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Suspected Levetiracetam-Induced Rhabdomyolysis: A Case Report and Literature Review

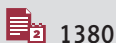
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 22-year-old
Final Diagnosis: Rhabdomyolysis
Symptoms: Creatine-kinase elevation
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Unusual or unexpected effect of treatment**Background:** Levetiracetam (LEV) is an anticonvulsant commonly used for treatment of generalized and partial seizure disorder. Some of the common side effects associated with levetiracetam include somnolence, dizziness, headaches, and mood changes. Rhabdomyolysis and increase in creatine kinase (CK) levels is one of the rarely reported effects of LEV.**Case Report:** We report a case of a 22-year-old man admitted for evaluation of new-onset generalized tonic-clonic seizures. The patient was started on levetiracetam 500 mg twice a day, after which his CK levels started to increase, with maximum level of 21 936 IU/L noted on day 5. No improvement in CK levels was observed even with aggressive intravenous hydration. In the absence of any other obvious cause, the persistent elevation in patient's CK levels was suspected to be due to LEV. Our suspicion was supported by significant decrease in CK levels (from 21 936 IU/L to 11 337 IU/L) after about 30 h of discontinuation of LEV. We reviewed cases of LEV-induced rhabdomyolysis reported in the literature over the last decade and found 13 cases with almost similar correlation between initiation of LEV and increase in CK levels.**Conclusions:** Our case report stresses the importance of close monitoring of CK levels and kidney functions after initiation of LEV, and to consider changing the anticonvulsant medication if CK levels are noted to be significantly high to avoid kidney injury.**MeSH Keywords:** Creatine Kinase • Rhabdomyolysis • Seizures**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/926064>

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Background

Levetiracetam (LEV) is a second-generation antiepileptic medication being used for the treatment of generalized and partial seizures either as monotherapy or in combination with other antiseizure medications, and for myoclonic seizures as adjunctive therapy [1]. Common adverse effects associated with LEV include fatigue, somnolence, behavioral changes such as irritability and nervousness, minor infections, and thrombocytopenia [2,3]. LEV has rarely been observed to cause elevated creatine kinase (CK) levels, and only a few cases of LEV-associated rhabdomyolysis have been reported in the literature. Rhabdomyolysis involves breakdown of skeletal muscle fibers leading to release of cellular contents including CK and myoglobin into the bloodstream [4]. The most sensitive serologic finding of rhabdomyolysis is an elevated serum CK level [5]. We report a case of 22-year-old man who developed significantly and persistently elevated CK levels after administration of LEV for new-onset generalized tonic-clonic seizure in the absence of any other known underlying cause.

Case Report

A 22-year-old man with no significant past medical history presented to the emergency department (ED) for evaluation of a new-onset single episode of generalized tonic-clonic seizure at home lasting for about 2–3 min, followed by fall and brief syncopal episode. In the ED, the patient was found to be completely oriented and neurologically intact without postictal confusion. He was administered 1 dose of 500 mg intravenous (IV) LEV in the ED and was admitted for further evaluation and management. The patient was started on oral LEV at 500 mg twice a day. Imaging studies, including computed tomography of the head and magnetic resonance imaging of the head, were unremarkable. Electroencephalogram (EEG) was unremarkable and did not show any focus of epileptiform activity. Neurology consultation was requested and although this was the patient's first seizure episode in his lifetime, continuation of LEV was recommended because of previously suspected seizurelike symptoms in the patient's history. The CK level obtained 10 h after hospital admission (and 8 h after first LEV dose) was found to be slightly elevated at 771 IU/L. The patient's mildly elevated CK level was presumed to be due to rhabdomyolysis secondary to the seizure episode. IV fluids were initiated and CK levels were monitored. Despite aggressive IV hydration at 150–200 mL/h for almost 72 h, CK levels continued to rise and reached a level above 20 000 IU/L on day 5. The patient's serum myoglobin was elevated at 594 ng/mL (normal: 28–72 ng/mL), but there was no evidence of acute kidney injury or myoglobinuria. In the absence of any obvious reason to explain this unexpected and persistent increase in CK level, LEV was then considered to be the cause

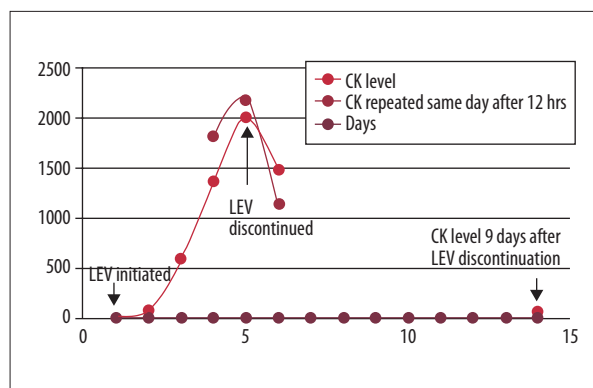


Figure 1. Creatine kinase (CK) level trend in relation to levetiracetam (LEV) dosing.

