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Levetiracetam-induced seizure aggravation associated with continuous spikes and waves during slow sleep in children with refractory epilepsies

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ABSTRACT – We present a patient with cryptogenic focal epilepsy and another with Dravet syndrome, who experienced seizure aggravation and negative myoclonus, associated with continuous spikes and waves during slow sleep, induced by levetiracetam. For both patients levetiracetam was discontinued, and there was significant improvement of this particular electroclinical picture.

Key words: aggravation, continuous spikes and waves during slow sleep, Dravet syndrome, negative myoclonus, levetiracetam

Levetiracetam (LEV) is chemically unrelated to any of the other current antiepileptic drugs (AEDs). LEV is a new AED approved as monotherapy for new-onset focal epilepsy in patients older than 16 years of age (Brodie *et al.*, 2007) and as adjuntive treatment for focal epilepsy in adults and children (Glauser *et al.*, 2006). LEV has also been approved for myoclonic seizures in patients with juvenile myoclonic epilepsy and for generalised tonic-clonic seizures in patients with idiopathic generalised epilepsy (Berkovic *et al.*, 2007).

Worsening of seizures by AEDs is a well-documented phenomenon, although there are few reported systematic studies. A paradoxical effect of LEV was previously reported in both children and adults with epilepsy (Nakken *et al.*, 2003).

Here, we present two patients, one with cryptogenic focal epilepsy and another with Dravet syndrome, who experienced negative myoclonus and increased seizure frequency associated with continuous spike-waves during slow-sleep (CSWSS), induced by LEV.

Case report 1

The patient was a 10-year-old girl whose parents were non-consanguineous and in good health. There was no family history of epilepsy. Pregnancy and delivery were normal, but the child had a mild developmental delay. At age 13 months, she apparently had a generalised tonic-clonic seizure. Carbamazepine 20 mg/kg/day was prescribed. Between the ages of two and

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five years, the child presented with right motor focal seizures with or without secondary generalisation every two months. Interictal awake and sleep EEG showed occasional bilateral spikes with left predominance. Carbamazepine was discontinued. The patient was administered phenobarbital and sodium valproate, but control of seizures was incomplete. Neurological examination showed moderate mental retardation. Physical and fundus examination were normal and no focal neurological signs were found. Routine laboratory investigations and brain CT scan were also normal. When the patient was seven years old, the number of focal seizures increased. Other AEDs, such as oxcarbazepine and lamotrigine were tried, but without a good response. MRI, metabolic investigations, and karyotype were normal.

At eight years of age, seizures continued to be frequent and the EEG recording did not show CSWSS. Oxcarbazepine was withdrawn and two months later LEV 1,500 mg/day was added to the lamotrigine treatment. The number of focal seizures with secondary generalisation increased and the patient developed gait instability. The interictal EEG showed frequent bilateral spikes predominating in anterior regions during wakefulness and increasing during sleep. The patient became unable to walk and developed behavioural disturbances. At that time, her weight was 35 kg. Serum LEV levels were not monitored.

The girl had frequent, discontinuous seizures compatible with negative myoclonus, but we were unable to perform a polygraphic EEG recording to document this particular type of seizure. Negative myoclonus involved the neck muscles and trunk. The involvement of these parts of the body provoked head drops and gait instability. This encephalopathic state lasted for four months. The EEG showed CSWSS *(figure 1A, B)*. The spike-and-wave index was more than 85%, calculated during all nap/sleep EEG recording.

At 8.5 years of age, LEV was discontinued and the patient slowly recovered her gait and the CSWSS disappeared within approximately two months. The interictal EEG recording during sleep showed bilateral spikes predominantly in the left hemisphere *(figure 2)*.

At her last examination at the age of 10 years, she had motor focal seizures occurring every four months with normal gait and moderate mental retardation. Her last EEG recording showed occasional bilateral spikes predominantly confined to the anterior left regions.

Case report 2

The patient was a 9.5-year-old boy without significant personal or familial antecedents whose parents were non-consanguineous. At the age of five months, he presented with a generalised tonic-clonic seizure (GTCS) during a febrile illness. From then on he had monthly moderate and prolonged GTCS and, less frequently, hemiclonic and focal motor seizures associated with febrile events that lasted during the first two years of life. In the same period he also experienced generalised tonic-clonic and hemiclonic status epilepticus associated with febrile events, and admission to an intensive care unit was necessary on three occasions. He initially received phenobarbital and subsequently valproic acid was introduced, but the latter drug was discontinued after he developed thrombocytopenia. The interictal EEG recordings were normal.

