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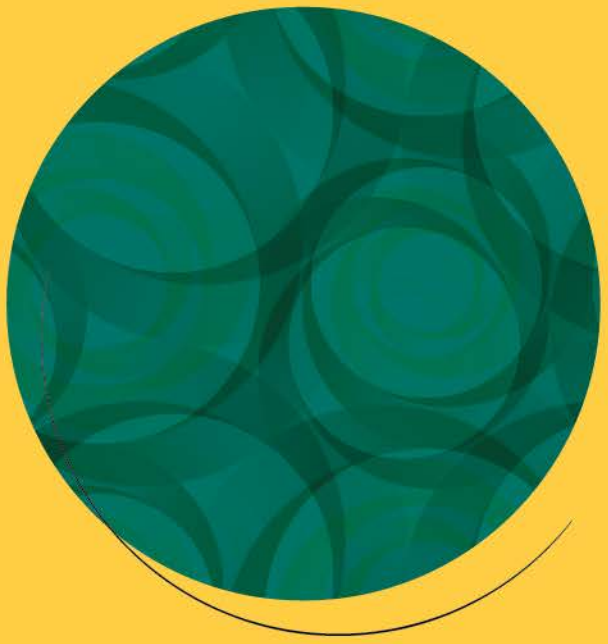

USE OF EPIDYOLEX®
in patients with Lennox-Gastaut syndrome or Dravet syndrome, within an early access program (EAP)

CASE REPORTS

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FOREWORD

Exploring a new class of antiseizure medications: purified cannabidiol oral solution (Epidyolex®)

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Keywords: cannabidiol, epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, antiseizure medications

Epilepsy is one of the most common neurological disorders, affecting around 70 million individuals worldwide, and its management is mainly symptomatic [1, 2]. One-third of patients continue to experience seizures despite adequate treatment, and the burden of refractory epilepsy has remained stable over recent decades despite increasing therapeutic resources, including third-generation antiseizure medications [3]. Hence, there is still a need to search for new effective options.

Cannabis has been used to treat epilepsy since antiquity, and interest in cannabis-based therapies has recently grown. However, the recent legal prohibition of cannabis, its biochemical complexity and variability, quality control issues, the previous dearth of appropriately powered randomized controlled trials, and the lack of pertinent education have all conspired to leave clinicians in the dark as to how to advise patients pursuing this treatment [4]. Cannabidiol (CBD), a major chemical of the resin of the *Cannabis sativa* plant, is a 21-carbon terpenophenolic compound formed following decarboxylation from a cannabidiolic acid precursor. CBD lacks psychoactive effects and, compared with conventional drugs, has a distinctive chemical structure and mechanism of action due to negligible affinity or activity at the cannabinoid receptors at clinically meaningful concentrations. It elicits its antiseizure properties by acting on multiple molecular targets, including antagonism of G protein-coupled receptor 55 (GPR55), desensitization of transient receptor potential of vanilloid type 1 (TRPV1) channels, and inhibition of adenosine reuptake [4, 5].

A plant-derived pharmaceutical formulation of purified CBD oral solution (Epidyolex®) has been recently approved by the US Food and Drug Administration and by the European Medicines Agency as adjunctive therapy in conjunction with clobazam for seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients aged 2 years and older.

The efficacy and safety of adjunctive CBD in these syndromes has been demonstrated in large multicenter, randomized, double-blind, placebo-controlled trials [2, 5, 6], showing a reduction of seizure frequency and generally good tolerability. Moreover, the results of an open-label extension trial (GWPCARE5; ClinicalTrials.gov number, NCT02224573) and an expanded access program provided further supporting evidence of the long-term effectiveness of add-on CBD in patients with drug-resistant epilepsy [7].

Controlled studies in other types of epilepsy, including refractory focal epilepsy, are warranted to further explore and fully understand the therapeutic potentialities of CBD. Nevertheless, the authorization of CBD for the treatment of childhood epilepsy is a milestone in the history of the medical use of cannabinoids to treat epileptic disorders. So far, Epidyolex® is the only pharmaceutical product deriving directly from the cannabis plant rather than produced synthetically that has undergone review through the approval processes, and it represents the first in a new class of antiseizure medications. Of interest, results cannot be transferred to other cannabis-derived products and non-purified forms of medical marijuana or its components.

This issue features a collection of five case reports illustrating the real-world utilization of Epidyolex® and guiding the use of oral CBD in everyday practice. A new class of medicine is probably born.

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Efficacy of CBD oral solution in an adult patient with Dravet syndrome and long-lasting drug-resistant epilepsy

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ABSTRACT

Background. *Our patient is a 24-year-old woman affected by Dravet syndrome due to a de novo SCN1A truncating variant. Her epilepsy began in the first year of life with recurrent febrile and afebrile seizures and episodes of focal motor status epilepticus. Despite many trials with appropriate antiepileptic drugs, she continued to have multiple weekly polymorphic seizures (absence-like, focal clonic and tonic with sporadic evolution to generalized tonic-clonic seizures).*

Methods. *In June 2019, when the patient was 23 years old, highly purified oral GW-cannabidiol (CBD) was added to the ongoing treatment (valproic acid and clobazam). CBD was started at 2.5 mg/kg twice daily for the first week and then 5 mg/kg twice daily with a concomitant reduction of clobazam.*

Results. *All types of seizures rapidly and progressively decreased and, after the first four months of CBD treatment, the patient presented only one nocturnal tonic seizure twice a week. This condition had remained unchanged at the last follow-up at 12 months. Caregivers reported increased irritability, and consequently CBD was slightly decreased to 4 mg/kg twice daily. Her behavior returned to the previous condition; seizures were reported to occur two to three times a week, mainly tonic during sleep with rare brief atypical absences during wakefulness. A slight increase of hepatic enzymes was observed, and valproic acid was reduced from 1000 mg/day to 800 mg/day with normalization of the blood results. No other side effect was reported.*

Conclusions. *The patient is currently taking CBD 4 mg/kg twice daily in combination with valproic acid 800 mg/day and clobazam 20 mg/day. Her seizures decreased globally by 90% with an associated positive impact on daily activities and a clear improvement of quality of life of the whole family.*

