Pediatric Neurology 52 (2015) 544–547

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Pure Cannabidiol in the Treatment of Malignant Migrating Partial Seizures in Infancy: A Case Report

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ABSTRACT

BACKGROUND: Malignant migrating partial seizures in infancy is a devastating pharmacoresistent epileptic encephalopathy of unknown etiology characterized by onset in the first 6 months of life, continuous migrating focal seizures with corresponding multifocal electroencephalographic discharges, developmental deterioration, and early mortality. Recent widespread interest in the nonpsychoactive component of the cannabis plant, cannabidiol, as a potential treatment for refractory devastating epilepsies has led to individual trials initiated by families or physicians in states that have legalized medical marijuana with anecdotal success. **PATIENT DESCRIPTION:** We describe a now 10-month-old boy with malignant migrating partial seizures in infancy who made developmental gains and demonstrated sustained seizure reduction with the addition of cannabidiol to his antiepileptic regimen. **CONCLUSION:** This report supports a role for cannabidiol in the treatment of malignant migrating partial seizures in infancy.

Keywords: migrating partial seizures, malignant migrating partial epilepsy, CBD, cannabidiol, ketogenic diet

Pediatr Neurol 2015; 52: 544-547

Introduction

Malignant migrating partial seizures in infancy (MMPSI) is a devastating pharmacoresistent epileptic encephalopathy of unknown etiology characterized by onset in the first 6 months of life, continuous migrating focal seizures with corresponding multifocal electroencephalography (EEG) discharges, developmental deterioration, and increased early mortality.

Medications with reported benefit in individuals with MMPSA, either alone or in combination, include levetiracetam, valproic acid, benzodiazepines, stiripentol, bromides, rufinamide, and possibly a ketogenic diet.[1-4]

Cannabinoids have recently gained attention in the treatment of devastating childhood epilepsies with anecdotal success in individual trials of children with Dravet syndrome and Lennox-Gastaut syndrome.[5,6] There are no reports of the use of cannabinoids in the treatment of MMPSI.

We describe a 10-month-old boy with MMPSI who made developmental gains and demonstrated sustained seizure reduction with the addition of cannabidiol to his antiepileptic regimen.

Patient Description

This boy was born at 39 weeks' gestation to a 25-year-old primigravid mother via emergency Cesarean section resulting from failed vacuum extraction. Apgar scores were 8 at 1 minute and 9 at 5 minutes.

Periods of apnea and desaturation on his first day of life were confirmed to be seizures originating from the left posterior region on video EEG monitoring. Evaluation for infection including cerebrospinal fluid for herpes simplex virus polymerase chain reaction was normal. Other normal investigations included echocardiogram, head ultrasound and head magnetic resonance imaging, urine organic acids, plasma amino acids, cerebrospinal fluid for glucose, amino acid, neurotransmitters, and redox panel. Genetic testing (infantile epilepsy panel (Gene Dx, MD) and chromosome microarray were normal.

He was treated with phenobarbital but required frequent boluses to achieve seizure control. He was discharged from the neonatal intensive care unit on day 27 of life on phenobarbital and levetiracetam but continued to have breakthrough seizures.

Article History:
Received December 12, 2014; Accepted in final form February 11, 2015

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http://dx.doi.org/10.1016/j.pediatrneurol.2015.02.008

