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Cannabidiol in children with treatment-resistant epilepsy with myoclonic-atonic seizures

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ABSTRACT

Purpose: This multicenter study aimed to evaluate the efficacy and tolerability of add-on cannabidiol (CBD) in treatment-resistant patients with epilepsy with myoclonic-atonic seizures (EMAtS) (n = 22) and Sturge Weber syndrome (SWS) with myoclonic-atonic seizures (n = 4).

Methods: Patients who met the diagnostic criteria of treatment-resistant EMAtS or SWS with myoclonic-atonic seizures were included. Cannabidiol was added in doses ranging from 8 to 40 mg/kg/day. Efficacy was assessed by comparing seizure frequency before and after initiating CBD therapy.

Neurologic examinations, brain magnetic resonance imaging, repeated prolonged electroencephalography (EEG) and/or video-EEG recordings, and neurometabolic studies were performed in all patients, and genetic investigations in 15.

Results: After a mean follow-up of 19 months, 15/26 patients (57.7%) who received add-on CBD had a >50% seizure decrease; three (11.5%) became seizure-free. The remaining 11 patients (42.3%) had a 25–50% seizure reduction. Drop attacks, including myoclonic-atonic seizures and generalized tonic-clonic seizures, as well as atypical absences and nonconvulsive status epilepticus responded well to CBD. In SWS patients, focal motor seizures without consciousness impairment and focal non-motor seizures with consciousness impairment were recognized in two each; in three a 30% reduction of focal seizures was observed. Side effects were mild and did not lead to CBD discontinuation.

Conclusion: This study evaluating the use of add-on CBD in children with EMAtS or SWS with myoclonic-atonic seizures found that 15/26 (57.7%) had a >50% seizure reduction with good tolerability; three (11.5%) became seizure-free.

1. Introduction

Cannabidiol (CBD), a non-psychoactive derivative of the cannabis plant, has increasingly been shown to be a valid option for epilepsy patients who do not respond to other treatments. Different double-blind, randomized, and long-term open-label extension trials have provided evidence for the safe and effective use of add-on CBD in patients with Dravet [1,2] and Lennox–Gastaut syndromes (LGS) [3–5], tuberous sclerosis complex [6,7], and other treatment-resistant epilepsies including Doose syndrome [8,9].

Epilepsy with myoclonic atonic seizures (EMAtS), also known as myoclonic astatic epilepsy or Doose syndrome, is a rare childhood epilepsy syndrome accounting for 2% of all childhood epilepsies. Onset is between 2–6 years of age and boys are affected twice as often as girls, except in those with onset in the first year of life when the sexes are equally divided [10]. Before seizure onset, development is normal in two-thirds of the patients; 25% of the children have a history of febrile seizures [11].

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Epilepsy with myoclonic atonic seizures is characterized by multiple seizure types, including myoclonic-atonic, atonic, absence, or generalized tonic-clonic seizures. Myoclonic-atonic seizures, the mandatory seizure type for diagnosis, manifest with sudden, brief myoclonic jerks in the proximal muscles, followed by a very brief atonic component associated with a subtle head drop or an abrupt fall [12].

Status epilepticus, both non-convulsive and myoclonic, is common. Generalized tonic-clonic seizures with or without fever are the presenting seizure type preceding the myoclonic-atonic and atonic seizures in around two-thirds of the children [12,13]. A so-called "stormy phase", a period of increased frequency of many different seizure types and worsening of the EEG often associated with non-convulsive status epilepticus, is observed in around 50% of the patients [14].

The outcome is variable. Remission is seen in two-thirds of the patients at around 3 years after seizure onset [12]. Development may return to normal, but moderate intellectual disability has been reported in 34%-60% of the patients [13,15,16]. Epilepsy with myoclonic-atonic seizures may also evolve into epileptic encephalopathy with drug-resistant seizures associated with developmental arrest or regression, behavior disorders, including hyperactivity and aggression, ataxia, and sleep disturbances [12].

A genetic etiology is suspected; however, although pathogenic variants in different genes have been reported, the number of patients identified for each gene is small [16] and it has been suggested that the underlying cause of EMAtS is multifactorial [16,17].

Treatment options include valproic acid, levetiracetam, lamotrigine, ethosuximide, topiramate, clobazam, rufinamide, and felbamate. Good response has also been achieved with ketogenic diet therapy (KDT) [14,15,18] and. recently, cannabidiol-enriched medical cannabis has proved to be effective as an add-on treatment in patients with EMAtS [19].

Considering that an important number of children with EMAtS are resistant to pharmacological and non-pharmacological treatment and based on the efficacy of CBD in drop-attacks [3], in 2019 our group started to use CBD in patients with treatment-resistant EMAtS. In addition, while most patients with Sturge-Weber syndrome (SWS) have focal epilepsy, some may develop generalized seizures including myoclonic-atonic seizures resulting in drop attacks [20]. Although these patients do not meet the inclusion criteria of the diagnosis of EMAtS [12], we also tried CBD in children with SWS associated with myoclonic-atonic seizures.

