

Case Report

A case of rhabdomyolysis in which levetiracetam was suspected as the cause



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ABSTRACT

Several studies have reported rhabdomyolysis induced by various drugs but not by the antiepileptic drug levetiracetam. We present a case of suspected levetiracetam-induced rhabdomyolysis. A 29-year-old woman was hospitalized for generalized tonic–clonic seizure and given levetiracetam for the first time. One day after starting levetiracetam, she developed myalgia, particularly backache, and weakness in both lower limbs. Based on her clinical symptoms and blood test results indicating hyperCKemia, our diagnosis was levetiracetam-induced rhabdomyolysis. Withdrawal of levetiracetam immediately improved the clinical symptoms and hyperCKemia. This first report of suspected levetiracetam-induced rhabdomyolysis provides important information for treating patients early in levetiracetam administration.

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1. Introduction

Levetiracetam is a relatively new antiepileptic drug that achieves its antiepileptic action by binding to synaptic vesicle protein 2A (SV2A) [1]. It was approved for clinical use in the United States in 1999 and in Japan in 2010 as a combination therapy with other antiepileptic drugs for partial-onset seizures (including secondary generalized seizures), for which other antiepileptic drugs are ineffective. The rate of adverse effects observed in patients taking levetiracetam in a clinical trial in Japan was 90.2% in adults and 58.9% in infants [2]. The major adverse effects reported were nasopharyngitis (53.0%), somnolence (35.5%), headache (19.9%), dizziness (17.5%), diarrhea (13.8%), and constipation (10.9%), while other serious adverse effects included Stevens–Johnson syndrome, Lyell syndrome, serious blood dysfunction, liver failure, hepatitis, pancreatitis, aggressiveness, and suicide attempt [2]. However, no cases of rhabdomyolysis have been reported with its use. Here, we report a case of rhabdomyolysis in a 29-year-old woman administered levetiracetam for the first time, and we provide a brief review of the literature.

1.1. Case report

A 29-year-old woman was admitted to our hospital in late September 2013 for generalized tonic–clonic seizure after a prolonged non-convulsive seizure. She had been medicated at our hospital for

idiopathic epilepsy that started at 14 years of age. She had no clinical symptoms such as rhabdomyolysis or hyperCKemia when intravenous phenytoin was administered for her last seizure, which occurred in mid-January 2010. Epilepsy was being well controlled by oral sodium valproate (VPA) 1000 mg daily and clobazam 20 mg daily since her last attack. During this treatment, a blood test revealed a normal serum creatine kinase (CK) level (69 IU/L) and an optimal blood VPA concentration (82.2 µg/mL). As she recently expressed a desire to conceive, we reduced the VPA dose from 1000 mg to 800 mg daily in mid-April 2012 because no spikes had been observed on electroencephalography (EEG) and no clinical seizures had occurred in the past 2 years. We further reduced the VPA dose to 600 mg daily in late December 2012 and to 400 mg daily in mid-March 2013 because she had not experienced any seizures with tapering the VPA dose (Fig. 1).

In late September 2013, she developed transient disturbance of consciousness without convulsion for around 5 min while at work. An ambulance was called for, but as her consciousness had returned by the time the ambulance arrived, she walked to the outpatient clinic at our hospital. However, around 4 h later, she developed a generalized tonic–clonic seizure during an EEG in the outpatient examination room and was consequently hospitalized. Electroencephalography revealed paroxysmal diffuse polyspike–waves following diffuse rhythmic waves in the tonic phase and a diffuse spike and slow-wave complex in the clonic phase (Figs. 2A–D). She was a nonsmoker, did not drink, and had no past history of allergic diseases. Idiopathic epilepsy was the only remarkable factor in her past history.

On first presentation, blood pressure was 102/51 mm Hg, and pulse was regular at 117 beats/min. Respiratory rate was 12 times/min, and SpO₂ was 100% in an air-conditioned room. General physical findings