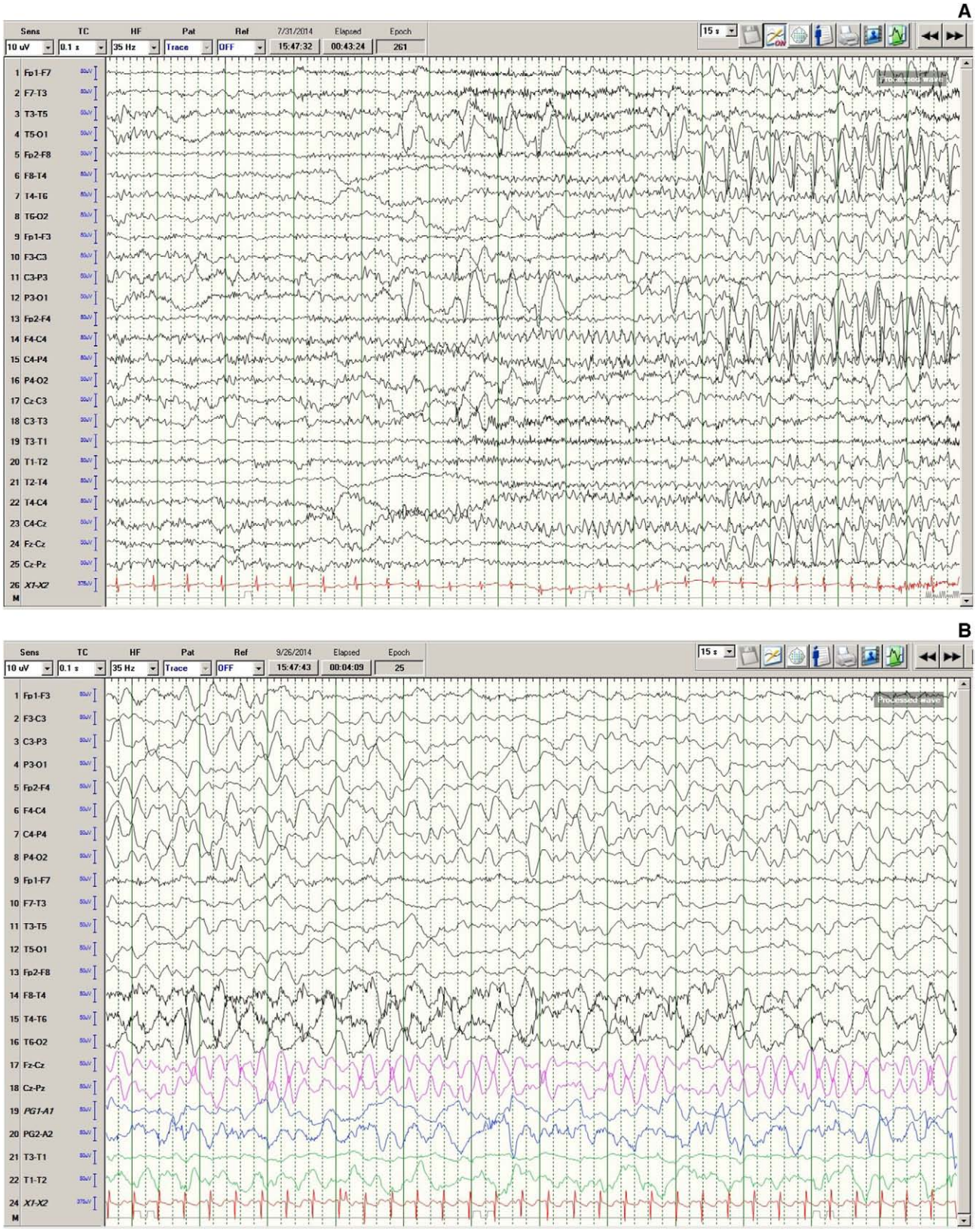

FIGURE.
(A) EEG at 4 months of age with seizure showing electrodecrement in the first 4 seconds, followed by the left occipital sharp waves then by a new seizure in the right frontotemporal region. (B) Follow-up EEG 2 months after start of cannabidiol showing slow background for age and background asymmetry with right posterior quadrant slowing but no ongoing seizure activity. (The color version of this figure is available in the online edition.)

By 2 months of age, he had developed two additional clinical seizure types: tonic spells with generalized stiffening and shaking and spells of rightward eye rolling and unresponsiveness. Carbamazepine was unsuccessful and was replaced by daily clonazepam.

By 3.5 months of age, he was drowsy with significant axial and appendicular hypotonia and absent vocalization, smiling, visual fixation, or tracking. A repeat video EEG showed continuous independent multifocal seizures consistent with the diagnosis of MMPSI.