The main differential diagnosis of EMAtS is LGS, which can be distinguished by the presence of early-onset tonic seizures and slow spike-wave discharges at <2.5 Hz and generalized paroxysmal fast activity during sleep in the EEG recording. Children with LGS may have a history of infantile epileptic spasms syndrome and developmental delay is often seen before seizure onset [12].

The aim of this retrospective, open-label, non-randomized, multicenter study was to evaluate the efficacy, safety, and tolerability of purified CBD as an add-on treatment in 22 patients with EMAtS and four with SWS associated with myoclonic-atonic seizures, who were resistant to other ASMs and/or non-pharmacological treatment, including vagus nerve stimulation (VNS) and KDT.

2. Material and methods

We retrospectively analyzed the medical records of 22 patients with EMAtS and four patients with SWS associated with myoclonic-atonic seizures treated with CBD at six epilepsy centers between May 2021 and February 2023. In all patients, CBD was started as add-on therapy.

2.1. Inclusion criteria

The following inclusion criteria for EMAtS were used: (1) normal or abnormal development and cognition before the onset of epilepsy; (2) seizure onset between 6 months and 6 years of age (peak, 2–4 years); (3) myoclonic-atonic seizures; (4) generalized spike-wave discharges at 2–3 Hz without persistent focal spike discharges on the EEG; (5) drop-attacks due to myoclonic-atonic, atonic, or myoclonic-flexor seizures associated with generalized spike-wave discharges; 6) absences and generalized tonic-clonic seizures may occur. Four patients with myoclonic-atonic seizures due to Sturge-Weber syndrome were also included. In this subgroup, structural abnormalities, clinical findings, and an EEG pattern of focal abnormalities ruled out the diagnosis of EMAtS. Treatment with VNS (minimum 2 years) and/or KDT (minimum 1 year) was not a reason for exclusion.

2.2. Exclusion criteria

Children with other myoclonic epilepsy syndromes or other epileptic encephalopathies, including LGS, Dravet syndrome, and epileptic encephalopathy with spike-wave activation in sleep, and those with the progressive neurological or systemic disease were excluded from the study. Patients with non-SWS-related myoclonic-atonic seizures secondary to a structural cause and patients with glucose transporter 1 (GLUT1) deficiency were also excluded. Gene panels were performed in 15/22 to rule out other epileptic encephalopathies and progressive neurological diseases and in all 22 patients with EMAtS lumbar puncture was performed to evaluate CSF to blood glucose ratio to rule out GLUT1 deficiency.

2.3. Interventions

Eligible patients were treated with purified CBD 100 mg/ml oral solution (convupidiol®, Alef Medical Argentina) diluted in sesame oil. The product was evaluated and approved by the Argentine National Drug, Food, and Medical Technology Administration (ANMAT). The initial CBD dose was 2 mg/kg/day given twice daily, which was gradually increased over two-weekly intervals until intolerance or a maximum of 40 mg/kg/day.

2.4. Clinical evaluations and questionnaires

Physical and neurological examinations and laboratory studies, including liver and kidney function tests, were done prior to CBD initiation and during follow-up. Seizure frequency, type, and duration were evaluated. The seizures were classified according to the 2017 Revised Classification of Seizures of the International League against Epilepsy [21]. The parents or caregivers of all patients were taught how to recognize the different seizures and kept a seizure diary to record seizure types and frequency before and after CBD initiation.

2.5. Investigations

All patients underwent sleep and awake EEG or video-EEG of at least 1 hour prior to CBD initiation and periodically afterwards. Improvements on the EEG were evaluated by the treating neurologist considering a more or less than 50% reduction of the slow spike-waves, diffuse fast rhythms, and multifocal spikes mainly during the maximum sleep stage in a video-EEG recording of at least 2 hours. Nevertheless, due to the retrospective and multicenter nature of the study, no systematic mathematical and statistical analysis could be performed.

Neurodevelopment was not systematically assessed before and after CDB initiation. Data on cognition, behavior, and school perfor-

mance were collected from reports by parents, occupational therapists, and teachers, and neurodevelopmental status was evaluated by the treating neurologist. The efficacy of CBD was evaluated by comparing seizure frequency before and after treatment initiation and a good response was defined as a ≥50% decrease in seizure frequency. Adverse effects, recorded at each follow-up visit, were also assessed.

2.6. Statistical analysis and study approval

For statistical analysis, the two-tailed Wilcoxon rank-sum and the Fisher exact tests were used. A p-value of less than 0.05 was considered significant. The study was approved by the ethics committee at each participating center.

3. Results

3.1. General characteristics

Before starting CBD, the patients were receiving a mean of four ASMs (range, 3–7). The month previous to CBD initiation was considered the baseline period for data comparison.

Brain computed tomography (CT) scan was performed in 13 and magnetic resonance imaging (MRI) in all patients. Genetic studies including gene panels for epileptic encephalopathies were performed in 15/22 patients. In 13 patients, the results of whole exome sequencing are pending.

Twenty-six patients (16 male and 10 female), aged between 5 and 12 years (mean 7 and median 8.5 years) with a mean age of 2.5 years (range, 1–6 years) at seizure onset who received CBD for treatment-resistant EMAtS and SWS with myoclonic-atonic seizures were evaluated. The patients were treated with add-on CBD for a mean period of 15 months (range, 10–23 months). We waited at least 3 years to see if the children entered into spontaneous remission.

