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Absence status induced by lacosamide adjunctive therapy

Charles Ákos Szabó, Lola C. Morgan, Suzanne Sonnenberg, Kameel M. Karkar

Department of Neurology and South Texas Comprehensive Epilepsy Center, UT Health San Antonio, San Antonio, Texas

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ABSTRACT – Since lacosamide was approved as an adjuvant agent for the treatment of medically refractory focal epilepsy over ten years ago, it is becoming more widely used for the treatment of idiopathic (genetic) generalized epilepsies. Several studies have demonstrated efficacy in reducing primary generalized tonic-clonic seizures (GTCS), but efficacy is less well-characterized for myoclonic and absence seizures. A 29-year-old man with juvenile myoclonic epilepsy and medically refractory GTCS on a combination of levetiracetam and topiramate was started on lacosamide adjunctive therapy with the plan to replace topiramate. While his GTCS became controlled, he was witnessed to have confusional episodes, with waxing and waning responsiveness, lasting a few days, several times a month. After eight months of adjunctive lacosamide therapy, he was admitted to the epilepsy monitoring unit, where paroxysms of generalized spike-and-wave complexes, lasting for 30-90 minutes, were recorded, interrupted only by sleep. During these periods, he demonstrated psychomotor slowing and disorientation on examination. The absence status was successfully broken by lorazepam, and lacosamide was discontinued. The patient had no further confusional episodes at the most recent follow-up visit, four months after discharge.

Key words: lacosamide, absence status, idiopathic generalized epilepsy, antiepileptic medications, seizure aggravation

Lacosamide was initially approved as an adjunctive agent for the treatment of medically refractory focal-onset seizures in adults in 2007 (Ben-Menachem *et al*., 2007; Chung *et al*., 2010). Since it was introduced, its indications have increased to include children and adolescents, and even as monotherapy in adults (Vimpat US Prescribing Information, 2018). Similar to carbamazepine, phenytoin or lamotrigine, lacosamide targets voltage-gated sodium channels, but instead of blocking rapidly depolarizing currents, it enhances slow inactivation of the channels. There are reports regarding the efficacy of lacosamide for the treatment of idiopathic generalized epilepsy syndromes, juvenile myoclonic epilepsy in particular (Afra and Adamolekun, 2012). A recent study demonstrated short-term efficacy for the treatment of GTCS, which was further improved during the course of a 59-week open-label extension of this study (Wechsler *et al*., 2017). Absence and myoclonic seizures were also reduced in the open-label phase, as well as a decrease in the overall burden of generalized spike-and-wave discharges. Nonetheless, five patients

Correspondence:
Charles Ákos Szabó
Department of Neurology,
UT Health San Antonio,
7703 Floyd Curl Drive,
San Antonio, TX, USA
<szabo@uthscsa.edu>

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in the pilot study experienced an increase in absence or myoclonic seizures, two of whom exhibited absence seizures for the first time. In the extended study, only one patient experienced an increase in absence seizures at a dose of 800 mg/day, but these resolved with dose reduction, and another demonstrated a self-limited period of increased myoclonic seizures. There have been no reports of absence status to date. In this report, we present a patient with a history of juvenile myoclonic epilepsy who experienced control of his GTCS with lacosamide adjunctive therapy, but also developed frequently recurring confusional episodes consistent with absence status.

Case study

The patient was a 29-year-old right-handed man presenting for video-EEG evaluation, with a history of epilepsy beginning at age six years old. He initially presented with absence seizures, developing myoclonic seizures, and GTCS in adolescence. The GTCS occurred only a few times per year, but were always followed by a prolonged period of confusion, which could last from hours to days.

He had no family history of epilepsy but was born prematurely in the 28th week of gestation, weighing two pounds and seven ounces. He denied a history of focal neurological abnormalities postnatally but suffered from mild developmental delay and was eventually treated for attention deficit disorder.

Other co-morbidities included hyperlipidaemia which was treated with fenofibrate and obstructive sleep apnoea with CPAP. He had chronic insomnia requiring a combination of 100 mg trazodone and 50 mg hydroxyzine at night.

