■ Clinical commentary

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Exacerbation of eyelid myoclonia in patients with epilepsy and eyelid myoclonia receiving cannabidiol

Ifrah Zawar, Linfa Franic, Prakash Kotagal, Elia Pestana Knight

Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA

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ABSTRACT

Epilepsy with eyelid myoclonia or Jeavons Syndrome (JS) is a childhood genetic generalized epilepsy. Its clinical features include eyelid myoclonia (hallmark) with or without brief absences, eyelid closure-induced seizures and/or electroencephalographic (EEG) paroxysms (generalized polyspikes and/or generalized spike-wave activity at 3-6 Hz, elicited by closure of eyelid) and photosensitivity. Broad-spectrum anti-seizure medications are often utilized for the management of JS patients. A wide variety of medications may be utilized especially in refractory cases. Efficacy or safety of cannabidiol (CBD) for JS has not been studied. We describe two cases of exacerbation of eyelid myoclonia in JS which correlated with CBD use and resolved after CBD discontinuation. These cases highlight that caution should be practiced when using CBD for JS as it can potentially worsen eyelid myoclonia.

Key words: Jeavons syndrome, eyelid myoclonia, generalized epilepsy, CBD, cannabidiol

Epilepsy with eyelid myoclonia or Jeavons Syndrome (JS) is a genetic generalized epilepsy (GGE). Its clinical features include eyelid myoclonia with or without absence seizures, eye closure-induced EEG paroxysms (generalized polyspikes or spike-wave-complexes) and photosensitivity [1]. Frequent seizure types include eyelid myoclonia, absence seizures and GTCs. Broad-spectrum anti-seizure medications (ASMs) are frequently used for the treatment of this syndrome. Efficacy or safety of cannabidiol (CBD) for JS has not been studied. We describe two unique cases of eyelid myoclonia exacerbation in JS which correlated with CBD use and resolved after CBD discontinuation. IRB approval was obtained.

Case 1

A 20-year-old female with JS was admitted to the epilepsy monitoring unit (EMU) with poorly controlled seizures (*table 1* table 1). Despite being tried on multiple ASMs, she continued to have daily seizures with clusters. Around five to six months prior to admission, she had self-initiated artisanal CBD oil at 4 mg three times daily as adjunct therapy without any improvement of seizures. After the initiation of CBD oil, the family had noted an increase in frequency of eyelid myoclonia.

During video-EEG, normal posterior dominant rhythm and sleep structures were seen. Runs of seizures characterized by prolonged and frequent eyelid

• **Correspondence:**
Elia Pestana Knight
Epilepsy Center
Cleveland Clinic
9500 Euclid Avenue, S-5
Cleveland, OH 44195, USA
<pestane@ccf.org>

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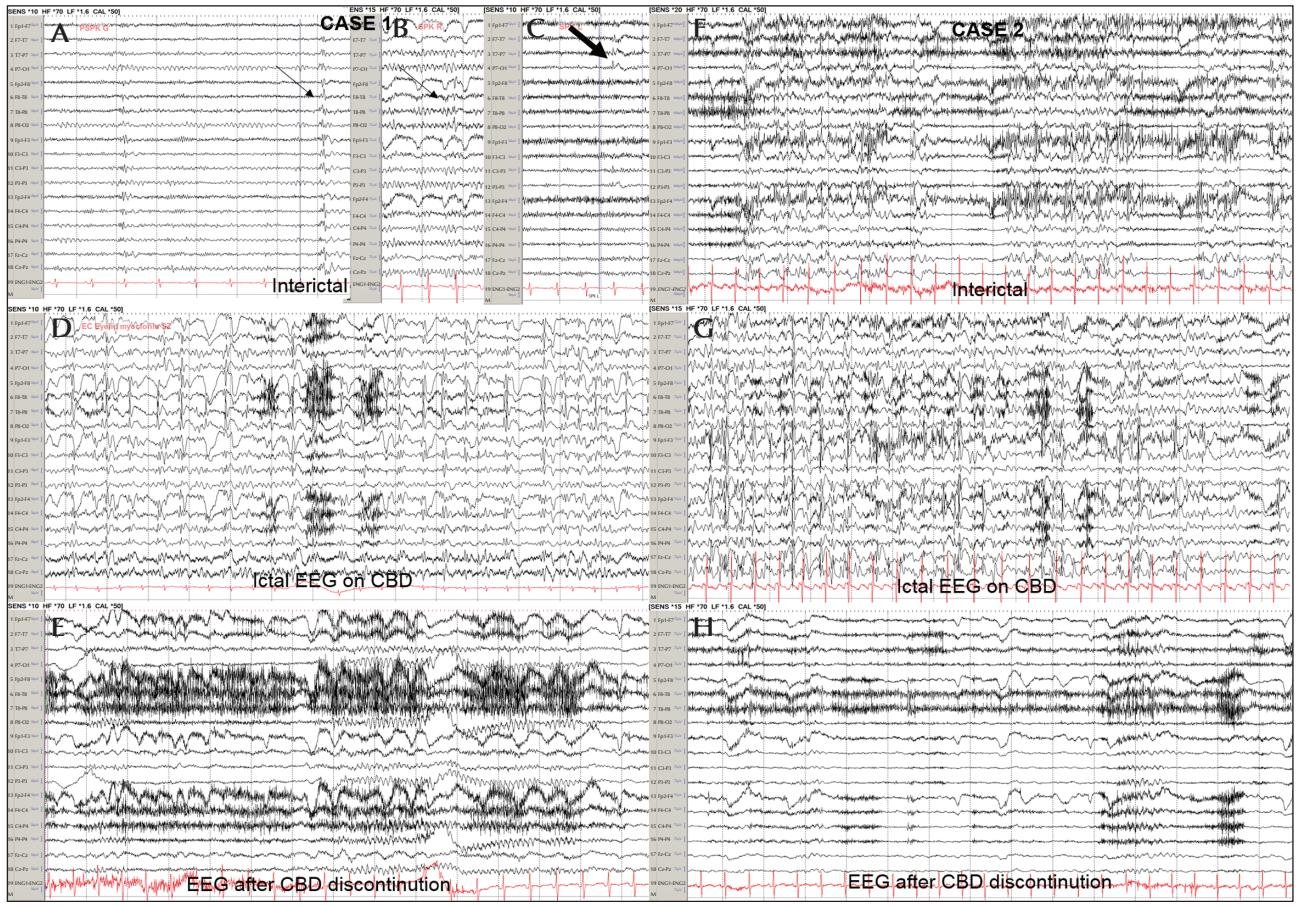
▼ **Table 1.** Baseline clinical characteristics of the patients.

