

Response to lacosamide monotherapy in a patient with medically refractory Jeavons syndrome: a case report and review of the literature^{*}

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ABSTRACT – Jeavons syndrome is a childhood genetic generalized epilepsy characterized by eyelid myoclonia with or without absences, eyelid closure-induced epileptiform discharges and/or seizures and photoparoxysmal response. This syndrome accounts for up to 12.9% of generalized epilepsies, however, it is frequently under-reported. The utility of lacosamide in genetic generalized epilepsy and Jeavons syndrome is unclear. We present a case of a 15-year-old female with medically refractory Jeavons syndrome with seizure resolution in response to lacosamide monotherapy at standard daily doses. She had failed treatment with adequate trials of ethosuximide, valproic acid, lamotrigine, topiramate and the ketogenic diet, either as monotherapy or in combination. The frequency of seizures was confirmed in the epilepsy monitoring unit. She was treated with a loading dose of 200 mg of intravenous lacosamide and started at a maintenance dose of 100 mg, twice daily. The EEG showed a dramatic response with resolution of seizures and dramatic improvement in interictal discharges. She remained seizure-free for 11 months on lacosamide monotherapy after which seizures recurred in the setting of medication non-compliance. This highlights the potential role of lacosamide as an option in this syndrome if other drugs are ineffective or not tolerated.

Key words: Jeavons syndrome, eyelid myoclonia, lacosamide, generalized epilepsy

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Jeavons syndrome or eyelid myoclonia with absences (EMA) is a childhood genetic generalized epilepsy which was first reported in 1932, the main features of which were clearly described by Jeavons in 1977 (Striano *et al.*, 2009). It is responsible for 2.7-12.9% of generalized epilepsies and up to 2.7% of all epilepsies (Smith *et al.*, 2018). However, it is frequently under-reported and under-recognized (Smith *et al.*, 2018). Onset is typically between 2-14 years of age with female predominance (Striano *et al.*, 2009; Smith *et al.*, 2018). It is characterized by:

- eyelid myoclonia (hallmark) with or without brief absences;
- eye closure-induced seizures or electroencephalographic (EEG) paroxysms (brief generalized polyspikes and/or generalized spike-wave activity at 3-6 Hz, elicited by eyelid closure which may disappear in the dark);
- and photosensitivity or photoparoxysmal response (eyelid myoclonia provoked by photic stimulation which may disappear when eyes are closed in total darkness) (Striano *et al.*, 2009; Smith *et al.*, 2018). Generalized tonic-clonic seizures may frequently occur (23.3%) and rarely, patients may have myoclonic seizures (Striano *et al.*, 2009; Smith *et al.*, 2018).

Several years after its launch onto the market, the importance of lacosamide in genetic generalized epilepsies including Jeavons syndrome is still uncertain, but pathophysiological mechanisms, along with some case reports and uncontrolled trials, suggest plausible efficacious benefits (Strzelczyk *et al.*, 2018). To our knowledge, there are no previous reports of lacosamide monotherapy in medically refractory Jeavons syndrome. We describe a patient with medically refractory Jeavons syndrome with highly favorable response to lacosamide monotherapy.

Case study

A 15-year-female presented with uncontrolled absence seizures that initially started at nine months of age. Seizures were characterized by arrest of activity with blank stare, unresponsiveness and eyelid fluttering lasting from 5 to 30 seconds each. She had no history of generalized tonic-clonic seizures. She carried the diagnosis of childhood absence epilepsy since the age of three years.

Her past medical history was significant for attention deficit hyperactivity disorder, oppositional defiant disorder, anxiety, obsessive compulsive disorder and history of head trauma at the age of one year without loss of consciousness. She had normal birth and development and a previous MRI performed at the age of six years was within normal limits.

Between the ages of 3 and 12, she was given adequate trials of ethosuximide, valproic acid, lamotrigine, topiramate and the ketogenic diet, either as monotherapy or in combination without adequate seizure control.

Between the ages of 12 to 14, she remained off anti-seizure drugs because of poor seizure control on medications and medication-related behavior and mood side effects. She continued to have multiple daily absence seizures (up to 25 per day). At the age of 14, she was admitted to the Pediatric Epilepsy Monitoring Unit to clarify the diagnosis of her epileptic syndrome, as childhood absence epilepsy is generally expected to resolve by this age.