He received bolus intravenous levetiracetam (40 mg/kg), fosphenytoin (20 mg/kg), and topiramate (2 mg/kg) for migrating partial status epilepticus. Intravenous pyridoxine challenge of 100 mg was ineffective. A stiripentol trial resulted in a dramatic increase in seizure frequency and was interrupted.

Ketogenic diet was initiated at 4 months of age with 3.5:1 ketogenic formula, but he returned 2 weeks later with nearly continuous electrical and clinical seizures involving desaturation and encephalopathy and requiring nasogastric tube placement (Figure A). Given the continued deterioration and his parents' interest in a cannabidiol trial, we obtained local institutional review board and Food and Drug Administration approval for emergency use of pure cannabidiol (CBD; also called Epidiolex, GW Pharma UK) and started oral CBD 25 mg/mL at 10 mg/kg/day divided twice daily. Dose was increased to goal of 25 mg/kg/day divided twice daily over 15 days with no observed side effects (standardized protocol per sponsor). During the first week after initiation of CBD, he became more alert and was able to maintain oral nutrition. By the second week, his parents described him as a "new baby."

Six months after initiation of CBD, he remains on levetiracetam (80 mg/kg/day) and daily clonazepam (0.5 mg at bedtime). His parents discontinued the ketogenic diet on their own by initiating baby foods when he was 7 months old. His seizure frequency decreased from 10-20 per day to 5 per week with up to 9 days of clinical seizure freedom. His EEG continues to show generalized slowing with right occipital epileptiform abnormalities, but no subclinical seizures (Figure B). He is now alert during the day, opens his eyes, looks, and tracks briefly. He reaches for nearby objects with his left arm, coos, and smiles. His head circumference continues to grow along the 85th percentile.

Discussion

This child fulfilled the clinical and electrical criteria for MMPSI, including initial partial seizures with multifocal interictal epileptiform EEG followed by polymorphous partial seizures evolving to nearly continuous seizures involving multiple independent areas of both hemispheres and developmental arrest.[7]

Three phases have been identified in the natural history of this syndrome. The initial phase is between the first week of life and about 7 months of age, during which seizures are sporadic, occurring at weekly to monthly intervals. Seizures are usually focal motor with or without secondary generalization, and autonomic manifestations such as apnea and flushing are frequent. Interictal EEG shows diffusely slowed background with multifocal discharges. During the second phase or "stormy phase" (between 3 weeks and 10 months), seizures become polymorphous with daily clusters or are almost continuous over days to weeks. Hypotonia, lethargy, feeding difficulty, absence of visual response, and loss of skills but with some improvement in mental status between seizure clusters. Seizure control during this phase may improve development.[8,9] EEG shows hallmark focal migrating discharges involving independent areas in the same or opposite hemisphere simultaneously or in sequence. Seizures quiet down during the third phase (from 1 to 5 years), but clusters or status epilepticus are triggered by intercurrent illnesses. By that time, most children have severe developmental delay and acquired microcephaly. Mortality is increased because of status epilepticus and respiratory failure.[1]

Our patient's progression was successfully halted during the stormy phase with interruption of nearly continuous migrating seizures; developmental gains and continued normal head circumference growth resumed shortly after initiation of CBD.

His seizures proved refractory to traditional antiepileptic drugs. We tried all the medications reported to be useful in MMPSI.[1-4] Phenobarbital boluses were beneficial initially, but seizure control was unsustained on maintenance dosing. Clonazepam decreased clinical seizure frequency but caused excessive sedation. Stiripentol exacerbated clinical seizures. Rufinamide is approved in the United States only for children older than age 4 years with the Lennox-Gastaut syndrome[10] and was therefore denied by insurance. We could not procure potassium bromide at our hospital. Ketogenic diet was started at 4 months of age with documented ketosis but continued worsening seizures. We added CBD 2 weeks later when our patient was seizing continuously with frequent desaturation, encephalopathy, and inability to maintain oral nutrition.

