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Case Report

Myoclonic super-refractory status epilepticus with favourable evolution in a teenager with FIRES: Is the association of vagus nerve stimulation and cannabidiol effective?

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Abstract

Background: Febrile infection-related epilepsy syndrome (FIRES) is a rare and catastrophic clinical syndrome occurring in previously healthy patients. Aetiology is still unknown and outcome usually poor. We describe a case of myoclonic prolonged super refractory status epilepticus (P-SRSE) in FIRES in a patient admitted to the paediatric intensive care unit of Padova, Italy.

Case report: A previously healthy 14-year-old girl with onset of myoclonic status epilepticus after a mild febrile illness was admitted to our hospital with a diagnosis of FIRES. Extensive diagnostic work-up was inconclusive. Status epilepticus and electroclinical seizures recurred every time weaning from anaesthetic agents was attempted. Eventually, a vagal nerve stimulator (VNS) was implanted and cannabidiol (CBD) administered, 43 days and 70 days after P-SRSE onset, respectively. Two days after CBD introduction, status epilepticus weaned and the girl rapidly regained complete consciousness showing a brilliant and unexpected recovery. At last follow-up, 12 months later, she is 8-months seizure free on multiple antiseizure medications, has only mild neuropsychological impairment with no neurological and intellective deficit.

Conclusions: To our knowledge, this represents a unique case with an extremely favourable evolution with a possible effect of the association of VNS and CBD to traditional antiseizure medications.

Keywords: Vagus nerve stimulation; Cannabidiol; Status epilepticus; Paediatrics; FIRES; Febrile infection-related epilepsy syndrome

Abbreviations: CBD, cannabidiol; FIRES, febrile infection-related epilepsy syndrome; KD, ketogenic diet; NORSE, new-onset refractory status epilepticus; RSE, refractory status epilepticus; VNS, vagal nerve stimulation

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1. Introduction

Febrile infection-related epilepsy syndrome (FIRES), recently included in the "Developmental and Epileptic Encephalopathies or Epileptic Encephalopathies with Onset in Childhood" by the International League Against Epilepsy (ILAE) task force [1], is a rare and catastrophic clinical syndrome characterized by de novo impetuous onset of refractory status epilepticus (RSE) soon after a febrile infectious disease occurring between 2 weeks and 24 h before the onset of RSE, without a clearly identifiable acute or active cause [2]. Outcome is extremely severe, with most patients presenting long-term sequelae, cognitive impairment and chronic refractory epilepsy, with a mortality rate of about 12% in children [3].

Aetiology and pathogenesis remain unknown in most cases, despite extensive work-up. Generally, the mainstay of treatment is immunotherapy, even if its efficacy is still under debate [3]. Due to the high case fatality, off-label treatments are often prescribed even without robust evidence of efficacy. Vagal nerve stimulation (VNS) and cannabidiol (CBD) have increasingly been used with variable, yet promising, results.

Here we report a case report of prolonged myoclonic super refractory status epilepticus (P-SRSE) in FIRES in a previously healthy teenager, who had an unexpected and brilliant recovery after the association of VNS and CBD.

2. Materials and methods

We describe a case report of a patient presenting with P-SRSE in FIRES at the tertiary care referral hospital of Padova, Italy.

All data are published anonymously and the identity of the patient described cannot be retrieved from the data provided in the present case report.

CBD was used off-label with parents' and hospital pharmacy's consent, according to the current clinical practice for off-label medications in our hospital.

Written informed consent for publication was obtained from the patient's parents.