During 24-hour video-EEG (electroencephalography) monitoring, we captured nine clusters of her typical seizures. On EEG, normal awake and sleep background rhythms were interrupted by bursts of generalized polyspikes and generalized spike-wave complexes of 3-4 Hz, most of which were elicited by eyelid closure (EEG paroxysms) and associated with eyelid myoclonia. She was noted to have frequent eyelid myoclonia, some of which evolved into absence seizures, and eyelid closure-induced absence seizures were seen on the EEG characterized by 3-4-Hz spike-wave complexes (*figure 1A*). These EEG changes associated with eyelid closure were not evident in the dark. Hence, her epilepsy was re-defined as generalized epilepsy with eyelid myoclonia (Jeavons syndrome).

Given her failure of response to multiple medications in the past and her psychiatric history, a trial of lacosamide was decided. She was loaded with 200 mg of lacosamide and started at a maintenance dose of 100 mg twice daily. The EEG showed a dramatic response with resolution of seizures and dramatic improvement in interictal discharges (*figure 1B*). She remained seizure-free for 11 months on lacosamide monotherapy, after which seizures recurred in the setting of medication non-compliance.

Discussion

Jeavons syndrome is generally a lifelong condition with up to 80% of patients experiencing drug-resistant epilepsy and requiring polypharmacy (Smith *et al.*, 2018). Therefore, it is likely to be managed by both pediatric and adult epileptologists (Smith *et al.*, 2018). Hence, it is a significant syndrome for all neurologists to identify in order to manage appropriately (Smith *et al.*, 2018).

There is limited literature on anti-seizure drug treatment for Jeavons syndrome (Parissis *et al.*, 2014; Smith *et al.*, 2018). There have been no randomized controlled trials. Treatment decisions are generally based on anecdotal evidence and case reports (Parissis *et al.*, 2014). Valproic acid, lamotrigine, ethosuximide,

