

## Repeated Occurrence of HyperCKemia After Levetiracetam Administration

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### Abstract

It is often difficult to identify the specific cause of hyperCKemia when treating epilepsy patients, due to frequent use of multiple antiepileptic drugs and possibility of seizure-related rhabdomyolysis. Levetiracetam-induced hyperCKemia is a rarely encountered adverse event, which has been recognized recently. Previously reported cases showed merely possible association between the use of levetiracetam and rhabdomyolysis. We report a 40-year-old epilepsy patient who showed repeated hyperCKemia after levetiracetam readministration, confirming 'probable' causal relationship between levetiracetam and hyperCKemia, by showing positive response after dechallenge and rechallenge.

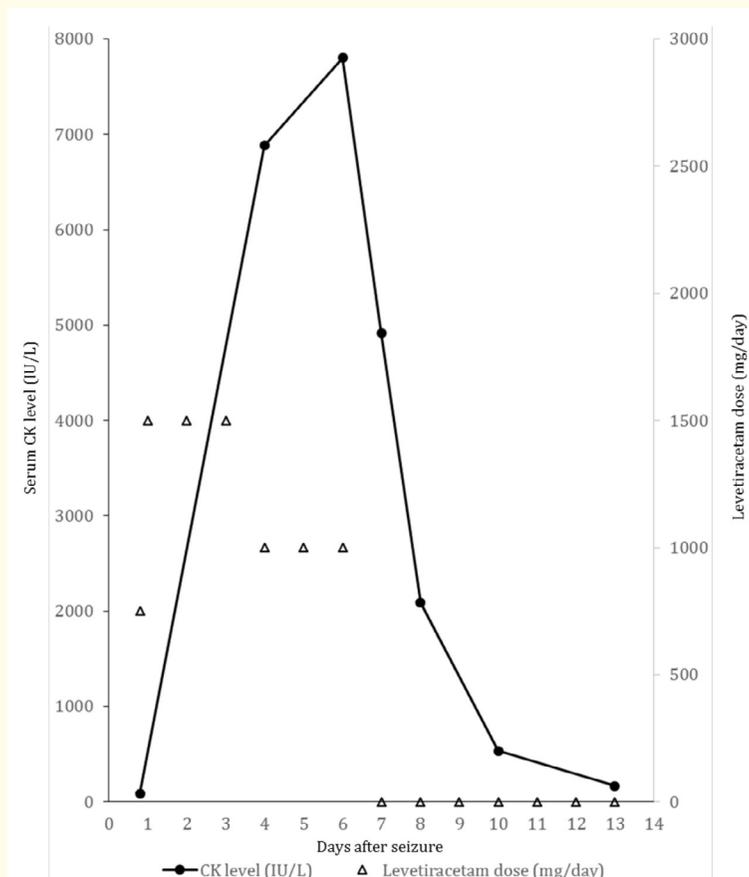
**Keywords:** Levetiracetam; Adverse Events; Hyperckemia; Rhabdomyolysis

### Introduction

Levetiracetam is widely used in treatment of various type of seizures, including generalized epileptic seizure as well as focal seizures. Among other anti-epileptic drugs (AEDs), levetiracetam use is steeply increasing due to its favorable pharmacokinetics and safety. Common adverse events of levetiracetam include somnolence, asthenia, dizziness, mood changes, kidney dysfunction, minor infections and thrombocytopenia [1]. Rhabdomyolysis after levetiracetam administration has been reported anecdotally; however, all of the previous reports failed to credibly prove the causality. Herein, we report a patient who showed repeated hyperCKemia after levetiracetam readministration.

