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SHORT RESEARCH ARTICLE

Cannabidiol in the acute phase of febrile infection-related epilepsy syndrome (FIRES)

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Abstract

Febrile infection-related epilepsy syndrome (FIRES) is a prolonged refractory status epilepticus (SE) that develops among healthy individuals after a febrile infection. FIRES treatment is challenging due to its poor response to antiseizure medications (ASMs) and anesthetic drugs. The use of cannabidiol (CBD) as an adjunctive treatment has been suggested, albeit data about its role in the acute phase is lacking. This report describes the use of purified CBD in the acute phase of two pediatric cases of FIRES and their long-term outcome. Both children were treated with several ASMs, immunomodulators, anesthetics, and nonpharmacological treatment (ketogenic diet). CBD was administered, as an adjunctive treatment, through nasogastric tube about 30 days after onset. SE resolved within 3 days of reaching the target dose and both were seizure-free for 1 year after. Although it is difficult to define the extent to which each previous therapy contributed to recovery, in both cases CBD therapy was a turning point, reinforcing its potential role as add-on treatment in the acute phase of FIRES.

KEYWORDS

CBD, cytokine, neuroinflammation, status epilepticus

1 | INTRODUCTION

Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy affecting previously healthy individuals. Its occurrence is extremely rare, with an estimated incidence of one per million.[1] FIRES is characterized by the onset of new-onset refractory status epilepticus (NORSE) between 2 weeks and 24 h after a febrile infection.[2-4] Typically, seizures increase in frequency and duration and show minimal response to antiseizure

medications (ASMs) over a period of 2–7 days after onset.[5] High rates of mortality in the acute phase of FIRES are described and delays in diagnosis and administration of appropriate therapies may contribute to poor prognosis, with frequent evolution into chronic, drug-resistant epilepsy and severe cognitive and behavioral impairment.[2,3,4,6] Therefore, the achievement of timely therapeutic success is crucial in the acute phase of the syndrome.

Other than the early administration of traditional ASMs and immune modulatory drugs, the use of cannabidiol (CBD) has been suggested at any time during the course of the disease as an adjunctive treatment to modulate epileptogenesis.[3,5,6,7] Nevertheless, literature evidence about its use in the acute phase of FIRES is poor and very few cases have been reported with uncertainty regarding the efficacy. Long-term outcome data are also lacking.[6,8]

Here we report the use, efficacy, and tolerability of highly purified CBD in the acute phase of two pediatric cases of FIRES and their long-term outcome.

2 | CASE 1

A four-year-old boy with no personal or familial history of neurological disease presented with high fever and pharyngitis resolved in 3 days. Two days later, sleepiness and hyporeactivity appeared and the child was admitted to the Emergency Department (ED); while in ED he developed repeated focal impaired awareness seizures characterized by behavior arrest, upward deviation of the eyes, sialorrhea, and oral automatisms. Fever up to 38°C and low oxygen saturation were also found. After the failure of the first-line therapy, he underwent intubation and was transferred to the Pediatric Intensive Care Unit (ICU). The video-electroencephalogram (EEG) recording showed nearly continuous clinical and electroclinical seizures, and a diagnosis of FIRES was provided. The boy underwent different paraclinical investigations without any findings hinting at a specific etiology (Table 1).

Many therapeutic strategies were applied (Figure 1) with limited response. Even the induction of burst suppression electrical pattern with anesthetic agents did not stop the electrical seizures. On day 8, a ketogenic diet (KD) was started but soon after stopped because of hypertriglyceridemia.

On day 26 CBD and clobazam (CLB) were started via nasogastric tube (NGT), concomitant with phenobarbital dose rise. CBD was initially administered at a dosage of 6 mg/Kg/day, rapidly increasing up to 12 mg/Kg/day in 4 days. Electroclinical seizures gradually reduced in frequency until they disappeared on day 33. The boy was then extubated and transferred to the Child Neurology ward; after intensive rehabilitation, there was almost complete recovery of neuromotor, cognitive, and communicative competencies. He was seizure-free for 1 year when then presented with structural focal seizures as a consequence of hippocampal sclerosis.