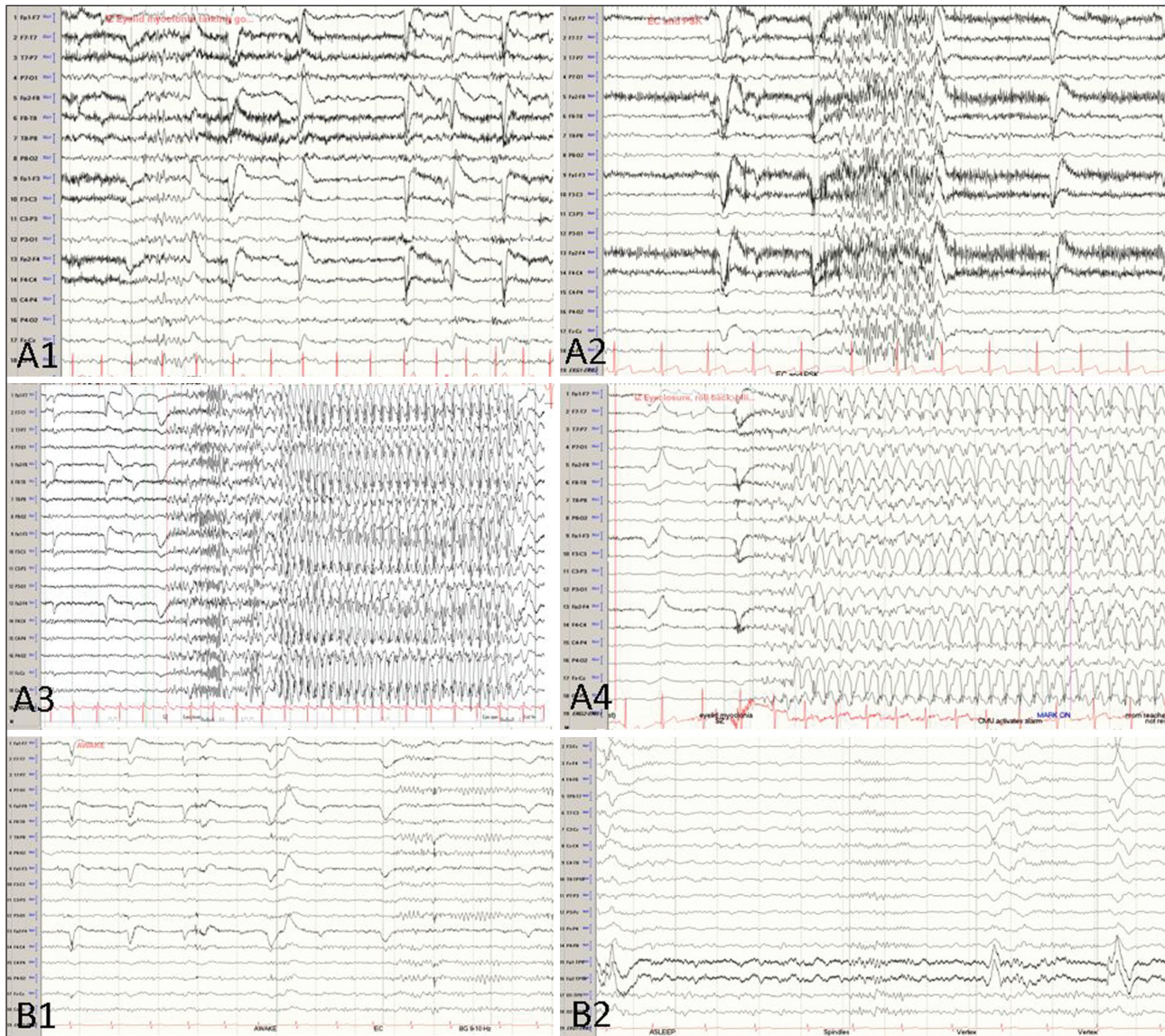


Figure 1. (A1-4) Before treatment; (B1-2) after treatment. (A1) Bursts of polyspikes associated with eyelid myoclonia. (A2) Eye closure-induced EEG paroxysms. (A3) Eyelid closure-induced seizures. (A4) Eyelid myoclonia evolving to dialeptic seizures. (B1) No epileptiform activity seen in association with eye closure following treatment. (B2) Sleep EEG following treatment without any interictal epileptiform activity.

levetiracetam, phenobarbital and benzodiazepines are commonly used with inconsistent efficacy, with drug-resistant cases requiring combination therapy (Parissis *et al.*, 2014; Smith *et al.*, 2018). A pilot open-label trial of levetiracetam use as monotherapy or adjunctive therapy demonstrated 80% response rate with acceptable tolerability (Biondi *et al.*, 2008). Lens therapy was deemed effective in up to 75-78% of patients with photoparoxysmal response in two studies, but no studies have been performed specifically for use in Jeavons syndrome patients. Dietary interventions and neuro-modulation have also not been thoroughly explored

(Smith *et al.*, 2018). Carbamazepine, phenytoin and vigabatrin may worsen seizures (Smith *et al.*, 2018).

A retrospective study at the Mayo clinic showed that even though lacosamide was not commonly used, among the four patients who were tried, two had effective response (50% response rate) although the details of whether this was monotherapy or a combination were not clear (Smith *et al.*, 2018).

Due to its efficacy and favorable side effect profile, several studies (Afra and Adamolekun, 2012; Zangaladze and Skidmore, 2012; Sodemann *et al.*, 2014; Yorns *et al.*, 2014; C. *et al.*, 2015; Strzelczyk *et al.*, 2018) have reported

Table 1. Response to lacosamide therapy in patients with genetic generalized epilepsy (excluding symptomatic generalized epilepsies) based on various studies.