BACKGROUND

Our patient is the only daughter of unrelated Italian parents. She was born in 1996, and pregnancy and delivery were unremarkable. No family history of epilepsy, febrile seizures or other neurological disorders

were reported. At 4 months of age, she had her first febrile seizure the day after a vaccination and, over the following two years, different seizure types, either afebrile or afebrile, developed: unilateral migrating focal clonic, generalized tonic-clonic seizures, atypical absences and repeated episodes of focal clonic status epilepticus. A concomitant marked developmental regression was evident with appearance of ataxic gait, mood disorder and irritability/aggressive behavior. Electroencephalograms (EEGs) showed bilateral multifocal spikes and spike-wave discharges prevailing in the frontotemporal regions and increased during sleep with frequent bilateral synchronized discharges. A diagnosis of epileptic encephalopathy was made [1]. Different antiepileptic drugs were used in different combinations (phenobarbital, valproic acid, topiramate, ethosuximide, various benzodiazepines) without any efficacy in reducing the frequency and severity of seizures. The molecular diagnosis was made in 2007, revealing a de novo *SCN1A* truncating variant, confirming the suspected clinical diagnosis of Dravet syndrome [2]. Stiripentol, an orphan drug for Dravet syndrome [3], was then added to valproic acid, clobazam and topiramate without any effect on the daily burden of seizures.

METHODS

In June 2019, at the age of 23, considering the recent advances in the treatment of this severe epileptic encephalopathy [4], highly purified oral CBD was added to the ongoing treatment (valproic acid 1000 mg/day and clobazam 30 mg/day). The patient was having about 30 seizures per week, of different types: nocturnal tonic seizures with sporadic evolution to generalized tonic-clonic and focal motor and atypical absence seizures in wakefulness. CBD was started at 2.5 mg/kg twice daily for the first week and then 5 mg/kg twice daily, with a concomitant reduction of clobazam from 30 to 20 mg/day.

RESULTS

All types of seizures rapidly and progressively decreased, and after the first 4 months of CBD treatment the patient presented only one nocturnal tonic seizure twice a week. Caregivers reported increased irritability after the increase of CBD to 5 mg/kg twice daily, and consequently CBD was slightly decreased to 4 mg/kg twice daily. Her behavior returned to the previous condition; seizures were then reported to occur two to three times a week, mainly tonic during sleep with rare brief absence-like seizures during wakefulness. After 6 months of CBD therapy, a slight increase of hepatic enzymes was observed (a few points over the normal range) and valproic acid was reduced from 1000 mg/day to 800 mg/day with normalization of blood results. No other side effect has been reported.

CONCLUSIONS

Our patient is currently taking CBD 4 mg/kg twice daily in combination with valproic acid 800 mg/day and clobazam 20 mg/day. After a 23-year history of epileptic seizures resistant to all previous antiepileptic drugs, the introduction of CBD resulted in a dramatic 90% decrease in her total seizures, with an associated positive impact on daily activities and a clear improvement in the whole family's

quality of life. CBD oral solution is an effective and safe treatment in this severe epileptic encephalopathy.

Disclaimer

This case report is related to Epidyolex®, and results do not apply to other CBD-containing products.

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Epidyolex® therapeutic drug monitoring in Dravet syndrome

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ABSTRACT

Background. *A patient with Dravet syndrome previously treated with several galenic cannabis products received add-on highly purified oral GW cannabidiol (CBD) to a stable antiepileptic drug regimen.*

Methods. *Therapeutic drug monitoring (TDM) by liquid chromatography with tandem mass spectrometry of CBD was performed in blood samples collected by volumetric absorptive microsampling.*

Results. *After 1 month of CBD treatment, the patient showed improved seizure control (>75%).*

Conclusions. *TDM may support therapeutic drug dosing during CBD therapy.*

BACKGROUND

The interest in cannabis-based therapies has increased, specifically in cannabidiol, which has antiseizure proprieties in the absence of psychoactive effects [1]. In June 2018, the US Food and Drug Administration approved Epidyolex®, a highly purified oral solution of CBD, for patients with Lennox-Gastaut syndrome and Dravet syndrome, two severe epileptic encephalopathies that manifest during early childhood [2, 3]. The pharmacokinetics of CBD show extensive variability in relation to route of administration (e.g., intravenous, oral, sublingual, oro-mucosal spray, inhalation, transdermal), type of product administered, concomitant intake of food, drug–drug interactions, and other factors [1, 4]. TDM of antiseizure drugs is an important clinical support tool that makes it possible to identify the individual concentrations associated with optimal response and to minimize drug-related toxicities [5-7]. We describe the clinical relevance of CBD plasma concentration in a patient with Dravet syndrome treated with CBD.

METHODS

The patient was the only child of Ecuadorian healthy non-consanguineous parents. He was born at 40 weeks of gestation after an

uneventful pregnancy and delivery (weight 4500 g; 50th percentile). At birth, a ventricular septal defect was detected and treated with conservative medical therapy. At 3 months of age, he was admitted to the local hospital due to focal to bilateral tonic-clonic seizures during fever. He was then discharged to the ward with a diagnosis of simple febrile convulsions. At 13 months of age, his EEG showed generalized spike-waves on slowed background activity and photosensitivity. Delayed psychomotor development was also evident, involving both motor and linguistic activities. Also, atypical absences and myoclonus at rest appeared from the age of 20 months.

At age 2 years and 9 months, he experienced five prolonged febrile and afebrile convulsive seizures, and valproate was added. Seizure control was almost complete with weekly atypical absences remaining. During the following years, he suffered from recurrent episodes of febrile convulsions despite treatment with several antiepileptic drugs (AEDs) used in various combinations, including valproate, topiramate, stiripentol, levetiracetam, lamotrigine, carbamazepine, vagus nerve stimulation (VNS), ketogenic diet, perampanel, and phenobarbital. The patient was referred to our hospital when he was 17 years old due to clusters of tonic-clonic seizures during sleep or on awakening (seven to eight times per night), often leading to convulsive status epilepticus. Laboratory investigations, including blood tests and routine metabolic screening, were unremarkable, as was brain magnetic resonance imaging (MRI). Echocardiography (ECG), ophthalmologic examination and physical examination were also unremarkable. He also suffered from constipation and gastroesophageal reflux disease treated with a proton pump inhibitor. The EEG showed background slowing with anterior sharp-wave complexes. At the last follow-up (26 years old), he showed severe intellectual disability and intact gross motor abilities but severe speech and language deficits. His neurologic examination revealed normal cranial nerves, tone and tendon reflexes of the limbs. During walking, he exhibited an anteflexed posture with crouch gait and resting tremors. Genomic DNA was extracted from peripheral blood lymphocytes and a heterozygous *de novo* mutation in exon 18(c.3614G>A) of the *SCN1A* gene was identified, confirming the diagnosis of Dravet syndrome. Following this diagnosis, at 23 of age, he started treatment with cannabis galenic product, i.e., Cannabis FM2 (tetrahydrocannabinol [THC] <8%; CBD <12%) [8], Bedrolite® (CBD <9%) and Bedrocan® or Bedrobinolo® (CBD <1%) [9] in several different combinations to ensure up to a maximum of 50.5 mg/day (3 mg/kg/day) of CBD; however, seizure control was not achieved, and the patient experienced drowsiness.