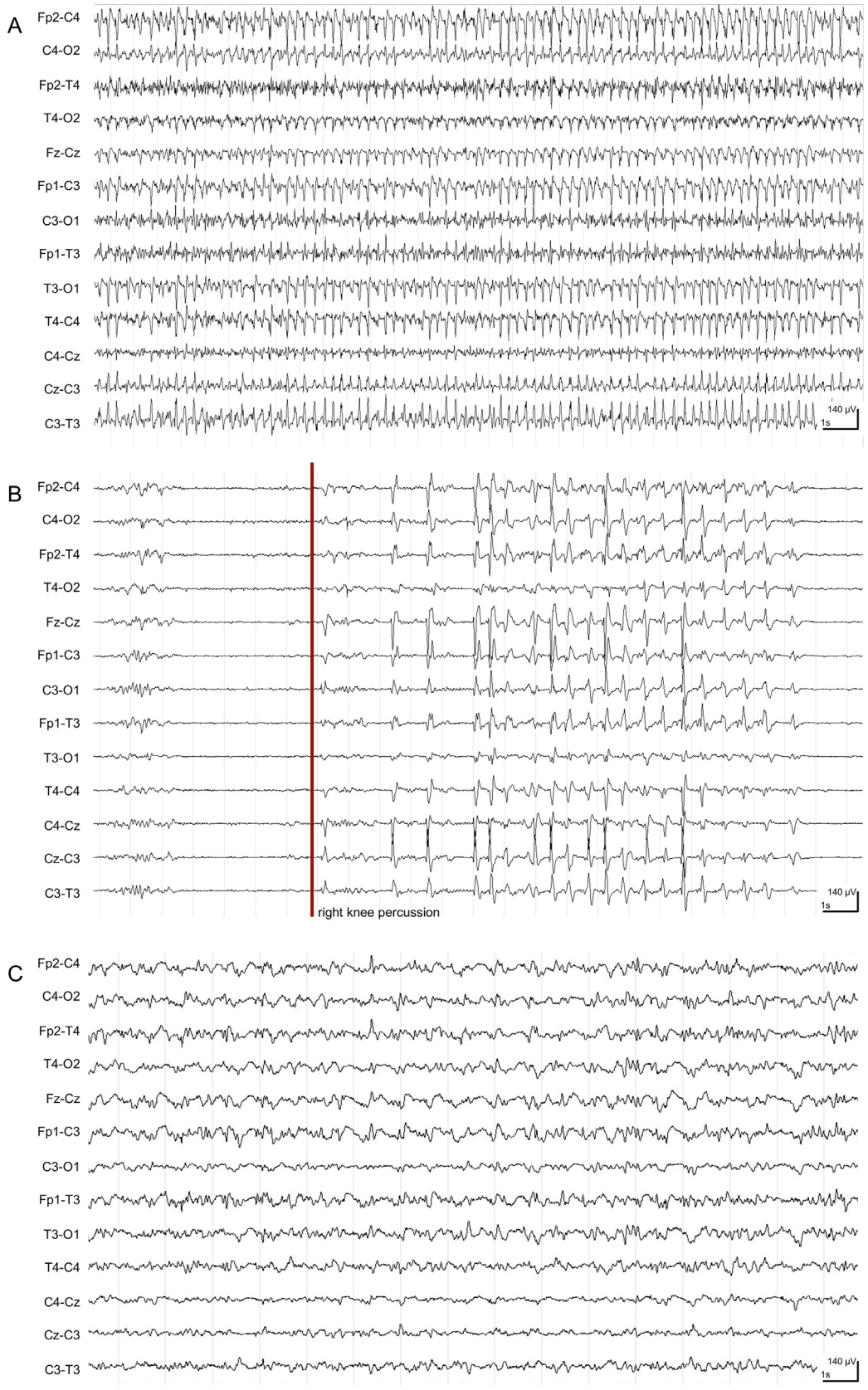
3. Case study

We report the case of a 14-year and 10-month-old, previously healthy girl who developed a P-SRSE 48 h after a mild infectious disease characterised by fever and gastrointestinal symptoms.

After admission to our paediatric intensive care unit in Padova, Italy, the clinical diagnosis of FIRES was made. She presented with myoclonic jerks of the buccal muscles and bilateral eyelid myoclonus coupled with diffuse and generalized myoclonic status epilepticus at continuous electroencephalography (cEEG) monitoring (Fig. 1a).

