Seizure: European Journal of Epilepsy 92 (2021) 238–243

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

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

Cannabidiol-enriched medical cannabis as add-on therapy in children with treatment-resistant West syndrome: A study of eight patients

Roberto Caraballo *, Gabriela Reyes Valenzuela

Neurology Department, Centro de Epilepsia (CEBA), Avenida Callao 1103, Combate de los Pozos 1881, Buenos Aires, Argentina

ARTICLE INFO

Keywords:
Antiseizure medication
Cannabidiol
Epileptic spasms
Treatment-resistant
West syndrome

ABSTRACT

Objective: Here we present a series of patients with WS that were refractory to antiseizure medications and the ketogenic diet and who were treated with cannabidiol-enriched cannabis oil (CBD) as add-on therapy analyzing efficacy, safety, and tolerability.

Material and methods: Medical records of eight patients with WS treated with CBD at a ratio of cannabidiol:Δ-9-tetrahydrocannabinol (CBD:THC) of 25:1 seen between May 2020 and March 2021 were retrospectively analyzed. In all patients CBD was started as add-on therapy.

Results: Eight patients (six female and two male) who received CBD for treatment-resistant WS were evaluated. Ages ranged from 16 to 22 months. The etiology was unknown in five and structural in three. Initial CBD dose was 2 mg/kg/day which was uptitrated to a median dose of 12 mg/kg/day (range, 2–25). Prior to CBD initiation, patients had a mean of 63 seizures per day (range, 31–79). After a follow-up of between 6 and 13 months, a 75–99% decrease in seizure frequency was observed in two patients, a 50–74% decrease in two, a less than 50% decrease in three, and no changes in seizure frequency were seen in the remaining patient. The index of EEG abnormalities improved between 20 and 80% in seven patients concurrently with the reduction in seizures. Adverse effects were mild and transient. Somnolence was observed in one patient, nausea and vomiting in one, and behavior disturbances and irritability in another patient.

Conclusion: This study evaluating the use of cannabidiol-enriched cannabis oil in children with WS showed that four (50%) of eight had a more than 50% seizure reduction with good tolerability.

1. Introduction

West Syndrome (WS) is an epileptic encephalopathy characterized by epileptic spasms (ES) in clusters, an EEG pattern of hypsarrhythmia in most of the cases, and developmental arrest or regression. The etiology of WS may be either genetic, infectious, metabolic, immune, or unknown as defined in the latest classification of the International League against Epilepsy (ILAE) [1]. The prognosis of WS regarding seizures, response to treatment, and cognitive development is variable [2].

In more than 70% of infants with WS an etiologic diagnosis can be identified which may lead to early initiation of a specific therapy possibly improving developmental outcome in the long term [3]. Hormone therapy with adrenocorticotropic hormone (ACTH) and prednisolone and vigabatrin (VGB) are the first-line treatment for WS. Unfortunately, only around 25% of children with WS become seizure free and have normal (or near-normal) intellectual outcomes. The remaining children are at risk of developing intellectual disability and treatment-resistant seizures that often evolve to other epilepsy syndromes [4].

Over the past years, cannabidiol (CBD), a non-psychoactive derivative of the cannabis plant, has been used as a last resort for epilepsy patients who do not respond to other treatments. There is increasing evidence that CBD is a safe, and effective add-on therapy for patients with Dravet [5] and Lennox–Gastaut syndrome (LGS) [6,7] as well as other treatment-resistant epilepsies [8–10].

Since in previous studies CBD was found to be effective in children with LGS [6,7] and particularly in those with LGS preceded by WS [11], we hypothesized that patients with refractory WS may be good candidates for treatment with CBD. Recently, a multicenter phase-2 study in patients with refractory WS treated with synthetic pharmaceutical grade CBD has been conducted [12].

Here we present a series of patients with WS refractory to antiseizure medications (ASM) and the ketogenic diet (KD) who were treated with CBD-enriched cannabis oil as add-on therapy analyzing efficacy, safety,

* Corresponding author.
E-mail address: rhcaraballo@arnet.com.ar (R. Caraballo).

https://doi.org/10.1016/j.seizure.2021.10.002
Received 21 July 2021; Received in revised form 15 September 2021; Accepted 2 October 2021
Available online 3 October 2021

and tolerability.