	Case 1	Case 2
Diagnosis	Jeavons Syndrome and focal epilepsy	Jeavons Syndrome
Age at seizure onset	9 years	1 year
Seizure types	Eyelid myoclonia, absence, generalized tonic-clonic seizures, focal unaware seizures	Eyelid myoclonia, absence, Generalized tonic clonic seizures, generalized myoclonic seizures
Seizure frequency	Daily in clusters	Daily eyelid myoclonia. The remaining seizures were occasional.
EEG findings	Generalized spike-wave complexes, polyspikes, right temporal spikes, left posterior temporal spikes, eye-closure sensitivity	Generalized Spike-wave Complexes, Generalized Polyspikes
Brain MRI	Left temporal pole hyperintensity	Normal
Age at the time of presentation	20 years	14 years
Duration of eyelid myoclonia upon awakening or after naps	2-3 hours of near continuous eyelid myoclonia lasting 2-3 seconds every 2-3 seconds recurring 3-4 times per day	6 hours of near continuous eyelid myoclonia each lasting 2-4 seconds every 1-3 seconds upon admission to video-EEG
Family history of epilepsy	None	None
ASMs at the time of presentation	Ethosuximide, clorazepate, rufinamide, acetazolamide, perampanel, cannabidiol oil, depo shots (for peri-menstrual cluster)	Ethosuximide, zonisamide, epidiolex, clonazepam
Prior ASM trials	Lamotrigine (worsened seizures), levetirecetam (depression, mood disorder), zonisamide (partial efficacy), clobazam (ineffective), modified Atkins (lack of efficacy)	Topiramate (weight loss), levetiracetam (severe rage), rufinamide (ineffective), valproate (severe anemia), zonisamide, ketogenic diet 4:1 (worsened seizures)
Genetics	Carrier of 2 *POLG* gene variants in CIS, paternally inherited (VUS), *ZEB2 (*VUS), *NRXN1* (VUS)	One heterogeneous polymorphism/variant reported in *DNA POLG1,* otherwise negative
Birth and development	Normal	Developmental delay
Associated conditions	Generalized anxiety disorder, learning difficulties, hypothyroidism, negative autoimmune epilepsy work-up	Autism

EEG: electroencephalography; MRI: magnetic resonance imaging; ASM: anti-seizure medications; VUS: variant of uncertain significance; NRXN1: neurexin 1; ZEB2: zinc finger e box-binding homeobox 2; POLG1: DNA polymerase subunit gamma; CIS: On the same side.

myoclonia and eye closure sensitivity were seen. Associated EEG demonstrated polyspikes that were maximum posteriorly and runs of left more than right-sided temporal sharp waves elicited by eye closure (*figure 1D*). Interictal EEG showed eye closure-elicited generalized polyspikes, generalized spikes, right posterior temporal polyspikes, temporal spikes (at times in runs) and left temporal spikes. Subjectively, on visual analysis, interictal EEG appeared worse and more frequent interictal spikes and polyspikes were noted when compared to previous video-EEGs prior to CBD initiation.