Subsequently, therapy with the galenic cannabis product was withdrawn and phenobarbital (100 mg/day) was added to the existing treatment. However, as no positive effect was achieved, he was then prescribed Epidyolex®, highly purified CBD oral solution, at the starting dose of 5 mg/kg/day divided into twice-daily administrations and gradually increased in 5 mg/kg/day increments after 1 week up to the maximum

dose of 20 mg/kg/day. CBD was added to the baseline antiseizure drug regimen with valproate 8 mg/kg/day, topiramate 3.7 mg/kg/day, stiripentol 21 mg/kg/day, clobazam 0.4 mg/kg/day and phenobarbital 0.7 mg/kg/day. To evaluate the potential role of TDM in monitoring CBD blood levels, we used the new volumetric absorptive microsampling (VAMS) technique (Mitra©, Neoteryx) in combination with liquid chromatography combined with tandem mass spectrometry.

RESULTS

Behavioral improvement and reduction in seizure frequency (<25%) and intensity was reached with a CBD dose of 10.5 mg/kg/day. Then, when a stable CBD dose of 20 mg/kg/day was reached, the patient showed a 50% reduction in monthly seizures from baseline, improvement of sleep–wake rhythm and participation in activities of daily living and social interactions. After a few weeks, phenobarbital was withdrawn without any side effects. Notably, the CBD plasma level was 1.4 ng/ml during Bedrolite® treatment and 203 ng/ml after 1 month of treatment with CBD 15 mg/kg/day.

CONCLUSIONS

Identification of the individual therapeutic concentration can be very useful in clinical management because it provides a useful reference value for informing management decisions if a change in the patient's clinical status occurs over time. Therefore, when a drug has a wide therapeutic range, it is generally considered safe and does not require monitoring.

The correlations between THC–CBD blood concentrations and the administered doses, with the inter-individual variability of pharmacokinetic parameters, support the need for TDM for medical cannabis, especially in patients with epilepsy, to optimize treatment [10].

This case supports the view that an increased plasma level of CBD leads to clinical improvement. TDM was helpful to support the identification of a safe and effective therapeutic drug dosage. In our patient, we used an innovative method, recently developed and validated in accordance with the European guidelines described by the European Medicines Agency, for determination of THC and CBD on capillary blood sampled with a VAMS device, which ensures rapid and efficient quantification of CBD and THC, with high specificity, accuracy, reproducibility, and linearity covering a wide range of concentrations. VAMS offers some benefits for patients, such as a less painful fingerprick (compared with venipuncture) and may also be considered safer than phlebotomy. Moreover, VAMS may allow a patient-centered experience where individuals can self-collect a precise quantity of blood, anywhere, with minimal training thus reducing the need for hospital visits. This opportunity can be particularly useful for patients living far away from specialized hospitals and to allow patients to be more responsive to their treatment scheme. Large series are needed to explore the impact of TDM on the individualization of treatment.

DISCLAIMER

This case report is related to Epidyolex®, and results do not apply to other CBD-containing products.

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Cannabidiol in monozygotic twins with Dravet syndrome

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ABSTRACT

Background. *We report on two male monozygotic twins with Dravet syndrome, almost completely concordant with respect to seizure onset, clinical manifestations of seizures and motor and mental development, and both refractory to the same polytherapy regimen.*

Methods. *The patients were treated with an add-on highly purified oral solution of GW cannabidiol (CBD) in the context of an Italian early access program.*

Results. *Both patients responded with a >50% reduction in seizure frequency without any side effect reported.*

Conclusions. *CBD was efficacious and well tolerated in these twins, who were almost completely concordant for epilepsy phenotype and treatment history.*

BACKGROUND

Male twins were born to a healthy mother, at 37 weeks by caesarean delivery without complications. No family history of epilepsy, febrile seizure or mental retardation was reported in the anamnesis. Clinical diagnosis was made at 18 months of age, and genetic evaluation performed at 24 months detected a *SCN1A* missens mutation p.Arg-101Trp. Cranial MRI revealed no abnormalities in either twin. EEG recordings during wake and sleep, from 18 months in both patients, showed rare and inconstant interictal generalized and focal abnormalities, such as multifocal spikes, spike and waves, polyspike and wave discharges and slowing of the background activity. Intermittent light stimulation was negative. Motor and mental development was normal for both twins until 20 months of age. For both, later development was characterized by ataxia, myoclonus, attention disorders and hyperactivity with some opposition behaviors; language was appropriate in terms of understanding and rich in production.

TWIN A

The first seizure occurred at age 5 months as a tonic-clonic seizure with eye deviation and brief duration, precipitated by fever. After that, five focal to bilateral seizures were repeatedly precipitated by fever until age 12 months. Therapy was started at 15 months with sodium valproate. At 18 months, ab-

sence seizures were also reported occasionally then confirmed at 20 months of age by video-EEG recording. At 2 years, a third type of seizure appeared, characterized by very brief shock-like muscle contractions or myoclonus confined to the upper extremities and, to a lesser extent, to the head and neck. At 2 years 9 months, multi-daily and repetitive tonic-clonic or clonic seizures occurred; adrenocorticotropic hormone (ACTH) treatment was effective. After this age, tonic-clonic and tonic seizures, prevailing during sleep, easily precipitated by fever, occurred several times with a frequency of 24-37 seizures per month. From the age of 2 years and 6 months, myoclonus in the extremities was observed, controlled partially by piracetam. Now the patient is 12 years and 3 months old and, after 10 months of treatment with CBD, is experiencing the following seizures: tonic and tonic-clonic seizures during sleep, rarely during wake, precipitated by fever and occurring with a frequency of 10-16 seizures per month.

TWIN B

The clinical course of twin B was similar to that of twin A.