2. Material and methods

Medical records of eight patients with WS treated with CBD seen at a private epilepsy center between May 2020 and March 2021 were retrospectively analyzed. In all patients CBD was started as add-on therapy.

The inclusion criteria were: (1) Infants aged 6 to 24 months, (2) a diagnosis of WS according to the ILAE classification of seizures and epilepsy syndromes [1], and (3) unresponsiveness to ACTH, corticosteroid therapy, and VGB, alone or in combination, and/or to other ASM, and the KD. Infants with ES in clusters without hypsarrhythmia were excluded.

Eligible patients were treated with a standardized plant extract of cannabis (Rideau® oral cannabidiol solution) with a CBD: Δ−9-tetrahydrocannabinol (THC) ratio of 25:1 diluted into medium-chain triglyceride oil provided by the Canadian laboratory Aphria. To ensure a consistent potency of the oil, quality and production steps were used. Analytical results within the specification range defined for the input material, in-process control, and finished product. The manufacturing process was validated to ensure consistency of each step and for the product to meet all required specifications. The resulting end product was tested by quality control. In addition, stability studies were performed to ensure that shelf life was within the specification range. The product was evaluated and approved by Health Canada and the Argentine national drug control agency (ANMAT).

The initial CBD dose was 2 mg/kg/day given twice daily. The dose was gradually increased during two-weekly office visits up to a maximum of 25 mg/kg/day until response and as long as the drug was well tolerated. Follow-up visits were monthly thereafter.

After CBD initiation, the ASM the patients were receiving were not modified and no other pharmacological or non-pharmacological treatments were added. At CBD initiation, the patients were receiving a mean of five ASM (range, 4–7). The month previous to CBD initiation was considered as the baseline period for comparison.

Physical and neurological examinations and laboratory studies as well as seizure frequency, type, and duration were assessed. The seizures were classified according to the Revised Classification of Seizures of the ILAE [13]. The ES were recorded in a seizure diary by the parents or caregivers of the patients and the association with other types of seizure was also considered. Improvements on the EEG were evaluated by the treating neurologist (RC).

A prolonged video-EEG of at least 6 h during sleep and while awake was performed at treatment initiation and regularly afterwards. EEG studies were compared to identify changes on the EEG before and after CBD was started. The epileptiform discharges were quantified considering the index of EEG abnormalities, including spikes, spikes and waves, polyspikes, slow waves, and voltage attenuation, including the presence, disappearance, or modification of the hypsarrhythmia pattern. The EEG abnormalities index was calculated during sleep and while awake in an EEG recording lasting one hour. Single epileptiform discharges as well as discharges with epileptic events that occurred over a longer period were counted separately.

The efficacy of CBD was evaluated comparing seizure frequency before starting treatment and after, and response was defined as (1) seizure freedom, (2) a 75%–99% decrease in seizure frequency, (3) a 50–74% decrease in seizure frequency, (4) a less than 50% decrease in seizure frequency, (5) no change, and (6) increase in seizure frequency. A seizure reduction of $\geq$ 50% was considered a good response.

Adverse effects, recorded at each follow-up visit, were also evaluated.

The study was approved by the ethics committee and a written informed consent form was signed by the caregivers of all the patients.

3. Results

3.1. General characteristics

Overall, eight patients (6 female and 2 male) who received CBD-enriched cannabis oil for treatment-resistant WS were evaluated. Mean age was 17 months (range, 10 to 22 months). The etiology was unknown in five and structural in three. Initial CBD dose was 2 mg/kg/day which was uptitrated to a median dose of 12 mg/kg/day (range, 4–25). None of the patients received concomitant clobazam. Mean follow-up was 9.5 months (range, 6 to 13 months).

Prior to CBD initiation, patients had a mean of 63 ES per day (range, 31–79) and of six focal seizures per week (range, 2–10), respectively. One patient had status epilepticus of ES lasting for 16 h (Fig. 1A and B). In this patient, who had Aicardi syndrome, the interictal EEG recording during sleep showed hypsarrhythmia alternating between one hemisphere and the other (Fig. 2). The EEG recording during sleep did not show paroxysmal abnormalities, except for background activity consisting of “alpha-like” rhythms in the left hemisphere and bilateral slow waves (Fig. 3).

