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SHORT RESEARCH ARTICLE

Successful management of refractory epilepsy in creatine transporter deficiency with cannabidiol and clobazam: A case report

Maria Borrell-Pichot[1] | **Carmen Fons**[2] | **Susana Boronat**[3,4] | **Alba Sierra-Marcos**[1,3]

[1]Neurology Department, Hospital Santa Creu i Sant Pau, Barcelona, Spain

[2]Pediatric Neurology Department, Sant Joan de Déu Hospital, Barcelona University, Institut de Recerca Sant Joan de Déu, Barcelona, Spain

[3]Epilepsy Unit, Hospital Santa Creu i Sant Pau, Barcelona, Spain

[4]Child Neurology Unit, Pediatrics Service, Hospital Santa Creu i Sant Pau, Barcelona, Spain

Correspondence
Maria Borrell-Pichot, Carrer Sant Quintí 89, 08041 Barcelona, Spain.
Email: mborrellpi@santpau.cat

Abstract

Creatine transporter deficiency (CRTR-D) is a rare X-linked inherited disease belonging to the group of cerebral creatine deficiency disorders. Major clinical features include developmental delay and epilepsy. To date, fewer than 200 individuals with CRTR-D have been reported. As a result, there is little evidence for effective treatment. Available therapies are creatine precursors, with a mild effect on disease progression. Concerning epilepsy, standard management is recommended and no specific anti-seizure medication (ASM) has been shown to be effective in refractory cases. We report the case of a 28-year-old male patient with CRTR-D and childhood-onset refractory epilepsy. He had an average of 10–20 focal motor seizures with impaired consciousness per month. He had tried several ASMs without significant improvement. Treatment with cannabidiol (CBD) and clobazam (CLB) in combination was added. The patient became seizure-free from the first week, and up to 1 year of follow-up. Behavioral improvement was also noted by his caregivers. No adverse effects were reported. Very few cases of CRTR-D with refractory epilepsy have been reported. This calls for more extensive research and suggests a possible role for CBD in cerebral creatine metabolism and transport and valuable option for future studies.

Plain Language Summary: Creatine transporter deficiency (CRTR-D) is a rare genetic disorder causing mental, behavioral, and movement problems. More than half of patients also have seizures, but because there are fewer than 200 known cases, it is difficult to know the best treatment options. We present a 28-year-old man with CRTR-D who had severe developmental delays and frequent seizures since childhood, despite trying many medications. After starting cannabidiol and clobazam, he has been seizure-free for a year. Sharing this success might help other people with CRTR-D benefit from similar treatments.

KEYWORDS
cannabinoid therapy, creatine deficiency disorders, developmental encephalopathy, metabolic epilepsy, precision medicine

1 | INTRODUCTION

Cerebral creatine deficiency disorders are inborn errors in creatine metabolism and transport. Creatine transporter deficiency (CRTR-D) (OMIM #300352) is an X-linked inherited disorder that belongs to this group. Major clinical features in affected males include developmental delay, speech and behavioral disorders, hypotonia, and epilepsy.[1] Other non-neurological clinical features may be present and include dysmorphic features, poor weight gain with chronic constipation, and prolonged QTc interval. Heterozygous females are generally either asymptomatic or present with mild intellectual disability.[2]

Creatine plays a key role in cellular energy buffering and is used mainly by the muscle and brain. It is converted to the high-energy compound phosphocreatine (PCr) by the enzyme creatine kinase (CK). PCr is then used to buffer the ATP to ADP ratio in the cytosol and for local ATP consumption.[3] Recent research also supports the role of creatine as a neuromodulator. It is released in an excitotoxic and action potential-dependent manner, acts as a gamma-aminobutyric acid A ($GABA_A$) agonist, interacts with serotonergic and dopaminergic systems, and is able to stimulate synaptic glutamate uptake.[4] This, together with the fact that patients with CRTR-D paradoxically have normal to slightly elevated CSF creatine levels, leads to the hypothesis that creatine deficiency in CRTR-D results from neuronal depletion due to defective creatine reuptake after release.[5] Under physiological conditions, creatine is taken up into the cell by a sodium-dependent membrane-bound creatine transporter (CRTR). This transporter is expressed in capillaries and neurons and is encoded by the SLC6A8 gene located on Xq28.[6] A pathogenic variant in the *SLC6A8* gene, in hemizygosity in males or in heterozygosity in some females, results in a deficient transport of creatine.

