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Off-label use of cannabidiol in genetic epileptic and developmental encephalopathies: A case report

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ABSTRACT

Developmental Epileptic encephalopathies (DEEs) are severe neurological conditions where cognitive functions appear modulated by both seizure and interictal epileptiform activity. Cannabidiol (CBD) has been shown to be highly effective in the treatment of drug-resistant seizures in patients with DEEs. Along with its antiseizure effects, CBD demonstrated clinical beneficial effects in patients' quality of life, sleep and numerous adaptive behaviors. However, based on the available phase III studies, the indications for this treatment have so far been restricted to Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS) and tuberous sclerosis complex (TSC) by regulatory authorities. We present the case of a 30-year-old girl with a rare genetic DEE, experiencing relevant seizure frequency reduction together with striking improvement in sleep quality, mood, behavior, language and motor skills after introducing off-label CBD.

Introduction

Developmental and epileptic encephalopathies (DEEs) are severe, early-onset syndromes characterized by refractory seizures, developmental delay or regression commonly associated with persistent epileptic activity and poor prognosis. DEEs are often associated with other neuropsychiatric comorbidities and/or movement disorders, frequently requiring aggressive management and treatment [1,2]. A higher risk for sudden-unexpected death in epilepsy (SUDEP) is also described in DEEs [3]. Due to inner complexity of these conditions, the goal of antiepileptic treatment in DEEs, together with seizure control, should, more than ever, focus on ameliorating quality of life, mood, quality of sleep and daytime interactions.

In 2018 the first plant-derived, purified, pharmaceutical-grade cannabidiol treatment (CBD) was approved by Food and Drug Administration (FDA) for two DEEs, namely Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) [4]. In 2020, tuberous sclerosis complex (TSC) has been added to the indications of the drug. Its utilization for other DEEs is still based on off-label individual authorization.

We describe the case of an Italian woman with 12q trisomy associated with drug-resistant epilepsy experiencing astonishing benefit with CBD, in terms of epileptic seizures control, daytime functioning and quality of life.

Case report/Clinical vignette

AS is a 30-year-old Italian woman affected by a rare genetic DEE caused by partial 12q trisomy with intellectual disability, drug-resistant focal epilepsy, insomnia and severe behavioural and sleep disturbances. Her medical history was also remarkable for type 1 diabetes mellitus and bilateral neurosensorial hypoacusis. Born after prolonged labour dystocia, she presented her first absence seizure twelve days after birth. By the age of 8, she began experiencing focal non motor seizures with staring, right head deviation and loss of consciousness, sometimes with bilateral tonic-clonic evolution. During adolescence, she was subjected to weekly atypical absence seizures with staring and blinking, particularly during the evening and night periods, with a frequency increase during catamenial periods. She also developed one episode of non-convulsive status epilepticus during a viral gastroenteritis. Hence, when she came to the attention of our adult epilepsy center, she had

