—Case Reports—

A Girl with Idiopathic Epilepsy Showing Forced Normalization after Levetiracetam Administration

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Background: Forced normalization has been reported in association with almost all anti-epileptic drugs.
Patient: We report on a 9-year-old girl with idiopathic epilepsy who showed forced normalization after administration of levetiracetam (LEV). She initially presented with generalized tonic-clonic seizures when she was 4 years old. Diffuse sharp and slow wave complexes (SWCs) were observed on electroencephalography (EEG). We prescribed sodium valproate (VPA) and benzodiazepines, but the seizures and EEG findings worsened gradually. Although subsequent administration of LEV stopped the seizures, the patient became subject to episodes of rage and violent behavior. Forced normalization was confirmed by the disappearance of SWCs on EEG. We reduced the dose of LEV and tried in various ways to resolve the situation, but finally we had to abandon LEV.
Conclusions: To the best of our knowledge, this is the first report of a patient with idiopathic epilepsy but without disabilities in everyday life showing forced normalization associated with LEV administration. (J Nippon Med Sch 2015; 82: 250–253)

Key words: idiopathic epilepsy, forced normalization, levetiracetam

Introduction

Landolt used the term "forced normalization" (FN) to describe the phenomenon of psychotic episodes occurring in people with epilepsy during treatment that has brought about the remission of seizures and disappearance of epileptiform discharges on electroencephalograms (EEGs)[1,2]. It has been reported that almost all anti-epileptic drugs (AEDs) induce FN, but few authors have observed this phenomenon in association with levetiracetam (LEV)[3,4]. We report a case of FN after administration of LEV in a girl with idiopathic epilepsy. Informed consent was obtained from the patient and her parents prior to the publication of this report.

Patient Report

The patient was a girl born uneventfully at 41 weeks' gestation and weighing 3,055 g. There was no family history of neurological disorders or epilepsy, and her developmental milestones were normal. She had the first unprovoked generalized tonic-clonic seizures when she was 4 years old and was brought to our clinic after the third episode. Electroencephalography (EEG) showed spike and wave complexes (SWCs) (**Fig. 1**), but magnetic resonance imaging of the brain revealed no abnormalities (data not shown). Idiopathic epilepsy was diagnosed, and oral sodium valproate (VPA) was administered. Although there were no significant changes in the EEG findings, the patient experienced no clinical seizures for the following two years. However, after entering elementary school (aged 6 years), she started having generalized seizures about once a week. Again, there were no changes in the EEG findings, so we administered benzodiazepine derivatives as add-on agents to VPA. We also administered clonazepam (CZP) but discontinued it because it caused excessive sleepiness in the patient. We tried clobazam (CLB) instead, and this combination of VPA and CLB was effective for a while. However, this combination of AEDs started losing its effectiveness

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when the patient was 9 years old. She had generalized seizures once a week again, with sleep EEGs showing increased frequency of SWCs over her previous records (**Fig. 2-A**), and waking EEGs also showing SWCs (**Fig. 2-B**). Therefore, we added LEV (500 mg per day) to the VPA/CLB combination. Thereafter, there was no recurrence of seizures, and, surprisingly, SWCs on both waking and sleep EEGs disappeared completely (**Fig. 3-A**, **B**). However, the patient became subject to rage and violent behavior, using rude language to her family, and turning on boys at school. On the basis of the criteria proposed by Krishnamoorthy[5], we diagnosed FN. Our first action was to reduce the dose of LEV by half to 250 mg per day. Three days later, her violent behavior had abated and family members were able to talk to her, but she still used rude language. Following Major's recommendations, we added oral vitamin B6 to her regimen[6]. We also reduced the dose of LEV by half again to 125 mg per day, but her behavior did not improve. Finally, therefore, we stopped administering LEV altogether, after which her behavior returned to how it had been before LEV was administered. On the Wechsler Intelligence Scale for Children (WISC III), the patient got scores of 92, 99, and 86, respectively, on full IQ, verbal IQ, and performance IQ after she stopped taking LEV.

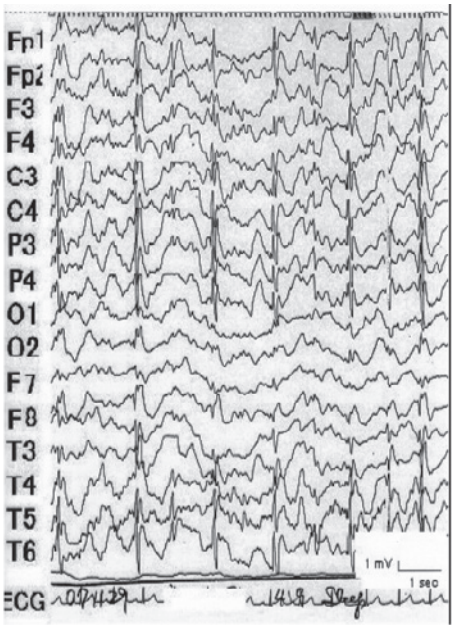

Fig. 1 The first EEG, when the patient was 4 years and 9 months old

Discussion

FN has generated heated debate since the term was first used by Landolt to describe the phenomenon of psychotic episodes occurring in people with epilepsy during treatment that has brought about the remission of seizures and disappearance of epileptiform discharges on EEGs[1,2].