Several different pharmacological treatments and immunotherapies were tried with no effect (Fig. 2). She persisted in barbiturate-induced burst suppression with thiopental for about two months. SE and electroclinical seizures, either myoclonic or focal motor, at cEEG recurred every time weaning from thiopental was attempted. She was started on enteral ketogenic diet (KD) twice, with reduction in electrical seizures on both occasions. KD had to be discontinued after about two weeks due to gastrointestinal intolerance, pancreatic enzyme increase and hypertriglyceridemia. Forty-three days after P-SRSE onset, a VNS was implanted (Sentiva1000, Cyberonics/Livanova MN-US). The stimulation was started immediately using the following parameters: I 0.25 mA, Fq 30 Hz, PW 250 μs and DC 10%. The output current was increased every 12–24 h of 0.25 mA up to 2.25 mA; DC was set at 16% on the eighth day. No adverse events were recorded; cEEG showed no immediate improvement. Twenty-seven days after surgery, off-label CBD was added (galenic oil preparation derived from pure crystals, 2.5 mg/kg/day, titrated every 5 days up to 12.5 mg/kg/day, later shifted to Food and Drug Administration (FDA) and Agenzia Italiana del Farmaco (AIFA)-approved pharmaceutical drug in oral solution). Forty-eight hours after CBD introduction, status epilepticus (SE) weaned and seizures stopped, and it was possible to wean off all anaesthetics in another month. Antiseizure medications (ASMs) were continued with phenobarbital, lacosamide and topiramate. Surprisingly, the girl regained consciousness 15 days after CBD introduction, showing a rapid and unexpected recovery (about 4 months after P-SRSE onset). One month after SE cessation, she had mild neuropsychological deficits characterised by emotional dysregulation, with mood deflection, anxiety and oppositional behaviour, sleep-wake cycle disturbance and avoidant restrictive food intake disorder with emetophobia. She had mild difficulty collecting and