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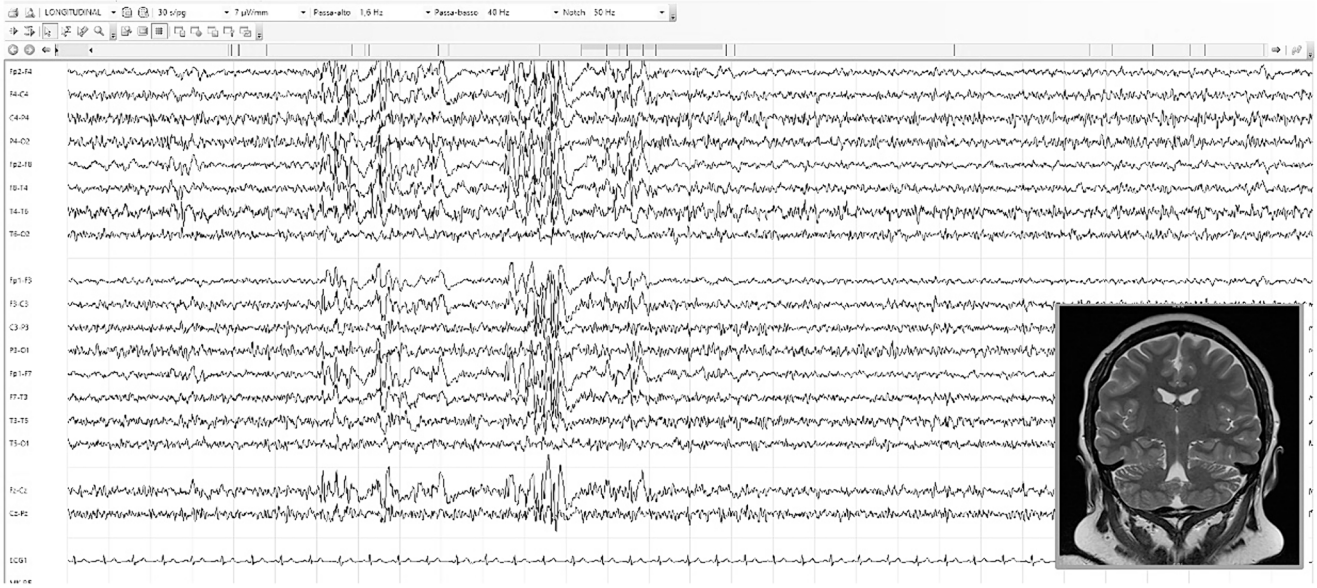

Fig. 1. Patients' EEG (longitudinal, 30 sec/page, 7 μV/mm) and brain MRI (high-resolution 2D T2 image). Notice the abundant generalized high-voltage sharp-waves predominant in the anterior regions in particular in the right hemisphere. Background activity shows theta rhythm (7–8 Hz) with a good reaction to eyes' opening.

experienced both focal (at the time with an estimated weekly frequency) and rare generalized epileptic manifestations.

Her brain magnetic resonance imaging (MRI), performed respecting the International League Against Epilepsy Neuroimaging Task Force recommendations (HARNESS protocol) [5] was deemed as unremarkable, while her electroencephalogram (EEG) showed numerous spikes, sharp and spike-waves located over fronto-temporal areas, with right predominance and occasional generalized 3 Hz spike and waves complexes (Fig. 1). Over the years, she has been treated with several anti-seizure drugs, either in monotherapy or in combination, including valproic acid, lamotrigine, topiramate, lacosamide and clobazam, but never reached seizure-freedom.

Given the persistence of monthly recurrent focal and generalized seizures, in April 2023, CBD was prescribed, starting with 5 mg/kg twice per day, titrated up to 7.5 mg/kg twice per day. At that time, the patient was on poly-therapy with topiramate (500 mg/day) lacosamide (600 mg/day) and clobazam (the latter used only as perimenstrual prophylaxis). Shortly after the drug introduction, her parents noticed some huge multi-level changes: she was more reactive and prone to social interaction, with improved language skills. In parallel, her sleep was described as more refreshing and continuative, with less awakenings during the night. Her behavioral disturbances, including attention-related difficulties and hyperactivity, greatly improved. She also experienced a significant benefit in terms of seizure frequency which changed from monthly before the introduction of CBD to sporadic; over 1 year of follow-up her parents reported only three brief non-motor seizures with staring and right head deviation (no seizure diary was available). A moderate reduction of epileptiform discharges on her interictal EEG was also noticed. Unfortunately, given her important behavioral and cognitive difficulties, neither the administration of conventional test to objectively measure some of her clinical improvement nor a full-night video-polysomnographic recording were feasible. Remarkably, no side effects associated with CBD were reported.

Discussion

Our patient, with a rare genetic DEE, besides a noteworthy reduction in seizure frequency, presented substantial improvement in language, social behavior and sleep after the authorized off-label introduction of CBD. She is affected by a balanced parental translocation between chromosome 2 and 12, with monosomy for the segment 2q37.3-2qter and trisomy for the segment 12q24.31-12qter. This condition is typically associated with severely retarded growth, intellectual disability and distinctive facial features, speech, communication and behavioural problems [6]. Lautaro Plaza-Benhumea and colleagues recently published the first case of a patient with a 12q24.21-12q24.33 duplication and drug-resistance epilepsy, which had been previously rarely described in patients with 12q trisomy [7].

