BRIEF COMMUNICATION

Potential Benefit of Add-on Δ9-Tetrahydrocannabinol in Pediatric Drug-Resistant Epilepsy: A Case Series

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ABSTRACT: We present five cases of pediatric drug-resistant epilepsy (DRE) that failed management using high cannabidiol (CBD) doses, but had significant reduction in seizure frequency with reintroduction or increasing doses of tetrahydrocannabinol (THC). There is growing evidence supporting the use of whole-plant CBD-rich extracts (containing THC and other cannabinoids) in the treatment of pediatric DRE. Based on our experiences and reports in the literature, we propose that, in patients who fail management with an initial trial of high-dose CBD-focused therapy, there may be a role for add-on THC-focused formulations.

RÉSUMÉ : Bienfait potentiel de l'adjonction de Δ9-tétrahydrocannabinol (THC) dans le traitement de l'épilepsie résistante aux médicaments chez les enfants : série de cas. Seront exposés dans l'article cinq cas d'épilepsie résistante aux médicaments (ERM) chez des enfants qui se sont montrés réfractaires à l'administration de fortes doses de cannabidiol (CBD) mais chez qui la reprise ou l'augmentation des doses de THC ont permis une réduction importante de la fréquence des crises d'épilepsie. De plus en plus de données probantes étayent l'emploi d'extraits de plantes entières, riches en CBD (contenant du THC et d'autres cannabinoïdes) dans le traitement de l'ERM chez les enfants. D'après l'expérience des auteurs et la documentation médicale, il y aurait lieu d'adjoindre des préparations contenant du THC chez les patients qui se montrent réfractaires à un essai initial de CBD seul, à forte dose.

Keywords: Cannabis, THC, CBD, Pediatric epilepsy

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Drug-resistant epilepsy (DRE) affects approximately 30% of people with epilepsy, with failure to control seizures being especially harmful to children[1]. Recently, cannabis has emerged as a promising treatment for DRE. The anticonvulsant effects of cannabidiol (CBD) have been reported in randomized control trials (RCTs), leading to the approval of the first cannabis-derived drug, Epidiolex©[2], which is 99% pure CBD. Other studies investigating CBD-rich extracts, where tetrahydrocannabinol (THC) and other cannabinoids are present in significant amounts, have also shown promising results[3,4]. However, the focus in these studies was on titrating CBD and minimizing the amount of THC exposure. High-quality evidence is lacking to support a role for THC alongside CBD in the treatment of DRE, and there is conflicting data regarding the role of THC as an antiseizure substance. We report our experience with add-on THC-focused cannabis formulations in five patients and discuss its relevance as a potential adjunctive therapy in poorly controlled pediatric DRE.

Case 1: A previously healthy 4-year-old female who developed drug-resistant, focal seizures. She presented at 2 years of age with tonic seizures (at least 5 per day, lasting 10–30 s). EEG showed epileptiform discharges in the right frontal and bilateral central regions (Figure 1). She was trialed on multiple AEDs without success including levetiracetam, valproic acid, and topiramate. She developed significant balance and coordination difficulties. Workup including brain MRI, MRI spine, metabolic testing, and genetic studies were noncontributory. One year after onset of seizures, she was started on an orally administered CBD-rich extract of 1:25 THC:CBD which was titrated up to 10 mg/kg/day of CBD (corresponding THC dose of 0.4 mg/kg/day). One

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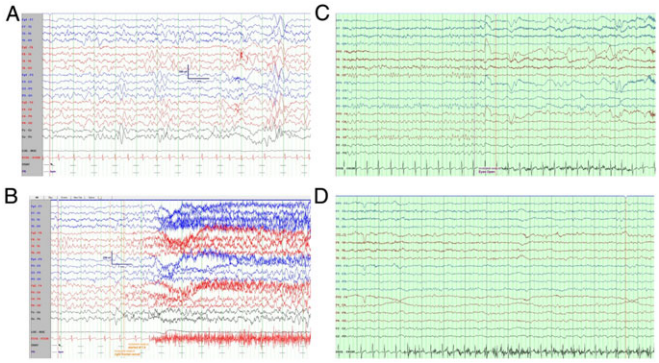