3 | CASE 2

A six-year-old boy with unremarkable personal and family medical history developed fever, dry cough, and maculopapular erythema of the lower limbs 17 days after measles-mumps-rubella and diphtheria-tetanus-pertussis vaccination. Symptoms resolved after ibuprofen and paracetamol administration at home but, 2 days later, he presented a first focal impaired awareness seizure characterized by behavior arrest, right deviation of the eyes, and ipsilateral clonus. The child was admitted to the local hospital and seizures rapidly evolved into refractory status epilepticus (SE); therefore, he was promptly transferred to the Pediatric ICU of our hospital, as a third-level regional hub. The EEG showed nearly continuous clinical and electroclinical focal seizures.

Although a diagnostic work-up was performed to rule out any infectious, autoimmune, and metabolic etiology, all investigations were unrevealing (Table 1). A diagnosis of FIRES was provided.

As in the previous case, several ASMs, anesthetic drugs, anti-inflammatory, and immunomodulatory agents were administered (Figure 1), with partial or no effect. Nineteen days after SE onset he started a standardized KD with a 3:1 ratio, which did not provide any improvement. CBD and CLB were started as add-on therapy 31 days after SE onset via NGT. CBD was initially administered at a dosage of 4 mg/Kg/day, increasing up to 20 mg/Kg/day in 11 days. After the introduction, he gradually improved, with a complete seizure recovery 3 days after reaching the full dose. Moreover, interictal epileptiform abnormalities on the EEG gradually disappeared. The child was then transferred to the neuropediatric ward and underwent intensive rehabilitation. He was discharged almost 3 months after the onset, seizure-free, with only mild cognitive difficulties. Since then, he has been seizure-free.

Both patients received the same plant-derived pharmaceutical formulation of highly purified CBD according to the local clinical practice for off-label medications. We obtained the consent of parents and local ethic committees.

4 | DISCUSSION

Our reports highlight the potential efficacy of highly purified CBD as add-on therapy in the acute phase of FIRES. In both our cases, SE persisted for a long time despite

TABLE 1 Investigations at onset, EEG characteristics, outcome, and follow-up.

		Case *n*°1	Case *n*°2
Investigations at onset	*CSF*	Leucocytes 11/mmc (98% lymph). Normal Link and barrier indexes.	Leucocytes 12/mmc (91.6% lymph). Normal Link and barrier indexes
	*Autoimmune screening on CSF and serum**	Negative	Negative except for weakly positive GluR3 on serum
	*Infectious screening on blood, CSF, and urine**	Negative	Ab Anti SARS Cov-2381 U/mL on serum
	Inflammatory markers	INF Score for INFα on blood: 26.77 (versus controls 4.67)	Cytokines on CSF: IL1β, IL12p70 and TNF-α not detectable, IL6 295 pg/mL, IL8 2152 pg/mL, IL10 2 pg/mL
	Brain MRI	Day 2: MRI T2 hyperintensity in left hippocampus. Mild cortical alterations in right F-insular area. Day 13: evolution in left hippocampal sclerosis; mild diffuse atrophy or pseudoatrophy	Day 2: Normal Day 6: Normal Day 20: Normal Day 59: Normal
EEG characteristics	*Epileptiform discharges*	Focal high amplitude spikes and waves (FT mostly right with SG)	Focal right FT fast activity followed by rhythmic spike and spike-and-wave complexes, then shifting to the contralateral side
	Burst suppression achieved (days since onset)	3	8
	Duration of burst suppression	5	7
Outcome and follow-up	*Status epilepticus recovery (days since onset)*	33	45
	Duration of ICU stay (days)	37	44
	Duration of hospital stay (days)	54 + rehabilitation center	96
	Outcome at discharge (MRS score)	moderate disability (3/5)	mild disability (2/5)
	Last FU (months since onset)	24	13
	Outcome at last FU (MRS score)	No disability (1/5): Short-term memory difficulties and speech fluency disorder	No disability (1/5): Difficulties in visual reasoning skills and verbal memory; speech fluency disorder
	ASMs *at last FU*	CBD, CLB, OXC, LEV	CBD, CLB
	EEG at last FU	Focal left T and F abnormalities	Normal
	MRI at last FU	Left hippocampal sclerosis	Normal

Note: *further details are provided in the supplements.