At the age of three years, the boy started with myoclonias, absences, and non-febrile focal and generalised motor seizures. At the same time, he also developed behavioural and language disturbances. The interictal EEG recordings showed frequent generalised polyspikes and slow waves and occasional focal spikes in anterior regions. Physical and fundus examinations were normal. Routine laboratory investigations, CT scan, and MRI were normal. The electroclinical picture and evolution were compatible with the so called "Dravet spectrum".

At 4.5 years of age, the seizures were refractory to classic and new antiepileptic drugs. The EEG recording showed occasional polyspikes and slow waves while awake and during sleep. Neurometabolic investigations and karyotype were normal. The patient was not tested for the *SCNIA* gene. LEV 1,000 mg/day was added to clobazam and topiramate, and one month later the boy presented with negative myoclonus and the number of generalised motor seizures increased. The EEG recording showed bilateral spikes and polyspikes and waves while awake and continuous spikes and waves during sleep *(figure 3)*. The spike-and-wave index was more than 85%, calculated during all nap/sleep EEG recording. The encephalopathic state, from the onset of negative myoclonus and CSWSS until LEV was discontinued, lasted 3.5 months. After LEV was discontinued the patient improved significantly, the negative myoclonus disappeared, the frequency of the other seizures diminished, and even the EEG abnormalities improved over a period of one and a half months. The EEG recording showed isolated bilateral polyspikes and waves. Between the ages of five and nine years, the patient presented once- or twice-monthly non-febrile and, less frequently, febrile seizures.

At his last examination, at age the age of nine years, he experienced two-monthly GTCS, hyperkinetic behaviour, language disturbances, and moderate mental retardation. He was refractory to the ketogenic diet. His last EEG recording showed occasional bilateral spikes and polyspikes and waves while awake and during sleep.

Discussion

The two patients presented here, the first with electroclinical features of cryptogenic focal epilepsy and