3.2. Efficacy

After a follow-up of between 6 and 13 months, a 75–99% decrease in seizure frequency was observed in two patients, a 50–74% decrease in two, a less than 50% decrease in three, and no changes in seizure frequency were seen in the remaining patient. The ages of the four patients who responded were 12, 13, 14, and 15 months, respectively. None of the patients became seizure free and in none of the patients the seizure frequency increased. The index of EEG abnormalities improved between 20 and 80% in seven patients concurrently with the seizure reduction; in three of four patients who had a more than 50% response, the hypsarrhythmia pattern disappeared. In the remaining patient, the pattern of hypsarrhythmia was modified. In the four non-responders, hypsarrhythmia remained unchanged. In one (12.5%) patient CBD was discontinued after a period of 6 months because no changes in the seizure frequency and EEG abnormalities were observed.

All patients received corticosteroid therapy; ACTH was given in seven patients and oral corticosteroids in one. In addition, eight patients received vigabatrin, associated with corticosteroids in four of them. Furthermore, topiramate was given in five, valproic acid in five, levetiracetam in five, zonisamide in three, rufinamide in three, lamotrigine in two, and sulthiame in two patients. The ketogenic diet was tried in all eight patients.

3.3. Adverse effects

Adverse effects were mild and transient. Somnolence was observed in one patient, nausea and vomiting in one, and behavior disturbances and irritability in another patient. Liver enzymes were not found to be increased in any of the patients. In none of the patients CBD was discontinued due to severe adverse events.

Table 1 lists the etiology, seizure reduction, and improvement of the EEG features in our series of eight patients with WS.

3.4. Follow-up

In all seven patients who continued on CBD, efficacy was maintained over a mean follow-up of 9.5 months. Four of eight patients (50%) had a greater than 50% decrease in seizures and in two patients with a seizure reduction of less than 50%, communication and sleep patterns improved.

