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Cannabidiol for treatment of refractory childhood epilepsies: Experience from a single tertiary epilepsy center in Slovenia

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ABSTRACT

Purpose: Refractory epilepsies in children present a major burden for patients and their families. Cannabidiol (CBD) has been suggested as a potential treatment for refractory epilepsies. The aim of this study was to evaluate the effectiveness of add-on therapy with CBD for the treatment of refractory childhood epilepsies.

Method: Patients with childhood-onset refractory epilepsy, treated at the tertiary epilepsy center of the University Children's Hospital Ljubljana, Slovenia, were included in the study. Add-on therapy with CBD was initiated once the child's epilepsy was categorized as pharmacoresistant to other antiepileptic drugs/therapies. The dosage of CBD was gradually increased to at least 8 mg/kg/day. The effect of CBD treatment was evaluated by the reduction in seizure burden and presence of side effects (positive and negative). Serial electroencephalography was performed in some children.

Results: Sixty-six patients were included in the analysis. Thirty-two (48.5%) patients had a more than 50% improvement regarding seizure burden, 14 of whom (21.2%) became seizure-free. None of the patients reported worsening of seizure frequency, but CBD had no effect in 15 (22.7%) patients. Some patients reported less vigorous seizures, shorter duration of seizures, shorter time to recovery, and other positive side effects of CBD treatment. Adverse effects were reported in 5/66 children.

Conclusions: In our cohort of patients, CBD was found to have potential benefits as add-on therapy for refractory childhood epilepsies, mainly by reducing seizure burden.

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1. Introduction

There is no simple and uniform definition of refractory (pharmacoresistant, intractable) epilepsy. In very broad and general terms, pharmacoresistance is the failure of seizures to come under complete control or acceptable control in response to antiepileptic drug (AED) therapy [1,2]. When AEDs fail, other treatment possibilities are available, such as ketogenic diet (KD), epilepsy surgery, vagal nerve stimulation, and, recently, treatment with extracts of cannabis containing cannabinoids [3–5].

The cannabis plant contains more than 100 cannabinoids that can have an effect on the human body through various mechanisms [6]. Cannabinoids that are derived from the plant are termed phytocannabinoids, and a wide range of synthetic cannabinoids has already been produced. The biological effects attributed to cannabis have mainly been linked to the phytocannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), both of which are present in cannabis in very high concentrations. However, other

cannabinoids are also present in cannabis in smaller amounts and are thought to be involved in the subtle modulation of medicinal effects (sometimes referred to as the entourage effect or synergy). This effect may be the result of their independent biological activity or through synergy with THC and CBD [7].

Compared with THC, CBD is frequently characterized as a nonpsychoactive or nonpsychotropic substance; however, these terms are inaccurate because CBD has prominent beneficial pharmacological effects on anxiety, schizophrenia, addiction, and possibly even depression [8]. A more accurate designation would be “nonintoxicating” substance as CBD is lacking the associated reinforcement, craving, compulsive use, and similar effects that are well-known for THC and that indicate drug abuse liability [8,9]. Until now, it has not been proven that CBD can be converted into THC in the human body, although under certain (extremely acid) conditions, this has been confirmed in “in vitro” studies [8]. In contrast to other newly developed AEDs, CBD remains an intriguing agent of unparalleled diversity of pharmacological effects without severe side effects [8]. Furthermore, there is a long list of new AEDs which have not improved the outcome of refractory epilepsies and show several side effects that influence the quality of life (QoL) of patients with epilepsies (as well as their families) nearly as much as the seizures themselves [10].