Our patient had no underlying disease other than epi-

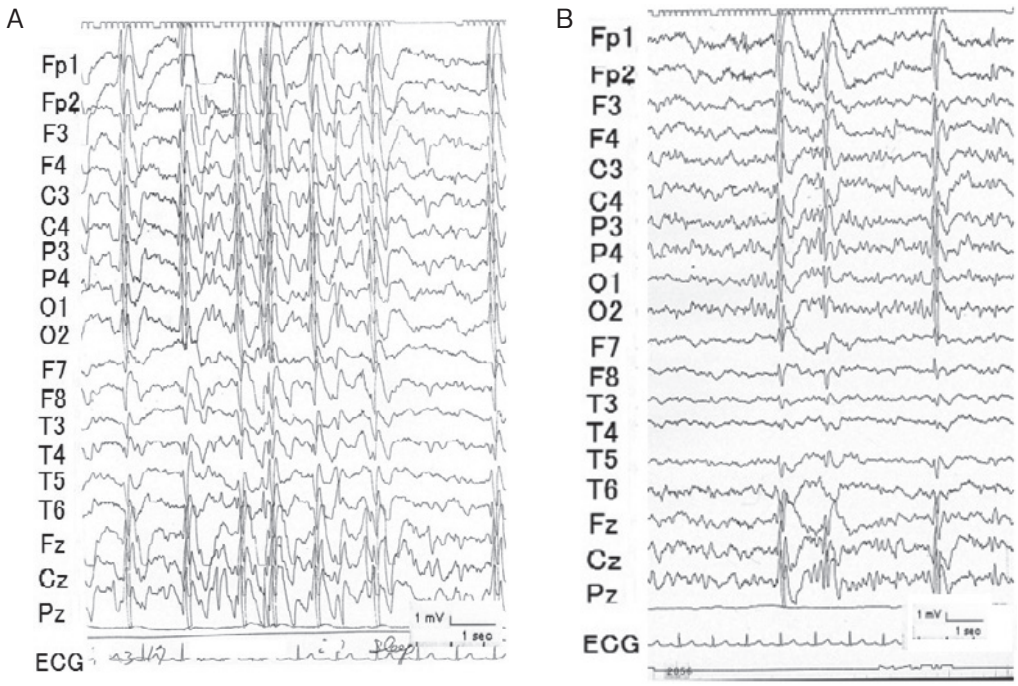

Fig. 2 EEG just before first administration of LEV, when the patient was 9 years and 1 month old (A: sleep, B: waking)

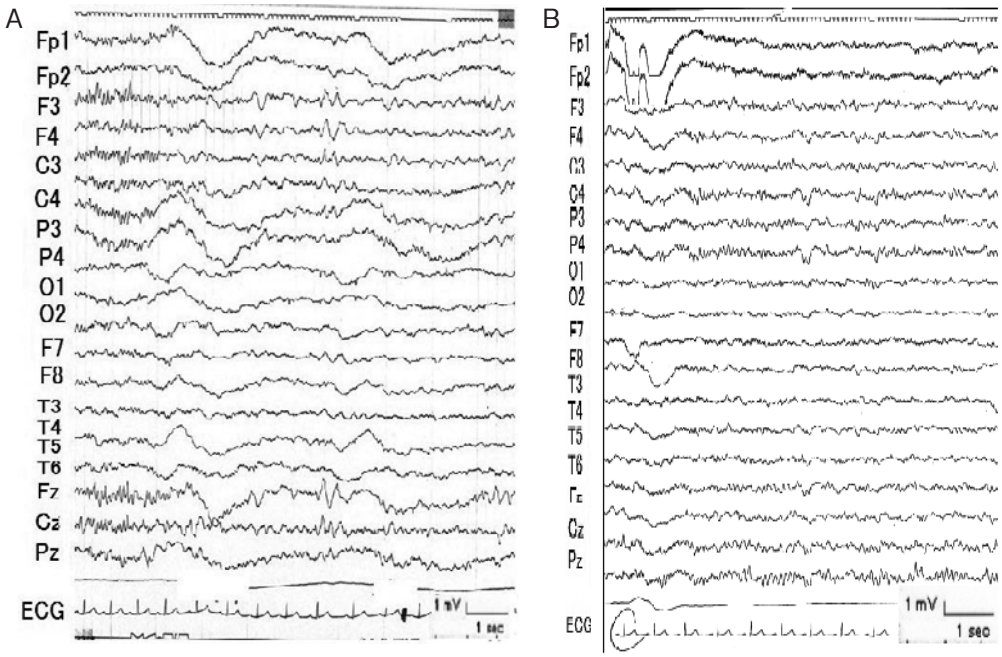

Fig. 3 EEG right after administration of LEV (A: sleep, B: waking)
α waves (9–10 Hz) are observed in the central and parietal areas in Fig. 2-B and Fig. 3-B.

lepsy, and blood tests showed no abnormal findings before the use of LEV. Although combinations of VPA and CZP or CLB had little clinical effect, LEV stopped the seizures promptly. In addition, paroxysmal epileptiform discharges were completely attenuated, not only on sleep EEGs but also on waking EEGs. Because she met the diagnostic criteria the patient was diagnosed with FN[5].

FN is known to be induced by almost all AEDs and so-called "new anticonvulsant drugs"[7–9]. We know of two case reports of FN induced by LEV, one in a mentally retarded patient[3], and the other in a patient with severe disabilities caused by comorbidity of epileptic encephalopathy[4], but the case we have reported here was in a patient with normal IQ. Psychotic episodes including rudeness or impulsivity have been reported as adverse effects of LEV, but EEG findings in affected patients have not been described. To the best of our knowledge, this is the first report of FN associated with LEV administration to a patient with idiopathic epilepsy but without disabilities in everyday life.

The pathophysiology of FN is still unknown. Some neurotransmitters including dopamine may reportedly play a role in the relationship between the psychotic symptoms and epileptic seizures[5], an observation that seems to be supported by a recent report that the psychiatric side effects of LEV are associated with variations in single nucleotide polymorphisms in some dopamine metabolic enzymes[10]. Further case reports and investigations into FN are eagerly awaited.

Conflict of Interest: No conflict of interest is declared.

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