Because patients who are most likely to respond to the ketogenic diet typically do so within the first 14 days,[11] it is not unreasonable to speculate that CBD had an antiepileptic effect in our patient, in conjunction with or independently of continued ketosis. This is further supported by his sustained decrease in seizure burden and his slow but steady developmental gains 5 months after initiation of CBD and 3 months after discontinuation of the diet.

The exact mechanism of action of CBD, the major nonpsychoactive component of cannabis, in epilepsy remains unknown. It has been shown to have an antiepileptic effect in animal models of acute epilepsy[12,13] and reports of patients with Dravet syndrome improving with high cannabidiol content preparations are encouraging.[5,6] Although MMPSI is genetically heterogenous,[14] some patients are reported to have SCN1A mutation—also found in Dravet syndrome.[15,16] Our patient was SCN1A negative.

The ideal dose, tolerability, and time to improvement with CBD have not been established. Most patients have responded to 200-300 mg per day of CBD.[17] We dosed our patient twice a day by mouth per the protocol provided by the sponsor. He responded to a total dose of 150 mg per day and did not exhibit sedation, vomiting, or diarrhea.[17]

This patient suggests that cannabidiol may be beneficial as an adjunctive medication in controlling seizures and improving developmental outcome in MMPSI. The data for patients who used CBD in the expanded access program through GW Pharma are being analyzed, but there are no reports of the use of CBD for MMPSI.

Further research is needed to determine whether CBD is beneficial in devastating epileptic encephalopathy.

References

1. Coppola G. Malignant migrating partial seizures in infancy. *Handb Clin Neurol*. 2013;111:605-609.
2. Djuric M, Kravljanac R, Kovacevic G, Martic J. The efficacy of bromides, stiripentol and levetiracetam in two patients with malignant migrating partial seizures in infancy. *Epileptic Disord*. 2011;13:22-26.

3. Vendrame M, Annapurna P, Loddenkepmer T, Kluger G, Coppola G, Kothare V. Treatment of malignant migrating partial epilepsy of infancy with rufinamide: report of five cases. *Epileptic Disord*. 2011; 13:18-21.
4. François LL, Manel V, Rousselle C, David M. Ketogenic regime as anti- epileptic treatment: its use in 29 epileptic children. *Arch Pediatr*. 2003;10:300-306.
5. Maa E, Figi P. The case for medical marijuana in epilepsy. *Epilepsia*. 2014;55:783-786.
6. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav*. 2013;29:574-577.
7. Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. *Epilepsia*. 1995;36:1017-1024.
8. Caraballo RH, Fontana E, Darra F, et al. Migrating focal seizures in infancy: analysis of the electroclinical patterns in 17 patients. *J Child Neurol*. 2008;29:497-506.
9. Marsh E, Melamed SE, Barron T, Clancy RR. Migrating partial seizures in infancy: expanding the phenotype of a rare seizure syndrome. *Epilepsia*. 2005;46:568-572.
10. Wier HA, Cerna A, So TY. Rufinamide for pediatric patients with Lennox-Gastaut syndrome: a comprehensive overview. *Paediatr Drugs*. 2011;13:97-106.
11. Kossoff EH, Laux LC, Blackford R, et al. When do seizures usually improve with the ketogenic diet? *Epilepsia*. 2008;49:329-333.
12. Robson PJ. Therapeutic potential of cannabinoid medicines. *Drug Test Anal*. 2014;6:24-30.
13. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55:791-802.
14. Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology. *Epilepsia*. 2009;50: 49-51.
15. Carranza Rojo D, Hamiwka L, McMahon JM, et al. De novo SCN1A mutations in migrating partial seizures of infancy. *Neurology*. 2011; 77:380-383.
16. Freilich ER, Jones JM, Gaillard WD, et al. Novel SCN1A mutation in a proband with malignant migrating partial seizures of infancy. *Arch Neurol*. 2011;68:665-671.
17. Gloss D, Vickrey B. Cannabinoids for epilepsy. *Cochrane Database Syst Rev*. 2014;3:CD009270.