Abbreviations: ASMs, anti-antiseizure medications; CBD, cannabidiol; CLB, clobazam; CSF, cerebrospinal fluid; EEG, electroencephalogram; F, frontal; FU, follow-up; ICU, intensive care unit; LEV, levetiracetam; lymph, lymphocytes; MRI, magnetic resonance imaging; MRS, modified Rankin scale; OXC, oxcarbazepine; SG, secondary generalization; T, temporal.

several ASMs, immunomodulatory or anesthetic drugs, or KD, but resolved within 3 days after the achievement of CBD's target dose.

Despite the recent proposal to consider the use of CBD at any time during the course of the disease,[5] there are only four reports in the literature regarding its therapeutic application in the early stages of the disease: Gofshteyn et al. described two children treated with CBD and CLB after 19 and 33 days from the syndrome onset: SE ceased in one patient; the other experienced a change in seizure frequency but passed away a few days later due to isoflurane-related multiorgan failure.[6] Sa et al. reported two cases of

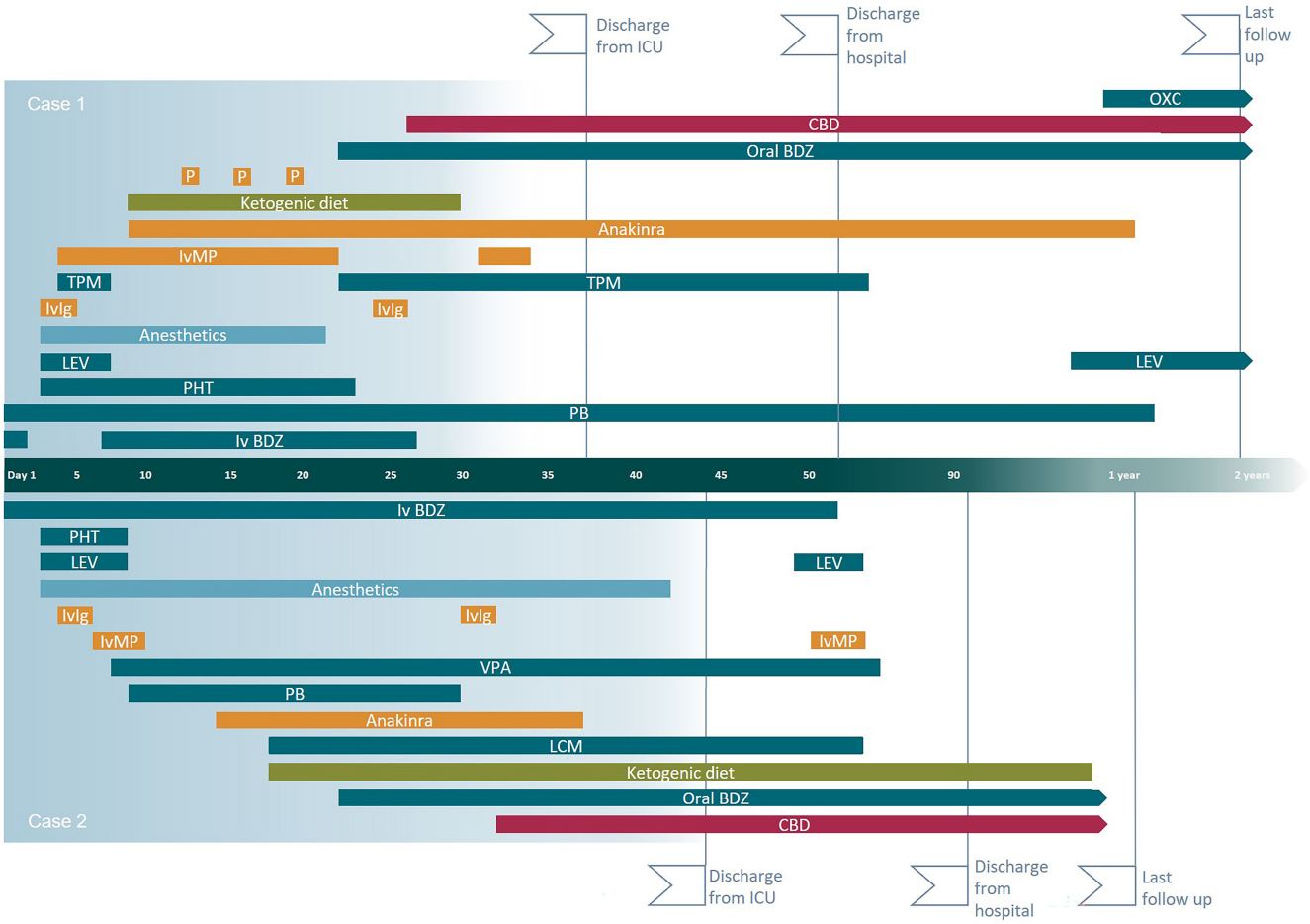

FIGURE 1 Treatment timeline. Case 1 is represented above the timeline and case 2 below. The different treatments are graphically arranged in order of use from oldest to newest from bottom to top for case 1 from top to bottom for case 2. BDZ, benzodiazepines; CBD, cannabidiol; ICU, intensive care unit; IvIg, intravenous immunoglobulins; IvMP, intravenous methylprednisolone; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; P, plasmapheresis; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproate.

FIRES in which CBD was added to KD or Anakinra in the acute phase (day 14 and 20 from the onset, respectively), with no clear-cut efficacy in reducing seizure frequency, consequently, other therapeutic strategies (i.e., deep brain stimulation) were pursued.[8]

The rationale of CBD's therapeutic role in the syndrome's acute phase is unclear and remains to be determined; this implies a deeper understanding of the still debated etiopathogenesis(s) of FIRES and the mechanisms leading to poor acute and long-term outcomes.