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At present, some clinical evidence exists that CBD can ameliorate epilepsy in both adults and children who are affected by refractory epilepsies, epilepsy syndromes, or epileptic encephalopathies and has a favorable side effect profile [10–12]. The only two randomized control trials published to date in peer-reviewed journals are trials on the efficacy of CBD for Dravet syndrome and Lennox–Gastaut syndrome [13, 14]. In the first study, 120 young adults with drug-resistant convulsive seizures due to Dravet syndrome were included. The median decrease in seizures in the treatment group was 38.9% versus 13.3% in the placebo group. In the second study (171 patients, aged 2–55 years), add-on CBD was found to be efficacious for the treatment of patients with drop seizures associated with Lennox–Gastaut syndrome and was generally well tolerated. For other indications such as tuberous sclerosis, phase 3 trials have also been completed, which suggests that CBD may also benefit patients with these syndromes [15]. Some anecdotal case reports describe dramatic improvement of seizure control [16,17]. It has also been shown recently that CBD may have a beneficial effect on a child's QoL, an effect which is independent of the seizure-reducing effect [18].

The main aim of this paper was to present our experience with a synthetic CBD preparation for treatment of the most severe cases of refractory childhood epilepsies in a single, third-level epilepsy center in Slovenia. We also describe particular cases where such treatment provided a significant improvement not only in the frequency and severity of the seizures but also in other aspects of the patient's wellbeing.

2. Materials and methods

In this retrospective study, electronic patient records of children, adolescents, and young adults who were given CBD preparation for treatment of refractory epilepsy in the period between February 1st, 2015 and July 31st, 2017 were reviewed. Patients were treated and followed up at the Department of Child, Adolescent and Developmental Neurology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia. The only Slovenian tertiary level epilepsy unit is a part of our department.

The CBD preparation we have used consisted of crystalline cannabidiol powder (>98% pure) produced by Bionorica®. This powder was mixed by our hospital pharmacy into an oily solution containing 100 mg of CBD per 1 ml. Cannabidiol was used exclusively as an add-on therapy. The request for CBD treatment was always raised by the child's parents who learned about this possibility from other parents or the media. Before the initiation of CBD treatment, basic blood tests were performed (full blood count, electrolytes, liver enzymes, ammonia). After the introduction of the CBD preparation into the treatment, all of the patients continued to receive their previous AEDs for at least 6 months before potential further modifications of treatment or discontinuation of CBD.

The starting dosage of CBD was 1–3 mg/kg/day, raising gradually each week up to a dosage that controlled the seizures or to a maximum of 16 mg/kg/day. Patients were clinically followed up regularly, at least 2 times during the initial 6 months of treatment. Once the CBD treatment has reached the therapeutic dosage, we repeated blood investigations and a follow-up electroencephalogram (EEG), and if clinically relevant, we repeated this at further follow-ups.

Seizure control was categorized as follows: no seizures, >90% improvement, 75%–90% improvement, 50%–75% improvement, 25%–50% improvement, <25% improvement, no improvement, and worsening of seizures, as reported by parents. The number of seizures per period of time was translated into categories of percentage of improvement. Parents were asked to report any possible side effects and any other (beneficial) effects.

Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS software version 24 (SPSS Inc., Chicago, IL, USA). To assess the relationship between a particular AED and an outcome, Pearson's chi-square test was used. As data

were not normally distributed, the Mann–Whitney *U* test was used for 2-group comparisons to get exact 2-tailed *p* values. Graphical data are presented as median with 95% confidence intervals (CI). A *p* value of <0.05 was considered as statistically significant.

All parents signed informed consent at the start of the treatment with CBD. The study was approved by Slovenian National Ethics Board No. 103/10/13.

3. Results

We have identified 70 patients who met the study inclusion criteria. Of these, 39 were boys (57%) and 31 were girls (43%); M/F ratio was 1.3:1. The median age of inclusion was 8.0 years, ranging from 0.5 year to 23.0 years. During the study period, 2 patients died: one had multiple cavernomas and died suddenly during sleep while the other had a confirmed genetic epileptic encephalopathy (SPTAN1 mutation) and died because of bronchopneumonia. Two patients were lost to follow-up. The final number of patients included in the analysis was 66.