Study	Number of patients	Number of seizure free patients, n (%)	>50 % seizure reduction	Number of patients on lacosamide monotherapy	Type of epilepsy
Miskin <i>et al.</i> , 2016	13	5 (38.5)	2 (15.4)	3	GGE
Yorns <i>et al.</i> , 2014	40	NA	23 (57.5) with improvement	3 on monotherapy, 20 on adjunct	GGE
Verrotti <i>et al.</i> , 2013	16	6.3-12.5 %	-	0	GGE
Rastogi and Ng, 2012	2	0	1	0	GGE
Afra and Adamolekun, 2012	3	3 (100%)	NA	1	JME
Zangaladze and Skidmore, 2012	2	2 (100%)	NA	0	JME, GTC only
Sodemann <i>et al.</i> , 2014	1	1 (100%)	NA	0	ASE
Reif <i>et al.</i> , 2018	1	1 (100%)	NA	0	ASE

ASE: absence status epilepticus, GGE: genetic generalized epilepsy, JME: juvenile myoclonic epilepsy, GTC: generalized tonic-clonic seizure, NA: not applicable.

successful treatment of genetic generalized epilepsy including juvenile myoclonic epilepsy (JME), generalized tonic-clonic seizure only, and some refractory cases of absence status epilepticus with lacosamide as monotherapy or an adjunct therapy (table 1 summarizes the response to lacosamide therapy in genetic generalized epilepsy based on various studies in the literature).

Medications that are traditionally used in Jeavons syndrome and other generalized epilepsies are broad-spectrum and it is not known which mechanisms are most responsible for their efficacy in these epileptic syndromes.

Lacosamide exerts its action by selectively enhancing slow inactivation of the sodium channel, unlike traditional sodium channel anti-seizure drugs (Rogawski *et al.*, 2015). It may be possible that the method by which it inactivates sodium channels plays a role in its efficacy as treatment for this syndrome or that it has a mechanism that we are not yet familiar with.

In 2017, the ILAE recognized eyelid myoclonia with epilepsy as a generalized seizure type, as a non-motor (absence) category along with eyelid myoclonia (Fisher *et al.*, 2017). However, studies have shown phenotypic overlap between JME and Jeavons syndrome (Smith *et al.*, 2018). Therefore, Smith *et al.* suggested that this may be a type of myoclonic epilepsy (Smith *et al.*, 2018). GABA-A and chloride channelopathies

have been associated with JME, but not sodium channel abnormalities (Zangaladze and Skidmore, 2012). Based on twin studies, a genetic etiology of Jeavons syndrome has been suggested (Smith *et al.*, 2018). Although, in general, Jeavons syndrome is thought to be caused by polygenic variants with or without environmental influence, monogenic variants and genetic mutations have been reported to manifest with a Jeavons syndrome phenotype, including unique variations in *CHD2* (chromo-domain helicase DNA binding protein 2) (Smith *et al.*, 2018), *KIAA2022* mutation (Samanta and Willis, 2020), *KCNB1* mutation (Marini *et al.*, 2017) and *NAA10* mutation (Valentine *et al.*, 2018). Even though no sodium channelopathies to date have been reported in association with Jeavons syndrome, it is interesting to note that sodium channel abnormalities have been reported in some generalized epilepsies phenotypically overlapping with JME (Zangaladze and Skidmore, 2012). Therefore, it may be possible that some patients with Jeavons syndrome could have unknown sodium channelopathies which could explain the efficacy of lacosamide in this syndrome. Unfortunately, our patient was unable to undergo genetic testing due to current medical insurance limitations for genetic testing in older children and adults with epilepsy.

In conclusion, we present a case of medically refractory Jeavons syndrome (EMA) with seizure resolution

in response to lacosamide monotherapy at standard daily doses. This highlights the potential role of lacosamide as an option for this syndrome if other drugs are ineffective or not tolerated.

Moreover, given the favorable side effect profile and low teratogenic potential, lacosamide could be considered as an add-on anti-seizure medication or as one of the initial treatment options for Jeavons syndrome in certain patient populations or for those whose comorbid conditions do not allow the use of other drugs. This case highlights the need for randomized prospective controlled studies with a large sample size to better elucidate efficacy and potential utility of this drug, both as initial or adjunct therapy for this syndrome and other generalized epilepsy syndromes. □

Supplementary data.

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

Disclosures.

Dr Pestana Knight is co-PI for a HRSA grant that is not relevant to this case report. None of the other authors have any conflict of interest to declare.

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TEST YOURSELF



- (1) What is the mechanism of action of lacosamide?
- (2) What are the three characteristic features of Jeavons syndrome?
- (3) What are some of the common treatment options used in Jeavons syndrome patients?

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".