

## Intermittent levetiracetam treatment in five patients with catamenial epilepsy

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### Abstract

Catamenial epilepsy is a periodic increase in seizure frequency in women with epilepsy during menstruation, or at any specific point in the menstrual cycle. We present five cases who attended the epilepsy outpatient clinic at the Sichuan Provincial People's Hospital, China, and who suffered catamenial epilepsy and received intermittent Levetiracetam (LEV) treatment 1 week prior to and post-menstruation around each menstrual period. The patients responded positively and seizures were controlled with a dose of 0.5g, twice daily in 3(67%) patients, and by a dose of 0.75g twice daily in the remaining 2(33%) patients, indicating that intermittent LEV therapy could be an effective strategy for the treatment of catamenial epilepsy.

**Keywords:** Catamenial epilepsy, Levetiracetam, Intermittent treatment.

### Introduction

Catamenial epilepsy, first reported in 1881,<sup>1</sup> is commonly defined as a periodic increase in seizure frequency in women with epilepsy during menstruation, or at any specific point in the menstrual cycle.<sup>2</sup> Studies have reported the prevalence of catamenial epilepsy in epileptic patients to be 31-60%.<sup>3-5</sup> In other words, at least 1 in 3 women with epilepsy develops this condition. Although neither conventional antiepileptic drugs (AEDs)<sup>6</sup> nor hormonal therapy<sup>7</sup> are successful for most patients with catamenial epilepsy, but benzodiazepine derivative clobazam, administered intermittently 20 or 30mg/day for 10 days around menstruation in successive menstrual cycles, has been proved effective.<sup>8</sup> However, clobazam may produce adverse side effects such as sedation, depression, etc., which makes it an undesirable therapy<sup>9</sup>. Therefore, we planned to find an alternative AED to get better responses and fewer side effects. After observing results of 5 patients treated with intermittent Levetiracetam (LEV), we propose that LEV might also be an effective therapy for catamenial epilepsy.

### Case Reports

All the five patients of catamenial epilepsy in our series received intermittent LEV treatment at the epilepsy

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outpatient clinic of Sichuan Provincial People's Hospital, China, from November 2011 to January 2012 (Table). Detailed clinical information was obtained from medical records and through patient interview.

### Case-1

A 28-year-old woman was diagnosed with symptomatic epilepsy (generalised tonic-clonic) at the age of 5 after leaving our hospital with Japanese encephalitis. The symptoms were controlled by sodium valproate (VPA; 0.2g, twice daily) and the frequency of seizures was kept at 2 to 3 times a year. However, by the age of 15, the frequency of her seizures went up to 2-3 times a month. The patient then was additionally administered with carbamazepine (CBZ) (0.1g, three times a day) but she did not respond well. By the age of 20, most seizures began on the second day of her menstruation with a frequency of 2 to 3 times per month. CBZ was replaced by lamotrigine (LTG; 50mg twice daily) but no further improvements were recorded. The patient received clonazepam (1mg, twice daily) together with VPA and the frequency of seizures still remained at 2 to 3 times a month. By the age of 26, the patient underwent magnetic resonance imaging (MRI) scan and no brain abnormalities were found. The electroencephalography (EEG) examination indicated that sharp waves or slow waves emerged at both sides of brain. The seizure mainly began on the second day of her menstruation. Since then, the patient began to take intermittent treatment with LEV (0.5g, twice daily) 1 week pre- and post-menstruation. The follow-up assessments at the 3rd, 6th and 12th month indicated that seizure frequency had reduced to once a month.

### Case-2

A 32-year-old woman was diagnosed with temporal epilepsy accompanied by onset of oropharyngeal chewing and unconsciousness for 4 years. After undergoing combination treatment with CBZ (0.1g, three times a day) and VPA (0.5g, twice daily), her symptoms of seizures were not completely blocked and still occurred on the first day of her menstruation with a frequency of 3-4 times a month. At the age of 30, the patient began to receive LEV (0.5g, twice daily) intermittently 1 week pre- and post-menstruation. Three months later, seizure frequency was reduced to 1-2 times a month. And then, LEV was increased to 0.75g, twice daily. The follow-up assessments at the 6th and 12th month recorded no seizures.

**Table-1:** Clinical information for 5 patients with catamenial epilepsy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Enrolled date	Nov.2011	Dec.2011	Dec.2011	Jan.2012	Jan.2012
Age (years)	28	32	27	42	41
Age of onset (years)	5	28	15	39	29
Weight (kg)	40	50	46	52	50
Aetiology of epilepsy	Japanese encephalitis	unknown	Herpes simplex encephalitis	Developed after resection of cerebral vascular malformations	unknown
Seizure type	Symptomatic epilepsy	Temporal epilepsy	Symptomatic epilepsy	Symptomatic epilepsy	Frontal lobe epilepsy
Frequency of seizures (before LEV treatment)	2-3 times per month	3-4 times per month	2-3 times per month	Once per month	Once per month
Menarche (years)	15	14	14	14	15
Period(days)	4-5	4-5	5-6	5-6	5-6
Catamenial epilepsy type	post-menstrual	pre-menstrual	pre-menstrual	post-menstrual	pre-menstrual
MRI	normal	normal	normal	normal	normal
EEG	abnormal	abnormal	abnormal	abnormal	abnormal
AEDs taken before LEV	VPA, CBZ, LTG, Clonazepam	CBZ, VPA	CBZ, TPM, LTG	Oxcarbazepine	CBZ, VPA
Dose of LEV (mg/day)	0.5g bid	0.5g bid to 0.75g bid	0.5g bid	0.5g bid	0.5g bid to 0.75g bid
Seizure control	Reduced to once a month during 3-, 6-, and 12-months of follow-up	No occurrence during 6- and 12-months of follow-up	No occurrence during 12-months of follow-up	No occurrence during 3-, 6-, and 12-months of follow-ups	No occurrence during 6-, and 12-months of follow-up

VPA: Valproic Acid. CBZ: Carbamazepine. LTG: Lamotrigine. TPM: Topiramate. MRI: Magnetic Resonance Imaging. EEG: Electroencephalography. LEV: Levetiracetam.