4. Discussion

Over the past decade, CBD has been increasingly used as a last-line

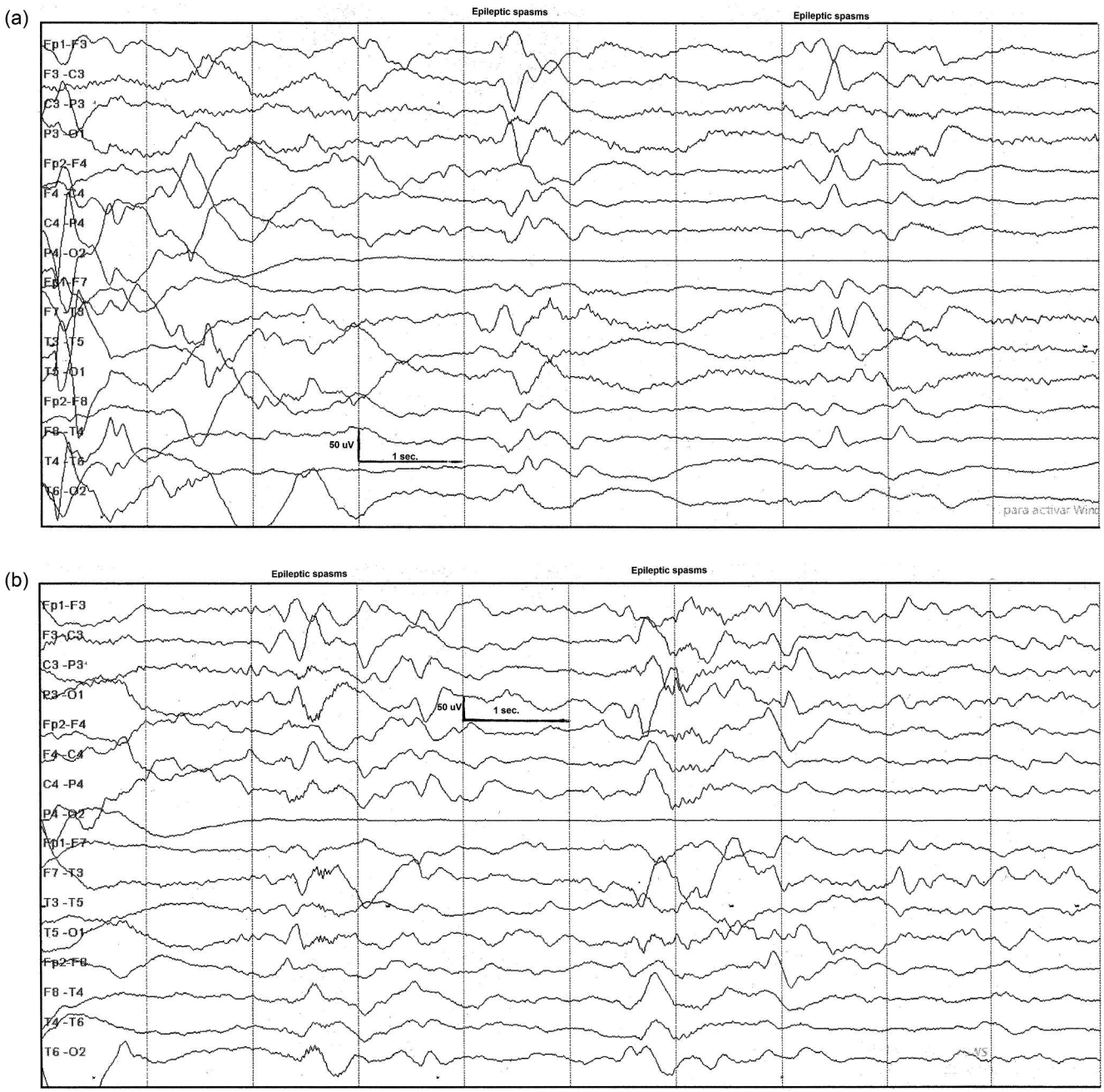

Fig. 1. A 13-month-old girl with Aicardi syndrome. The EEG recording shows repetitive epileptic spasms associated with diffuse slow waves in clusters during status epilepticus 30 min after ES onset. Fig. 1B: The EEG recording of the same patient shows status epilepticus of ES associated with diffuse slow waves 3 h after onset.

option for patients with treatment-resistant epilepsy, particularly epileptic encephalopathies. A good response to purified CBD was found in patients with Dravet syndrome [5] and LGS [6,7] and specific etiologies, such as CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes [8–10].

Here we report our preliminary findings regarding efficacy and tolerability of CBD added to ASM in a group of eight patients with treatment-resistant WS. Four (50%) of eight patients had a more than 50% seizure decrease, of whom two had a 75–90% decrease in seizures; therefore, response was considered to be good in these four cases. CBD was started between 6 and 14 months after initiation of the first-line treatment.

In our previous study evaluating patients with treatment-resistant encephalopathies treated with add-on CBD-enriched cannabis oil [11], 38 patients had LGS of whom 29 (76.3%) were responders with a more than 50% seizure decrease. Twenty-four of 38 patients previously had WS. Of this subgroup of 24 patients, 18 (75%) had a more than 50% seizure reduction. Interestingly, two of these patients had Aicardi syndrome and two lissencephaly, all four of whom had a more than 75% decrease in seizures. Our patient with Aicardi syndrome in the present study had a 75–90% improvement in seizure frequency. In the study by Devinsky et al. [9], in the subgroup of 19 patients with Aicardi syndrome 71% had $a \geq 50\%$ response to purified CBD. These findings suggest that patients with treatment-resistant WS secondary to severe malformations of cortical development and Aicardi syndrome may respond well to CBD.

In an open-label investigational-new-drug study, Herlopian et al. [14] enrolled nine patients with refractory ES in addition to other seizure types. Response of the ES to purified pharmaceutical CBD was good, with a success rate in attaining ES freedom of 33% at two weeks and 56% at 12 weeks.