To date, fewer than 200 individuals have been identified with a pathogenic variant in *SLC6A8*.[1,7,8] Epilepsy occurs in almost 60% of affected males, with an average age of onset of 4.5 years. Seizure types include generalized tonic–clonic and focal seizures with or without loss of consciousness.[5] Drug-resistant epilepsy has been described in fewer than 10 individuals.[7,9]

Creatine monohydrate and creatine synthesis precursors, arginine and glycine, are used as an attempt to slow disease progression.[9–11] Regarding epilepsy, no specific anti-seizure medication (ASM) has been demonstrated to be effective, and standardized treatment by an experienced neurologist is recommended.[7]

Key points

- Epilepsy affects 60% of patients with creatine transporter deficiency (CRTR-D).
- Evidence for effective anti-seizure medication (ASM) in CRTR-D is limited, which is challenging in cases of drug-resistant epilepsy (DRE).
- We present a 28-year-old man with CRTR-D and DRE who became seizure-free upon treatment with cannabidiol (CBD) and clobazam (CLB).
- This case highlights CBD as a potential alternative to conventional ASM in patients with creatine deficiency disorders and DRE.

When traditional ASMs fail to manage drug-resistant epilepsy, new therapeutic approaches must be explored. One of these options is cannabidiol (CBD), which according to current literature, has not been studied in creatine disorders yet. CBD is a nonpsychotropic cannabinoid that has been recently approved as an add-on anticonvulsant drug for patients with Lennox–Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex (TSC),[12,13] as several clinical trials have demonstrated significantly greater reductions in total seizure frequency when compared to placebo, especially when associated with clobazam (CLB).[14] CBD has multiple proposed anticonvulsant mechanisms of action. The most well-studied ones are G-protein-coupled receptor 55 (GPR55) antagonism, transient receptor potential cation channel subfamily V member 1 (TRPV1) desensitization, and the elevation of extracellular adenosine levels.[15] Moreover, CBD has shown neuroprotective properties, as well as anti-inflammatory, antiemetic, and antipsychotic effects.[12,16]

We report a 28-year-old male with CRTR deficiency and refractory epilepsy who has been seizure-free for 1 year upon treatment with CBD and CLB. The use of CBD provides important insights into potentially effective seizure

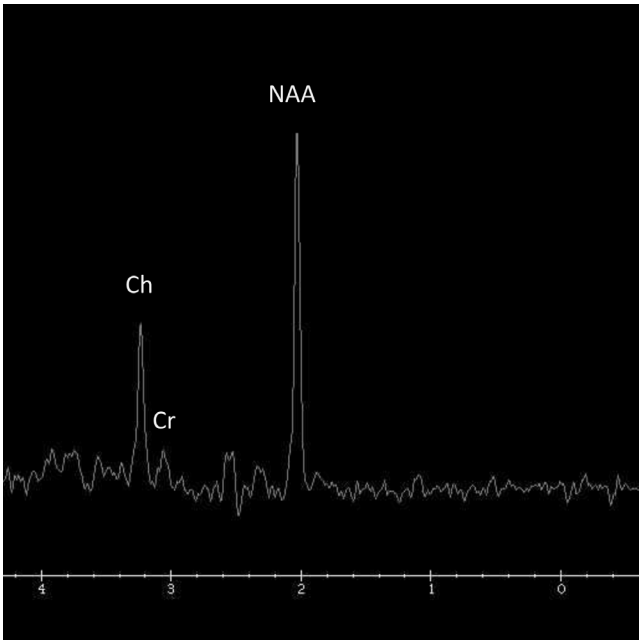

FIGURE 1 Magnetic resonance spectroscopy of the left thalamus shows a nearly undetectable creatine peak relative to the choline peak, suggesting creatine deficiency.

treatments in creatine disorders, where evidence remains limited due to the rarity of these conditions.