### Case-3

A 27-year-old woman was diagnosed with symptomatic epilepsy (partial epilepsy secondary to Generalized tonic-clonic seizures) for 12 years. At the age of 15, she was diagnosed with herpes simplex encephalitis. She reported occasional spasm on the right hand and loss of consciousness 2-3 times a month. After receiving treatment with CBZ (0.1g, three times a day), the patient reported that the frequency of seizure was reduced to twice a year. At age 19, she was administered with topiramate (TPM, 50 mg, twice daily) and LTG (50mg, twice daily) and her seizures nearly disappeared. Four years later, the patient made a decision by herself to stop taking TPM and LTG because of the disappearance of seizures. However, when she was 26, she was attacked again by similar seizures which mainly occurred on the day prior to menstruation and with a frequency of 2-3 times per month. Examinations showed that no lesions were revealed by cranial MRI, but slow wave activity was observed by routine EEG. From then on, she took intermittent LEV (0.5g, twice daily) treatment 1 week pre- and post-menstruation. The follow-up assessments at the 3rd month showed that seizure frequency had reduced to 1-2 times per month; at the 6-month follow-up, it was reduced to once a month; and at the 12-month follow-up, no seizures were reported.

### Case-4

A 42-year-old woman was diagnosed with epilepsy with symptomatic epilepsy (partial onset) for 3 years. At age 39, the patient suffered from spasms at left extremities after resection of cerebral vascular malformations found after subarachnoid

haemorrhage. The frequency of seizures was 4 times every month. After 1-year treatment with oxcarbazepine (0.45g, twice daily), the frequency was reduced to once per month and the seizures mainly occurred on the second day post-menstruation. At age 41, the patient received additionally intermittent LEV (0.5g, twice daily) treatment. During 3rd, 6th and 12th month follow-up, seizures had been fully controlled.

### Case-5

A 41-year-old woman was diagnosed with frontal lobe epilepsy for 12 years. At age 29, she suffered from spasms and loss of consciousness. The seizures mainly occurred at night and each seizure lasted approximately 10 seconds. She was administered CBZ (0.1g, three times a day) treatment and the seizure frequency was reduced to 1-2 times per month. After VPA (0.5g, twice daily) was added, the frequency was further reduced to once every month and the seizure mainly occurred on the day prior to menstruation. At age 40, her symptoms got worse. Cranial MRI scan indicated no abnormalities, but EEG examination revealed bilateral sharp and slow complex wave activity in the frontal zone. Intermittent LEV treatment (0.5g, twice daily) was added. Three months later, no improvement was found. Then the dose of LEV was increased to 0.75g, twice daily. The follow-up assessments at the 6th and 12th saw no seizures.

### Discussion

To date, there is no specific drug treatment approved by the US Food and Drug Administration (FDA) for catamenial epilepsy though many therapeutic interventions, including

hormonal agents (Medroxyprogesterone acetate,<sup>10</sup> Clomiphene,<sup>11</sup> Triptorelin,<sup>12</sup> Leuprolide,<sup>13</sup> Progesterone,<sup>14-16</sup> Goserelin<sup>17</sup>), Non-hormonal agents (Acetazolamide,<sup>18</sup> Clobazam,<sup>8,9</sup> Lamotrigine<sup>19</sup>) and Neurosteroid-based agents (Ganaxolone<sup>20</sup>) have been tested with varying degrees of success. The reason was that most patients with catamenial epilepsy did not respond well to conventional AEDs, and, on the other hand, both conventional AEDs and hormonal agents may affect a woman's hormones which will cause undesirable hormonal side effects.

As show by our series, LEV, administered intermittently 1 week before and after menstruation, could be useful for controlling catamenial seizures. This outcome is similar to that of a previous study in which CBZ, 20 or 30 mg/day, was administered intermittently for 10 days around menstruation in successive menstrual cycles<sup>8,9</sup>). Given the fact that LEV has little effect on hormone level of females,<sup>21</sup> it seems to be an alternative choice when the patients with catamenial epilepsy are found resistant to conventional AEDs. In addition, catamenial seizures exhibit at least 3 patterns: perimenstrual, periovulatory within ovulatory cycles, and entire luteal phase within anovulatory cycles.<sup>22</sup> Earlier studies demonstrated that Ganaxolone would be a specific drug for perimenstrual catamenial epilepsy other than all the 3 patterns.<sup>23,24</sup> In order to provide simple intervention to patients with catamenial epilepsy, we employed a single treatment regimen for all patterns of catamenial epilepsy in this series. Based on clinical data, we found surprisingly positive responses to intermittent application of LEV in all five patients even though catamenial seizures occurring pre-menstruation (3 cases) or post-menstruation (2 cases) were resistant to conventional AEDs, such as VPA, CBZ, LTG, TPM, oxcarbazepine or clorazepam. The fact that Case 2 and 5 presented a better response to LEV after its dose was increased from 0.5g, twice daily, to 0.75g three times a day, suggests that dose would be an important factor to be considered for intermittent treatment.

## Conclusion

The current study only provides preliminary evidence that intermittent LEV treatment can be a new strategy for catamenial seizures. However, convincing evidence from large-scale clinical trials or multiple randomised clinical trials are needed to authenticate our results.

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