The etiologies of epilepsies were as follows: a known chromosomal/genetic abnormality in 14 patients, morphological brain abnormality in 10 patients, hypoxic–ischemic brain injury in 6 patients, metabolic/mitochondrial disorder in 5 patients, known epileptic syndrome in 4 patients, postinfectious brain injury in 2 patients, and an undefined etiology for a refractory epilepsy in 25 patients. Of the patients with a known epileptic syndrome, 2 patients had Lennox–Gastaut syndrome, one had Landau–Kleffner syndrome, and one had Ohtahara syndrome. None of the patients in our cohort had Dravet syndrome, for which CBD therapy has been previously shown to be beneficial [19]. Patients were followed up for a median of 14.0 months, ranging from 6.0 to 29.3 months.

Patients were treated with 1–14 (median: 3) AEDs and/or a vagus nerve stimulator (VNS) prior to start of CBD treatment. Cannabidiol was added to 1–4 (median: 2) AEDs and/or VNS at the start of CBD treatment. Fig. 1 represents antiepileptic therapy used at the start of CBD treatment. Out of all patients included in the study, VNS was implanted in 4. The parameters of the VNS were not changed 6 months prior to or after the initiation of CBD treatment. None of the patients were on KD at the onset of CBD treatment although several have been on KD before the introduction of add-on CBD treatment.

The median starting dosage of CBD was 2.5 mg/kg/day (range: 0.5–5.0 mg/kg/day), divided into two daily dosages. In infants below 2 years of age, the daily dosage was divided into three dosages. The median therapeutic dosage was 8.3 mg/kg/day (range: 3.0–22.0

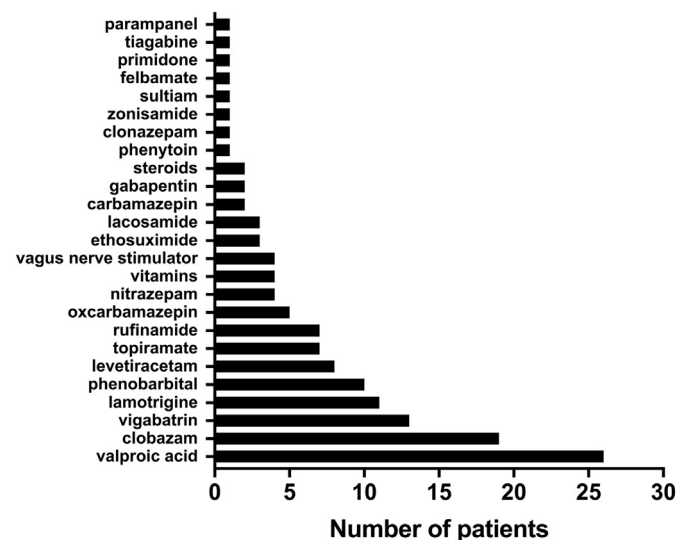


Fig. 1. Number of patients treated with a particular AED or VNS at the onset of CBD treatment.

mg/kg/day). The therapeutic dosage was considered to be 8 mg/kg/day; 53/66 patients reached either this (21/66 patients) or a higher daily dosage (32/66 patients). All parents were instructed to give CBD treatment separately from the other AEDs with a time gap of at least 1 h to avoid drug interaction. In some patients in whom at least 50% reduction of seizures was achieved, we have attempted to decrease the dosages of other AEDs at least six months after the start of CBD.

The outcome of CBD treatment regarding the frequency of seizures is presented in Table 1. Of all 66 patients, 32 (48.5%) had a 50% improvement or higher, 14 of whom (21.2%) became seizure-free. None of the patients reported worsening seizure frequency, although CBD treatment had no beneficial effect on seizure frequency in 15 (22.7%) patients. Fig. 2 represents the distribution of outcome regarding seizure frequency compared with the etiology of seizures. The number of patients in certain subgroups is too small to allow statistical analysis, but CBD therapy seemed to be more effective in the metabolic/mitochondrial etiology subgroup of seizures (4/5 patients) while it was not effective in any patient (0/4) with a defined epileptic syndrome. In some patients, there was no improvement regarding the seizure frequency; however, the parents observed less vigorous seizures in 6, shorter duration of seizures in 4, and shorter time to recovery in 4 patients.