The first seizure appeared at 5 months during fever, in the form of a focal to bilateral prolonged seizure, repeated after 1 month. Since that time and up to the age of 2 years and 1 month, he showed tonic-clonic seizures with focal components several times a year, precipitated by fever, despite various AED treatments. At 2 years 6 months, myoclonic and absence seizures appeared. At the same age as twin A, he experienced repetitive tonic-clonic or clonic seizures treated with ACTH. After this, tonic-clonic and tonic seizures with focal components, prevailing during sleep and easily precipitated by fever, occurred several times with a frequency of 20-41 seizures per month. From the age of 2 years and 9 months, myoclonus in the extremities was observed, partially controlled by piracetam. At 12 years and 3 months of age and after 15 months of treatment with CBD, he is experiencing the following seizures: tonic and tonic-clonic seizures during sleep, rarely during wake, precipitated by fever and occurring several times with a frequency of 6-13 seizures per month.

METHODS

Both twins were treated with multiple polytherapy.

In twin A, at the age of 24 months, levetiracetam was added to sodium valproate and clobazam and stopped at 28 months when stiripentol was added, resulting in an approximately 50% reduction in seizures. At the age of 23 months, a worsening in seizures was observed with topiramate. At 11 years and 5 months of age, the seizures were of the tonic and tonic-clonic type and rarely appeared during wake: CBD was added to sodium valproate 650 mg/day, clobazam 20 mg/day and stiripentol 750 mg/day, up to 10 mg/kg/day through a titration schedule of 2.5 mg/kg twice daily increments every 2 weeks. At present, we have 10 months of follow-up.

In twin B, stiripentol was added to sodium valproate at the age of 2 years and 6 months, resulting in an approximately 50% reduc-

tion in seizures. At the age of 2 years and 11 months during add-on levetiracetam, mood change and irritability was observed, which disappeared after withdrawal. At 3 years and 7 months, clobazam was added. At the age of 5 years 6 months, a worsening in seizures was observed with topiramate. At 11 years of age, the seizures were of the tonic and tonic-clonic variety and rarely appeared during wake: CBD up to 10 mg/kg/day, titrated with increments of 2.5 mg/kg twice daily every 2 weeks, was added to sodium valproate 500 mg/day, clobazam 20 mg/day and stiripentol 750 mg/day. At present, we have 15 months of follow-up.

RESULTS

Before starting CBD, the seizures were of the tonic-clonic and tonic type. At 4 weeks before starting CBD, twin A and twin B had 35 and 25 seizures, respectively. Both twins showed an improvement in seizure intensity and frequency, with a >50% reduction; no side effects were observed, in particular no drowsiness, gastrointestinal problems or weight loss. In both twins, seizure frequency increased approximately two-fold when stiripentol was reduced to 500 mg/day, but it returned to the pre dose-reduction frequencies within 7 days of restoring the previous dose of 750 mg/day.

DISCUSSION

Dravet syndrome is an autosomal dominant genetic epileptic encephalopathy characterized by prolonged seizures and frequent episodes of convulsive and non convulsive status epilepticus, cognitive impairment, ataxia and high mortality [1-4]. The first clinical sign is frequent febrile seizures in infancy that often develop into status epilepticus. Afebrile seizures occur later, followed by myoclonic seizures and focal seizures [1]. Early psychomotor development is normal, but developmental regression occurs after the onset of epileptic seizures [5].

The most common target of Dravet syndrome mutations is the *SCN1A* gene [6]. Fujiwara et al. reported on monozygotic twins with severe myoclonic epilepsy in infancy who were almost completely concordant regarding seizure onset, clinical seizure symptomatology, EEG results and seizure prognosis [7]. The twins reported herein, consistent with the previously described twins, are also almost completely concordant with respect to seizure onset and clinical seizure symptomatology, as well as motor and language development.

A similar good response, >50% reduction in seizures after treatment with CBD, was also concordant. Neither twin experienced side effects, apart from a worsening of seizures when stiripentol was reduced, though control was regained when the dose was restored. However, no plasma drug assays were collected for interpretation. CBD seems to be an efficacious and safe option in the treatment of Dravet syndrome also in the long term. The story of these twins suggests that the clinical course of Dravet syndrome and the response to AED therapy is strictly genetically determined.

DISCLAIMER

This case report is related to Epidyolex®, and results do not apply to other CBD-containing products.

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Use of Epidyolex® in a case of Lennox-Gastaut syndrome: experience in clinical practice

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ABSTRACT

Background. *We report on a case of Lennox-Gastaut syndrome with genetic etiology. The patient presented highly frequent and severely drug-resistant multiple seizure types (focal seizures, absences with eyelid myoclonia, generalized tonic and tonic-clonic seizures).*

Methods. *The basic antiepileptic treatment was clobazam 20 mg/day and sodium valproate 1300 mg/day. Epidyolex®, highly purified GW-cannabidiol in oral solution (CBD), was combined with valproate and clobazam.*

Results. *The maximum dose of CBD 20 mg/kg/day was reached, resulting in improved seizures and excellent tolerability.*

Conclusions. *We believe it was possible to achieve this goal by following a personalized CBD program of titration and modification of the concomitant AEDs in relation to changes in serum transaminase levels and the appearance of adverse events.*

BACKGROUND

Our patient was a 20-year-old male, the second-born from healthy non-consanguineous parents. The pregnancy was regular and the birth was spontaneous but with respiratory distress for the child. The patient presents severe cognitive delay and associated autism spectrum disorder.

At the ages of 11 and 14 months, he presented complex febrile seizures. From the age of 3 years, the patient began to present morpheic seizures in apyrexia described as left hemisomatic motor focal seizure and absence seizures with eyelid myoclonia. The frequency was multi-daily. From the age of 15 years, he experienced onset of atonic seizures lasting a few seconds with rapid recovery, at high frequency.

The last diagnostic workup in January 2018 included:

- EEG: generalized 1.5–2 Hz slow spike and wave discharges
- MRI: normal
- Genetic evaluation: positive for mosaic mutation of *KCNB1* (c.l045G> T) and of the variant of the *SCL6A1* gene (c.589A> G) in heterozygosity.

As a *KCNB1* mutation can result in early-onset epileptic encephalopathy [1], a diagnosis of Lennox-Gastaut syndrome with genetic etiology was established.

Previous treatments included carbamaze-

pine, etosuccimide, levetiracetam, perampanel, topiramate, lamotrigine, rufmamide, lacosamide, stiripentol and diazepam (rectal). The boy's parents refused to let him undergo VNS.