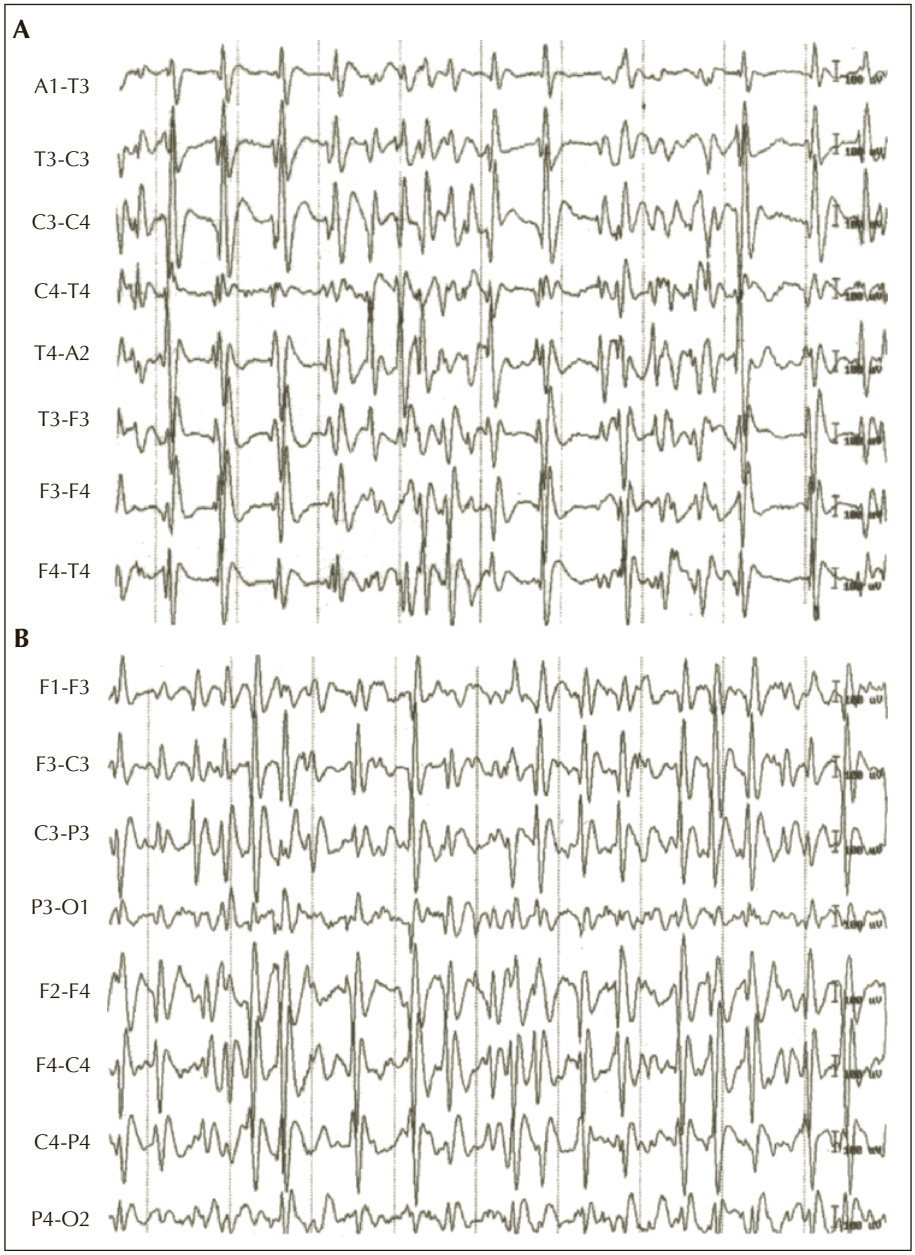

Figure 1. (Case report 1) **A**) EEG recording in a transversal montage during slow sleep shows diffuse CSWSS activity following introduction of LEV. **B**) The same EEG recording of *figure 1A* in longitudinal montage shows CSWSS.

seizures associated with a probable frontal lobe origin and the second with Dravet syndrome, developed a peculiar clinical evolution characterized by increased seizure frequency, negative myoclonus, and behavioural disturbances associated with CSWSS. These characteristics were induced by LEV which, to our knowledge, has not been described previously. In our opinion, two mandatory requirements were met to confirm the hypothesis of a strict correlation between LEV use and occurrence of adverse events. The first was the appearance of clinical symptoms when the AED was introduced, and the second, their disappearance soon after AED was discontinued.

In some cases, a paradoxical increase in seizure frequency may be observed as a consequence of drug intoxication, however, this is not the explanation for our patients. In other settings, seizure exacerbation seems to be the result of an adverse interaction between the mode of action of the drug and the pathogenetic mechanisms underlying specific seizure types or syndromes. Some cases are even more

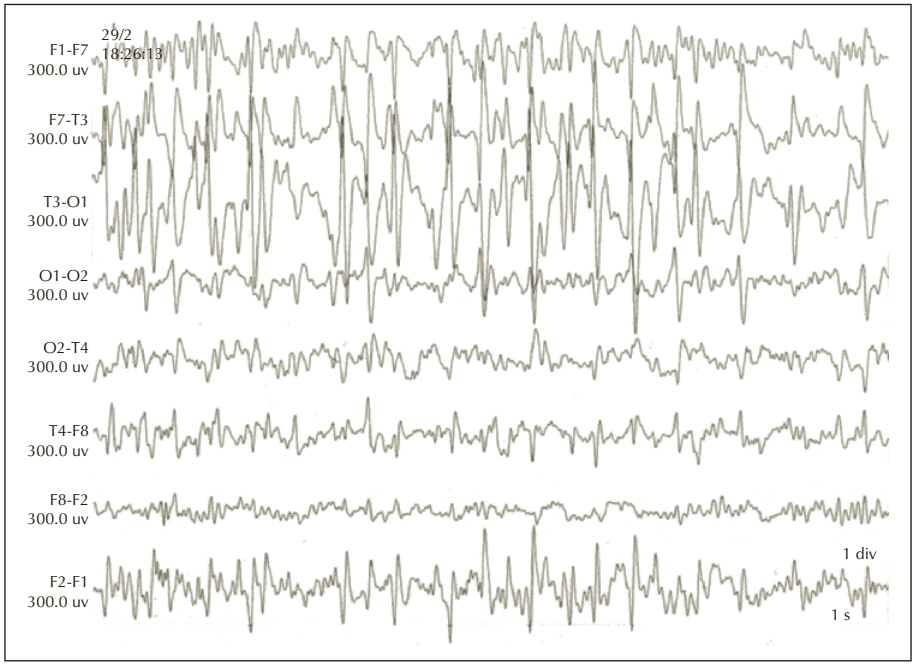

Figure 2. (Case report 1) Following discontinuation of LECV the EEG recording during slow sleep shows bilateral spikes predominantly in the left hemisphere.