of rhabdomyolysis in this patient. LEV was discontinued on day 5, with CK levels peaking to 21 936 IU/L about 12 h after the last LEV dose, followed by significant decrease in CK level to 11 337 IU/L the next day (Figure 1). Our suspicion of LEV-induced rhabdomyolysis was strongly supported by the following facts: (1) the patient was not on any other medications; (2) he remained seizure free since his hospital admission; (3) he had no known underlying musculoskeletal disorder; (4) the patient denied any recent viral respiratory tract or gastrointestinal infection; (5) the patient's serum electrolytes, including phosphorus, calcium, and potassium, were within normal limits and his urine drug screen was negative for cocaine/amphetamines; (6) his CK levels declined significantly from 21 936 IU/L to 11 337 IU/L within 24 h of discontinuation of LEV. Throughout his hospital stay, the patient did not complain of myalgias; he remained neurologically intact and seizure free. We did not check the patient for genetic musculoskeletal or mitochondrial disorders as the patient declined family history of musculoskeletal disorders. The patient was discharged home in stable condition on day 6 without antiepileptic medication. The neurologist's decision to monitor the patient off antiepileptic medication was based on the fact that this was the patient's first seizure episode, in addition to having a normal EEG during his hospital stay. The patient was advised to follow up with the neurologist as an outpatient within 1–2 weeks of discharge, and he reported no further seizure episodes. Repeat EEG after 14 days of hospital discharge also did not show any epileptiform activity. The CK level was repeated 8 days after hospital discharge (9 days after discontinuation of LEV) and it was found to be 330 IU/L, further supporting our provisional diagnosis.

Discussion

LEV is a second-generation antiepileptic medication that was approved in the United States in late 1990s and is currently being used for the treatment of generalized and partial

Table 1. Data of reported cases of levetiracetam-induced rhabdomyolysis.

Reference	Year	Patient		Acute kidney injury	Myalgias	Peak CK (IU/L)	Time to peak CK
		Age (years)	Sex				
Thomas et al. [12]	2019	62	M	No	No	19 000	5 days
Rastogi et al. [13]	2018	42	M	Yes	Unknown	30 000	3 days
Mena-Martin et al. [20]	2018	28	M	Yes	No	1559	7 days
Kubota et al. [21]	2017	26	F	No	Yes	4396	15 days
Sohn et al. [22]	2017	40	M	No	Yes	7800	6 days
Di Lorenzo and Li [14]	2017	27	M	NR	No	49 539	5 days
Shahbaz et al. [23]	2016	43	M	No	No	29 750	7 days
Singh et al. [15]	2016	16	M	Yes	Yes	15 111	4 days
Ramon et al. [16]	2016	25	M	No	Unknown	15 811	4 days
Sivasambu and Yogarajah [17]	2015	30	M	NR	No	37 622	4 days
Akiyama et al. [6]	2014	29	F	NR	Yes	2410	4 days
Isaacson et al. [24]	2014	19	M	Yes	No	29 136	8 days
Spengler et al. [18]	2014	23	F	Yes	Yes	1368	4 days

NR – not reported; CK – creatine kinase.

seizures [6]. LEV promotes the release of synaptic neurotransmitter by binding to synaptic vesicle 2A (SV2A) protein [7] that is expressed widely in the brain and selectively in slow muscle fiber motor nerve terminals [8]. It does not possess cytochrome P-450 activity and therefore has minimal interaction with other drugs and has been reported to be fairly well tolerated [9]. Rhabdomyolysis is one of the rarely observed/reported side effects of LEV despite its widespread use. Some of the common causes of rhabdomyolysis include trauma (motor vehicle accident, crush injuries), strenuous exercise, seizures, hypothermia, malignant hyperthermia, electrolyte imbalances (hypokalemia, hypocalcemia, hypophosphatemia), autoimmune disorders such as polymyositis and dermatomyositis, and certain genetic disorders such as McArdle disease, Tarui disease, Duchenne and Becker muscular dystrophies, mitochondrial disorders, and certain drugs [10]. In addition to LEV, Kaufman and Choy in 2012 reported another anticonvulsant, pregabalin, as a cause of rhabdomyolysis when used in combination with simvastatin [11]. The patient in our case demonstrated a temporal relationship between exposure to LEV and onset of elevated CK levels followed by improvement in CK levels upon discontinuation of the medication. We reviewed cases of LEV-induced rhabdomyolysis reported in the literature over the last decade (Table 1).

Of interest, most of the reported cases of LEV-induced rhabdomyolysis were observed in young and adolescent patients

between the ages of 19 and 30 years, with only 1 patient being above the age of 60 years [12]. Peak CK levels observed in these cases were highly variable and ranged between 1368 IU/L and 49 539 IU/L. The difference in observed peak CK levels among the reported cases could likely be related to difference in muscle mass of the patients. Our patient weighed 64 kg and had a muscular body, which likely explains the significant increase in CK levels. In almost all of the cases included in our literature review, elevation in CK level was observed within 12–36 h of initiation of LEV, suggesting the need for close observation, particularly during the initial treatment phase. In most of the reported cases [6,12–18], the time elapsed from initiation of LEV to peak CK elevation was noted to be 3–5 days, after which the medication was discontinued, leading to improvement in CK levels. Symptomatic rhabdomyolysis (back pain, muscle aches) was reported in 5 of 13 cases; our patient, however, did not develop any symptoms of rhabdomyolysis.

The patient reported in our case continued to have increasing CK levels up to 5 days after his single seizure episode, which further supported our presumptive diagnosis of LEV-induced rhabdomyolysis as opposed to seizure-related rhabdomyolysis. Brigo et al. suggested that seizure-related rhabdomyolysis is usually associated with slight elevation of CK levels, with peak level noted at 36–40 h [19].

The exact mechanism by which LEV causes rhabdomyolysis is not clear. One proposed theory is the interaction of LEV with SV2A protein in motor nerve terminals of slow muscle fibers, causing enhanced cholinergic neurotransmission and increased stress in muscles, leading to rhabdomyolysis [8].

Conclusions

Although LEV has been known to be well tolerated, it has the potential to cause rhabdomyolysis in some patients. Therefore, clinicians need to be aware and vigilant about this rare side effect of LEV, particularly during the early phase of treatment.

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Conflict of interest

None.