The etiology was unknown in 18, genetic in four (two with *NEXMIF* and one with *SYNGAP1* gene mutations, and a 15q13.3 microdeletion in the remaining patient), and structural in four patients with SWS. The initial CBD dose was 2 mg/kg/day, which was up-titrated to a median dose of 18 mg/kg/day (range, 8–40). The mean follow-up was 16 months (range, 6 to 24 months).

A mean of eight ASMs was tried before CBD was started. Valproic acid was concomitantly used in 85%, levetiracetam in 70%, clobazam in 34%, topiramate in 40%, ethosuximide in 35%, brivaracetam in 20%, and lamotrigine in 20%. Ketogenic diet therapy and VNS were concomitantly used in 10 (38.5%) and four (15.3%) patients, respectively.

3.2. Clinical features

At baseline, all patients with EMAtS had myoclonic-atonic and myoclonic seizures at a frequency of daily and a short series of two to five events in all patients. The frequency of non-myoclonic-atonic and myoclonic seizures was weekly in 15 and monthly in seven. All four patients with SWS had daily myoclonic-atonic and myoclonic seizures and 3/4 had weekly focal seizures, consisting of focal motor seizures without consciousness impairment in two and focal non-motor seizures with consciousness impairment in one.

Drop attacks were secondary to massive myoclonic jerks or myoclonic-atonic seizures. The myoclonic jerks had a wide range of severity ranging from head nodding to falls. Eleven patients (50%) had generalized tonic-clonic seizures. Atypical absence seizures associated with an atonic component were observed in 14 patients (63.5%). Eight patients (36.5%) had nonconvulsive status epilepticus characterized by stupor and apathy associated with myoclonias of the face and limbs, lasting from 2 hours to several days, and occurring spontaneously. Atonic seizures were recognized in six patients (27.3%). Tonic seizures occurred in seven patients (31.8%).

3.3. Efficacy

After a mean follow-up of 16 months, 15 of 26 patients (57.7%) receiving add-on CBD had a greater than 50% seizure decrease, three of whom (11.5%) became seizure-free. In 11 patients (42.3%) the seizure reduction was 25–50%.

By this time, in 12 patients with a more than 50% response, the myoclonic-atonic and myoclonic seizures occurred daily but significantly less frequently in two, weekly in eight, and monthly in the remaining two. The frequency of non-myoclonic-atonic and myoclonic seizures was weekly in six and monthly in six others. All 11 patients with a 25–50% seizure reduction continued to have daily myoclonic-atonic and myoclonic seizures, but they were less frequent. Non-myoclonic-atonic and myoclonic seizures occurred weekly in all but were also less frequent. In three patients with SWS, focal seizures occurred once every 15 days to one month.

Considering the different seizure types, 12 of the 15 responders (77.7%), three of whom had SWS, had a greater than 50% reduction in drop attacks (myoclonic-atonic, atonic, myoclonic, and/or tonic seizures) and 7/14 (50%) had a greater than 50% decrease in atypical absences. In 3/11 patients (27.7%) who had generalized tonic-clonic seizures, a greater than 50% decrease was observed. Cannabidiol was effective in 4/8 patients (50%) with nonconvulsive status epilepticus. In all three patients with SWS, a 30% decrease in focal seizures was observed.

Overall, six patients received comedication with clobazam (CBL); however, no synergistic effects, either positive or negative, were observed. After CBD initiation, 2/4 of patients with VNS and 7/10 patients who received KDT had a greater than 50% decrease in all seizure types.

The interictal EEG abnormalities improved in all responders. The EEG normalized in one of the patients who became seizure-free and showed only isolated diffuse abnormalities in the other two (Fig. 1 A, B, and C, and Fig. 2 A and B).

No statistical differences were observed when comparing age at seizure onset, epilepsy duration, and age at CBD initiation between responders and non-responders.

Table 1 shows the general features, epilepsy syndrome, etiology, dose and age at initiation, and electroclinical improvement in our patients with EMAtS and SWS associated with myoclonic-atonic seizures treated with add-on CBD.

3.4. Adverse effects

The most common adverse events were decreased appetite in three and somnolence in three other patients. Nausea was observed in two and irritability in one patient. All adverse effects were transient and mild and did not lead to treatment discontinuation. In the majority of cases, the adverse effects were resolved with an adjustment of the CBD dose. No increase in seizure frequency was seen in any of the patients.

Laboratory tests were normal in all patients and no changes in blood levels of concomitant ASMs were observed after CBD was added.