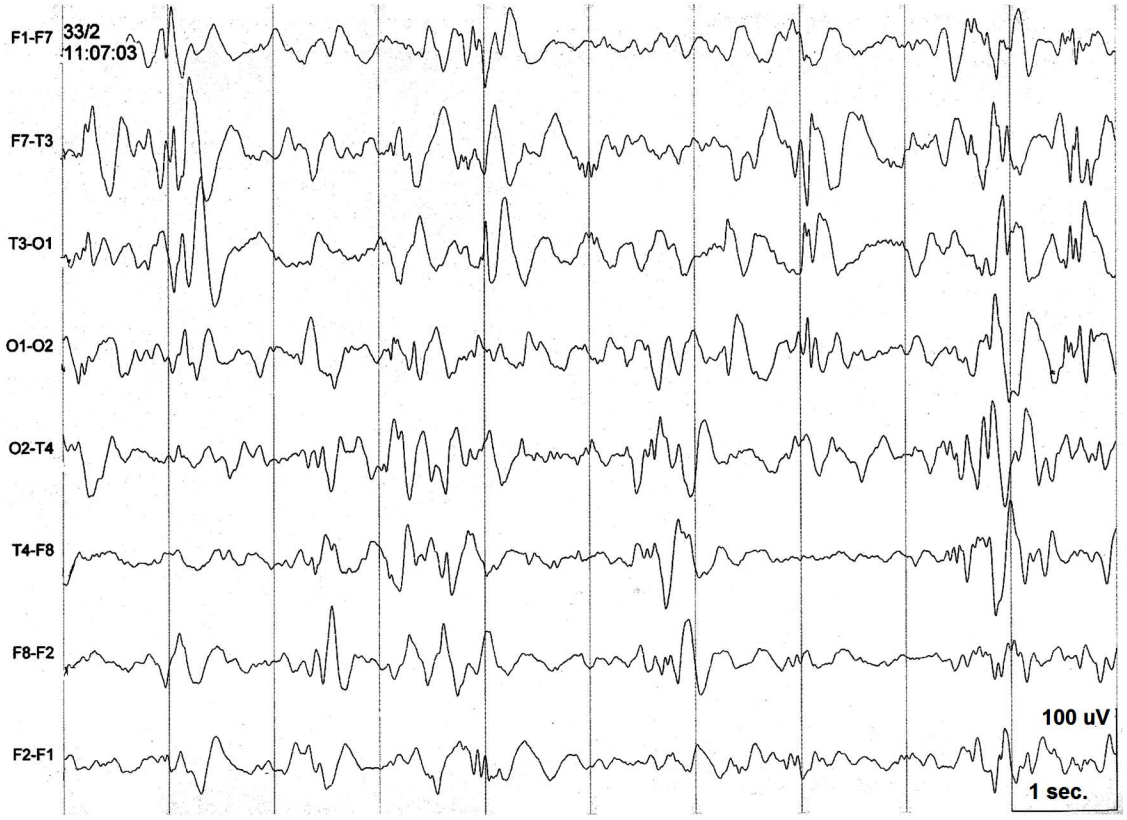

Fig. 2. The EEG recording during sleep shows hypsarrhythmia alternating between one hemisphere and the other in the patient with Aicardi syndrome.

