

# Levetiracetam-induced rhabdomyolysis: A case report and literature review

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## Abstract

Levetiracetam (LEV), a relatively new antiepileptic drug, is now frequently used for treating partial or generalized seizures. Among the adverse effects of LEV, rhabdomyolysis is rare. We describe here a case of LEV-induced rhabdomyolysis in a 26-year-old woman. The patient's seizures had been controlled with carbamazepine and phenobarbital for the previous 7 years. However, LEV was initiated at the age of 26 years because her seizures control deteriorated with seizures occurring monthly. She experienced lower limb weakness with a high level of creatine kinase 15 days after starting LEV. When LEV was discontinued, her creatine kinase levels decreased and her symptoms gradually improved. This case provide another example of rhabdomyolysis during the early phase of LEV treatment.

**Keywords:** Levetiracetam, rhabdomyolysis, intellectual disability

## INTRODUCTION

Levetiracetam (LEV) is a relatively new antiepileptic drug that is now frequently used in treating partial or generalized seizures of various etiologies. LEV acts by binding to synaptic vesicle protein 2A (SV2A).<sup>1</sup> Common adverse effects of LEV include nasopharyngitis, somnolence, dizziness, nervousness, irritability, asthenia, and fatigue.<sup>2</sup>

Rhabdomyolysis results from the damage of skeletal muscle fibers, which leads to leakage of muscle cell contents into the systemic circulation. The classical symptoms of rhabdomyolysis include myalgia, muscle weakness, and pigmenturia. The most common causes of rhabdomyolysis are substance abuse, medication, trauma, and epileptic seizures.<sup>3</sup> A few cases of LEV-induced rhabdomyolysis have been recently reported.<sup>4-6</sup> Here, we describe a case of rhabdomyolysis in a 26-year-old woman treated with LEV for the first time, and we present a review of the literature.

## CASE REPORT

A 26-year-old woman was diagnosed as having severe intellectual disability and syndromic epilepsy with complex partial and secondarily generalized seizures. No clinical seizures had occurred in the previous 7 years. Her seizures had been well controlled with oral carbamazepine

(CBZ) at a dose of 470 mg daily and phenobarbital (PB) at a dose of 100 mg daily. During this treatment, a blood test revealed normal serum creatine kinase (CK) levels. However, at the age of 26 years, epileptic seizures control deteriorated with seizures occurring monthly. CBZ and PB were continued and she was also given LEV 500 mg daily (Table 1). Fifteen days after starting LEV therapy, she was unable to stand up but showed no infection or trauma. On admission, physical examination revealed proximal muscle weakness in both legs. Laboratory results revealed a high level of serum CK (2,723 IU/L), with no renal failure. Electromyography was not performed due to her inability to cooperate with such the procedure because of her severe intellectual disability. LEV was withdrawn, while CBZ and PB were continued. Withdrawal of LEV gradually improved her lower leg weakness, and the high level of CK rapidly improved (75 IU/L) to within the reference range 11 days after admission. She was discharged 14 days after initial presentation. On hospital discharge, she had normal serum CK levels and her neurologic function had returned to baseline values. (Figure 1)

## DISCUSSION

In this report, we described a case of rhabdomyolysis in a patient with severe intellectual disability who

was receiving LEV. We diagnosed the patient as having rhabdomyolysis induced by LEV. Determining which medication is the cause of rhabdomyolysis can be difficult when several medications are being administered at the time of rhabdomyolysis onset, as it can develop in response to various medications. Cases of rhabdomyolysis have been reported with the administration of the antiepileptic drugs LEV, phenytoin, valproic acid, gabapentin and lamotrigine.<sup>4</sup> Our patient had been receiving CBZ, PB and LEV at the onset of rhabdomyolysis. However, among these drugs, LEV was thought to be the causal drug based on the following reasons. The patient had shown no symptoms during treatment with PB and CBZ and had normal serum CK levels while taking these drugs for several years. However, symptom onset occurred approximately two week after the initiation of LEV. LEV, which has a different mechanism, does not influence the serum concentration of any other antiepileptic drugs. The potential for rhabdomyolysis to be induced by PB or CBZ is low. In addition, there was no alternative explanation for a rhabdomyolysis, including no trauma, infection, or other new medications. Therefore, the temporal relationship between exposure to LEV and onset of symptoms and the immediate clinical and biochemical resolution after discontinuation of LEV suggested

that LEV was the most likely causal agent for rhabdomyolysis in our case.

Despite the widespread use of LEV, there have been few reports of LEV-induced rhabdomyolysis. In addition to the present patient, only 3 patients have been reported with LEV-induced rhabdomyolysis.<sup>5-7</sup> Details of these 4 cases are summarized in Table 1. The mean age of onset in the one male and 3 females was 22 years (range, 13–29 years). In all 4 cases, LEV administration was combined with other antiepileptic drugs. Development of rhabdomyolysis in all cases occurred during the loading dose phase of LEV. This suggests that rhabdomyolysis may occur even at low dose and that therefore patients should particularly be monitored during the initiation of LEV. The first signs of rhabdomyolysis was myalgia in 2 patients, weakness in both lower limbs in 2 patients, including our patient, and no signs in one patient. The mean peak serum CK level was 9,232 IU/L, but it was quite variable (range, 986–29,136). The differences in the peak CK levels may have been due to different muscle volumes. For example, the patient reported by Isaacson *et al.* had a muscular physique, unlike our patient.<sup>5</sup> The interval between the first exposure to LEV therapy and the symptoms of rhabdomyolysis varied (range, 1–15 days). The mean interval from the initiation of LEV to symptom onset

