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Case Report

Microseizures Induced by Topiramate

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A 22-year-old Japanese male with trisomy 21 was diagnosed with West syndrome at 4 months old. After the suppression of epileptic spasms using adrenocorticotropic hormone therapy, he had complex partial seizures and bilateral frontal epileptic discharges on EEG. Although the introduction of topiramate (TPM) decreased the seizures during wakefulness, frequent episodes of brief eye-opening appeared during sleep while the patient was taking TPM (400 mg/day). EEG showed fast activity at the times of eye-opening. The episodes of eye-opening during sleep and the fast activities disappeared upon TPM discontinuation. This is the first report of TPM-induced microseizures similar to benzodiazepine-induced microseizures.

Key words: topiramate, microseizures, paroxysmal fast activity, side effects, seizure aggravation

Benzodiazepines are known to induce microseizures during sleep, and these microseizures are associated with high amplitude fast activities on electroencephalography (EEG) [1,2]. We report the case of a patient with a similar phenomenon during topiramate (TPM) administration. To the best of our knowledge, this is the first report of microseizures induced by TPM.

Case Report

The patient was a 22-year-old Japanese male with trisomy 21. He was delivered at term by caesarean section because of cephalopelvic disproportion. Three days after birth, he underwent surgery for duodenal obstruction. A ventricular septal defect was also detected but it disappeared spontaneously. At 1 month of age, he underwent surgery for bilateral cataracts. Hypothyroidism was treated using thyroid hormone. At 4 months of age, he was diagnosed with West syndrome and received adrenocorticotropic hormone (ACTH) therapy. At 10 years of age, a gastrostomy was performed because of recurrent aspiration pneumonitis.

After the suppression of epileptic spasms using ACTH therapy, his seizure type changed to complex partial seizures. These seizures were accompanied by a loud cry and upper deviation of his eyes, bilateral elevation of the upper arms, and twisting of his body toward the right, followed by generalized clonic convulsions. These seizures continued for 1 to 2 min and often occurred several times in cluster, or they developed into status epilepticus, lasting for 15 to 30 min. These seizures continued to occur approx. 5×/month.

At 19 years of age, he was admitted to our facility. He was bedridden and had no sign of secondary sex characteristics. His height was 144 cm and weight was 21 kg. He was administered antiepileptic drugs consisting of 150-mg zonisamide, 6-mg clobazam, 55-mg

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lamotrigine, and 300-mg valproic acid daily. Clonazepam, carbamazepine and a ketogenic diet had no effect.

At admission, a brain computed tomography scan showed no gross abnormalities, and EEG showed bilateral frontal epileptic discharges. Although we increased the dose of lamotrigine from 55 mg to 70 mg per day, his seizures continued with the same frequency as before. When we added TPM and increased its dose to 100 mg, the seizure frequency dramatically decreased to 1×/month. At a daily dose of 150 mg TPM and a blood level 6.1 μg/ml measured at 21 years 6 months old, another EEG examination showed bilateral frontal epileptic discharges with left frontal dominance, as before (Fig. 1). However, soon thereafter the seizure frequency again increased to 12-15×/month. We then added levetiracetam, and increased its dose to 1,750 mg (76 mg/kg/day), and the seizure frequency decreased to 4×/month. Because TPM seemed to be effective temporarily and its dose had not reached the maximum level, we increased the TPM dose to 400 mg and observed a blood level of 21.6 μg/ml. The seizure frequency again decreased to 1×/month.

Another EEG examination revealed approx. 50 μV, diffuse fast activities (12-14 c/sec) frequently appearing during sleep in addition to bilateral frontal and occipital epileptic discharges. These fast activities occurred 29 times during the EEG examination while the patient was asleep, and 13 of the 29 fast activities were accompanied by brief eye-opening (Fig. 2). These episodes resembled the reported microseizures induced by benzodiazepines in their clinical and EEG manifestations and also in their mode of appearance. We thus suspected that these microseizures might be induced by TPM, and we discontinued the TPM. Two months after the discontinuation, diffuse fast activities had disappeared on EEG, although bilateral frontal epileptic discharges remained. The microseizures during sleep also disappeared, but the seizure frequency during wakefulness increased to the level before the introduction of TPM. We therefore increased the daily dose of zonisamide to 300 mg and added perampanel 6 mg per day.

Discussion

Ohtahara *et al.* reported newly recognized microseizures that appeared to be related to the increase in the benzodiazepine dose in 21 patients with Lennox-Gastaut syndrome, in 1982 [1] and 1983 [2]. The main clinical symptoms were opening the eyes and respiratory suppression during sleep, and ictal EEGs showed peculiar bursts of hypersynchronous rapid activities (8-18 Hz). Because these microseizures were suppressed by the decrease or discontinuation of benzodiazepines, those authors concluded that the microseizures were induced by benzodiazepines.