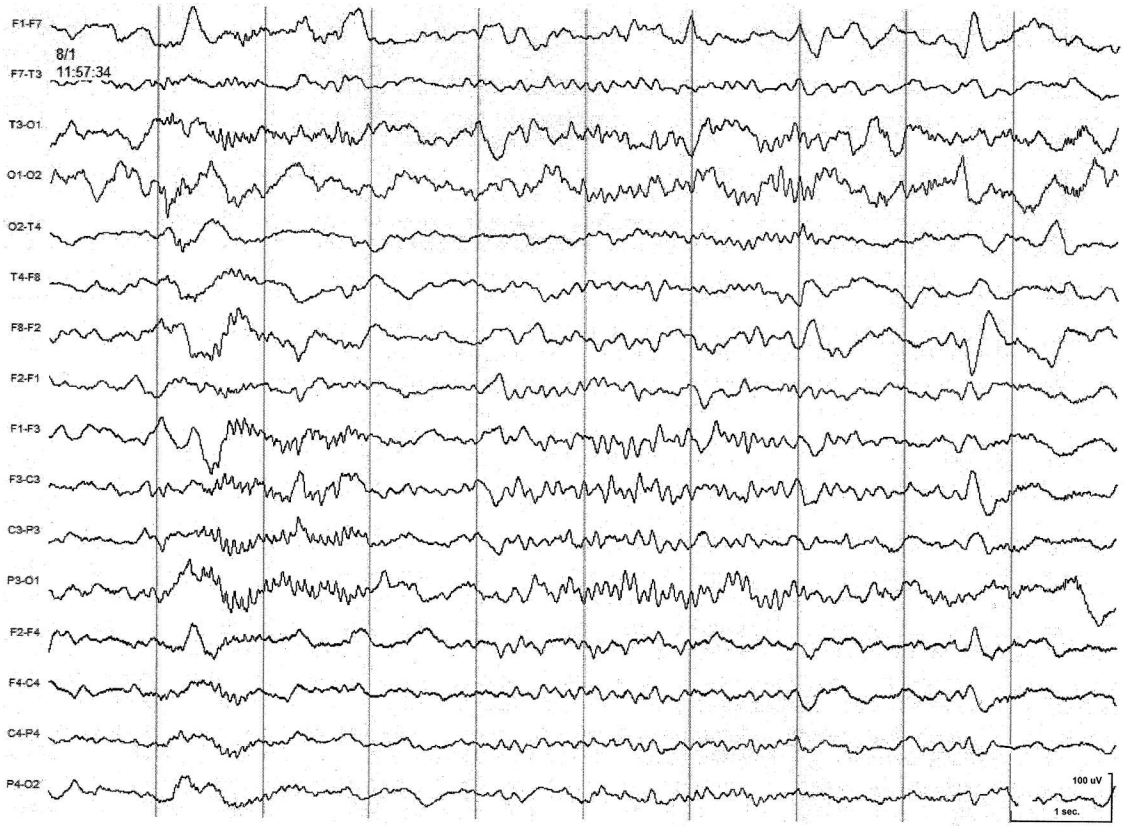

Fig. 3. The EEG recording during sleep of the same patient as in Figs. 1 and 2 does not show paroxysmal abnormalities, except for background activity consisting of "alpha-like" rhythms in the left hemisphere and bilateral slow waves.

Table 1
Etiology, seizure reduction, improvement of the EEG features, CBD dose, adverse effects and follow-up in eight patients with WS treated with **CBD-enriched cannabis oil** as add-on therapy.

West SyndromeEtiology	Seizure reduction (%)	Improvement on the EEG (%)	CBD(dose)	Adverse effects	Time of Follow-up (months)
Unknown	No changes	No changes	25 mg/kg/day	Somnolence	6
Unknown	< 50%	25%	8 mg/kg/day	——	8
Aicardi syndrome	75–90%	80%	20 mg/kg/day	——	13
Hydrocephalus	50–75%	50%	12 mg/kg/day	——	11
Unknown	75–90%	75%	13 mg/kg/day	——	9
Hypoxic-ischemic encephalopathy	< 50%	30%	10 mg/kg/day	Nausea and vomiting	10
Unknown	< 50%	30%	18 mg/kg/day	——	7
Unknown	50–75%	50%	4 mg/kg/day	Behavior disturbances and irritability	12

Abbreviations: CBD: cannabidiol; EEG: electroencephalogram.

Hussain et al. [12] studied nine children 6 to 36 months of age with IS that had failed treatment with both ACTH and VGB and subsequently received synthetic pharmaceutical grade CBD. Their results were poor with only one patient responding to therapy and eight patients exhibiting neither clinical nor electrographic response. The authors hypothesized that younger patients with shorter duration of IS and fewer treatment failures may respond better to CBD.

Although much remains unclear, differences in response to different treatments of patients at different ages may be explained by brain maturation, receptors, and epileptic syndromes. Receptors play a prominent role in brain function, as they are the effector sites of neurotransmission at the postsynaptic membrane. They exert regulatory action in presynaptic sites for transmitter reuptake and feedback, and modulate various functions on the cell membrane. This might explain why CBD may be more or less effective at a certain age [15].

Timing of CBD initiation in children with WS has to be analyzed for each case in particular, considering etiology. CBD may also be tried in patients with treatment-refractory WS later in the course of the disease when the clinical and electrographic features of WS are still present or in the period of transition of WS to LGS [16].