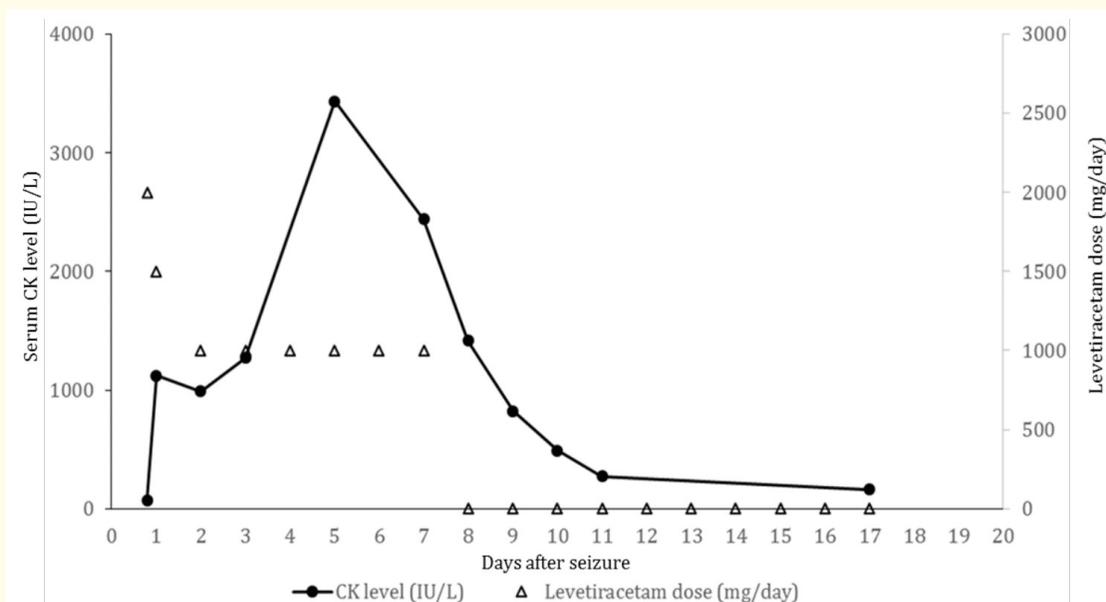
### Case Report

A 40-year-old male presented to the emergency room in March 2016 after an episode of generalized tonic clonic seizure. He rapidly recovered from postictal confusion, but he complained of chest discomfort. Initial serum creatinine kinase (CK) level was normal at 78 IU/L (reference range: 26-200 IU/L). Cardiologic evaluation including electrocardiogram, echocardiogram, cardiac enzyme was normal. He was admitted to the department of neurology for seizure etiology work-up. Subsequent evaluation including brain magnetic resonance imaging, cerebrospinal fluid analysis, electroencephalography showed negative results. Under clinical impression of idiopathic epileptic seizure, levetiracetam administration was started, considering its cardiologic safety profile. The dose of levetiracetam was gradually increased from daily dose of 750 mg to 1500 mg. On hospital day 3, he complained of severe headache around the forehead and generalized myalgia. Laboratory findings on day 4 revealed serum CK level of 6881 IU/L. At that time, it was thought that the cause of hyperCKemia was due to seizure, hence levetiracetam administration was maintained. Aggressive intravenous hydration was started, and we reduced levetiracetam dose to 1000mg daily. However, a blood test drawn on hospital day 6 revealed a CK level of 7800 IU/L and normal serum creatinine level. The possibility of levetiracetam-induced hyperCKemia was considered; from day 7, we stopped levetiracetam and switched to sodium valproate. Then CK level gradually decreased, and reached normal value at 1 week after discontinuation of levetiracetam (hospital day 13) (Figure 1a).



**Figure 1a:** Trends in serum CK levels during the first hospitalization. Levetiracetam (shown in open triangle) was given until hospital day 6. Serum CK reached normal value one week after discontinuation of levetiracetam.

The patient presented again to our hospital on March 2017, despite he had been seizure-free for one year on oral sodium valproate maintenance. The second seizure was witnessed by medical staffs in the emergency room (ER). After a brief ictal vocalization, generalized tonic-clonic seizure occurred with a duration of 6 minutes. He was diagnosed as status epilepticus, and was given 8 mg of lorazepam (4 mg twice) and 5 mg of diazepam intravenously, but the patient did not recovered. Tongue bite and postictal voiding was noted. Although a loading dose of intravenous levetiracetam 2000mg was given, the seizure continued. After intravenous phenytoin 1200 mg was given subsequently, the patient finally recovered. The initial serum CK level measured during ER stay was normal at 74 IU/L. For prevention of seizure recurrence, levetiracetam and phenytoin was maintained for 1 week at a daily dose of 1000 mg and 300 mg, respectively. CK level began to rise from the next day, reaching 1273 IU/L on hospital day 3, despite massive intravenous fluid hydration. The patient complained of mild diffuse myalgia without asthenia. Serum creatinine on day 3 was 0.56 mg/dL (reference range: 0.50 - 1.10 mg/dL), along with normal straw colored urine. Serum CK level stayed high, reaching a maximum of 3432 IU/L (on day 5) while on levetiracetam, and began to decrease exponentially after discontinuation (Figure 1b).