METHODS

In February 2019, the patient had a series of drop seizures (atonic and/or tonic-clonic) occurring three to four times/month and absence seizures with eyelid myoclonia at very high frequency (30–40/day). He took clobazam 20 mg/day and sodium valproat 1300 mg/day. Laboratory tests were all normal, and EEG showed a continuous succession of synchronous and asynchronous hypervolted p, pw and pp-w. There were rare incidences of very short bouffes of generalized p-w at 3.5 Hz (**Fig. 1**).

CBD was added at the recommended [2] starting dose of 2.5 mg/kg twice daily and subsequently increased over about 2 months to the dose of 7.5 mg/kg/day and then 10 mg/kg/day (March 2019), with no change in seizure frequency. In these 2 months, the patient's clinical and laboratory parameters were closely monitored. Because of drowsiness, the clobazam dose was reduced to 10 mg/day, and this side effect rapidly disappeared.

Subsequently, the dose of CBD was increased very slowly by 2.5 mg/kg/day every 20 days with concomitant assessment of laboratory parameters and tolerability. At a dose of 12.5 mg/kg/day, an increase in serum transaminase levels over twice the normal limits was observed so the sodium valproate dose was reduced to 1000 mg/day without changes in CBD and clobazam. The serum transaminase levels were checked every 15 days with stable therapy until normalization occurred after 2 months. Despite the persistence of high transaminase values, the dose of CBD and clobazam was kept unchanged in consideration of the lack of evidence of an increasing trend of the same.

After normalization of the laboratory parameters, the CBD dose was increased to 15 mg/kg/day and then steps of 2.5 mg/kg/day were carried out every month until the maximum dose of 20 mg/kg/day was reached. This increase was made gradually and took another 2 months.

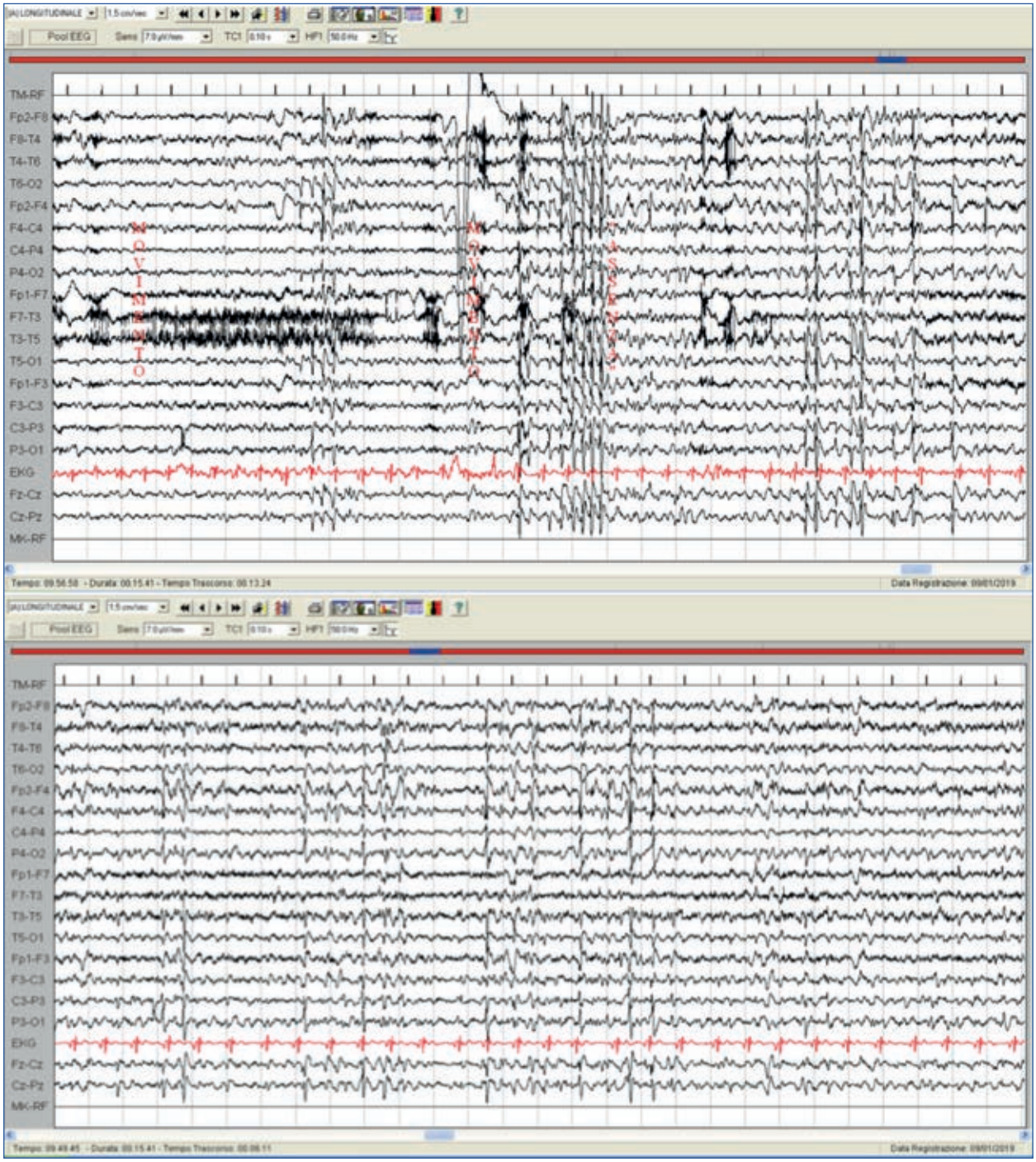
RESULTS

The patient reached the maximum dose of CBD (20 mg/kg/day) in 6 months, and each dose increase took place after checking the laboratory parameters.

A reduction in frequency of seizures was evident starting from the 15 mg/kg/day dose, showing a dose-dependence with respect of the subsequent increases. At a dose of 20 mg/kg/day, the patient presented drop seizures three to four times per month (baseline: three to four times per month) and absence seizures with eyelid myoclonus two to three times per day (baseline: 30–40/day). The dramatic reduction in the frequency of absence seizures led to an improvement in patient participation with subsequent improvement of the parents' reported quality of life. When checked 11 months after reaching the maximum dose, the patient had the same seizure frequency.

