Epilepsy & Behavior Case Reports 2 (2014) 152–155

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

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

Hisanao Akiyama *, Yoshiteru Haga, Naoshi Sasaki, Toshiyuki Yanagisawa, Yasuhiro Hasegawa

Department of Neurology, St. Marianna University School of Medicine, Japan

ARTICLE INFO

Article history:
Received 4 July 2014
Received in revised form 20 July 2014
Accepted 5 August 2014
Available online 16 September 2014

Keywords:
Levetiracetam
Rhabdomyolysis
Myalgia
Weakness
HyperCKemia

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.

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 nonconvulsive 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 SpO_2 was 100% in an air-conditioned room. General physical findings

* Corresponding author at: Department of Neurology, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan. Tel.: +81 44 977 8111; fax: +81 44 976 8516.
E-mail address: h2akiyama@marianna-u.ac.jp (H. Akiyama).

http://dx.doi.org/10.1016/j.ebcr.2014.08.001

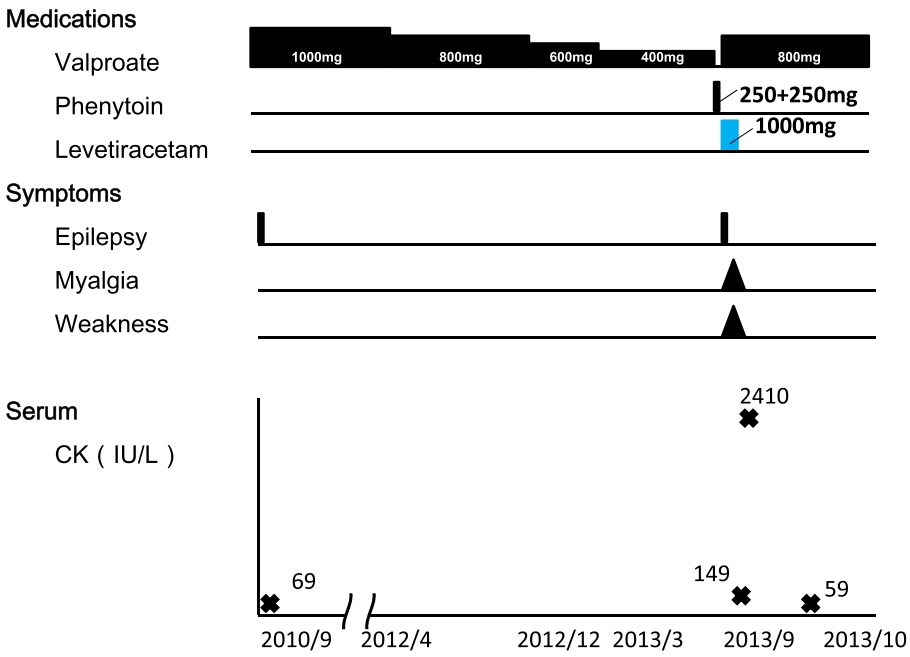

Fig. 1. Sodium valproate dose was gradually reduced to 400 mg daily in mid-March 2013 because she had not experienced any seizures during tapering.

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 μg/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 KEEPER™[1] trial, the SKATE™ 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