**Figure 1b:** Trends in serum CK levels during the second hospitalization. Levetiracetam (shown in open triangle) was given until hospital day 7. Serum CK level began to decrease exponentially after discontinuation of levetiracetam.

### Discussion

HyperCKemia is considered as a nonspecific marker of muscle damage, since CK is a sarcoplasmic protein that reflects muscle membrane integrity [2]. Indeed, hyperCKemia might reflect a less severe form of rhabdomyolysis. Depletion of adenosine triphosphate within the muscle cells and consequent pump failure that leads to intracellular calcium accumulation is believed to play a major role in the pathomechanism of non-traumatic rhabdomyolysis [3]. The safety profile of levetiracetam is excellent in general. Previously conducted large multicenter clinical trials on levetiracetam reported somnolence, asthenia, irritability, dizziness, headache, and fatigue as major side effects, but there was no rhabdomyolysis [4-6].

The occurrence of hyperCKemia in our patient was very likely due to levetiracetam, since not only hyperCKemia occurred after administration but also persisted during maintenance of the drug, and normalized after discontinuation. Temporal relationship of hyperCKemia after levetiracetam administration was within 1 to 4 days in our case, which was in line with previous reports [4,7,8,10]. In typical rhabdomyolysis, serum CK rises within 2 - 12 hours after skeletal muscle injury, peaks around 1-3 days, and decline approximately over 3 - 5 days [7]. Seizure-related rhabdomyolysis was not thought to be the cause, as CK continued to rise beyond 5 - 7 days after seizure. Furthermore, hyperCKemia reoccurred after reintroducing levetiracetam in our case, confirming the causality by showing positive dechallenge and rechallenge.

Detailed clinical data of possible levetiracetam-induced rhabdomyolysis were available in 5 cases [4,7-10]. All reports were published recently, after year 2014. All of the reported cases were epilepsy patients aged less than 30 years old, who were otherwise healthy. Administered dose of levetiracetam ranged from 500 mg/day (20 mg/Kg/day) in a child [8] to 2000 mg/day [9], leading to mild renal compromise in 2 cases [7,9]. Only one patient (out of 5) received levetiracetam monotherapy [8]; other patients received multiple AEDs or medications that may cause rhabdomyolysis [10]. All of the mentioned reports only provided 'possible causality' [11] according to Naranjo adverse drug reaction scale [12], in contrast with our case which provides evidence of 'probable causality'.

The pathomechanism of levetiracetam-induced hyperCKemia needs to be elucidated. One explanation was proposed by Carnovale, *et al* [11]. The authors focused on potentiation of cholinergic neurotransmission via synaptic vesicle protein SV2A binding of levetiracetam, thereby exerting high stress in muscles, leading to rhabdomyolysis [11]. Another hypothesis – direct toxicity of levetiracetam on muscle membrane - can be made considering that levetiracetam-induced hyperCKemia showed similar temporal course as quinolone-related rhabdomyolysis [4]. In quinolone induced rhabdomyolysis, a direct toxicity to muscle fascia, tendon sheath and synovial membrane was shown, resulting in hyperpermeability of blood vessels and infiltration of mononuclear cells with localized edema [13]. It is somewhat different from statin-induced rhabdomyolysis, known to be probably due to mitochondrial dysfunction [14], which occurs weeks after statin administration. Additionally, levetiracetam is well known to exert less mitochondrial toxicity among AEDs, therefore considered as a preferentially administered agent in patients with mitochondrial disorders [15]. Therefore it is less likely that levetiracetam-induced rhabdomyolysis is mediated by mitochondrial toxicity.

### Conclusion

The authors present a case of levetiracetam-induced hyperCKemia which reoccurred after readministration. Although its pathomechanism should be elucidated, we believe that our case confirms the relationship of between CK elevation and levetiracetam administration. To the best of our knowledge, this is the first case providing evidence of probable causality. When treating patients with levetiracetam, clinicians should closely monitor serum CK level, since levetiracetam-induced rhabdomyolysis may be potentially harmful to susceptible patients.

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