Regarding tolerability, drowsiness regressed with the reduction of the clobazam dose and no longer occurred.

Figure 1. Baseline EEG characteristics

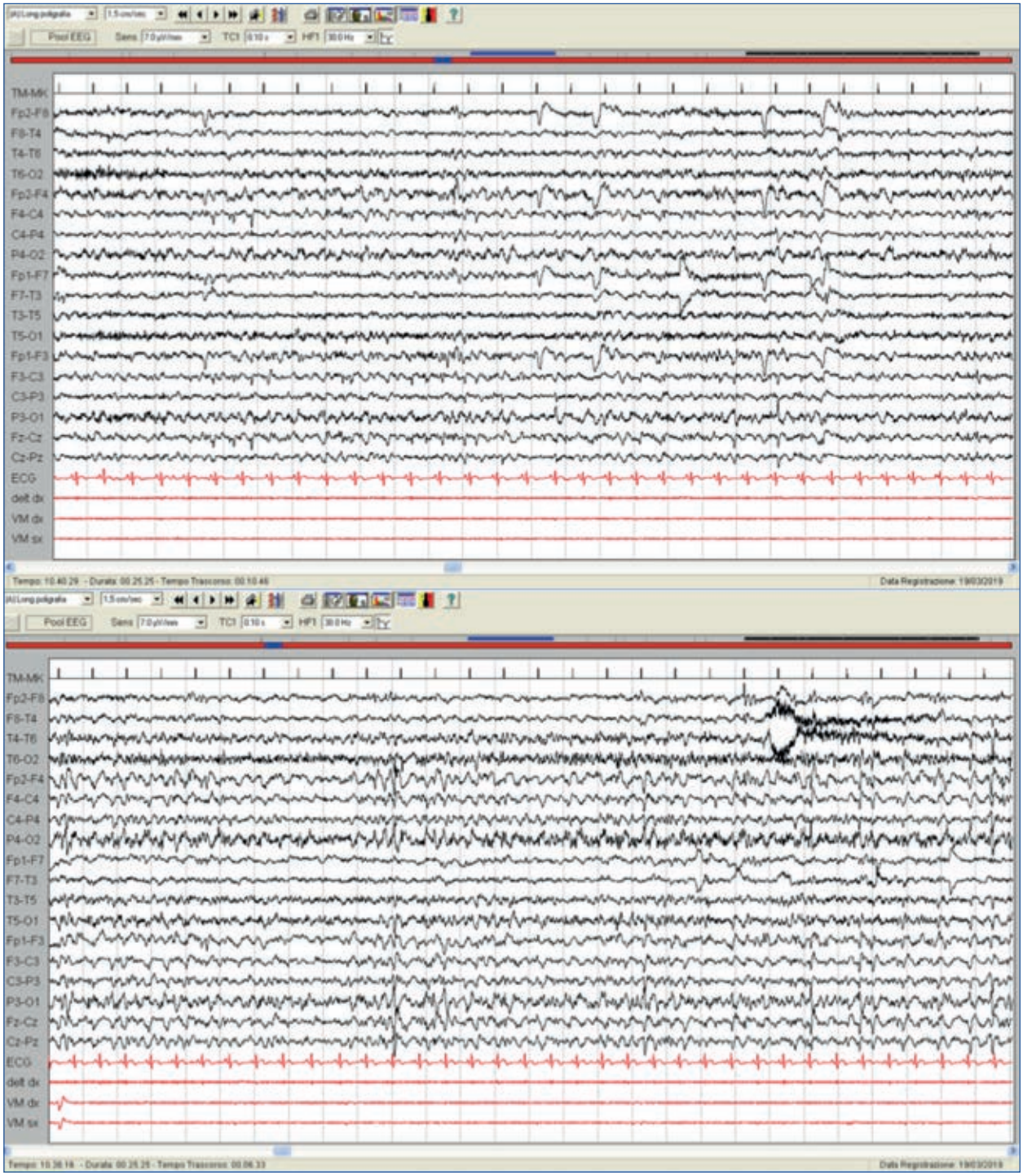


The increase in serum transaminase levels regressed with reduction of the sodium valproate dose. It should be noted that complete normalization took about 2 months after sodium valproate dose reduction. During this period, the therapy was not changed and the patient underwent laboratory checks every 15 days.

No other adverse events occurred.

At the last check-up, 11 months after reaching the maximum dose of CBD, the laboratory parameters were within normal ranges

Figure 2. EEG characteristics during CBD treatment



and the EEG showed evident reduction of paroxysmal anomalies (**Fig. 2**).

CONCLUSIONS

CBD is a novel therapeutic option for Lennox-Gastaut syndrome. In randomized controlled trials, drowsiness and increased serum transaminases represented the most frequent adverse event [3]. More than two-thirds of aminotransferase elevations occurred in patients taking concomitant sodium valproate, and some cases resolved while on CBD after

the sodium valproate dose was decreased. As CBD has no meaningful effects on sodium valproate concentrations, pharmacodynamic interactions may explain this finding. The incidence of drowsiness is higher in patients concomitantly taking clobazam, and the pharmacokinetic interaction leading to an increased serum level of clobazam and its metabolites is likely to contribute to the risk.

The patient described was taking sodium valproate and clobazam and therefore presented a risk of both drowsiness and increased serum transaminase levels.

On the basis of this consideration, it was decided to proceed with a CBD titration tailored to the patient's characteristics. Specifically, a particularly slow titration of the drug was planned with concomitant checking of laboratory parameters and clinical situation. The parents were informed in advance of this choice, which would require longer times to obtain any result in terms of efficacy but would better protect the patient in terms of tolerability, and they accepted. This strategy would also allow us to test the drug in our patient, who had no other therapeutic (pharmacological or surgical) options.

The patient experienced both drowsiness and increased serum transaminase levels; the former was quickly overcome by reducing the clobazam dose. Normalization of serum transaminase levels after sodium valproate dose reduction required 2 months of constant therapy. This latency could be related to the fact that the side effect appears to be linked to a pharmacodynamic interaction and that liver damage requires a certain interval of time to resolve.

Following this observation, after finding an increase in serum transaminase levels and after a sodium valproate dose reduction, it should be possible to carry out a clinical laboratory observation over time with stable therapy for at least 2 months, unless a trend is observed of further increase in transaminase values.

DISCLAIMER

This case report is related to Epidyolex®, and results do not apply to other CBD-containing products.