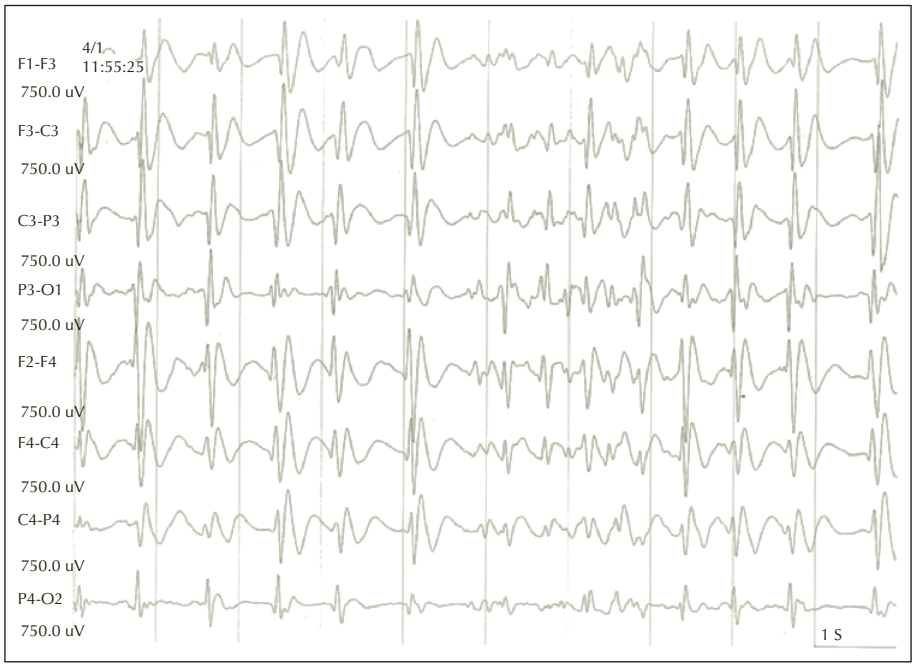

Figure 3. (Case report 2) EEG recording in longitudinal montage shows diffuse CSWSS discharges.

intriguing, because exacerbation of seizures occurs at therapeutic dosages and in patients with types of epilepsy which normally respond favourably to the offending drug. In our patients, the latter mechanism may be involved.

LEV is an effective AED when used as adjunctive treatment to control focal seizures in children (Glauser *et al.*, 2006). Moreover, a reduction of EEG abnormalities and improvement in cognition or behaviour and even complete recovery in children with CSWSS have been described (Capovilla *et al.*, 2004; Aeby *et al.*, 2005).

There is evidence that classic AEDs, particularly carbamazepine, may induce aggravation of EEG and clinical symptoms in patients with focal epilepsies especially in idiopathic forms (Caraballo *et al.*, 1989; Guerrini *et al.*, 1995; Prats *et al.*, 1998). In two cases with benign focal epilepsy with centrotemporal spikes, negative myoclonus associated with CSWSS was induced by carbamazepine (Caraballo *et al.*, 1989). The negative myoclonus was documented by polygraphic recording and in one of these cases, CSWSS disappeared after discontinuation of carbamazepine and reappeared on reintroduction of that AED (Caraballo *et al.*, 1989). Among the new AEDs, oxcarbazepine, lamotrigine, and topiramate were also reported as involved in inducing CSWSS (Montenegro and Guerreiro, 2002; Grosso *et al.*, 2003; Cerminara *et al.*, 2004).

Conclusion

To the best of our knowledge, these are the first reported patients who, in spite of having very different epilepsy syndromes, experienced seizure aggravation associated with CSWSS induced by LEV. This particular electroclinical picture should be corroborated. □

Disclosure.

All co-authors have had a significant role in designing, executing, and/or analyzing data from the study, and/or in writing the manuscript, and they have seen and approved the final version of the paper and accept responsibility for the data presented.

None of the authors has any conflict of interest to disclose.

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