3.5. Follow-up

Over a mean follow-up of 16 months, the efficacy of CBD was maintained in 14/15 patients who had a greater than 50% seizure decrease. Three patients who had become seizure-free remained

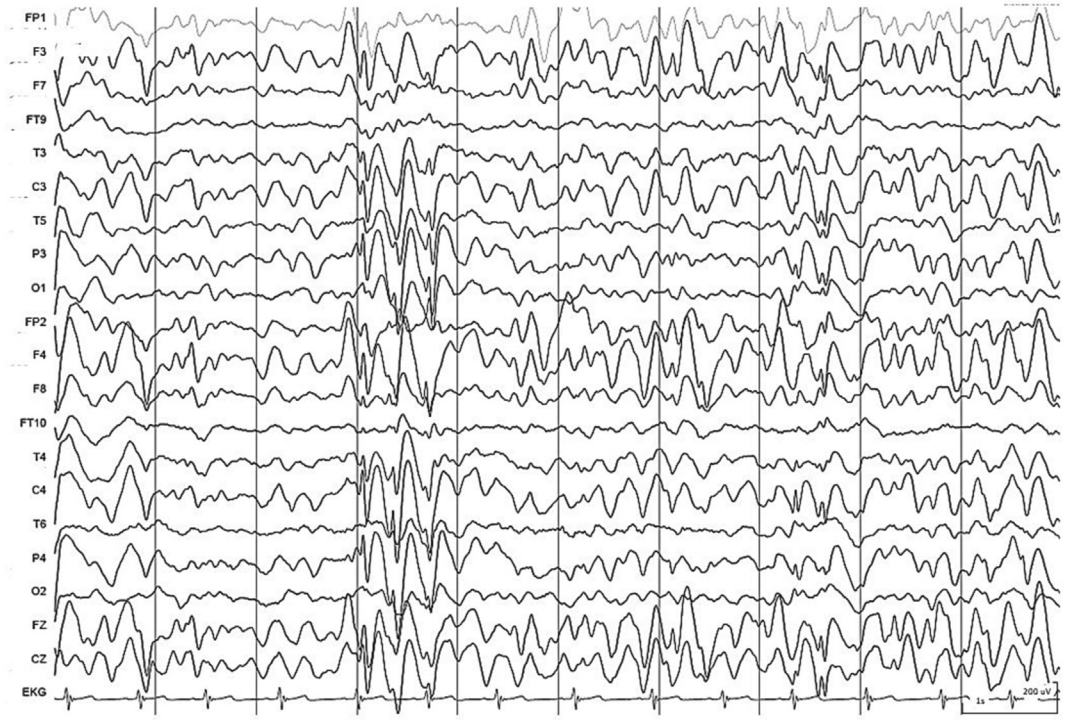


Figure 1A. A 6-year-old girl with EMAtS. The EEG recording during sleep shows generalized spikes and waves. Figure 1B: The ictal EEG recording shows generalized spikes and waves associated with a myoclonic atonic seizure in the same patient. Figure 1C: After 16 months of follow-up, the girl became seizure-free. The EEG was normal.

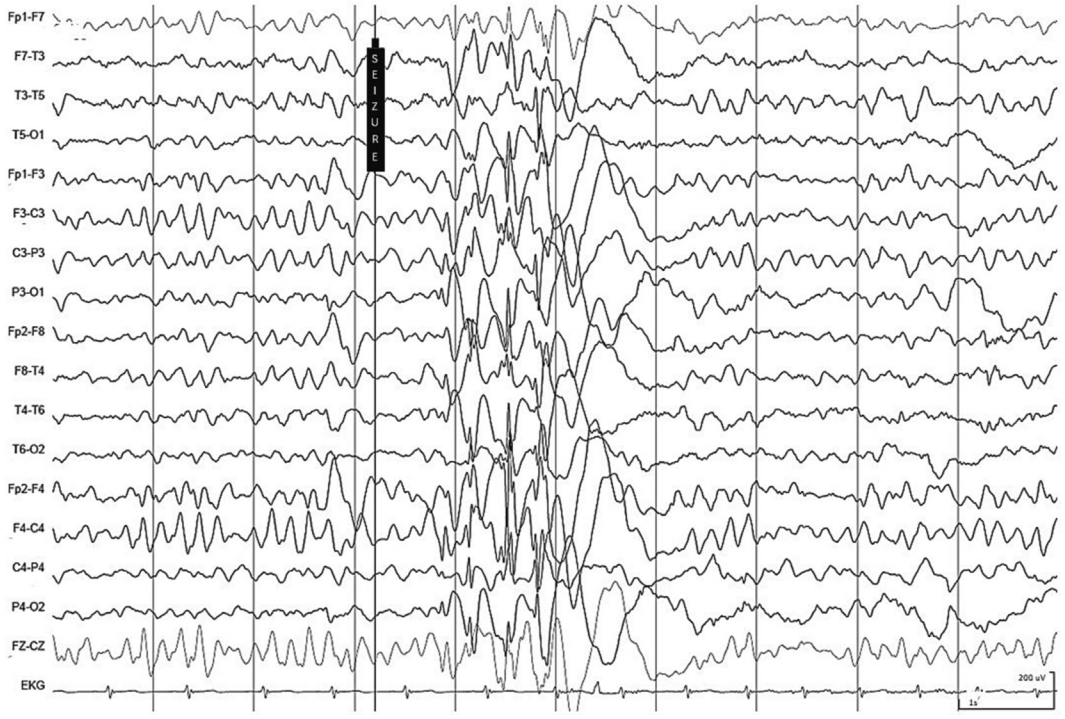
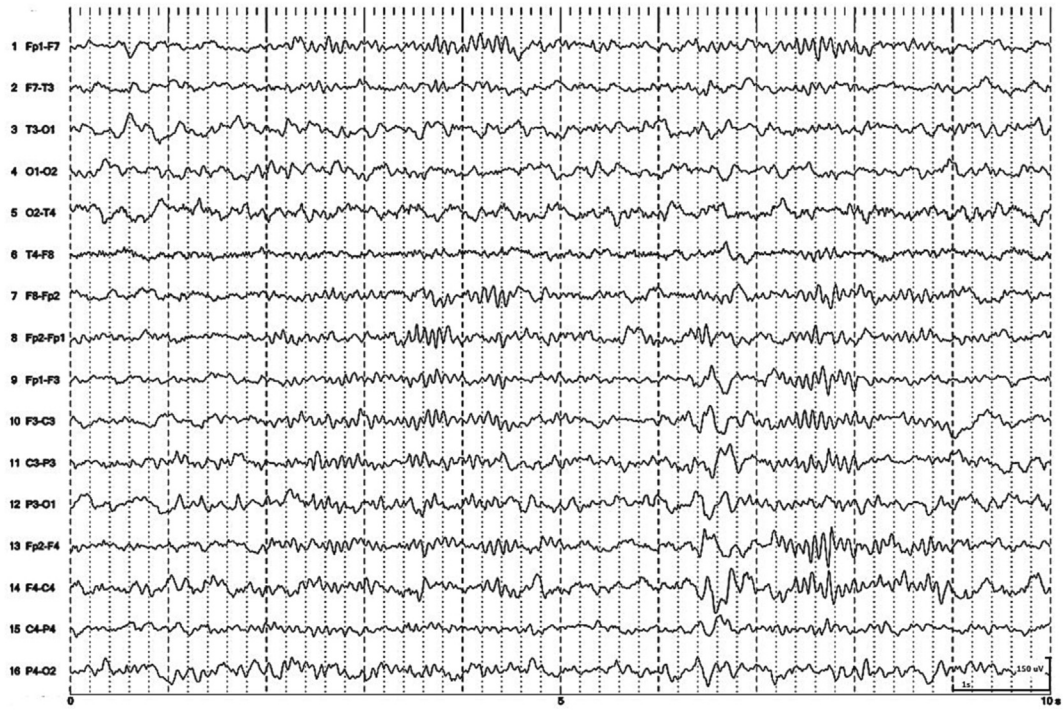