Fig. 1. EEG recording of our patient. (a) Generalized myoclonic status epilepticus at transfer to our hospital (day 1). Ongoing medications: midazolam 1.5 mg/kg/h, propofol 3 mg/kg/h, lacosamide 200 mg x2/day, brivaracetam 100 mg x2/day. (b) Stimulus-induced rhythmic, periodic or ictal discharge (SIRPID) caused by percussion of the right knee (day 30). Ongoing medications: thiopental 1.5 mg/kg/day, midazolam 0.2 mg/kg/h, ketamine 50 mcg/kg/min, lacosamide 200 mg x2/day, topiramate 200 mg x2/day, perampanel 12 mg x1/day, methylprednisolone 30 mg x2/day. (c) Resolution of the status with reappearance of organised background activity with interspersed multifocal low voltage epileptiform spikes (day 72), two days after introduction of cannabidiol (50 mg × 2/day) and twenty-nine days after vagal nerve stimulation implantation (at present 2.25 mA, Fq 30 Hz, PW 250 μs and DC 16%). Ongoing medications: i.v. ketamine 70 mcg/kg/min, i.v. midazolam 0,6 mg/kg/h, i.v. thiopental 3 mg/kg/h, i.v. lacosamide 200 mg × 2/day, topiramate nasogastric tube (NGT) 200 mg × 2/die, perampanel NGT 12 mg/die, i.v. methylprednisolone 30 mg × 2/day.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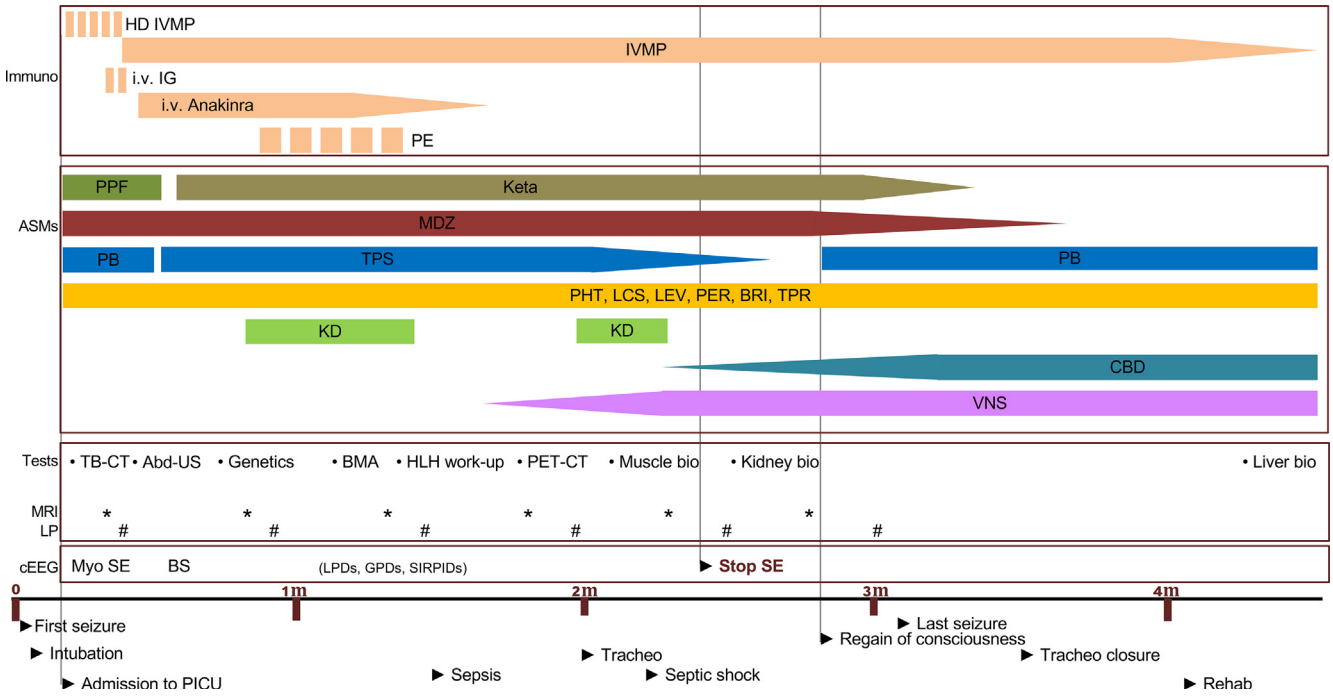

Fig. 2. Timeline of the case. each time lp was performed all these lab tests were analyzed and resulted negative: broad viral PCR tests, interleukins (IL-1, IL-2, IL-4, IL-6, IL-8, TNFa), neuronal autoantibody (anti-NMDAR, anti-MOG, anti-VGKC, anti-GAD, anti-LG1, anti-GABA-B, anti-AMPA, anti-aquaporin-4) and oligoclonal bands. In the third LP, onconeural autoantibodies, anti-GABA-A, anti-glycine and anti-dopamine-2 receptor autoantibodies were searched and resulted negative. Legend and dosages: abd-US: abdominal ultrasound; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASMs: antiseizure medications; bio: biopsy; BMA: bone marrow aspirate; BRI: brivaracetam (200 mg/day); BS: burst suppression; CBD: cannabidiol (up to 12.5 mg/kg/day); cEEG: continuous electroencephalography; GABA-A: gamma aminobutyric acid-A; GABA-B: gamma aminobutyric acid-B; GAD: glutamic acid decarboxylase; GPDs: generalized periodic discharges; HD IVMP: high-dose intravenous methylprednisolone (30 mg/kg x5 days); HLH: hemophagocytic lymphohistiocytosis; IG: immunoglobulins (1 g/kg x2 days); IL: interleukin; immuno: immunological therapies; i.v.: intravenous; IVMP: intravenous methylprednisolone (2 mg/kg/day); KD: ketogenic diet (3:1); keta: ketamine (up to 100 mcg/kg/min); LCS: lacosamide (up to 400 mg/day); LEV: levetiracetam (up to 60 mg/kg/day); LG1: leucine-rich glioma-inactivated 1; LP: lumbar puncture; LPDs: lateralized periodic discharges; m: months; MOG: myelin oligodendrocyte glycoprotein; MRI: magnetic resonance imaging; myo: myoclonic; NMDAR: *N*-methyl-D-aspartate receptors; PB: phenobarbital (7–10 mg/kg/day, up to blood level of 200–250 μmol/L); PCR: polymerase chain reaction; PE: plasma exchange; PER: perampanel (6–12 mg/day); PET-CT: positron emission tomography-computed tomography; PHT: phenytoin (up to 10 mg/kg/day); PICU: paediatric intensive care unit; PPF: propofol (1–5 mg/kg/day); SE: status epilepticus; SIRPIDs: stimulus-induced rhythmic periodic ictal discharges; TB-CT: total body-computed tomography; TNFa: Tumor necrosis factor alfa; TPR: topiramate; TPS: thiopental (3–5 mg/kg/day); tracheo: tracheostomy; VGKC: voltage-gated potassium channel; VNS: vagal nerve stimulation.