The most current evidence suggests a dysregulation of innate immunity with a functional deficiency of anti-inflammatory pathways: among predisposed individuals, febrile infections may induce a fulminant cytokine-mediated inflammation in the central nervous system (CNS) resulting in seizure threshold reduction.[4,5,9,10] The onset of recurrent seizures provokes acute receptor changes (such as internalization of GABA receptors, reduction of presynaptic adenosine A1 receptors, and NMDA expression increase) that contribute to the development of a vicious cycle of aberrant hyperexcitability and refractory SE.[5,11,12] Eventually, this will result in neuronal death caused by intracellular calcium accumulation, adenosine triphosphate (ATP) depletion due to mitochondrial dysfunction, and excessive reactive oxygen species (ROS) production through NADPH.[13] The frequent finding of proinflammatory cytokine profiles and the efficacy of anti-inflammatory and anticytokine therapies in treating the condition support this hypothesis.[3,9,10,14-19]

In both of our cases, there was evidence to suggest a cytokine storm: interferon score for IFN alpha (i.e., quantitative measure for IFN alpha cascade gene expression) was measured in Case 1 as a research protocol proving six times higher than controls, confirming a cytokine-mediated pathway of inflammation.[20] In Case 2, cytokines were measured on CSF and serum at different stages of the disease, and interleukin (IL)-6 was increased on CSF in the acute phase, consistently with literature data.[21]

Interestingly, the mechanisms underpinning CBD's modulatory effect on neuroexcitability seem to target

several key molecules involved in the pathogenesis of FIRES and its acute and long-term outcomes. Indeed, CBD reduces microglia-mediated neuroinflammation by decreasing proinflammatory cytokines and chemokines (TNF-α, IL-1β, IL-6) through inhibition of TLR4-NFkB and IFN-b-JAK–STAT pathways.[22,23] Moreover, CBD's TNF-a suppressive effect is linked with the inhibition of adenosine reuptake anti-inflammatory effects and reduction of neuroexcitability.[23,24] CBD also activates and desensitizes the microglial transient receptor potential vanilloid type 1 (TRPV1) channel, whose activation is shown to mediate persistent neuroinflammation.[23,24] Ultimately, CBD reduces ATP release, intracellular calcium accumulation, and ROS production through the inhibition of NADPH oxidase.[23]