Figure 1B (*continued*)

so during follow-up and cognitive development returned to pre-morbid levels. In 11 patients who had a less than 50% decrease in seizure frequency, some improvement in development and cognition was also seen.

Overall, we tried to make as few changes as possible in the treatment scheme, except if necessary, as is usual in our clinical practice once we start a new medication. Rescue medications were needed in two patients who had non-convulsive status epilepticus.



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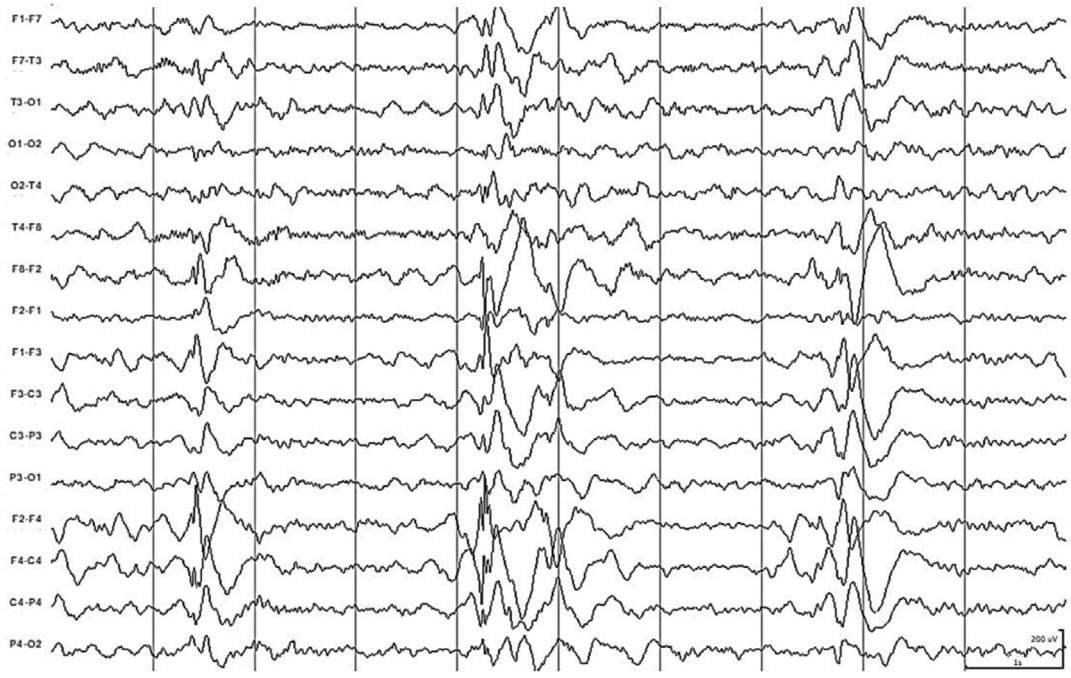

Figure 2A. A 7-year-old boy with EMAtS. The EEG recording showed frequent generalized paroxysms of spikes and polyspike waves during sleep. Figure 2B: After a period of seizure freedom of 11 months, the EEG showed isolated generalized spikes and waves.