Patients who became seizure-free did not have significantly higher maximum dosages compared with all other patients (median: 9.0 mg/kg/day vs. 8 mg/kg/day, respectively; $p = 0.32$). However, all patients who eventually became seizure-free received 6 mg/kg of CBD or more. There was no statistically significant difference in maximum CBD daily dosage between the group of patients who showed a $\geq 50\%$ improvement and the group that showed $< 50\%$ improvement ($p = 0.65$). Also, there was no significant difference in outcome between children receiving CBD dosage of 8 mg/kg/day and those receiving higher dosages ($p = 0.46$). Fig. 3 shows the relationship between outcome and 5 most frequently used AEDs before initiation of add-on CBD therapy. We did not observe any significant relationship between outcome (seizure improvement of 50% or higher) and any of the AEDs patients have received prior to add-on CBD therapy.

Electroencephalogram was not routinely performed as many of the patients had a severe encephalopathy with motor problems, which rendered EEG recording difficult to perform without sedation. Therefore, EEG has been performed only in patients in whom it could have been done without sedation or by using sleep deprivation. Electroencephalogram was recorded in 20 patients before and after the introduction of CBD. We have found that CBD may or may not improve EEG background activity and the frequency of epileptiform discharges, but these changes are not necessarily related to the presence of clinical seizures. Fig. 4 demonstrates a case where improvement of seizure frequency was accompanied by the improvement of EEG findings, and Fig. 5 demonstrates a patient in whom there was a dramatic improvement in seizure frequency, although the EEG results remained severely abnormal.

Adverse effects were reported in only 5/66 children (7.6%). One patient was adynamic, floppy, and not able to walk at a dosage of 20 mg/kg/day – after lowering the dosage to 10 mg/kg/day, the symptoms resolved. One patient, who was morbidly obese (100 kg) and was

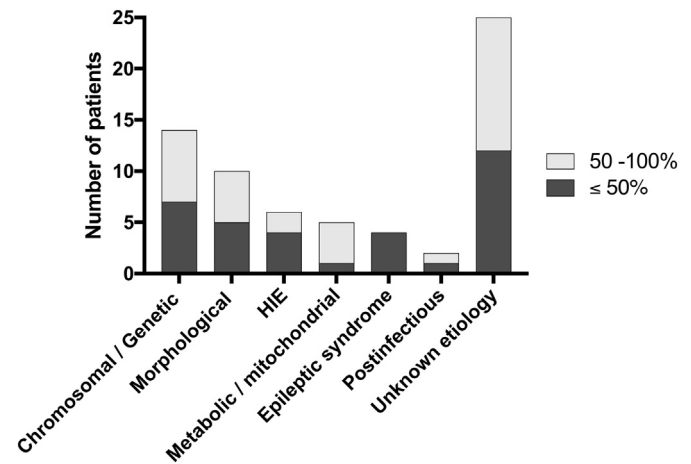


Fig. 2. Outcome in seizure frequency (more than 50% improvement or 50% improvement or less) related to seizure etiology.

receiving high dosages of CBD (1000 mg/day), reported nocturnal enuresis and appeared sedated – after decreasing the dosage to 800 mg/day, the symptoms resolved. Eosinophilia was found in one patient so the CBD treatment was discontinued even though the association between eosinophilia and CBD was not clear. The parents of one patient reported a yellowish skin discoloration but since bilirubin levels were found to be normal, the patient remained on CBD treatment. One patient complained about stomach pain, which was associated with slightly elevated liver enzymes that returned to normal when the dosage of CBD was lowered. In all of these patients, levels of concomitant AEDs were also measured in the blood but were within normal therapeutic ranges.

Other positive effects that were not related to seizure improvement were as follows (with some patients reporting more than one of these effects): improved behavior in 7, better sleep in 7, better gross motor functions in 5, increased alertness in 5, better cognitive functions in 3, better appetite in 3, increased joyfulness in 3, better speech in 3, better communication in 2, and better eye-to-eye contact in 2.