Figure 1: *AP bipolar EEG montages from Case 1, (A-B) during period of frequent breakthrough seizures (pre add-on THC) and (C-D) during period of seizure freedom post add-on THC. (A) shows interictal epileptiform discharges over bilateral central regions and right frontal region, and a brief interval of diffuse spike wave discharges. (B) demonstrates a captured electroclinical seizure starting from the right frontal-central region, with clinical correlate consisting of tonic stiffening. (C-D) shows normalization of the EEG, with resolution of interictal abnormalities and symmetric background.*

week after initiation of cannabis, she became seizure-free, development normalized, neurological deficits resolved, and EEG showed resolution of previous epileptiform activity and became normal (Figure 1); all other AEDs were weaned and discontinued.

She remained free of seizures for one year then developed breakthrough seizures and recurrence of her encephalopathic picture. Parents abruptly discontinued cannabis and she was slowly re-titrated up to 5.3 mg/kg/day CBD with a corresponding THC dose of 0.1 mg/kg/day, without significant effect on seizures. Instead of continuing to titrate CBD, THC was added at night (dose of 0.1 mg/kg), to reach a total THC dose of 0.2 mg/kg/day. Briefly following this adjustment, without any other interventions, the patient became seizure free once again and repeat EEG demonstrated complete normalization.

Case 2: A 12-year-old female who was referred due to uncontrolled seizures on carbamazepine. At the time, she was suffering from multiple left focal sensorimotor seizures occurring daily. She also had generalized tonic clonic seizures (GTCs), occurring daily to once every few weeks, disabling fatigue, and academic difficulties. Her workup revealed an unremarkable 3T MRI and PET scan. EEG showed right frontal-central interictal discharges. Seizures captured on EEG appeared as runs of rhythmic spikes from central sagittal and vertex regions.

She was trialed on multiple other AEDs without good effect. While on clobazam and lamotrigine, she was started on an orally administered CBD-rich extract (1:25 THC:CBD) at 5 mg/kg/day of CBD and titrated to 12.5 mg/kg/day (corresponding THC dose of 0.5mg/kg/day). She had no further GTCs and had infrequent focal seizures, with seizure freedom for up to 8 weeks at a time. Her energy improved, she started attending school again, and her repeat EEG normalized.

Due to cost concerns, she was switched to purified CBD (containing no THC), without altering her other AEDs, and was titrated to 20 mg/kg/day. She subsequently developed increased seizure frequency, fatigue, and mood fluctuations. She was ultimately switched back to a CBD-rich extract (1.44:23.4 THC:CBD) at 8.64 mg/kg/day of CBD (corresponding THC dose of 0.53 mg/kg/day) with the purpose of reintroducing THC. Her dosing was adjusted to three times daily, with a higher dose at nighttime, and she became seizure free.

Other Cases: We describe three cases who were initially treated with CBD-rich extracts but developed seizure recurrence. In all cases, families pursued high THC formulations through their local dispensary. Details regarding dosing, timing, and titration of cannabis formulations acquired through dispensaries are unavailable.

The first case is a 4-year-old male who first experienced epileptic spasms at 4 months with hypsarrhythmia on EEG. He was found to have simplified gyri on MRI and SPTAN1 mutation. He then started experiencing daily focal seizures and multiple AEDs were ineffective. At age 3, he began 2 mg/kg/day of 1:20 THC:CBD oil (administered orally) which was titrated to 3.2 mg/kg/day of CBD (corresponding THC dose of 0.16 mg/kg/day) with good effect. Unfortunately, focal seizures recurred. The patient was weaned from the oil but then started taking THC:CBD suppositories twice daily, of varying ratios (1:1 or 1:0 THC:CBD). This stabilized his seizure frequency to one seizure every 3–4 d.

Next, a 13-year-old girl suffered from drug-resistant focal seizures, epileptic spasms, and GTCs for 11 years. Various AED combinations and ketogenic diet failed to achieve lasting seizure control. By age 10, she was experiencing up to 15 seizures per night and subsequently began 2mg/kg/day of 1:20 THC:CBD oil administered orally. Despite an initial positive response, daytime and nocturnal tonic seizures re-occurred. Through a local dispensary, she began taking 1:0 THC:CBD suppositories, with reports of seizure reduction by 50%.