According to current ILAE definition, in patients with DEEs seizures, both interictal epileptiform activity and the whole neurobiological process underlying epilepsy are involved in the establishment of patients' cognitive profile, thus it is mandatory to introduce an aggressive treatment to reduce the overall burden of epilepsy and mitigate the EEG anomalies [2].

The underlying mechanism of CBD in humans is still partially unknown: it is supposed to be multimodal, involving also non-cannabinoid pathways, which may explain its strong anti-inflammatory and neuroprotective activity. So far, around 56 different neurological molecular targets of CBD including enzymes, ion channels, ionotropic, and metabotropic receptors have been identified [8,9]. Besides molecular changes, some important variations in the brain connectivity profile had also been observed. These involved in particular modifications of brain resting-state functional connectivity, with stronger changes in the inter-regional connections between the vermis, amygdala, hippocampus and frontal cortex [10]. Similarly, CBD have been proved to modulate the attention processing by influencing the functional connectivity between the superior frontal gyrus and insula/middle frontal gyrus [11]. In our patient, unfortunately, we do not dispose of neuro-functional data to confirm these preliminary observations, due to her limited cooperation.

Evidence on the clinical benefits of CBD beyond its antiepileptic properties is still scarce, although there is growing scientific interest in this topic. To date, CBD has been authorized by EMA only for treatment of DS, LGS, and TSC [12–14]. However, several studies, mainly case reports and open-label studies, suggest the existence of neurological benefits also beyond these three epileptic syndromes [13,15–18]. Rosemberg et al. published in 2017 an open-label clinical study showing a significative improvement in the caregiver-reported QoLCE (Quality Of Life of Childhood Epilepsy; 8.2 +/− 9.9 points of difference) in a subset of 48 children and young adults affected by severe drug-resistant epilepsy after 12 weeks of therapy with CBD [19,20]. Similarly, another

Table 1
. Main clinical outcomes of CBD according to epilepsy condition or etiology (adapted from Lattanzi et al. 2021).

Epilepsy condition/ etiology	Population	Main findings
Tuberous Sclerosis Complex	N = 224, N = 2, N = 18, N = 25, N = 3	Reduction in TSC-associated seizure frequency: 47.5 % (CBD50), 48.6 % (CBD25), 26.5 % placebo (26.5 %) Cognitive gains 12/14 (85.7 %), behavioral improvement 6/9 (66.7 %)
Aicardi syndrome	N = 19	Median decrease in convulsive seizure frequency: 58.3 %-59.2 %
CDKL5 deficiency	N = 1, N = 20, N = 5	Seizure frequency reduction: 100 %
Doose syndrome	N = 2, N = 8	Seizure frequency reduction: 54–100 %
Dup15q syndrome	N = 1, N = 8	Seizure frequency reduction: 26 %
Sturge-Weber syndrome	N = 5	Seizure frequency reduction: 12–100 % All patients reported improvements in quality of life, speech and cognitive abilities, level of alertness, vocalization and communication, mood and behavior
SYNGAP1 DEE	N = 3	Seizure frequency reduction: 0–85 % (M2), 80–95 % (M9)
SCN8A EE	N = 1	CBD dose was reduced for side effects and discontinued after 25 months for inefficacy
Rett syndrome	N = 1	CBD dose reduction for side effects and discontinued after 6 months for inefficacy.