4. Discussion

Our results suggest that CBD has potential antiepileptic properties as it can decrease seizure burden in patients with refractory epilepsy while having a favorable side-effect profile. In 48.5% of all patients in our cohort, CBD treatment induced a 50% or higher improvement with regard to seizure frequency, and 21.2% of all patients became seizure-free, while none of the patients reported worsening of their seizures after

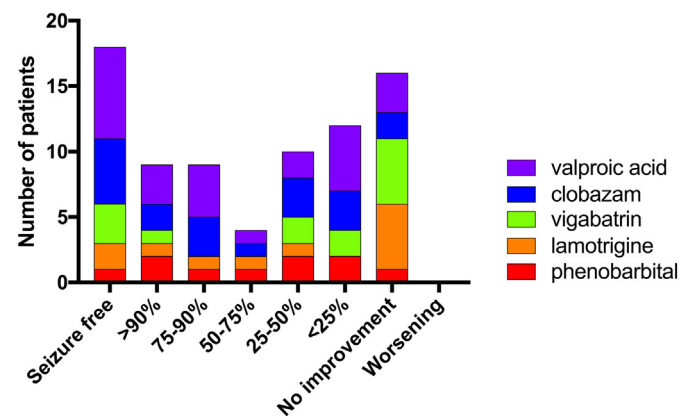


Fig. 3. Outcome related to the five most commonly used AEDs at the beginning of CBD treatment.

Table 1

Outcome regarding the percentage of seizures in a cohort of 66 patients treated with CBD.

Outcome	No. of patients (%)
Seizure-free	14 (21.2%)
>90% improvement	7 (10.6%)
75%–90% improvement	8 (12.1%)
50%–75% improvement	3 (4.5%)
25%–50% improvement	9 (13.6%)
<25% improvement	10 (15.2%)
No improvement	15 (22.7%)
Worsening of seizures	None