The ictal clinical and EEG manifestations observed in our patient were similar to these previously reported benzodiazepine-induced microseizures. His microseizures appeared with an increase in the TPM dose and disappeared when the TPM was discontinued. We thus suspected that our patient's microseizures were induced by TPM. On the other hand, there is a possibility that concomitant antiepileptic drugs other than TPM, especially clobazam (a type of benzodiazepine), might have had some influence on the occurrence of his microseizures. To evaluate the changes in the blood level of each antiepileptic drug, we analyzed the patient's blood levels before and after the increase in TPM dosage. We found no increase in the blood levels of clobazam or N-desmethylclobazam (Table 1). Accordingly, we concluded that the main cause of our patient's microseizures was the increase in the dosage and blood levels of TPM.

Comparing benzodiazepine-induced microseizures and TPM-induced microseizures, TPM-induced microseizures were observed in a patient with frontal lobe epilepsy, while benzodiazepine-induced microseizures were observed in those with Lennox-Gastaut syndrome. For ictal EEGs, amplitude has tended to be higher in benzodiazepine-induced microseizures. TPM-induced microseizures appeared mainly during sleep stage 1, whereas benzodiazepine-induced microseizures appeared mainly during sleep stage 2 or thereafter.

Common characteristics of benzodiazepine-induced microseizures and TPM-induced seizures are that they appeared exclusively during sleep and were associated with newly appearing peculiar fast activities, whereas the original seizures during wakefulness dramatically decreased in our patient with TPM-induced maicroseizures and those with benzodiazepine-induced microseizures. We suggest that these two types of microseizures might have some common mechanisms of occurrence. Yagi *et al.* reported mild clinical attacks manifested alongside a high-voltage spike discharge during sleep in

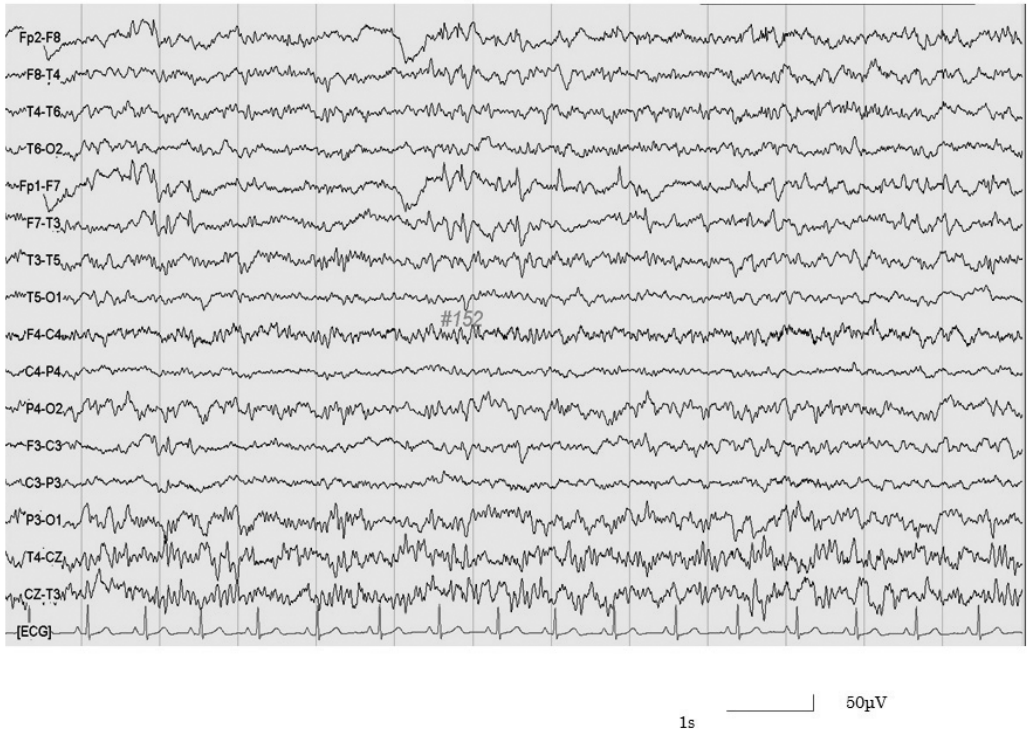

Fig. 1 Interictal EEG during the patient's sleep at age 21 years 6 months. The EEG shows bilateral frontal spikes, predominantly at the left frontal pole. Characteristic fast activities (Fig. 2) were not observed on this EEG. The plasma TPM concentration was 6.1 $\mu g/ml$.