retelling recent memories. She showed postural tremor and paresis of the lower limbs due to atrophy and critical illness neuropathy.

Five months later, the intensity of stimulation was decreased from 2.25 to 1.75 mA due to tachycardia and frequent coughing.

At twelve-month follow-up, she is 8-months seizure free on multiple ASMs, talks properly and fluently and has resumed home schooling. She is regaining walking with assistance.

As regards neurophysiology, the initial EEG recording showed a generalized myoclonic SE (Fig. 1a). During the evolution, despite pharmacological burst suppression, multiple daily seizures either generalized, or arising from multifocal sites, mainly from the occipital lobes, were recorded by cEEG. Generalized periodic discharges (GPDs), lateralized periodic discharges (LPDs) and stimulus-induced rhythmic periodic ictal discharges (SIRPIDs) were also recorded (Fig. 1b) during the acute phase of the SE. After VNS and CBD introduction, later associated with high-dose phenobarbital (blood level up to 220–250 μ mol/L), cEEG showed improvement of background activity (Fig. 1c), restoration of sleep architecture with complete resolution of the epileptiform discharges, despite abundant rapid activity, due to the ongoing pharmacological treatment.

An extensive diagnostic work-up was inconclusive (Fig. 2). The first lumbar puncture revealed mild pleocytosis (monocytes 34/μL) with negative cerebrospinal fluid oligoclonal bands and anti-neuronal antibody searches – including *N*-methyl-D-aspartate receptors (anti-NMDAR) antibodies -, but five subsequent lumbar punctures did not reveal any abnormalities.