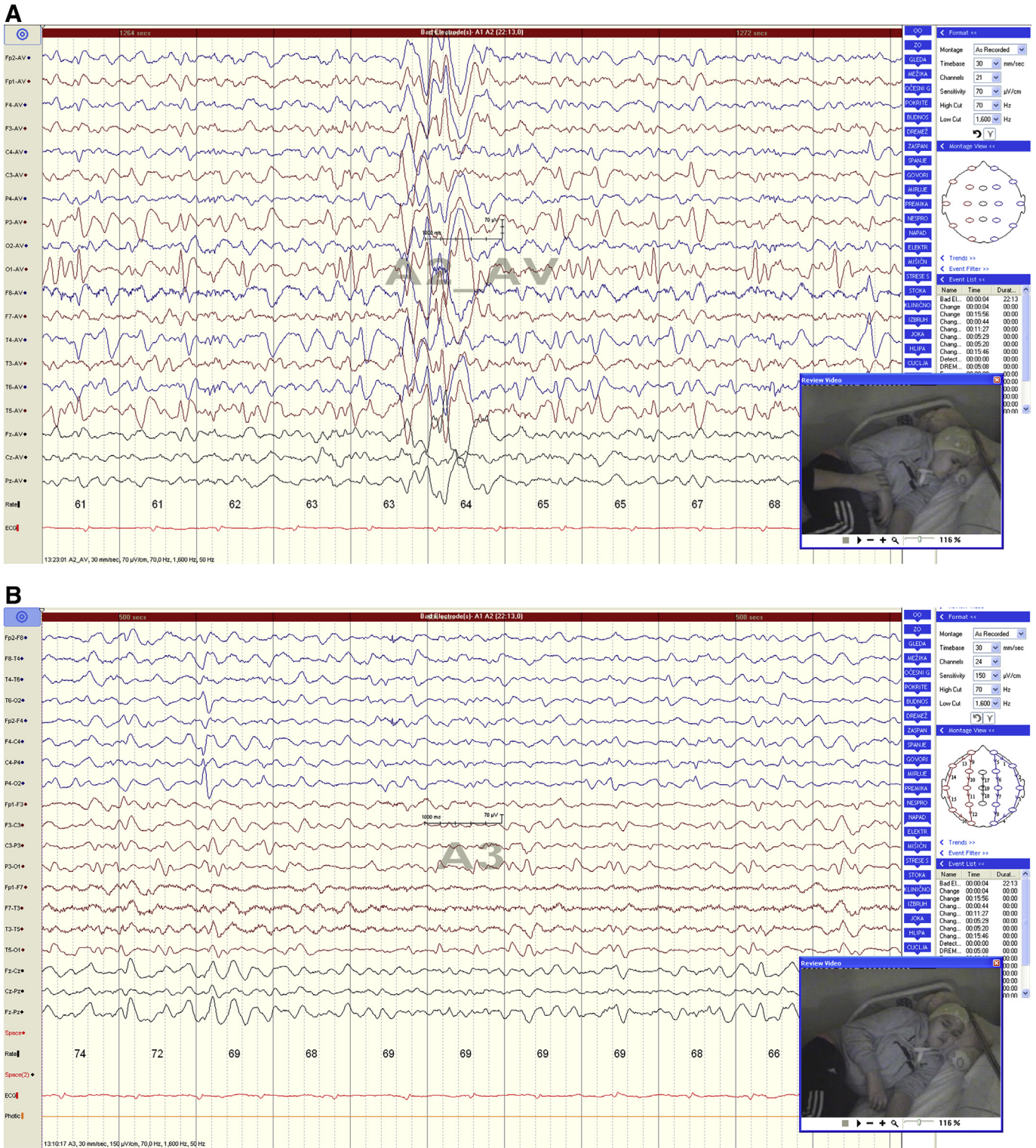


Fig. 4. A. An EEG record of a patient from the group with postencephalitic epileptic encephalopathy before the start of add-on CBD treatment: he had been on several AEDs before but at the start of CBD, he has concomitantly been taking clobazam and rufinamide and has had VNS implant. He had up to 30 seizures per day, mainly in the form of drop attacks. There are constant focal discharges over Lt occipital region and generalized discharge of spike and wave complexes. B. EEG recording of the same patient 6 months after add-on CBD treatment: more than 90% of the seizures were reduced. Still, few focal sharp waves are seen; otherwise, EEG is grossly improved.

the introduction of CBD. Some patients (5/66) did exhibit side effects not related to seizure frequency, for which parents discontinued CBD treatment.

A multicenter study from the USA published in 2016 revealed similar beneficial effects; however, the authors have used much higher dosages of CBD, up to 50 mg/kg/day [11]. We did not find any benefit in increasing

the dosage above 8 mg/kg/day, which was the median dosage in our cohort of patients. In fact, with dosages of 20 mg/kg/day and above, adverse effects appeared, which required lowering of the daily dosage of CBD. Similarly, in the study by Tzadok et al. [12], they have used CBD-enriched cannabis (with a CBD:THC ratio of 20:1) in a similar population of children with severe and intractable epilepsies. In their study, the CBD