2 | CASE PRESENTATION

2.1 | Patient information

A 28-year-old Caucasian male patient was referred to our epilepsy clinic. He had no relevant family history of epilepsy. There were no complications during pregnancy or delivery. Before the age of 1 year, he showed global development delay. He started walking at the age of 1.5 years with instability and numerous falls. Later, he was diagnosed with autism spectrum disorder at the age of 3, with severe receptive and expressive language impairment. Currently, he uses a wheelchair when outside the house due to lower limb weakness and generalized hypotonia, and needs help eating because he has difficulty using cutlery.

The first seizure was generalized tonic–clonic (GTC) at the age of 2.5 years. Since then, he had highly frequent seizures (between 20 and 40 per month) and two episodes of status epilepticus at 3 and 4 years of age, requiring an induced barbiturate coma. The maximum seizure-free period was 1.5 years (from 8 to 9 years). Since adulthood, he no longer had GTC seizures, but focal motor seizures with impaired consciousness, including manual and oromandibular automatisms and dystonic posturing of the left hand. The average duration was 1–4 min. The average seizure frequency at the time of our visit was 10–20 per month.

2.2 | Clinical findings

Cranial magnetic resonance imaging (MRI) on T2 showed diffuse hyperintense subcortical areas consistent with hypomyelination. Gadolinium enhancement was negative. Spectroscopy showed nearly undetectable creatine levels in the left thalamus (Figure 1).

Only a limited number of EEG recordings were obtained due to a lack of cooperation. Most of them were normal or showed diffuse slowing with low reactivity. Only one EEG, obtained when the patient was 11 years old, showed a focal delta rhythm in the temporo-occipital region of the left hemisphere.

Urine analysis showed a consistently elevated creatine/creatinine ratio in serial determinations (2.45 mmol/mmol; reference range 0.03–1.44 mmol/mmol) and normal guanidinoacetate levels in plasma and urine. Creatine uptake test in fibroblasts also showed altered results (5.7 pmol/μg protein at 500 μM creatine; reference range 20–60 pmol/μg protein).

The diagnosis of CRTR-D was established by DNA sequence analysis of the *SLC6A8* gene, which revealed a hemizygous variant consisting of a three-nucleotide deletion in exon 6 (c.942_944delCTT), predicted to be likely pathogenic. This variant was first reported in our patient and later identified as a heterozygous mutation in another unrelated clinically affected female.[17] His mother is a heterozygous carrier who remains completely asymptomatic and has completed secondary education. She underwent MRI with normal spectroscopic creatine levels, and neuropsychological testing with the Wechsler Adult Intelligence Scale (WAIS) with normal scores.

2.3 | Therapeutic intervention

At the age of 10, he was treated with creatine, arginine, and glycine supplements without improvement in cognitive or behavioral symptoms, nor seizure frequency. He had tried several ASMs in combination (carbamazepine, oxcarbazepine, ethosuximide, valproic acid, topiramate, phenobarbital, lacosamide, CLB) and a classical ketogenic diet without significant reduction in seizure frequency. Current treatment prior to intervention was brivaracetam 300 mg/day, lamotrigine 600 mg/day, and phenytoin 300 mg/day.

We introduced CLB (20 mg/day) and progressively increased CBD from 5 to 15 mg/kg/day.

2.4 | Follow-up and outcomes

The patient became seizure-free from the first week of treatment with CLB and CBD. At 1 year follow-up, he was

still seizure-free. Phenytoin was successfully progressively removed. His caregivers and teachers described improvements in his behavior, particularly increased attention and participation. No adverse effects were reported.

He underwent a new EEG upon 3 months of starting treatment, which showed a well-structured alpha rhythm and the absence of epileptiform activity (Figure 2).