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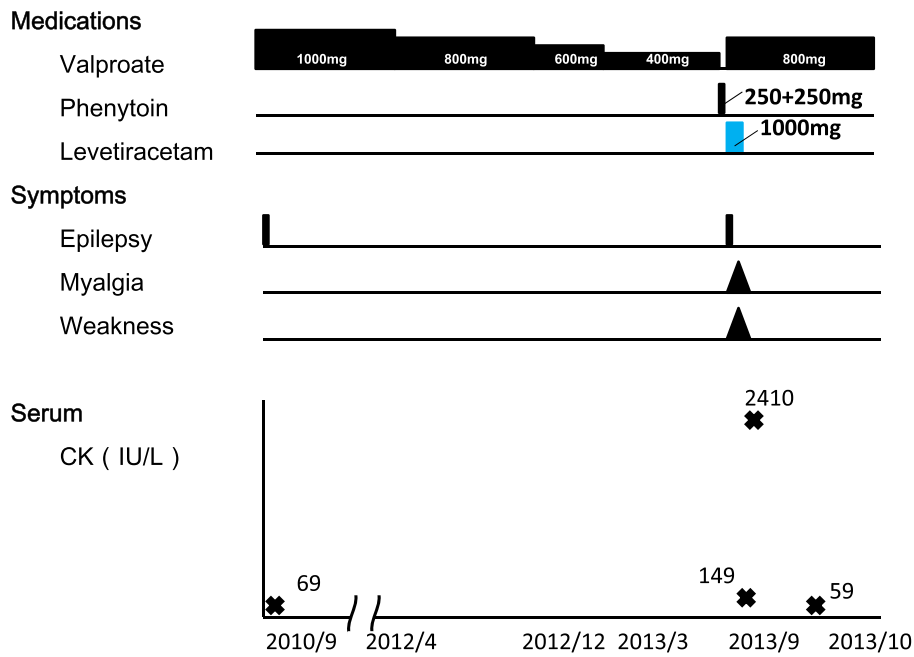


Fig. 1. Sodium valproate dose was gradually reduced to 400 mg daily in mid-March 2013 because she had not experienced any seizures during tapering.

and neurological findings were normal. Blood values were within normal limits, including a normal serum CK level (149 IU/L), and chest X-ray and ECG findings were also normal. Plain computed tomography of the head revealed no intracranial abnormalities or sinusitis.

The patient was admitted to our department because of the generalized tonic-clonic seizure, which developed during the EEG, and after this episode, she was started on intravenous phenytoin 250 mg daily. She had not experienced any seizures since starting intravenous phenytoin. A single dose of phenytoin 250 mg was given on hospital day 2, and intravenous medication was discontinued the same day (total phenytoin dose, 500 mg over 2 days). Levetiracetam 1000 mg daily and VPA 800 mg daily were started from hospital day 3. She developed myalgia, particularly backache, and weakness in both lower limbs after starting levetiracetam and VPA on hospital day 4. However, she was discharged because of improved clinical symptoms and because she wished to return to work. Initial seizure control was complete, and drug adherence was good after discharge. However, myalgia and weakness were gradually aggravated, and she revisited our hospital 3 days later. A blood test revealed hyperCKemia of 2410 IU/L and a low blood VPA concentration of 33.6 $\mu\text{g}/\text{mL}$, and levetiracetam was immediately withdrawn. Sodium valproate 800 mg daily was continued. Withdrawal of levetiracetam immediately improved the myalgia and weakness, and hyperCKemia improved rapidly to a normal level; CK was 59 IU/L 28 days after discharge. We did not measure serum myoglobin levels but diagnosed the patient as having rhabdomyolysis induced by levetiracetam based on the clinical course (Fig. 1).

2. Discussion

Levetiracetam is an antiepileptic drug marketed since 2000. The mechanism of action by binding to SV2A of levetiracetam is different from that of other antiepileptic agents. Here, we report the first case of rhabdomyolysis in a patient treated with this new antiepileptic drug, which, despite its short history of use in Japan, is now widely prescribed due to its efficacy. The present case reveals the importance of being aware that rhabdomyolysis may develop, albeit rarely, while on levetiracetam.

Rhabdomyolysis is often caused by traumatic events such as accident and injury or by nontraumatic events such as dehydration

and administration of medication. Its mechanism is known to involve fusion and necrosis of skeletal muscle cells, which causes myalgia and weakness [3,4]. Although rhabdomyolysis can develop in response to various agents, it is often caused by statins, fibrates, antibiotics, neuroleptics, and traditional Chinese medicine, and its incidence is low in users of antiepileptics. Among the limited number of antiepileptic agents, a few cases of rhabdomyolysis with VPA, zonisamide, and phenytoin have been reported [5–7]. However, no studies have reported this adverse effect with levetiracetam. Furthermore, the medical and pharmacological product survey forms for the medication at the time of its approval showed that the rate of adverse effects in adults in the clinical trial in Japan was 90.2%, while that for children was 58.9%, but there were no cases of rhabdomyolysis reported [2]. Similarly, large-scale clinical trials on levetiracetam, including the KEEPERTM trial, the SKATETM study, and the Asia SKATE II study [8–10], reported somnolence (12.8–30.3%), asthenia (8.3%), dizziness (7.2–14.7%), headache (5.9–10.3%), and fatigue (6.0–13.7%) as major adverse effects but no cases of rhabdomyolysis (Table 1). However, although rhabdomyolysis is not specifically indicated, the adverse effects described on the medical interview form for levetiracetam possibly denote rhabdomyolysis because the occurrence of backache is 3% and that of myalgia and pain in the extremities, neck, or shoulder is <1–3% [2]. To the best of our knowledge, few studies have reported hyperCKemia [11,12]. However, all of these reported cases were asymptomatic without rhabdomyolysis. As such, the present study is the first reported suspected case of levetiracetam-induced rhabdomyolysis, clinicians should consider this possibility under the appropriate clinical circumstances.