Last, a 5-year-old male, ex-27-weeker, who had epilepsy secondary to bilateral periventricular/intraventricular hemorrhages. He began having right focal seizures and spasms at 3 months. By age 3, he failed the ketogenic diet and multiple AEDs. His parents independently tried orally administered CBD-rich extracts (1:20 THC:CBD) through a dispensary which reduced seizures from 30 per day to fewer than 10 per week. Over time, the patient had increasing frequency of seizures and 1:1 THC:CBD suppositories were introduced. The patient became seizure-free and his other AEDs were weaned.

We present five cases of DRE that failed management focused on achieving high CBD doses, but who had reduction in seizure frequency with reintroduction or increasing doses of THC. These cases bring forward the need for investigating the role of THC in pediatric seizure management.

Animal studies have shown that THC has antiepileptogenic properties; however, there is variability in the effect between different animal models which has made clinical application difficult[6]. We now know that THC plays an important role in the modulation of neuronal excitability, through its effects on the endocannabinoid system.

Clinical evidence for medical cannabis as a therapeutic agent in DRE has focused on purified CBD (Epidiolex©) which is now approved in the USA for tuberous sclerosis (TSC), Lennox Gastaut syndrome (LGS), and Dravet syndrome. In Europe, it is approved for LGS and Dravet syndrome only with concomitant use of clobazam. RCTs have shown significant reductions in seizures with doses ranging between 10 and 50 mg/kg/day. With higher doses, common side effects such as somnolence, diarrhea, decreased appetite, and fatigue were described[2].

There are a growing number of reports suggesting that cannabis extracts may be more effective in the treatment of

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seizures when compared to purified cannabinoids[5]. The phenomenon described in preclinical studies is the entourage effect, where the pharmacological effects of all cannabinoids combined in the whole plant extract are superior to the effect of any individual cannabinoid alone[6]. The interpretation of preclinical work on THC is complicated by the fact that different studies have found both pro- and anticonvulsant effects of THC[7]. Although there is some evidence that this effect occurs through the CB1/CB2 receptors, it is likely that this effect can be mediated or enhanced through different, indirect pathways[8].

It has been brought to light that patient caregivers are independently dosing cannabis extracts in the hope of better managing their children's epilepsy. In a study looking at parental reports of formulations that have been rated as effective, it was noticed that most formulations rated as effective contained THC[9]. Prospective open-label studies have examined the effect of CBD-rich extracts containing THC and have shown significant reduction in seizure frequency and improvements in quality of life in patients with DRE. A recent meta-analysis concluded that patients taking CBD-rich extracts (containing THC) reported better seizure control (71% vs 46%) and fewer side effects compared to those taking purified CBD[10].

Without disregarding possible adverse long-term effects, it would seem that THC-containing cannabis formulations, specifically from whole plant extracts, could be beneficial for certain DRE cases. The use of add-on THC focused formulations to pure CBD regimens may be beneficial and should be considered in patients with severe epilepsy who fail management with an initial trial of high dose, CBD-exclusive therapy (up to 20 mg/kg/day CBD). Furthermore, we are seeing increasing numbers of families obtaining cannabis through local dispensaries. Consultation from a neurologist would be beneficial to guide dosing, observe for efficacy, and monitor adverse events (such as the cognitive effects of THC) in a controlled setting. For this reason, we suggest that there is an unfilled need for rigorous well-designed trials of THC-containing cannabis formulations in the treatment of pediatric, drug-resistant epilepsy.

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Statement of Authorship

MN: Conception, data collection, and interpretation of Toronto cases, primary article drafting, and final approval of the version to be published.

PLD and EL: Design of the work, critical revision of the article, and final approval of the version to be published.

SB-T: Conception, data collection and interpretation of Montreal cases, article drafting, and final approval of the version to be published.

AGW, JB, P-OC and NTS: Interpretation of clinical data of Montreal cases, article drafting, and final approval of the published version.

ES and PM: Provided clinical expertise regarding Montreal cases and final approval of the version of to be published.

FOH: Provided information and expertise regarding dispensary preparations and final approval of the version to be published.

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