4. Discussion

Over the past decade, CBD has been increasingly used as a last resort for patients with treatment-resistant epilepsy. Most studies on the use of add-on CBD have reported patients with epileptic encephalopathies, such as Dravet syndrome [1,2], LGS [3–5], and tuberous sclerosis complex [6,7], but children with other developmental and epileptic encephalopathies with or without specific etiologies have also been described [9,19,22].

In our retrospective study, purified CDB (convupidiol®, Alef Medical Argentina) showed good long-term efficacy and tolerability in 22 children with EMAtS and four patients with SWS associated with myoclonic-atonic seizures who failed to respond to at least five other ASMs and non-pharmacological treatment. Seizure

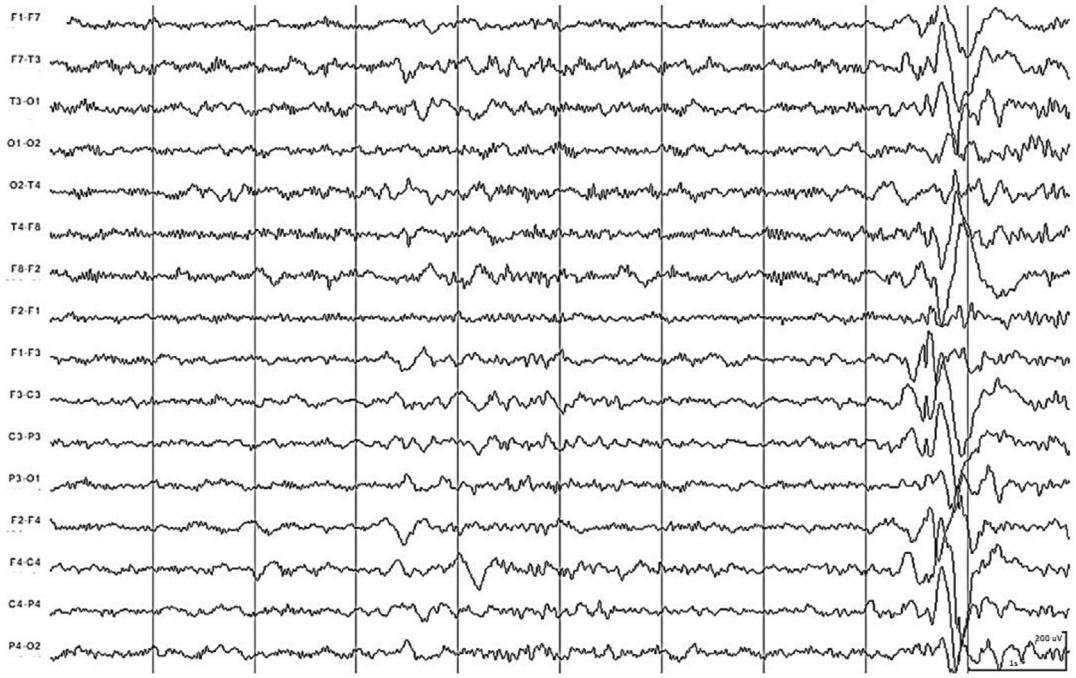

Figure 2B (*continued*)

frequency was found to be reduced by more than 50% in 57.7% of the patients.

Drop attacks, but also atypical absences, tonic-clonic, and tonic seizures, and nonconvulsive status epilepticus responded well to CBD. Similar results were found in patients with EMAtS [19] and LGS [3–5], both of which are associated with the characteristic seizure type of the former syndrome (myoclonic-atonic seizures) but generally without myoclonic seizures in the latter. Therefore, the drop attacks in EMAtS and LGS may be secondary to the same seizure type. In addition, the efficacy of CBD has been shown in atypical absences and nonconvulsive status epilepticus [19]. Patients with other childhood myoclonic epilepsies and patients with epileptic encephalopathies with myoclonic seizures who responded well to CBD have also been reported [19].

Three of our patients became seizure-free; the EEG normalized in one and showed isolated paroxysmal abnormalities in the other two while cognition and development returned to baseline levels. In the remaining 12 patients who had a seizure reduction of $\geq$50%, the EEG abnormalities and neurocognitive development improved.

In an open-label study evaluating the compassionate use of CBD for the management of patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes, eight patients with EMAtS had a response rate of 43% by week 12 and 57% by week 48 [9].

In our study, four patients with SWS were included. Although rare, patients with SWS may have myoclonic-atonic seizures. Ewen et al. describe one patient with SWS and myoclonic-atonic seizures and mention eight other cases reported in the literature [20]. The authors suggest that the mechanism of secondary bilateral synchrony from focal seizures may explain the development of myoclonic-atonic seizures. On the other hand, both EMAtS and SWS may be associated with resistance to ASMs.

Cannabidiol was previously tried in patients with SWS with good results by Kaplan et al. [23]. In a further study by the same authors based on an open-label, prospective oral drug trial of Epidiolex® in 10 subjects significant improvements in SWS neuroscore, patient-reported quality of life, anxiety and emotional regulation, and bimanual ability were observed independently of seizure control [24].