Regarding the diagnosis of rhabdomyolysis, the incidence of this condition in clinical practice is low, and many medications are frequently being administered at the time of its onset. Consequently, it is often impossible to determine which medication caused the muscle damage. The etiology of rhabdomyolysis in our case was also thought to have been caused by 1) generalized tonic-clonic seizure or 2) intravenous phenytoin or oral VPA and levetiracetam administration.

It is difficult to determine the causative agent among the antiepileptic drugs of phenytoin, VPA, and levetiracetam in the present case. Given that rhabdomyolysis is a natural result of generalized tonic-clonic seizure, it is usual for myalgia or weakness to appear immediately after an epileptic episode. However, our patient was unaware of any

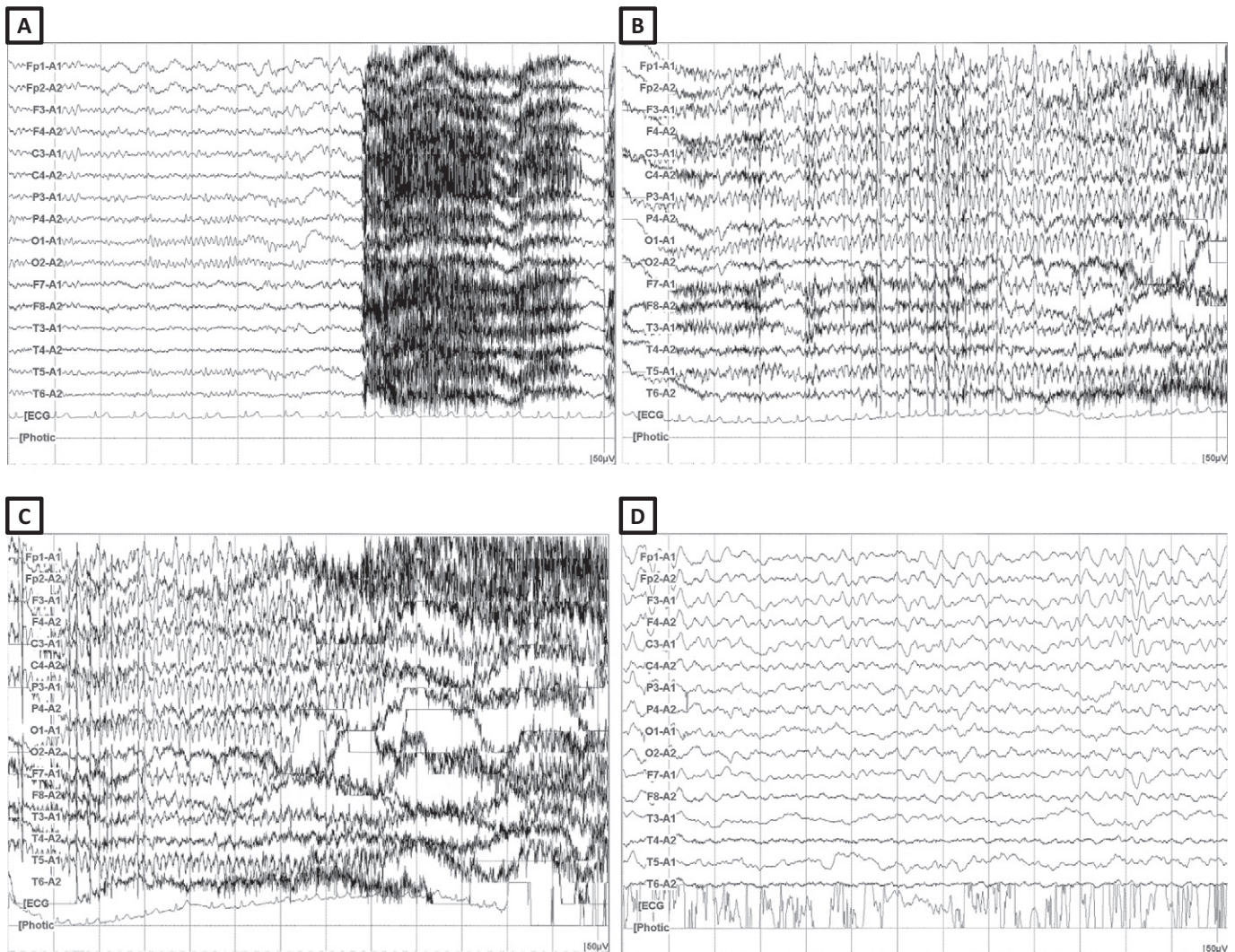


Fig. 2. Electroencephalography on admission showed paroxysmal diffuse polyspike-waves following diffuse rhythmic waves in the tonic phase and a diffuse spike and slow-wave complex in the clonic phase (A: tonic phase; B and C: clonic phase; D: after generalized tonic-clonic seizure).