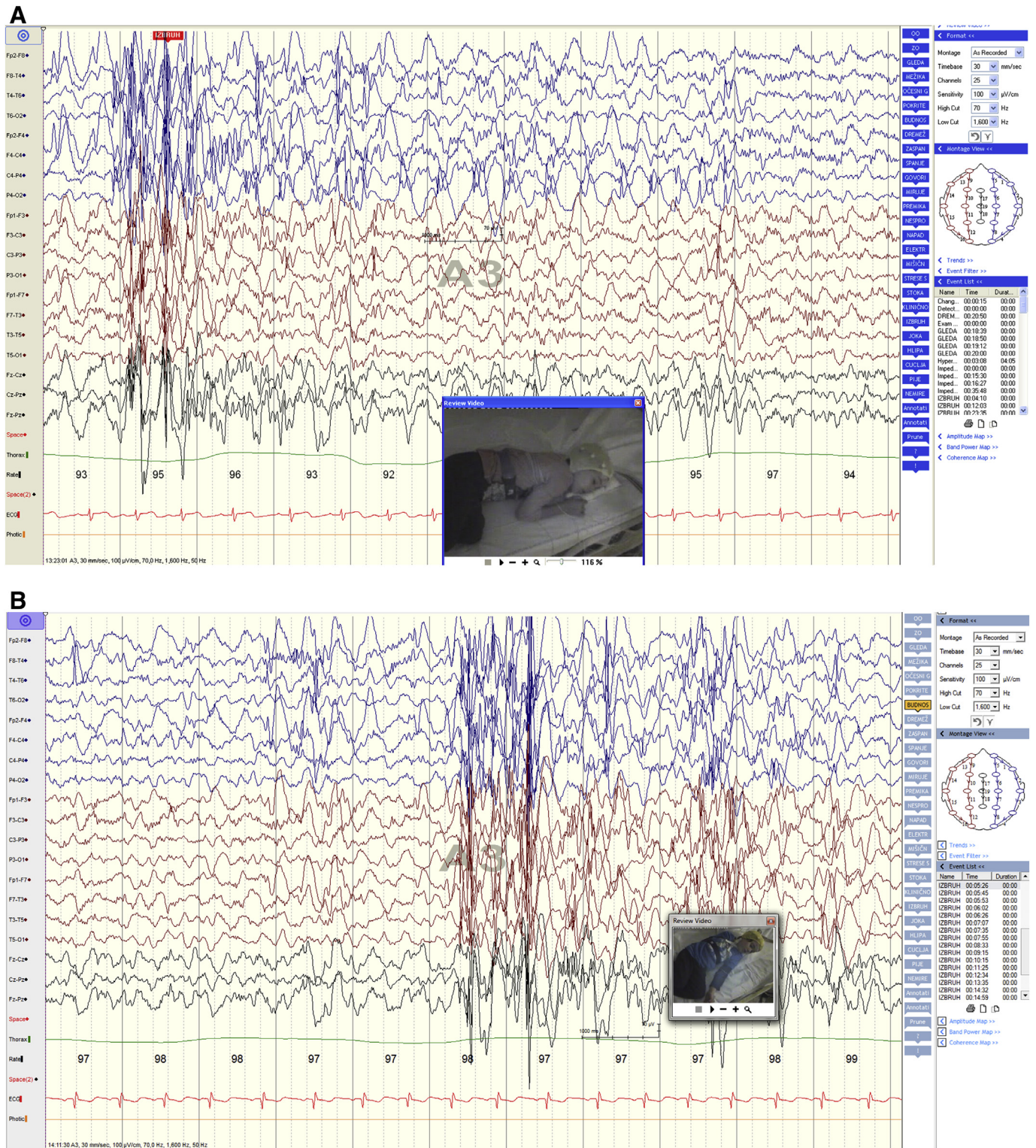


Fig. 5. A. An EEG record of one of the patients from the group with severe and intractable epilepsies/epileptic syndromes: he had absence epilepsy and has been treated with 4 AEDs before without much improvement. At the start of add-on CBD treatment, he has been concomitantly taking clobazam and lamotrigine and has had more than 3 absence seizures daily. His EEG is showing slow focal spike and wave complexes as well as generalized polyspike and wave discharges. B. An EEG record of the same patient 4 months after add-on CBD treatment: his seizures stopped completely; however, his follow-up EEG did not change at all.

dosage ranged from 1 to 20 mg/kg/day (two groups were formed: 1–10 mg/kg/day and 10–20 mg/kg/day). In our study as well as in theirs, dosages of CBD up to 10 mg/kg/day were found to be efficacious. Although the effect of treatment resulted in a similar seizure reduction (52% of the patients have had more than 50% reduction of seizures in an Israeli study), the results of failure are different (7% in their study vs. 22.7% in

ours, respectively). These results perhaps suggest that natural cannabis extracts exert a more beneficial effect because of the so-called “entourage effect” of other phytocannabinoids in natural cannabis, as claimed by some authors [9,20,21]. Recent studies support the notion that a combination of THC and CBD allows seizure control with much lower dosages of CBD [22,23].