3 | DISCUSSION

Very few cases of drug-resistant epilepsy have been described for CRTR-D, and even fewer report favorable therapeutic outcomes or specific seizure management data (Table 1). While Mercimek-Mahmutoglu et al. (2010) reported the case of a girl with drug-resistant epilepsy

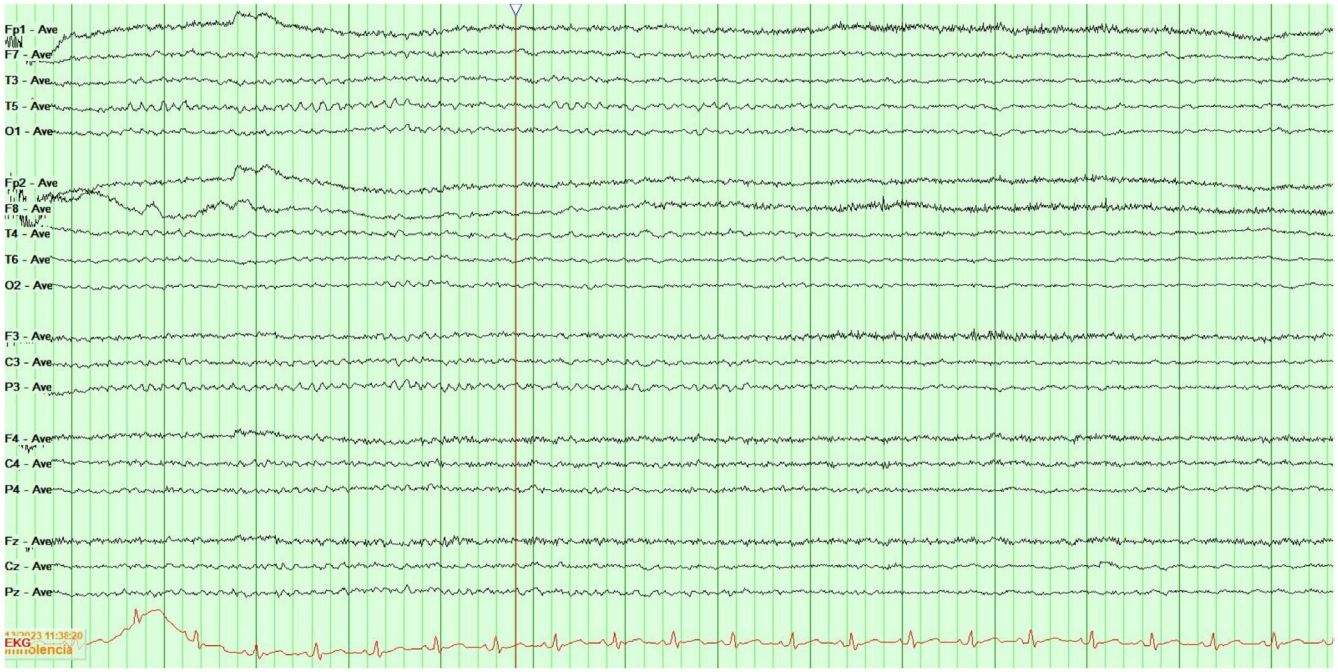

FIGURE 2 EEG of the patient, 2 months after initiation of treatment with CBD and CLB. Referential average montage at 25 mm/sec and 7 μV/mm. Background alpha activity and absence of epileptiform abnormalities.

TABLE 1 Literature summary of treatments tested in patients with CRTR-D and refractory epilepsy.

Author, journal (year)	Sex, age years	Treatment prior to intervention	Treatment after intervention	Results
Mancardi, Epilepsia (2007)[18]	M, 5 years	PB, VPA, CNZ, TPM	Prednisone + LEV, VPA, TPM	Daily seizures → 2–3/month
Mercimek, Mol Genet Metab (2010)[9]	F, 9 years	LTG	Cr + Arg + Gly + LTG	Seizure-free
Chilosi, Orphanet J Rare Dis (2012)[19]	M, 2 years	No treatment	L-Arg	"Mild electroclinical improvement" (unspecified)
Chilosi, Orphanet J Rare Dis (2012)[19]	F, 5 years	Polytherapy	L-Arg, monotherapy	Reduction in frequency (unspecified)
Chilosi, Orphanet J Rare Dis (2012)[19]	M, 17 years	Polytherapy	L-Arg, monotherapy	Reduction in frequency (unspecified)
Bruun, Metab Brain Dis (2018)[1]	M, 10 years	Unknown	Cr + Arg + Gly	No improvement
Bruun, Metab Brain Di (2018)[1]	M, 4 years	Unknown	Cr + Arg + Gly	No improvement

Note: To date, the majority of cases of refractory epilepsy in patients with CRTR-D reported in the literature have shown little or no improvement with multiple pharmacologic interventions. Almost all the drugs tested are creatine or creatine precursors, and studies with specific ASMs are lacking.