She was initiated on valproate and later levetiracetam. In addition, perampanel, acetazolamide and rufinamide were weaned off because of a lack of efficacy or side effects. These changes resulted in improvement of other seizure types but did not result in improvement of eyelid myoclonia. CBD oil was eventually



■ **Figure 1.** EEG findings of the patients. (A-E) Case 1. (A) Generalized polyspikes (thin black arrow). (B) Right temporal spike (thin black arrow). (C) Left temporal spike (thick black arrow). (D) Runs of eye closure-elicited eyelid myoclonia are noted with corresponding EEG showing generalized polyspikes, maximum posteriorly, and more predominant on the right than the left. (E) EEG following discontinuation of CBD oil and initiation of levetiracetam. (F-H) Case 2. (F) Note the generalized polyspike discharges elicited by eyelid closure. (G) Abundant seizures characterized by eye closure-induced eyelid myoclonia with corresponding EEG showing generalized polyspikes, maximum in the bilateral frontocentral region. (H) Improvement on EEG noted after epidiolex was tapered off and the initiation of lacosamide. All EEGs are shown in longitudinal bipolar montage.

discontinued. Soon after CBD oil discontinuation, her eyelid myoclonia terminated.

Case 2

A 14-year-old female with JS was admitted to the EMU with poorly controlled seizures. CBD (Epidiolex) had been added to her ASM regimen eight months prior to admission. This improved her absence seizures. However, two months later, she started experiencing "eye fluttering seizures" (*table 1*). CBD was titrated up from 5 mg/kg/day to 10 mg/kg/day. With increasing dose, her daily eyelid myoclonia worsened.

Her video-EEG showed abundant seizures with eyelid myoclonia elicited by eye closure lasting for 3-8 seconds every 5-10 seconds. Associated EEG demonstrated generalized polyspikes that were maximum in the bilateral frontocentral region, frequently in runs (*figure 1G*). Interictal EEG showed frequent generalized polyspikes elicited by eye closure (in runs), maximum over the bifrontocentral region.

Epidiolex was tapered and discontinued with resolution of eyelid myoclonia. Following this, she was loaded with 200 mg of lacosamide and started on 100 mg, twice daily, which improved polyspike frequency on video-EEG (*figure 1H*).

Discussion

Up to 80% of JS patients develop medically refractory epilepsy [2]. The existing literature on ASMs for JS is scarce [2, 3]. In addition to traditionally used medications including valproate, lamotrigine, ethosuximide, levetiracetam, phenobarbital and benzodiazepines, other medications are frequently tried in refractory cases.

Recently, the anti-epileptic property of CBD has attracted attention. Randomized controlled trials of uncontrolled epilepsy have shown CBD efficacy as adjunctive use for Lennox-Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex [4]. Hence, it has been FDA approved for these syndromes. More recently, its off-label use for other epilepsies has increased. The mechanism of action of CBD in epilepsy is unknown. It is thought to affect a multitude of receptors (including CB1 and CB2 cannabinoid receptors) and sodium channels, block T-type calcium channels, act as an agonist on serotonin receptors and an antagonist on GPR-55, modulate adenosine receptor, and affect neurotransmitter transporters and multiple 7-transmembrane receptors [4, 5]. Case reports have described both anti-seizure and pro-seizure effects of CBD [6]. Convulsions with CBD use have been reported [5]. Reports also exist on improvement of post-anoxic myoclonus with CBD [7]. However, the effect of CBD on eyelid myoclonia in JS patients has not been studied.

One of our patients showed an improvement in absence seizures which was possibly due to CBD blockade of T-type calcium channels. However, in both our patients, there was a temporal relationship between the adjunct use of CBD and the exacerbation of eyelid myoclonia which terminated with the weaning of the medication. Therefore, it is possible that this worsening of eyelid myoclonia in our patients was secondary to CBD use. The reason for worsening is unclear. It may be possible that the method by which CBD interacts with some of the other receptors may worsen eyelid myoclonus or alternatively un unknown mechanism may be involved.

The limitation of our findings is that correlation does not necessarily mean causation, especially in epilepsy patients for whom so many variables can influence seizure frequency. Therefore, no definitive statement is possible in the absence of a randomized placebo-controlled study. In addition, an attempt to re-introduce CBD to the anti-seizure medication list, to see if this resulted in worsening of eyelid myoclonia again, was not made for either of the patients. In addition, one of our patients was using artisanal CBD, the exact content of which was not known. Therefore, other constituents such as THC (tetrahydrocannabinol) and/or impurities may have potentially contributed to seizure worsening.

With the increasing utilization of CBD for various epilepsies, these cases highlight potential worsening of eyelid myoclonia in JS. Therefore, CBD should be used with caution in JS patients. Randomized controlled studies with larger sample sizes are needed to better understand the safety of CBD for JS. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors report any conflicts of interest to disclose.

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TEST YOURSELF

(1) What are the three characteristic features of epilepsy with eyelid myoclonia?

(2) What are the target receptors for cannabidiol?

(3) What are the concerns regarding cannabidiol use in patients with epilepsy with eyelid myoclonia?

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