It is, therefore, conceivable that CBD may have helped in counteracting the proepileptogenic mechanisms induced by both the initial immune dysregulation and the persistence of the SE itself. However, it is likely that several, not yet completely understood, mechanisms underlie the action of the endocannabinoid system in modulating epileptogenesis.[7]

Moreover, given the complex pathogenesis of the disease and its refractoriness to drugs, critically ill patients with FIRES undergo several therapies in the acute phase of the disease and the definition of the exact extent to which each therapy contributes to FIRES resolution is challenging. Both cases 1 and 2 started KD about 2 weeks before the administration of CBD. While the first rapidly discontinued it for adverse effects, the second was kept on it and SE persisted for 12 days after reaching ketosis. Ketogenic diet is currently a preferred treatment of choice for FIRES over prolonged drug-induced coma because of broad anti-inflammatory and neuroprotective properties mediated by ketone bodies, caloric restriction, polyunsaturated fatty acids, and gut microbiota modifications.[25] Nevertheless, an additive effect of KD and CBD cannot be excluded in this case.

Anakinra, a recombinant IL-1 receptor antagonist (RA), is also widely used in the acute phase of FIRES. Its role is pivotal in a subset of cases in which a functional defect of the endogenous IL-1RA leads to IL1β epileptogenic pathway activation.[10,16,26] High levels of IL-1RA in the CSF can predict such therapeutic response.[10] Unfortunately, laboratory tests for this cytokine were not available in Case 1 and Case 2. Conversely, IL-1β was tested in Case 2 and turned out normal. Anakinra was administered in both patients on days 8 and 14, respectively, with no clinical change in the following days. Case 1 received CBD together with Anakinra and other ASMs, after KD discontinuation, Anakinra and CBD's combined role against neuroinflammation may have contributed to the favorable outcome in this case.

In both cases, CBD was administered together with CLB. Multiple studies have demonstrated a bidirectional interaction between these two drugs, resulting in increased exposure to the active metabolite of each.[27-29] Moreover, pivotal trials on Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS) found CBD added on to pre-existing ASMs (mostly CLB) to be superior to placebo in improving seizure control, leading regulatory agencies to state the prescription of CBD together with CLB for these syndromes.[30,31] Conversely, more recently, both a pivotal clinical trial on CBD in Tuberous Sclerosis and a meta-analysis on CBD in DS and LGS supported CBD's independent antiseizure activity and efficacy from CLB.[32,33] Therefore, there is no conclusive data on this interaction and a synergic action cannot be excluded in our cases either.

Administration through nasogastric tube, despite the high lipophilicity of CBD, was effective in our cases, as assumed by the rapid clinical turnaround after initiation of therapy. However, the actual absorption rate could not be estimated, and blood levels of CBD are not used in clinical practice due to the lack of correlation with administered dose and antiseizure efficacy.[34]

Both children continued CBD therapy for a long time after discharge and are still on it with no evidence of side effects and almost complete recovery, suggesting good safety and efficacy profiles also in the follow-up. In the case where focal epilepsy of structural etiology occurred secondarily as a likely consequence of hippocampal sclerosis induced by the prolonged SE[35,36], however, additional therapy was required.

5 | CONCLUSIONS

In conclusion, we reported two cases treated with highly purified CBD in the acute phase of FIRES.

Our experience supports the use of CBD as an add-on therapy in the initial stage of FIRES, during which it may contribute to the resolution of SE by modulating proepileptogenic activity.

Further studies are needed to systematically investigate CBD effect on the pathways that drive neuroinflammation and neuroexcitability in FIRES, and the likely synergistic role with the other treatments.

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CONFLICT OF INTEREST STATEMENT

DC served as consultant for Alexion, GW Pharmaceuticals, PTC Therapeutics. The remaining authors have no conflict to disclose.

ETHICAL APPROVAL

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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