Considering that CBD is effective in patients with SWS regardless of the seizure type [23] and also in patients with myoclonic-atonic seizures [9,19,21], we may speculate that patients with SWS who have myoclonic-atonic seizures are good candidates for CBD.

In different systematic reviews evaluating the use of CBD in randomized controlled trials including patients with DS and LGS as well as different other epileptic conditions, tolerability was found to be good. The most commonly reported adverse events were somnolence, gastrointestinal symptoms, decreased appetite, and increased serum aminotransferases. In our series of children, similar to the literature [8], the adverse events were mild and did not require CBD discontinuation.

Although our results are based on a multicenter, retrospective analysis of a small cohort of patients without a control group and response was assessed based on the general impression of parents, our data may contribute to the knowledge about the role of CBD in the treatment of patients with treatment-resistant EMAtS and SWS associated with myoclonic-atonic seizures.

Regarding the efficacy of purified CBD in nonconvulsive seizures, such as atypical absences and nonconvulsive status epilepticus, further studies including other epileptic encephalopathies in which nonconvulsive seizures are pathognomonic are needed.

5. Conclusions

This study evaluating the use of add-on purified CBD in children with EMAtS and SWS associated with myoclonic-atonic seizures showed a more than 50% seizure reduction with good tolerability in 15 (57.6%) of 26. Three patients (11.5%) became seizure-free.

Further studies with a larger number of patients and a longer follow-up are necessary to evaluate if CBD is a good treatment option for treatment-resistant patients with EMAtS or SWS associated with myoclonic-atonic seizures.

Table 1
General features, epilepsy syndrome, etiology, dose and age at initiation, and electroclinical improvement of our patients with EMAtS and SWS treated with add-on CBD.

Number of patients and sex	Epileptic syndrome and etiology	Age at CDB initiation and dose	Concomitant treatment	Seizure reduction (%)	Improvement in EEG (%)
1M	EMAtS Unknown	4 years 18 mg	LEV, CLB	Seizure-free	No abnormalities
2F	EMAtS Unknown	5 years 8 mg	VPA, KDT	<50%	No changes
3M	EMAtS Unknown	7 years 10 mg	LEV, LMT, KDT	50–74%	50%
4F	EMAtS Unknown	4 years 15 mg	VNS, VPA	<50%	40%
5M	EMAtS Unknown	8 years 18 mg	ETM, BVT	50–74%	70%
6M	EMAtS Unknown	8 years 9 mg	VNS, BVT	<50%	30%
7F	EMAtS Unknown	7 years 8 mg	ETM, VPA	50–74%	50%
8F	EMAtS Unknown	9 years 19 mg	KDT, LEV	<50%	No changes
9F	EMAtS Unknown	5 years 10 mg	CLB, VPA	75–99%	80%
10M	EMAtS Unknown	4.5 years 11 mg	KDT, VPA, ETM	<50%	30%
11M	EMAtS Unknown	5.5 years 11 mg	LMT, VPA, VNS	75–99%	70%
12F	EMAtS Unknown	6 years 40 mg	KDT, ETM, LMT	50–74%	50%
13F	EMAtS Unknown	7 years 30 mg	KDT, LEV, CLB	50–74%	60%
14M	EMAtS Unknown	8 years 12 mg	KDT, LEV,CLB	75–99%	90%
15F	EMAtS Unknown	7.5 years 13 mg	VPA, CLB	75–99%	65%
16M	EMAtS Unknown	5 years 13 mg	KDT, LEV	Seizure-free	Isolated diffuse spikes and waves
17M	Unknown	4 years 14 mg	LMT, VPA	75–99%	75%
18F	Unknown	6.5 years 12 mg	KDT, ETM, LMT	75–99%	80%
19F	EMAtS *NEXMIF*	8 years 14 mg	BVT	Seizure-free	No abnormalities
20M	EMAtS *NEXMIF*	9 years 18 mg	LEV, LMT	50–74%	50%
21M	EMAtS *SYNGAP1*	9 years 17 mg	KDT, VPA	75–99%	70%
22F	EMAtS 15q13.3 microdeletion	6 years 25 mg	VNS, LEV, ETM	<50%	No changes
23M	SWS	5 years 28 mg	LMT,VPA	75–99%	90%
24M	SWS	7 years 30 mg	LEV, ETM	50–74%	40%
25M	SWS	6 years 25 mg	CBL, VPA	75–99%	80%
26F	SWS	5 years 22 mg	BVT,VPA	<50%	20%

Abbreviations: BVT, brivaracetam; CLB, clobazam; EMAtS, epilepsy with myoclonic-atonic seizures; ETM, ethosuximide; F, female; KDT, ketogenic dietary therapy; LEV, levetiracetam; LMT, lamotrigine; M, male; SWS, Sturge Weber syndrome; VPA, valproic acid; VNS, vagus nerve stimulation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] 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.

[2] Scheffer IE, Halford JJ, Miller I, Nabbout R, Sanchez-Carpintero R, Shiloh-Malawsky Y, et al. Add-on cannabidiol in patients with Dravet syndrome: Results of a long-term open-label extension trial. Epilepsia 2021;62(10):2505–17. https://doi.org/10.1111/epi.17036.