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The therapeutic challenge of co-occurrence of Lennox-Gastaut and long-QT syndrome: cannabidiol as an effective and safe treatment option

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ABSTRACT

Background. *Co-occurrence of Lennox-Gastaut syndrome and long-QT syndrome influences antiepileptic treatment and prognosis.*

Methods. *A patient was treated with highly purified add-on GW-cannabidiol (CBD) after several drugs had proved ineffective.*

Results. *Improvement of seizure control and motor and cognitive performance was observed, without any side effects.*

Conclusion. *CBD was an effective and safe option for a patient with Lennox-Gastaut syndrome and cardiac comorbidity.*

BACKGROUND

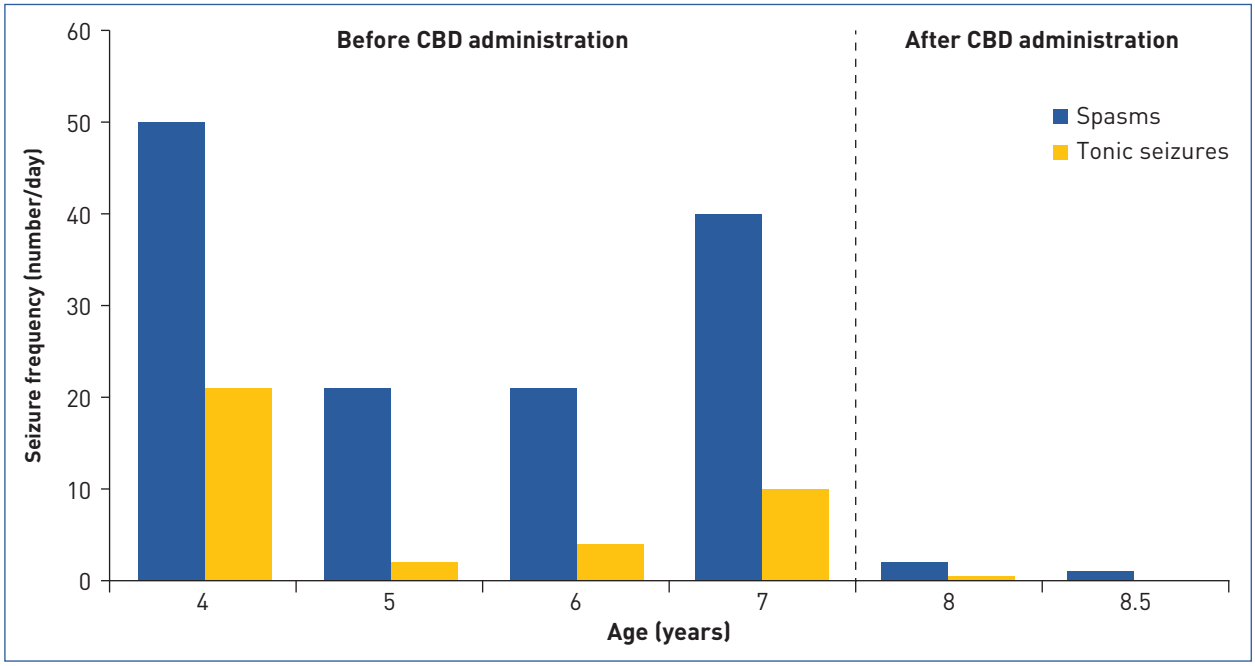
Lennox-Gastaut syndrome, a prototype of childhood-onset epileptic encephalopathy, represents a therapeutic challenge for clinicians and health care systems because of the difficult-to-treat epilepsy and the severe impact on daily life due to intellectual disability, psychiatric comorbidities and dangerous seizures with a high risk of injuries and polytraumas [1]. We report on the case of an 8-year-old girl with long-QT syndrome and Lennox-Gastaut syndrome, hemiparesis, cognitive impairment and behavior disorder provoked by diffuse hypoxic-ischemic encephalopathy due to cardiac arrest that occurred during the first year of life. The coexistence of long-QT syndrome complicated the clinical picture and prevented the use of specific therapeutic options, increasing the burden of epilepsy and disability on quality of life. The patient was born at term after an uneventful pregnancy; normal neurodevelopmental stages were reported in the first year of life. At the age of 9 months, she was diagnosed with long-QT syndrome and hypertrophic cardiomyopathy; treatment with propranolol was immediately started. At 11 months, she was resuscitated after cardiac arrest; this resulted in a diffuse hypoxic-ischemic encephalopathy with basal ganglia involvement and asym-

metrical distribution for predominant left hemisphere damage. At 12 months, she was implanted with a cardioverter defibrillator, and prophylactic treatment with phenobarbital was started. A few days after discharge, she was readmitted with repetitive focal seizures (left head deviations and tonic-clonic generalization); status epilepticus was stopped with midazolam infusion, and levetiracetam was started as an add-on therapy to phenobarbital. Genetic testing for *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1* and *KCNE2*, involved in cardiac arrhythmia, as well as comparative genomic hybridization array, were performed, but results were non-informative. Further genetic examination is ongoing.

METHODS

At our first observation, at 17 months of age, she presented with right hemiparesis, epileptic spasms with focal onset and developmental delay (nonverbal and not standing) with autistic features; the EEG showed hypsarrhythmia. She reached standing position at 22 months and started walking and babbling at 27 months. At the age of 18 months, tonic seizures and epileptic spasms with focal onset were reported; valproate, clobazam, vigabatrin (discontinued at 3 years of age), rufinamide and topiramate were alternatively added to the therapy. Rufinamide had some time-limited efficacy; other drugs had almost no effect on the seizure frequency, which remained daily during the follow-up. The more severe clusters of spasms and tonic or atonic seizures (two to three per week) caused the child to fall, leading to head traumas and hospitalizations. A Lennox-Gastaut syndrome was diagnosed (age 3 years) on the basis of seizure types, EEG features and progressive cognitive decline. Interictal EEG showed abnormally slow background activity with superimposed fast activities, multifocal spike-and-wave discharges in both hemispheres and intermittent diffuse and rhythmic slow spike-and-wave and polyspike-and-wave pattern. Vigabatrin was reintroduced with limited benefit, as well as prednisone 2 mg/kg/day and high-dose (20 mg/kg/day) pulse corticosteroid therapy with methylprednisolone. Lamotrigine was introduced, along with a shift from clobazam to clonazepam, with limited efficacy. Therapeutic options were discussed collectively; ketogenic diet and felbamate, considered effective treatment for Lennox-Gastaut syndrome epilepsy, were contraindicated for the arrhythmic risk in long-QT syndrome [2,3]. Resective/disconnective surgery was excluded because of the multifocality of recorded seizures and extensiveness of the cerebral damage evident on MRI and computed tomography scans. Eventually, in the absence of treatment alternatives, VNS was elected as a viable therapeutic option (age 4.5 years). VNS was effective and led to the longest seizure-free period after epilepsy onset; seizure control was associated with global clinical improvement. No changes in AEDs were made after VNS activation except for a benzodiazepine shift from clonazepam to nitrazepam and progressive withdrawal of topiramate. After 1 year, seizures relapsed and progressively increased. During follow-up, daily epileptic spasms in clusters and tonic seizures with disabling falls and weekly focal-to-bilateral tonic-clonic seizures occurred. At the same time, worsening of motor abilities and decline of cognitive performance were observed. The patient's AED treatment was