such symptoms during treatment with phenytoin or VPA and had not presented with hyperCKemia at any previous hospital visits while taking phenytoin or VPA. Furthermore, the total dose of intravenous phenytoin at this time was only 500 mg, which was administered in 2 doses over 2 days (250 mg on day 1 and 250 mg on day 2), and the blood VPA concentration when hyperCKemia appeared was too low. Regarding the drug interaction between levetiracetam and phenytoin or VPA, it has been reported that levetiracetam does not influence the serum concentration or pharmacokinetics of phenytoin or VPA [13]. Therefore, the possibility of rhabdomyolysis being induced by phenytoin or VPA is low. Our patient started to experience myalgia and weakness in both lower limbs, as well as hyperCKemia, immediately after being started on levetiracetam. According to medical interview forms, the serum concentration (i.e., C_{max}) of levetiracetam peaks 2–3 h after administration and reaches a steady state 3 days after administration when a repeat dose of levetiracetam should be given [13]. These pharmacokinetics coincide with the onset of clinical symptoms or hyperCKemia. Since her signs and symptoms improved quickly once levetiracetam was withdrawn, the adverse effects were likely due to this drug alone. In addition, other muscle diseases known to cause rhabdomyolysis, such as metabolic disorders (e.g., glycogen storage disease), lipid metabolism disorders, metabolic myopathy, dystrophinopathy, certain atypical types of mitochondrial disorders, and hypothyroidism, were clearly

ruled out based on the patient's clinical course. The most likely cause of the rhabdomyolysis was levetiracetam, as evidenced by the close temporal relationship between exposure to the drug and onset of symptoms and the immediate resolution of symptoms and hyperCKemia after levetiracetam withdrawal.

In terms of the incidence of rhabdomyolysis due to levetiracetam, it is difficult to determine the exact number of patients taking this drug. In addition, it is conceivable that not all cases of rhabdomyolysis have been reported, so it is difficult to calculate its incidence. However, based on the 157 patients at our hospital taking levetiracetam, the frequency of rhabdomyolysis was estimated to be at around 0.64%. According to marketing information on levetiracetam, the number of the patients taking the drug in Japan is around 80,000 to 100,000, and the incidence of rhabdomyolysis among them is reported to be 0.001 to 0.00125%, which is extremely low.

Finally, the timing of the onset of rhabdomyolysis is reported to vary depending on the types of medication involved. For example, with antibiotics, particularly quinolone, rhabdomyolysis often occurs within 1 to 6 days after commencing treatment [14], while with statins, it occurs within a few weeks to months. In the present case, the symptoms appeared within 24 h after starting levetiracetam treatment. Therefore, it is possible that levetiracetam, much like antibiotics, can cause rhabdomyolysis early in treatment.

Table 1
Review of the large-scale clinical trials.

Publication year	2003	2007	2010
Study name	The KEEPER™ ¹ trial	The SKATE™ study	The Asia SKATE II study
Total number of patients	1030	1541	251
Adverse effect			
Overall (%)	38.3	50.5	73.3
Serious adverse event (%)	0.29	1	4.4
Symptoms (%)			
Somnolence	132 (12.8)	290 (18.8)	76 (30.3)
Asthenia	86 (8.3)	–	–
Dizziness	74 (7.2)	123 (8.0)	37 (14.7)
Headache	61 (5.9)	159 (10.3)	16 (6.4)
Fatigue	–	211 (13.7)	15 (6.0)
Nausea	–	58 (3.8)	14 (5.6)
Convulsion	–	48 (3.1)	–
Sedation	–	–	15 (6.0)
Lethargy	–	–	11 (4.4)
Vomiting	–	–	9 (3.6)
Abnormal coordination	–	–	6 (2.4)
Blurred vision	–	–	6 (2.4)
Insomnia	–	–	6 (2.4)
Rash	–	–	6 (2.4)
Anger	–	–	5 (2.0)
Upper respiratory tract infection	–	–	5 (2.0)

3. Conclusions

We encountered the first case of rhabdomyolysis in which levetiracetam was suspected as the cause. As rhabdomyolysis has the potential to develop during the early phase of levetiracetam treatment, clinicians should pay attention to the possible development of rhabdomyolysis despite its rare incidence.

Consent

Written informed consent to publish this case report and any accompanying images was obtained from the patient. A copy of the written consent is available for review from the Editor-in-Chief of this journal.

Author contributions

All authors read and approved the final manuscript.

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None.

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Conflict of interest

The authors declare that they have no competing interests.

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