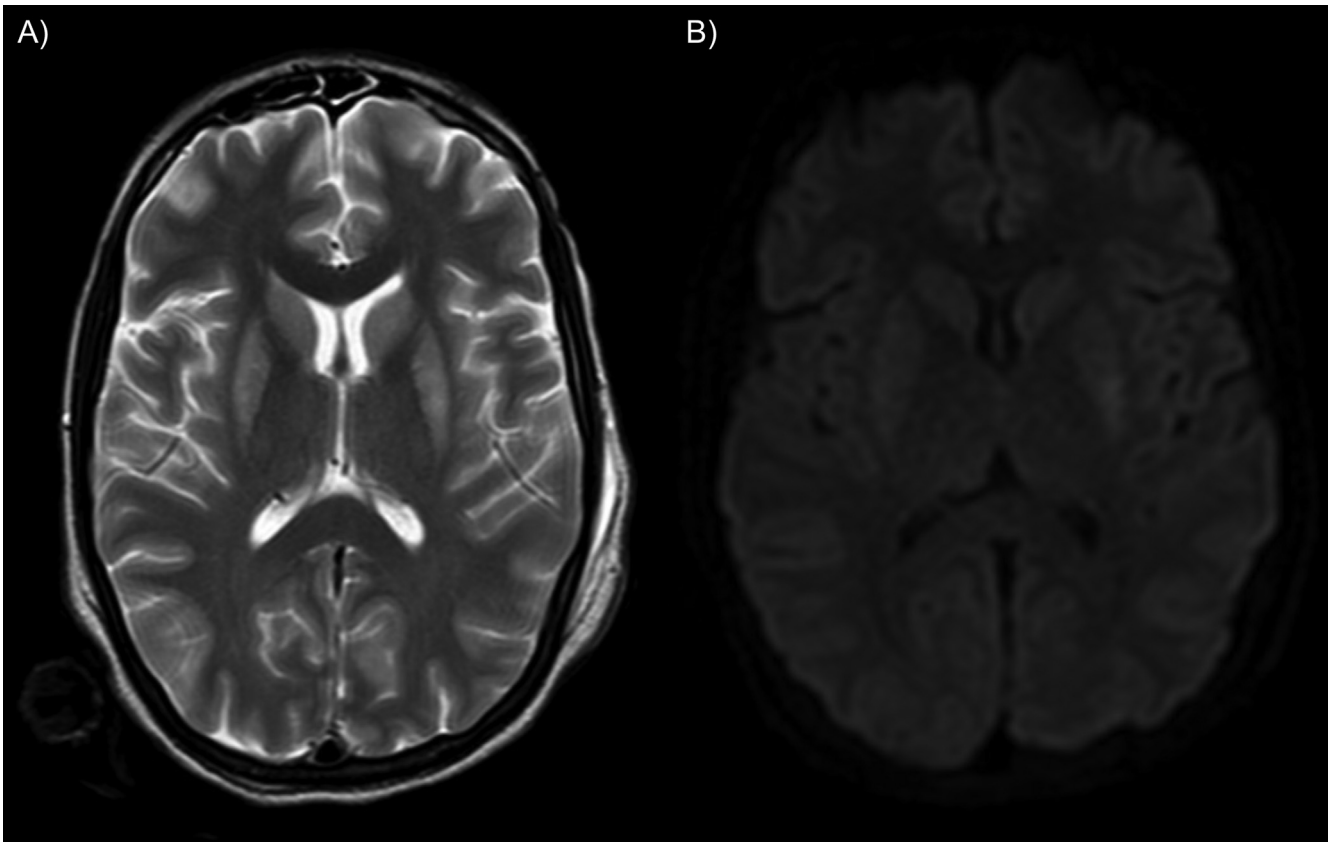

Fig. 3. MRI of the patient at onset. Axial-T2 (a) and axial-DWI (b) scans showing bilateral striatal oedema and reduction of diffusivity of the lenticular nucleus. Legend: DWI: diffusion weighted imaging.

Neuro-immunological, oncologic, infectious and endocrinological testing resulted persistently negative. Toxic causes were excluded by urine, blood and hair analysis. Liver, muscle and kidney biopsies were unremarkable. Genetic next generation sequencing panels for epilepsy, autoimmune disorders, mitochondrial diseases were inconclusive, whereas whole exome analysis is currently under investigation. MRI at onset (Fig. 3) showed bilateral non-specific T2-hyperintensities of the claustra which later evolved in atrophy of the lesions, consistent with MRI changes during FIRES already described in the literature [4]. Brain positron emission tomography with computed tomography (PET-CT), during the acute phase and general anaesthesia showed a global reduction of the metabolism with no focal area involved, which later normalised the follow-up.