Specific etiologies, such as genetic causes including malformations of cortical development and Aicardi syndrome, may respond better to CBD. Further studies, preferably randomized and double blind, with larger sample sizes and subdividing patients into different etiological categories are necessary to support our findings. In addition, timing of treatment initiation may be a factor to consider.

Furthermore, patients with other developmental epileptic encephalopathies, such as ES in clusters without hypsarrhythmia or other encephalopathies associated with ES that are refractory to ASM and KD, may be candidates for CBD therapy.

In different systematic reviews on the use of CBD in randomized controlled trials in DS and LGS as well as different other epileptic conditions tolerability of CBD was found to be good. The most commonly reported adverse events were somnolence, gastrointestinal symptoms, decreased appetite, and increased serum aminotransferases [10,17,18]. In our series of children, the adverse events, consisting of somnolence and nausea and vomiting, were mild. Behavior disturbances and irritability were observed in one of our patients.

In our study, we used an oil with a CBD/THC ratio of 25:1, different from the purified or synthetic CBD preparations used in other studies. In a clinical trial using CBD-enriched cannabis oil at a CBD:THC 20:1 for the treatment of different types of epilepsy, Tzadok et al. [19] suggested synergistic effects between CBD and THC, which was subsequently emphasized by Melchoulam [20]. An "entourage effect", in which different pharmacokinetic interactions between cannabinoids lead to potentiation of the properties of the cannabis plant, has been described [21]. In a epilepsy model of zebrafish [22] and in a mouse model of Dravet syndrome [23] it was found that when THC and CBD were applied together, they displayed a synergistic effect. These findings might explain why our results were better than those observed when purified or synthetic CBD was used. Whereas THC is known to directly activate the brain endocannabinoid system, little is known about the mechanism of action of CBD [24]. The intrinsic mechanisms of action of both components and their interactions need to be further investigated.

Clearly, the small sample size and retrospective analysis of the patients are limitations of this study; however, the results in this series of patients may contribute to further elucidate the role of CBD in the treatment of patients with treatment-resistant WS.

5. Conclusions

This study evaluating the use of CBD-enriched cannabis oil in children with WS showed that four (50%) of eight had a more than 50% seizure reduction with good tolerability.

CBD may also be tried later when the clinical and electrographic features of WS are still present or in the period of transition of WS to LGS.

Further research studies with a larger number of patients and a longer follow-up are necessary to evaluate if CBD is a good treatment option in patients with refractory WS. These studies may also allow us to assess which patients respond better to CBD in terms of etiology and dosage.

Declarations of Competing Interest

None.

References

[1] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512–21. https://doi.org/10.1111/epi.13709. Apr.
[2] Guzzetta F. Cognitive and behavioral outcome in West syndrome. Epilepsia 2006; 47(2):49–52. https://doi.org/10.1111/j.1528-1167.2006.00689.x. SupplPMID: 17105461.
[3] Shields WD. Infantile spasms: little seizures, BIG consequences. Epilepsy Curr 2006; 6(3):63–9. https://doi.org/10.1111/j.1535-7511.2006.00100.x. May-Jun.
[4] Hussain SA. Treatment of infantile spasms. Epilepsia Open 2018;3(2):143–54. https://doi.org/10.1002/epi4.12264. Oct 23Suppl Suppl.
[5] Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Cannabidiol in Dravet syndrome study group. Trial of Cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011–20. https://doi.org/10.1056/NEJMoa1611618. May 25.