Many parents share the opinion that a natural product is safer and more effective than a synthetic pharmaceutical agent [19]. However, CBD alone has a strong anticonvulsant effect, and it has no proconvulsant effect even at higher dosages, as 21 preclinical studies have shown [23]. In addition, none of the parents in our study reported worsening of seizures after the introduction of CBD. The use of pure CBD is more widely accepted by pediatricians as there are still many concerns related to expanded cannabis use [24]. It is also easier to use pure CBD because we know more about how it is metabolized and its interactions with other drugs than different combinations of CBD and THC in natural cannabis products [21,25–29].

Although CBD is mainly used to reduce seizure burden, it has other beneficial effects [23]. Cannabidiol can counteract many AED side effects, and many parents reported improved sleep, appetite, and development [23]. The same was found in our study as many children presented with beneficial side effects, which the parents considered important regardless of the effect of CBD on the seizure frequency. Some of the parents preferred to use CBD even if it had no significant effect on seizure burden as they were pleased with the beneficial effect of CBD on sleep, appetite, behavior, and cognitive functions. In our cohort of patients, the parents also observed shorter duration of seizures, less severe clinical presentation of seizures, and shorter time to recovery, all of which have been already reported in previous studies [23,30]. A recent report on QoL in pediatric patients who were enrolled in a study with cannabidiol has shown a significant improvement in caregiver-reported QoL in multiple domains, as well as in general [18].

There are not many reports on the effect of CBD or natural cannabis extracts on EEG. A short communication in JAMA reports the results of an intravenous infusion of CBD on the EEG activity of a patient with epilepsy [31]. The authors have shown in one patient that CBD did not decrease the abnormal epileptic activity and concluded that CBD might not have anticonvulsant effects on human epilepsy. However, in our study, CBD could have reduced seizure frequency, but this improvement was (Fig. 4) or was not (Fig. 5) related with the improvement of the EEG findings. The effect of CBD on EEG should be further evaluated by more elaborate studies. In the Israeli study that used enriched CBD, the dosage of other AEDs was gradually decreased once improvement was noted on EEG [12]. We lowered other AED dosages not according to EEG findings but according to seizure reduction. If the reduction was 50% or better six months after add-on treatment with CBD, other AED dosages were gradually reduced.

Our study has several limitations. As the study was retrospective, we did not have a baseline period with stable dosages of AEDs before starting the treatment with add-on CBD as some other studies had [11]. Our results could potentially be skewed towards overoptimistic conclusions about the efficacy of CBD because parents were the ones who needed to express their wish for their children to be treated with CBD and therefore could have been biased towards positive effects. Also, they were the ones who reported on the effect of CBD on seizure frequency. A control group of patients and blinded treatment, which we did not have in our study, could partially resolve such bias. The etiology of epilepsies could have been specific to our cohort of patients, which could influence the results as well. The EEG was planned to be done in all patients, but it was difficult to perform EEG recordings on the severely handicapped children without sedation, which could have altered the EEG background in addition to not being approved by some parents. Therefore, EEG has been performed only in patients in whom it could have been done without sedation or using sleep deprivation, which also proved to be quite feasible in children with cognitive and behavioral problems [32]. We were also not able to measure CBD concentration in the blood as this method still has to be developed in our laboratory. However, we did occasionally measure concentrations of some AEDs (especially in those who developed adverse effects after adding CBD) but never found levels increased over therapeutic limits. Finally, in the future, it would be interesting to make a crossover study comparing synthetic pure CBD and natural CBD-enriched cannabis.

5. Conclusions

Our data suggest that CBD can have a potentially beneficial therapeutic effect in refractory childhood epilepsy as it could reduce seizure burden with possible beneficial side effects and minimal negative side effects.

Conflict of interest

The authors do not have any conflict of interests to report.

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