4. Discussion

We present a highly comprehensive iconography and detailed history of a case with a peculiar and unexpected course of a catastrophic disease. FIRES onset with generalized myoclonic SRSE is extremely exceptional. FIRES mostly presents with focal onset seizures with multifocal epileptiform discharges on a delta-theta background at EEG. Farias Moeller and colleagues described three main EEG features in the hyperacute phase being (*i*) gradual increase in seizure burden, (*ii*) presence of recurrent extreme delta-brush, and (*iii*) distinctive seizure pattern [5]. All these characteristics were not observed in our patient, who presented from the beginning with a relentless generalized myoclonic SE. Therefore, we suggest that this pattern should also be included as one of the possible of FIRES debuts.

As regards therapy, P-SRSE treatment in FIRES is known to be extremely challenging [6,7]. As the SRSE persists, neuronal changes and internalisation of gamma-aminobutyric acid (GABA) receptors lead to refractoriness to conventional ASMs. Hence, the need to find novel therapies not targeting classic receptors. These include novel neuromodulation therapies such as KD, CBD and VNS, whose mechanisms of action on epilepsy need to be fully elucidated yet. In our patient, after KD discontinuation due to side effects, VNS and CBD were undertaken.

VNS is one of the most used neuromodulation approaches to treat pharmacoresistant epilepsy. Isolated

cases of successful VNS implantation are reported in literature in cases of SRSE, either new-onset refractory status epilepticus (NORSE) or FIRES, mainly in the adult literature [8]. According to a recent international consensus recommendation for management of FIRES [7], VNS may be effective for the post-acute epilepsy. In our patient, VNS was used after about 6 weeks of onset, due to inefficacy of several other therapeutic interventions, and based on a recent systematic review showing a success rate of acute termination of refractory SE with VNS of up to 76%, thus proposing VNS as an extremely promising therapy in the acute treatment of SRSE. However, more studies are warranted to improve protocols of implantation time, parameter titration and monitoring of efficacy in seizure reduction or SE termination [9].

On the other hand, CBD has emerged as a potential therapeutic strategy for epilepsy in the last five years [10,11]. Most studies in children were conducted in patients affected by genetic diseases, such as Dravet syndrome [12] and other developmental and epileptic encephalopathies. In a series of seven paediatric patients with FIRES, add-on CBD after failure of classic therapies, in both the acute and chronic phase, allowed the weaning of several ASMs [13]. However, according to a recent international consensus recommendation for management of FIRES [7], current evidence does not clearly support the usefulness of CBD in the acute phase of NORSE/FIRES, and this should not be used as a first-line treatment in this condition.

To date, reports and studies on the association of VNS and CBD are lacking. This association, to the best of our knowledge, has never been tried in paediatric FIRES before. CBD mechanism of action still needs to be fully elucidated, and is hypothesised to be associated with the activation of the endocannabinoid system possibly related to epileptogenesis. CBD also appears to have an anti-inflammatory effect in the nervous system by decreasing pro-inflammatory mechanisms in animal models [14]. We may infer that this anti-inflammatory mechanism, coupled with the neuromodulation effect of VNS, led to the control of SE and seizures in our patient, with a remarkable recovery and normalisation of both clinical status and EEG. Yet, this observation remains speculative at the moment and should be verified in future cases.

5. Conclusions

In conclusion, we reported the first paediatric case of P-SRSE caused by FIRES with successful recovery with the association of VNS and CBD with complete seizure control, EEG normalisation and with only minimal residual neuropsychological impairments.

Even if more studies are needed to confirm our observations, our case suggests the possibility of the synergic association of VNS and CBD in adjunction with traditional therapies in refractory cases, not responsive to immunotherapy, KD and traditional ASMs.

Author contributions

CMB and GMF performed clinical data collection, reviewed the literature, and drafted the manuscript. BG contributed in collecting data from patient's chart and from the literature. CL contributed to the acquisition and interpretation of the data. IT, MN, AP, CL and CB critically revised the manuscript. SS and AL conceived the idea for this case report, drafted and critically reviewed the manuscript, performed clinical data collection and interpretation and finally approved the manuscript.

Conflict of interest disclosures

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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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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