His most recent brain MRI was normal except for a Chiari I malformation. His EEG was normal just prior to starting lacosamide but generalized 3-5-Hz spike-and-wave as well as generalized polyspike-and-wave discharges resurfaced once started on lacosamide; findings that were mirrored by earlier EEG reports. He had failed topiramate, zonisamide, valproic acid, lamotrigine, phenytoin, carbamazepine, clonazepam, and gabapentin.

Lacosamide was introduced to replace topiramate as the adjunctive agent for levetiracetam and titrated to 500 mg daily. This combination controlled his GTCS for eight months, but he was witnessed as having 2-3-day periods of waxing and waning confusion. As these were occurring several times a month, he was no longer able to be gainfully employed.

At the time of his admission, his random levetiracetam level was 17 mcg/ml (normal range: 15-40 mcg/ml) and lacosamide level was 12.3 mcg/ml (normal range: 5-10 mcg/ml). He did not complain of any side effects on this regimen, and previous trough lacosamide levels were within the normal range. His metabolic profile demonstrated mild elevation of ALT/SGPT and AST/SGOT, but no other abnormalities.

His EEG at admission indicated prolonged paroxysms of 3-5-Hz generalized spike- and polyspike-and-wave discharges, occurring in runs of 20-30 seconds, with a brief 1-2-second interruption with transient return of his posterior background (*figure 1*). This EEG pattern lasted from 9:30 am into early afternoon, resolving briefly whenever he fell asleep. The absence status was finally aborted by two doses of lorazepam at 1 mg, with the EEG pattern responding within 10 minutes of its administration. During his absence status, he underwent bedside testing and was only oriented to place but not to person or the current date. He was not able to solve simple single-digit mathematical additions, suffered from short-term memory impairment, and could not recall what he had eaten for lunch that day. His partner confirmed that these symptoms were consistent with the confusional episodes he witnessed at home. Repeat testing after the absence status was aborted, with subsequent resolution of his disorientation to person and place and improvement in his dyscalculia and short-term memory deficits.

Lacosamide was held, while levetiracetam was increased to 1,000 mg twice daily to prevent GTCS. His EEG reverted to his normal awake and sleep background with brief generalized spike-and-wave discharges, not lasting longer than a second in duration (*figure 2*). Ethosuximide was also added prior to discharge to help control the absence seizures, but was poorly tolerated by the patient due to nausea and hiccoughs, requiring a dose reduction of 500 mg to 250 mg twice daily. His levetiracetam and ethosuximide levels were 11 mcg/ml and 26 mcg/ml (therapeutic range: 40-100 mcg/ml), respectively. According to the patient and his partner, he had no further confusional episodes in the four months since lacosamide was withdrawn.

Discussion

This case report describes a patient with juvenile myoclonic epilepsy presenting with recurrent bouts of absence status on lacosamide, despite improved control of his GTCS. While there is concern that lacosamide can aggravate absence and myoclonic seizures in some patients, absence status has not been reported to date (Wechsler *et al*., 2017). The patient started experiencing 2-3-day periods of confusion, several times each month, soon after lacosamide was introduced, despite complete control of his GTCS. The episodes did not recur afterwards, within four months following his discharge from hospital. Other

