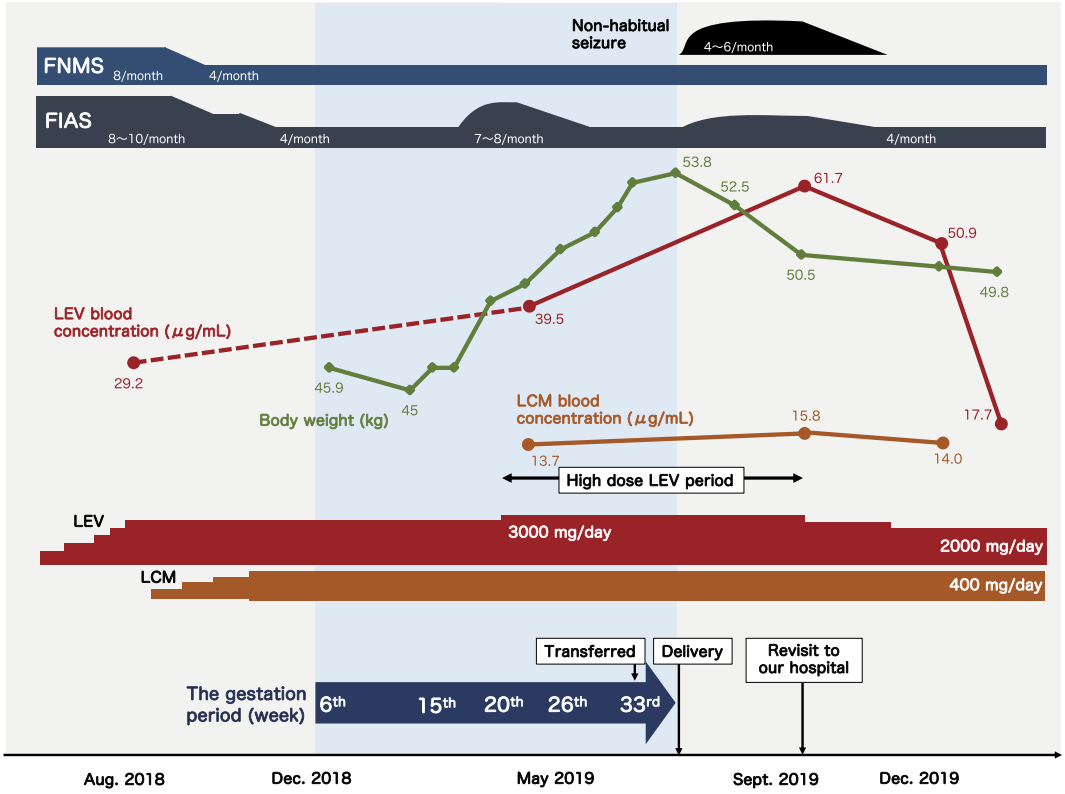

Figure 2. **Clinical course, including the peripartum period. The clinical courses of habitual seizures (FNMS and FIAS) and non-habitual seizures are illustrated. Bars indicate the frequency of each type of seizure, and the numbers in the bars indicate the frequency per month. The line graphs indicate changes in the body weight and blood concentration of the antiepileptic drugs during the peripartum period. Due to the long duration between the first and second examinations of the LEV blood concentration, the concentration changes during this period are shown by a red dashed line. FIAS: focal impaired awareness seizure, FNMS: focal aware non-motor seizure, LEV: levetiracetam, LCM: lacosamide**

habitual seizure frequency increase and a new non-habitual seizure appearance, as previously reported (2, 4, 5).

It should be noted that LEV can also cause a sense of rotation as an adverse event (6), similar to that observed with non-habitual seizures. This makes it difficult to discriminate between new non-habitual seizures and side effects of LEV. However, several facts supported the possibility of PE in the present case. First, although the sense of rotation might have been an adverse event of LEV, other typical adverse events of LEV, such as drowsiness, were absent in the present case. In addition, the duration of the sense of rotation was comparable to that seen in epileptic focal seizures (7). Second, while the sense of rotation emerged, the frequency of habitual seizures also slightly increased, suggesting that the epileptic condition had deteriorated. Finally, the semiology of non-habitual seizures was also comparable to that of epileptic seizures arising from the lateral temporal region (8).

The habitual FNMS in the present case was consistent with seizures that originated from the mesial temporal lobe. The location of epileptic discharges in the ictal and interictal EEG was also consistent with this diagnosis. In contrast, the non-habitual seizure was characterized by a sense of rotation in the horizontal plane around the patient's body axis, or Yaw plane illusions. The superior and mid temporal gyri, the opercular region, and parietal lobe are potentially responsible regions (8). The interictal epileptic discharge was prominent in the right anterior temporal region (T2); however, the lateral temporal region (T4 and T6) was also involved. These findings suggested that the epileptogenic lesion included a broad area that was centered at the temporal lobe, with the mesial temporal region having the lowest seizure threshold within the area, i.e. the seizure onset zone. The superior temporal cortex and surrounding cortices likely had the second-lowest threshold, i.e. probably the irritative zone (11). Thus, PE might reduce the seizure threshold of these areas which thus results in the non-habitual seizure being subsequently generated from the irritative zone, which normally does not generate a seizure with the LEV blood concentration at the appropriate level.

Understanding the peripartum pharmacodynamics of LEV is essential to clarify the relationship between the blood concentration of LEV and the timing of the event. LEV has a broad spectrum for seizure types among patients with epilepsy, including pregnant patients (1, 9). However, the LEV serum concentration fluctuates during the perinatal period. LEV is primarily eliminated through renal excretion (1, 10).

Since the glomerular filtration rate increases by approximately 50% during pregnancy, the serum concentration can be 40% of the baseline value, thereby resulting in a marked decrease in the serum concentration/dose (C/D) ratio (1). Within the first two weeks after delivery, the C/D ratio immediately increases to the baseline level. As the present patient continued to take high-dose LEV throughout the second trimester and during the postpartum period, there may have been a sharp increase in the LEV serum concentration after delivery due to the reduced renal LEV clearance.

Although the present patient reported no substantial increase in postpartum stress, several peripartum factors can influence one's seizure control, e.g. hormone levels and breast vs. formula feeding.

The present case with MTLE exhibited a new non-habitual seizure immediately after delivery. Her clinical course suggested that the continuation of LEV at the same dose before and after delivery dramatically increased the blood LEV concentration, thereby potentially leading to a deteriorated seizure condition. Therefore, clinicians should keep managing seizures carefully after delivery, depending on peripartum metabolic changes in patients with epilepsy. Inter-departmental cooperation is also critical in such cases.

The authors state that they have no Conflict of Interest (COI).

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