Figure 1. Epilepsy course

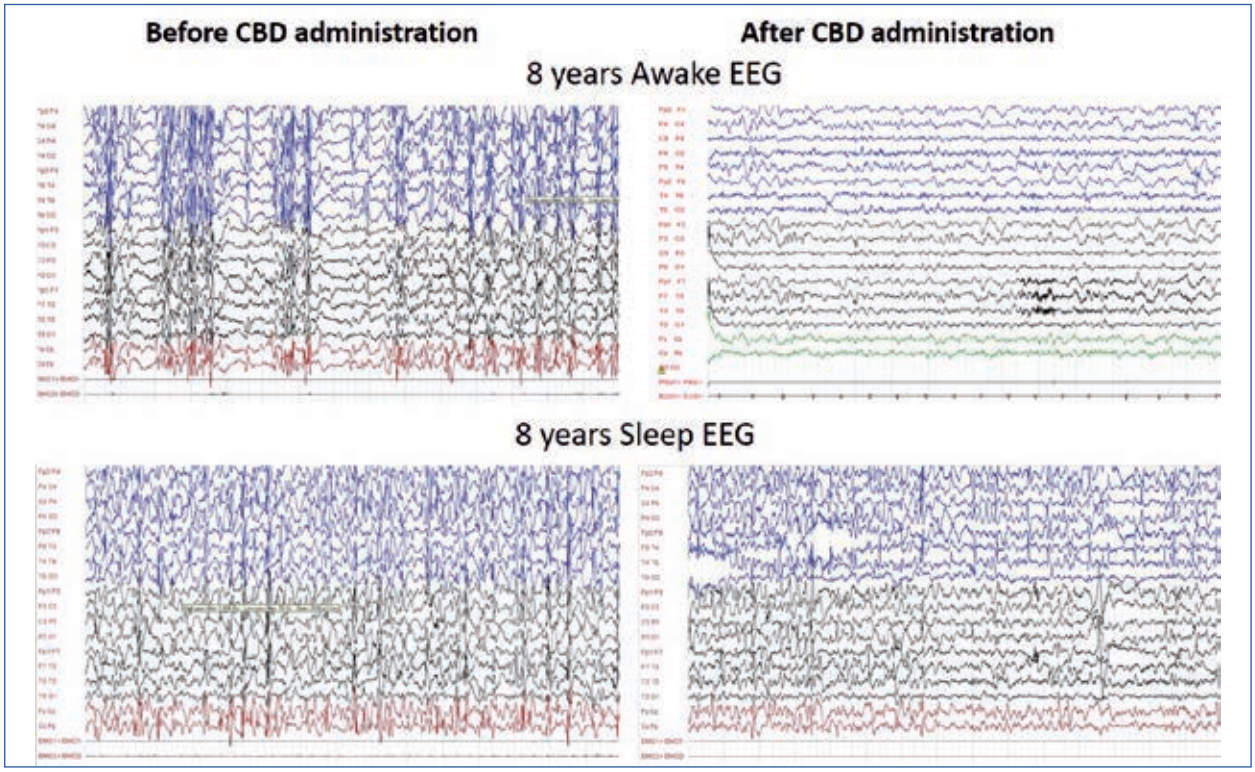


reviewed, and zonisamide, levetiracetam and acetazolamide were added. No efficacy was reported. At the age of 8 years, the patient started highly purified CBD in oral solution treatment at a dosage of 5 mg/kg/day. Concomitant therapy included sodium valproate, lamotrigine, clonazepam, acetazolamide and gabapentin.

RESULTS

Shortly after CBD treatment started, still during dose titration (starting at 1 mg/kg/day and increasing by 2.5 mg/kg every week until the target dose of 20 mg/kg), the family reported a dramatic reduction in the intensity and frequency of the spasms and tonic seizures (**Fig. 1**) [4, 5], along with improved alertness and interaction [6]. A significant improvement in behavior and motor and cognitive performance, with greater stability in walking, were observed. A drastic reduction of paroxysmal discharges during awake EEG (**Fig. 2**) confirmed the decrease of epilepsy severity. Acetazolamide and gabapentin treatments were progressively stopped. After reaching the CBD target dose, further clinical improvement was observed concurrently with clobazam treatment initiation (clonazepam discontinuation and switch to clobazam, starting at 2.5 mg until 7.5 mg) [7]. No side effects were reported. Serum transaminases and ECG monitoring showed no change from preceding evaluations. At the time of writing (8 months of follow-up), the patient is receiving therapy with CBD 20 mg/kg/day, alongside valproate 450 mg/day, lamotrigine 80 mg/day and clobazam 7.5 mg/day. Drop attacks are no longer observed. A reduction in tonic seizure frequency of 100% and in spasm frequency of 92.5% compared with the 6 months before CBD administration has been reported. Behavior, alertness, communication and motor improvement remains, and further development of motor skills and emotional intelligence is expected over the following months of treatment.

Figure 2. Awake and sleep EEG before and after CBD administration



CONCLUSION

Our report suggests that CBD as add-on therapy, especially in combination with clobazam, should be considered a viable option in patients with Lennox-Gastaut syndrome and cardiac comorbidities that preclude access to other pharmacological or neurosurgical treatments. Improvement in seizure control may be associated with additional benefits on behavior and cognitive and motor performance, with a positive impact on the quality of life of the patients and their families.

DISCLAIMER

This case report is related to Epidyolex®, and results do not apply to other CBD-containing products.

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