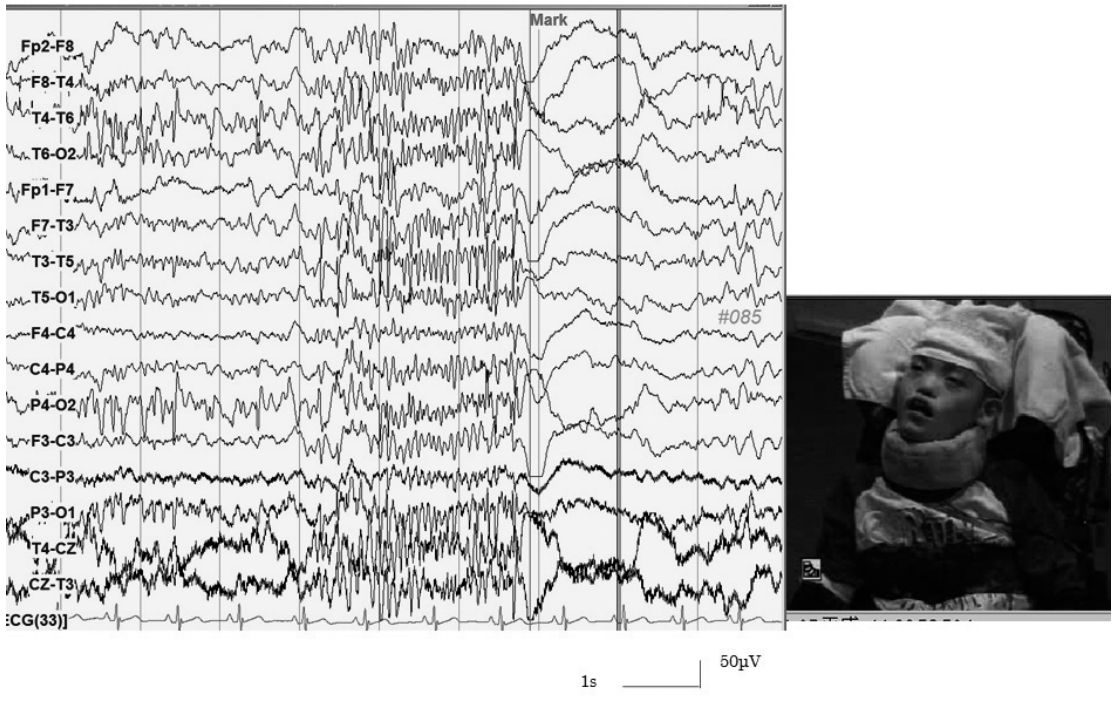

Fig. 2 Ictal EEG of a microseizure induced by TPM. The EEG shows diffuse fast activity during light sleep, which was associated with eye-opening. The plasma TPM concentration was 21.6 $\mu g/ml$.

Table 1 Blood levels of antiepileptic drugs before and after appearance of microseizures

Antiepileptic drugs	Daily dose (blood level)	Daily dose (blood level)
TPM	200 mg (12.4 μg/ml)	400 mg (21.6 μg/ml)
VPA	300 mg (72 μg/ml)	300 mg (43 μg/ml)
ZNS	150 mg (9.3 μg/ml)	150 mg (7.2 μg/ml)
LTG	70 mg (5.4 μg/ml)	70 mg (4.4 μg/ml)
LEV	1,750 mg (55.4 μg/ml)	1,750 mg (56.7 μg/ml)
CLB	6 mg (129 ng/ml)	6 mg (81 ng/ml)
desmethylCLB	(816 ng/ml)	(704 ng/ml)

TPM: topiramate, VPA: valproic acid, ZNS: zonisamide, LTG: lamotrigine, LEV: levetiracetam, CLB: clobazam

patients with Lennox-Gastaut syndrome [3]. Brenner *et al.* reported similar generalized paroxysmal fast activity in epileptic patients, mostly those with Lennox-Gastaut syndrome [4]. These previously reported seizures or characteristic EEG activities might be the same phenomenon as that underlying benzodiazepine-induced microseizures in Lennox-Gastaut syndrome.

Mesencephalic reticular formation and thalamic reticular formation are believed to play a critical role in the pathophysiology of Lennox-Gastaut syndrome. These structures are also closely related to sleep mechanisms. One of the main effects of benzodiazepines is a hypnotic effect; benzodiazepines may thus provoke characteristic microseizures by influencing sleep mechanisms.

A similar phenomenon might have been induced by TPM in our patient with frontal lobe epilepsy. He has a history of West syndrome, which belongs to age-dependent epileptic encephalopathies consisting of Ohtahara syndrome, West syndrome, and Lennox-Gastaut syndrome [5,6]. A transition from West syndrome to Lennox-Gastaut syndrome with age is often observed, and both epileptic syndrome share the common pathophysiological characteristics of corticoreticular epilepsy. Although our patient manifested frontal lobe epilepsy after West syndrome, an epileptogenic pathophysiology similar to Lennox-Gastaut syndrome might have continued after the suppression of West syndrome.

At a TPM serum concentration of 6.1 μg/ml, there were neither characteristic fast EEG activities nor microseizures which consisted of brief eye-opening during sleep.

The therapeutic range of the TPM blood level is considered to be from 2 to 25 μg/ml [7], but a blood level >25 μg/ml might sometimes be necessary. Because the microseizures in our patient appeared at a TPM blood level of 21.6 μg/ml, careful monitoring of the appearance of microseizures associated with characteristic fast activities on EEG may be needed during TPM therapy, especially during high-dose therapy.

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