Abbreviations: Arg, arginine; Cr, creatine; F, female; Gly, glycine; LEV, levetiracetam; M, male; y, years.

who became seizure-free with a combination of creatine, arginine, and glycine,[9] another study by Bruun et al. found no benefit in similar patients.[1] Mancardi et al. reported a man with intractable daily GTC seizures who showed a partial response to prednisone and levetiracetam in a multidrug regimen.[18] Chilosi et al. conducted a prospective study with L-arginine in five patients, three of whom had drug-resistant epilepsy, also obtaining partial seizure control.[19]

Despite the administration of a variety of ASM, ketogenic diet, creatine, arginine, and glycine supplements, our patient's seizures remained uncontrolled. However, upon treatment with CLB and CBD, we quickly observed a notable response. Other genetic disorders have already benefited from specific CBD mechanisms that target key physiopathological pathways, such as TRPV1 desensitization in SYNGAP1 encephalopathy[20] and suppression of mechanistic target of rapamycin (mTOR) activity in tuberous sclerosis complex.[13] In the case of creatine deficiency disorders, CBD has shown neuroprotective properties that target mitochondrial function, acting as an antioxidant agent and modulating energetic metabolism.[21] Hypothetically, this may compensate for creatine deficiency in the cell through indirect pathways that are still unknown. Moreover, at the synaptic level, the loss of creatine agonism at $GABA_A$ receptors may be partially compensated by the GABAergic properties attributed to CBD.[4] This could also be the case for serotonergic activity, as both creatine and CBD act as serotonin modulators, which may have an influence on cognitive and behavioral challenges.[22] However, these approaches are theoretical and more research is needed to understand the intrinsic mechanisms of CBD in relation to creatine metabolism.

This study is limited by a lack of access to the patient's early records due to poor digitization. In addition, the administration of CBD with CLB according to guidelines makes it difficult to determine the extent to which each agent contributed to seizure control. However, the patient had already been treated with CLB in the past without response, suggesting a key role for CBD in controlling seizures.

Given the limitations in ultrarare diseases to gather a large enough sample of patients to conduct trials, case reports or N-of-one trials are often the only option that remains. More evidence is needed to confirm whether this excellent response to CBD is reproducible in other individuals with CRTR-D. Nevertheless, its ability to target multiple pathways and its success in seizure control in other conditions such as Dravet and Lennox–Gastaut syndromes,[23] make CBD a valuable option to consider in epileptic and developmental encephalopathies where traditional therapies have not achieved seizure control.

4 | CONCLUSION

We present a case of a male with CRTR-D and drug-resistant epilepsy who achieved 1 year of seizure freedom after introducing treatment with CLB and CBD. Further research is needed to evaluate the reproducibility of this result in other patients with creatine deficiency disorders.

AUTHOR CONTRIBUTIONS

M.B.P.: Acquisition of data, drafting of the manuscript, accountability for all aspects of the work. C.F.: Acquisition of data, critically revising the manuscript for important intellectual content, final approval of the version to be published. S.B.: Critically revising the manuscript for important intellectual content, final approval of the version to be published. A.S.M.: Acquisition of data, critically revising the manuscript for important intellectual content, final approval of the version to be published, accountability for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. 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. This patient was previously included in a case series reported by Dr. Fons in 2009[24] (Patient 4). However, the current report focuses on different aspects of the patient's clinical course and treatment. This case is presented independently to highlight new therapeutic outcomes not previously discussed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Consent has been obtained from the patient's legal guardians to publish this brief communication.

ORCID

Maria Borrell-Pichot https://orcid.org/0009-0006-7917-3132
Carmen Fons https://orcid.org/0000-0001-7227-1350

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