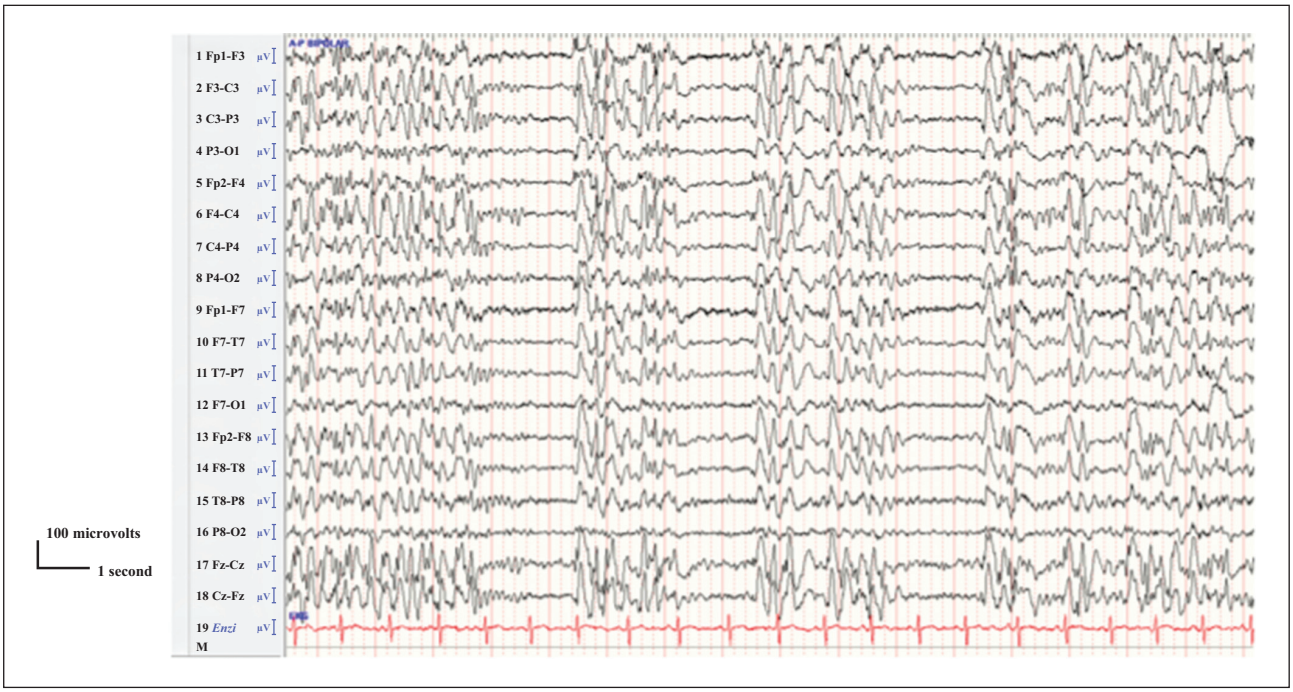

Figure 1. Absence status. Paroxysms of 3-5-Hz generalized spike- and polyspike-and-wave discharges are demonstrated on this 20-second EEG sample recorded using an anterior-posterior bipolar montage (Nihon-Kohden, Japan). Note the brief return of the patient's normal background activity between the paroxysms.