[6] Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. GWPCARE3 Study Group. Effect of Cannabidiol on drop seizures in the lennox-Gastaut syndrome. N Engl J Med 2018;378(20):1888–97. https://doi.org/10.1056/NEJMoa1714631. a May 17.
[7] Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391(10125):1085–96. https://doi.org/10.1016/S0140-6736(18)30136-3. Mar 17.
[8] Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, et al. CBD EAP study group. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. Epilepsia 2018;59(8):1540–8. https://doi.org/10.1111/epi.14477. Aug.
[9] Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav 2018;86:131–7. https://doi.org/10.1016/j.yebeh.2018.05.013. b Sep.
[10] Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, et al. Highly Purified Cannabidiol for epilepsy treatment: a systematic review of epileptic conditions beyond Dravet syndrome and Lennox-Gastaut syndrome. CNS Drugs 2021;35(3):265–81. a Mar10.1007/s40263-021-00807-y. Epub 2021 Mar 22.
[11] Caraballo R, Demirdjian G, Reyes G, Huaman M, Gutierrez R. Effectiveness of cannabidiol in a prospective cohort of children with drug-resistant epileptic encephalopathy in Argentina. Seizure 2020;80:75–80. https://doi.org/10.1016/j.seizure.2020.06.005. AugEpub 2020 Jun 6. Erratum in: Seizure. 2020 Jul 9;: PMID: 32544657.
[12] Hussain SA, Dlugos DJ, Cilio MR, Parikh N, Oh A, Sankar R. Synthetic pharmaceutical grade cannabidiol for treatment of refractory infantile spasms: a multicenter phase-2 study. Epilepsy Behav 2020;102:106826. https://doi.org/10.1016/j.yebeh.2019.106826. Jan.
[13] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position Paper of the ILAE commission for classification and terminology. Epilepsia 2017;58(4):522–30. https://doi.org/10.1111/epi.13670. Apr.
[14] Herlopian A, Hess EJ, Barnett J, Geffrey AL, Pollack SF, Skirvin L, Bruno P, Sourbron J, Thiele EA. Cannabidiol in treatment of refractory epileptic spasms: an open-label study. Epilepsy Behav 2020;106:106988. https://doi.org/10.1016/j.yebeh.2020.106988. MayEpub 2020 Mar 10. PMID: 32169600.
[15] Heiss WD, Herholz K. Brain receptor imaging. J Nucl Med 2006;47(2):302–12. FebPMID: 16455637.
[16] Calvo A, Buompadre MC, Gallo A, Gutiérrez R, Valenzuela GR, Caraballo R. Electroclinical pattern in the transition from West to Lennox-Gastaut syndrome. Epilepsy Res 2020;167:106446. Nov10.1016/j.eplepsyres.2020.106446.
[17] Lattanzi S, Brigo F, Trinka E, Zaccara G, Cagnetti C, Del Giovane C, et al. Efficacy and safety of Cannabidiol in Epilepsy: a systematic review and meta-analysis. Drugs 2018;78(17):1791–804. https://doi.org/10.1007/s40265-018-0992-5. NovPMID: 30390221.
[18] Lattanzi S, Zaccara G, Russo E, La Neve A, Lodi MAM, Striano P. Practical use of pharmaceutically purified oral cannabidiol in Dravet syndrome and Lennox-Gastaut syndrome. Expert Rev Neurother 2021;21(1):99–110. https://doi.org/10.1080/14737175.2021.1834383. b Jan.
[19] Tzadok M, Uliel-Siboni S, Linder I, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. Seizure 2016;35:41–4. https://doi.org/10.1016/j.seizure.2016.01.004.
[20] Mechoulam R. Cannabis and epilepsy. Epilepsy Behav 2017;70:278–9. https://doi.org/10.1016/j.yebeh.2017.01.014. Pt B.
[21] Anderson LL, Etchart MG, Bahceci D, Golembiewski TA, Arnold JC. Cannabis constituents interact at the drug efflux pump BCRP to markedly increase plasma cannabidiolic acid concentrations. Sci Rep 2021;11(1):14948. https://doi.org/10.1038/s41598-021-94212-6. Published 2021 Jul 22.
[22] Samarut É, Nixon J, Kundap UP, Drapeau P, Ellis LD. Single and Synergistic Effects of Cannabidiol and Δ-9-Tetrahydrocannabinol on Zebrafish Models of Neuro-Hyperactivity. Front Pharmacol 2019;10:226. https://doi.org/10.3389/fphar.2019.00226. Published 2019 Mar 20.
[23] Anderson LL, Low IK, McGregor IS, Arnold JC. Interactions between cannabidiol and Δ9 -tetrahydrocannabinol in modulating seizure susceptibility and survival in a mouse model of Dravet syndrome. Br J Pharmacol 2020;177(18):4261–74. https://doi.org/10.1111/bph.15181.
[24] Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. N Engl J Med 2015;373(11):1048–58. https://doi.org/10.1056/NEJMra1407304.