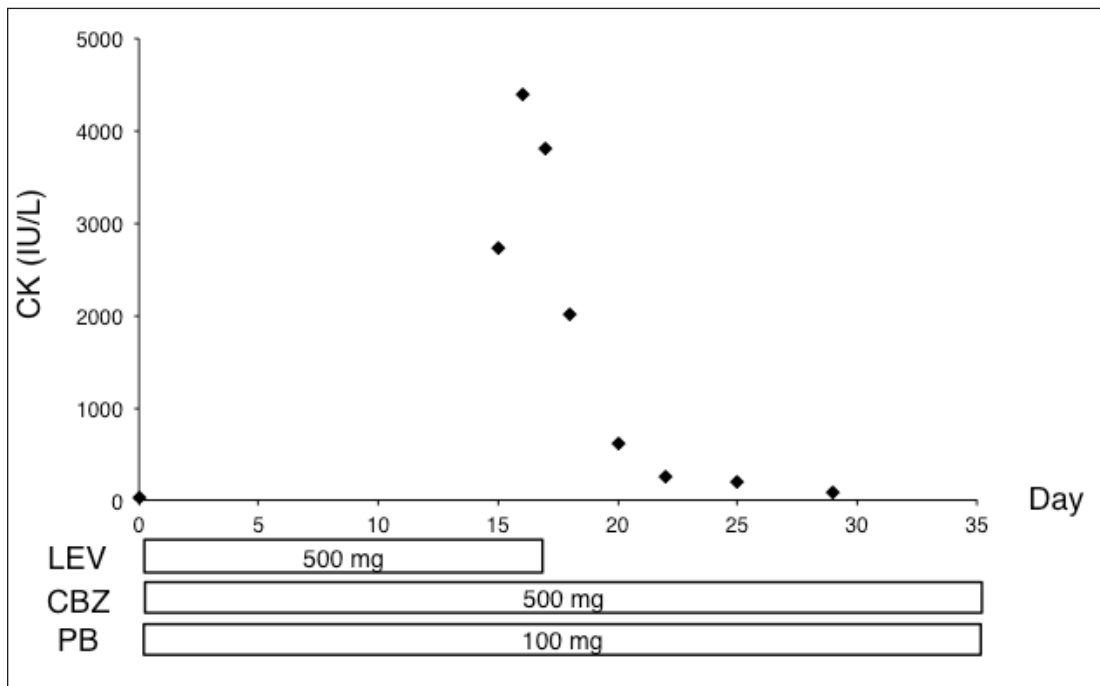


Figure 1. Prompt normalization of serum CK level after discontinuation of LEV. LEV, levetiracetam; CBZ, carbamazepine; PB, phenobarbital.

**Table 1: Summary of LEV-induced rhabdomyolysis**

case report	Akiyama H <sup>6</sup>	Isaacson JE <sup>5</sup>	Incecik F <sup>7</sup>	our case
year	2014	2014	2015	
Age	29	19	13	26
sex	female	male	girl	female
Disease	idiopathic epilepsy	right frontal arteriovenous malformation	benign epilepsy with centrottemporal spikes	syndromic epilepsy
Seizure type	generalized tonic-clonic seizure (after a prolonged non convulsive seizure)	complex partial seizure with secondary generalization	partial seizure with secondary generalized seizure	partial seizure with secondary generalized seizure
Amount of LEV	1000 mg	500 mg	500 mg (20 mg/kg)	500 mg
Other drugs on onset	PHT 500 mg, VPA 800 mg, CLB 20 mg	OXC 1500 mg, lorazepam 0.5 mg	none	CBZ 500 mg, PB 100 mg
Clinical presentation	myalgia, particularly backache, and weakness in both lower limbs	renal dysfunction	myalgia (mainly in lower extremities)	weakness in both lower limbs
Time of onset	1 day	4 days	7 days	15 days
Peak CK value(IU/L)	2410	29, 136	986 (on admission)	4396
Treatment	drug withdrawal	drug withdrawal	drug withdrawal	drug withdrawal

LEV, levetiracetam; PHT, phenytoin; VPA, valproic acid; CLB, clobazam; OXC, oxcarbazepine; CBZ, carbamazepine; PB, phenobarbital; CK, creatine kinase.

was 6.8 days, with our patient's symptom onset being above the mean. However, it was possible that she might have been unable to communicate her symptoms, such as myalgia, because of her severe intellectual disability, and this might have resulted in delayed diagnosis.

The mechanism of LEV-induced rhabdomyolysis is unclear. LEV has been reported to bind specifically with SV2A, which is mainly expressed in the brain, located in synapses within presynaptic terminals, presumably to modify neurotransmitter release.<sup>1</sup> However, SV2A has also been shown to be selectively localized in motor nerve terminals on slow (type I and small type IIA) muscle fibers in mice.<sup>8</sup> The presence of the receptor in the muscle fibers may suggest a mechanism for the LEV-induced rhabdomyolysis.

In conclusion, we described a rare case of LEV-induced rhabdomyolysis during the drug initiation. Since rhabdomyolysis has the potential to develop during the early phase of LEV exposure, close attention should be given to the potential for rhabdomyolysis, despite its rare incidence. If LEV is suspected as the causative agent, the drug should be discontinued immediately.

## DISCLOSURE

Conflict of interest: None

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