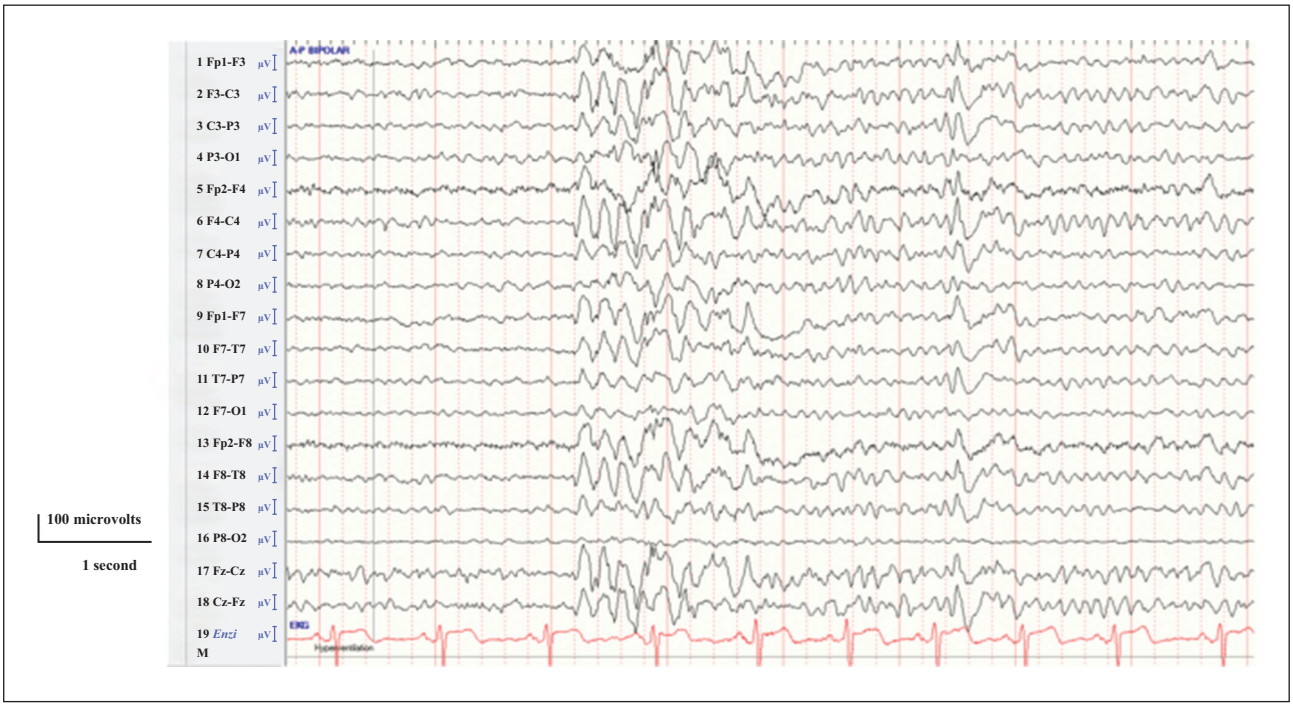

Figure 2. Interictal epileptic discharges triggered by hyperventilation. A 3-5-Hz generalized spike-and-wave discharge is triggered by hyperventilation after resolution of the absence status on this 10-second EEG sample, recorded using an anterior-posterior bipolar montage (Nihon-Kohden, Japan).

than the discontinuation of lacosamide, levetiracetam was increased by 500 mg a day at discharge, and ethosuximide was added. However, at the most recent follow-up visit, the levels of both of these medications were subtherapeutic, therefore less likely to be the cause of the prevention of absence status. Hence, based on the evidence that absence status started when lacosamide was introduced and resolved with its discontinuation, this is the most likely explanation of this adverse effect. Future case reports or series may be helpful to better characterize whether or not this lacosamide effect is dose-dependent.

The mechanism underlying the paroxysmal enhancement of spike-and-wave discharges is unclear. Several medications have been reported to trigger absence status including carbamazepine and oxcarbazepine (Genton *et al*., 2000; Gelisse *et al*., 2004), putatively as sodium-channel blockers, as well as vigabatrin and tiagabine (Panayiotopoulos *et al*., 1997; Knake *et al*., 1999) due to potentiation of $GABA_B$-receptor activation. While lacosamide's action on the sodium channel differs from that of carbamazepine and oxcarbazepine, the overall effect may be similar (Hebeisen *et al*., 2015). As in the case of carbamazepine and oxcarbazepine, it is still unclear why absence seizures would respond to lacosamide adjunctive therapy in most patients with idiopathic generalized epilepsy, yet worsen in a few patients, and, in this case, even evolve to absence epilepsy (Wechsler *et al*., 2017). The answers could include clinical, electrophysiological or even genetic factors. □

Key Points

In addition to focal-onset seizures, lacosamide may be helpful for the treatment of primary GTCS.
The efficacy of lacosamide for the treatment of other generalized seizure types is still being evaluated.
We report exacerbation of absence status epilepticus in a person with lacosamide adjunctive therapy.
Caution is advised when using lacosamide to treat idiopathic generalized epilepsy.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Which of the following medications can cause an aggravation of absence seizures in people with idiopathic generalized epilepsy?
A. Vigabatrin and tiagabine
B. Lacosamide
C. Carbamazepine and phenytoin
D. All of the above

(2) Lacosamide's main mechanism of action is due to enhancement of _____ of sodium channels.
A. Rapid activation
B. Slow inactivation
C. Rapid inactivation
D. Slow activation

(3) Lacosamide is a promising treatment for idiopathic generalized epilepsy, but caution is advised in patients with _____ seizures.
A. Bilateral convulsive seizures
B. Myoclonic seizures
C. Absence seizures
D. All of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".