DEE = Developmental and epileptic encephalopathy; EE = Epileptic encephalopathy; CBD25 = cannabidiol 25 mg/kg/day; CBD50 = cannabidiol 50 mg/kg/day; M2 = month2; M9 = month9; TSC = Tuberous sclerosis.

clinical trial reported positive results on quality of life and mood after one year of treatment, regardless of changes in seizure frequency, in an adult cohort of 53 patients affected by treatment-refractory epilepsy [21]. Moreover, in a large multicentric cohort study involving 311 patients, of whom 206 children and adolescents treated with CBD off −label due to epilepsy subtype, beyond a reduction in seizure frequency, patients experienced improvements in mood, sleep, development and concentration, as well as an increase in appetite and a reduction in spasticity. Interestingly, the results for patients with LGS, DS and TCS were not significantly different from other epilepsy subtypes [15]. Finally, a recently published systematic review analyzing 42 studies on the use of CBD in patients with epileptic syndromes other than those mentioned above, including rare genetic epileptic and developmental encephalopathies, showed that a good treatment response can be seen in patients across a broad range of epilepsy disorders and DEEs [12,16] (Table 1). In this review, the sustained seizures' reduction and stable EEG improvement suggested a protracted efficacy of the drug.

Our patient experienced a great amelioration in her behavior, mood and cognitive performances, with striking improvement in her interaction with people (see box 1 on patient experience), together with seizure improvement and EEG amelioration, with no relevant side effects. We believe that her clinical course may be representative of the complexity of DEEs in adults, given the co-existence of epileptiform disturbances with severe cognitive and behavioral disorders, associated with a rare genetic mutation. The off-label utilization of CBD lead to a massive global improvement and seizure reduction, that lasted up to 12 months of observation. Molecular genetics and neurobiology will play a pivotal role in the comprehension of the pathophysiological mechanisms involved in several DEEs paving the way to new targeted therapies [9]. Meanwhile, growing knowledge on drugs' efficacy and underlying genetic mechanisms in specific DEEs might help to better understand the pharmacodynamic properties of new drugs which in some cases is still unclear [22].

Conclusion

Besides its antiseizures effect, CBD might lead to clinical beneficial effects in patients' quality of life, sleep, cognition and numerous adaptive behaviors. Hopefully, the growing interest in the CBD antiepileptic activity will lead to its use in other developmental and epileptic encephalopathies. Moreover, the simultaneous discovery of new pathogenic genes is expected to increase knowledge on specific epileptogenic mechanisms and shed light on CBD antiepileptic, neuroprotective and anti-inflammatory role. Further studies are needed to extend the use of new drugs to rarer syndromes.

Ethical statement

Hereby, I Dr Elisa Mannini, consciously assure that for the manuscript *'Off-label use of cannabidiol in genetic epileptic and developmental encephalopathies: a case report'* the following are fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.

2) The paper is not currently being considered for publication elsewhere.

3) The paper reflects the authors' own research and analysis in a truthful and complete manner.

4) The paper properly credits the meaningful contributions of co-authors and co-researchers.

5) The results are appropriately placed in the context of prior and existing research.

6) All sources used are properly disclosed (correct citation).

7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

CRediT authorship contribution statement

Elisa Mannini: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Francesco Misirocchi:** Writing – review & editing. **Stefania Lazzari:** Writing – review & editing. **Giulia Balella:** Writing – review & editing. **Dario Bottignole:** Writing – review & editing. **Maddalena Frapporti:** Writing – review & editing. **Lucia Zinno:** Writing – review & editing. **Irene Florindo:** Writing – review & editing. **Liborio Parrino:** Writing – review &

BOX 1
. Patient's experience in her parents word.

"The beginning of this new treatment wasn't easy, as our daughter dislikes to drink drugs. The first clinical benefits appear after 45–50 days…but it was worth waiting! She became more collaborative and interactive, but the biggest improvement was in her language production, She did not present any seizure relapse. Even the 'smaller ones' disappeared. She slept more regularly, and her small episodes of anger disappeared. This great behavioral improvement was confirmed also by the social assistants working with her each day. They described her as deeply changed, with higher predisposition for laughing with other people and ready to join the discussion. Her life had a great leap in quality with this new treatment".

editing, Supervision. **Carlotta Mutti:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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.

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