[3] 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.

[4] 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.

[5] Patel AD, Mazurkiewicz-Bełdzińska M, Chin RF, Gil-Nagel A, Gunning B, Halford JJ, et al. Long-term safety and efficacy of add-on cannabidiol in patients with Lennox-Gastaut syndrome: Results of a long-term open-label extension trial. Epilepsia 2021;62(9):2228–39. https://doi.org/10.1111/epi.17000.

[6] Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. GWPCARE6 Study Group. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized

Clinical Trial. JAMA Neurol 2021;78(3):285–92. https://doi.org/10.1001/jamaneurol.2020.4607.
[7] Thiele EA, Bebin EM, Filloux F, Kwan P, Loftus R, Sahebkar F, et al. Long-term cannabidiol treatment for seizures in patients with tuberous sclerosis complex: An open-label extension trial. Epilepsia 2022;63(2):426–39. https://doi.org/10.1111/epi.17150.
[8] Szaflarski JP, Bebin EM, Cutter G, DeWolfe J, Dure LS, Gaston TE, et al. UAB CBD Program. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. Epilepsy Behav 2018;87:131–6. https://doi.org/10.1016/j.yebeh.2018.07.020.
[9] Devinsky O, Verducci C, Thiele EA, Laux LC, Parel AD, Filloux F. 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.
[10] Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Dev Med Child Neurol 2010;52(11):988–93. https://doi.org/10.1111/j.1469-8749.2010.03744.x.
[11] Doose H, Gerken H, Leonhardt R, Vozke E, Volz C. Centrencephalic myoclonic-astatic petit mal. Clinical and genetic investigations. Neuropediatrie 1970;2:59–78.
[12] Specchio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions. Epilepsia 2022;63(6):1398–442. https://doi.org/10.1111/epi.17241.
[13] Caraballo RH, Chamorro N, Darra F, Fortini S, Arroyo H. Epilepsy with myoclonic atonic seizures: an electroclinical study of 69 patients. Pediatr Neurol 2013;48(5):355–62. https://doi.org/10.1016/j.pediatrneurol.2012.12.022.
[14] Joshi C, Nickels K, Demarest S, Eltze C, Cross JH, Wirrell E. Results of an international Delphi consensus in epilepsy with myoclonic atonic seizures/Doose syndrome. Seizure 2021;85:12–8. https://doi.org/10.1016/j.seizure.2020.11.017.
[15] Nickels K, Kossoff EH, Eschbach K, Joshi C. Epilepsy with myoclonic-atonic seizures (Doose syndrome): Clarification of diagnosis and treatment options through a large retrospective multicenter cohort. Epilepsia 2021;62(1):120–7. https://doi.org/10.1111/epi.16752.
[16] Tang S, Addis L, Smith A, Topp SD, Pendziwiat M, Mei D, et al. Phenotypic and genetic spectrum of epilepsy with myoclonic atonic seizures. Epilepsia 2020;61(5):995–1007. https://doi.org/10.1111/epi.16508.
[17] Nickels K. Epilepsy With Myoclonic Atonic Seizures: Why Is the Yield of Genetic Testing for a "Presumed Genetic" Epilepsy Low? Epilepsy Curr 2020;20(6):351–2. https://doi.org/10.1177/1535759720948890.
[18] Caraballo RH, Cersósimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with myoclonic-astatic epilepsy. Epileptic Disord 2006;8(2):151–5. PMID: 16793577.
[19] Caraballo R, Reyes G, Demirdjian G, Huaman M, Gutierrez R. Long-term use of cannabidiol-enriched medical cannabis in a prospective cohort of children with drug-resistant developmental and epileptic encephalopathy. Seizure 2022;95:56–63. https://doi.org/10.1016/j.seizure.2022.01.001.
[20] Ewen JB, Comi AM, Kossoff EH. Myoclonic-astatic epilepsy in a child with Sturge-Weber syndrome. Pediatr Neurol 2007;36(2):115–7. https://doi.org/10.1016/j.pediatrneurol.2006.08.006.
[21] 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.
[22] Kühne F, Becker LL, Bast T, Bertsche A, Borggraefe I, Boßelmann CM, et al. Real-world data on cannabidiol treatment of various epilepsy subtypes: A retrospective, multicenter study. Epilepsia Open 2023. https://doi.org/10.1002/epi4.12699. Epub ahead of print. PMID: 36693811.
[23] Kaplan EH, Offermann EA, Sievers JW, Comi AM. Cannabidiol Treatment for Refractory Seizures in Sturge-Weber Syndrome. Pediatr Neurol 2017;71. https://doi.org/10.1016/j.pediatrneurol.2017.02.009. 18–23.e2 Epub 2017 Feb 22 PMID: 28454984.
[24] Smegal LF, Vedmurthy P, Ryan M, Eagen M, Andrejow NW, Sweeney K, et al. Cannabidiol Treatment for Neurological, Cognitive, and Psychiatric Symptoms in Sturge-Weber Syndrome. Pediatr Neurol 2023;139:24–34. https://doi.org/10.1016/j.pediatrneurol.2022.10.014.