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Clinical letter

High dose cannabidiol (CBD) in the treatment of new-onset refractory status epilepticus (NORSE)

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1. Introduction

New-Onset Refractory Status Epilepticus (NORSE) is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause [1]. Febrile Infection-Related Epilepsy Syndrome (FIRES) is a subcategory of NORSE, applicable for all ages, that requires a prior febrile infection starting between 2 weeks and 24 h prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus [1].

2. Case report

A 27-year-old man with past medical history of migraines presented as an outside transfer with subacute altered mental status. He was febrile a week prior to admission to 40 °C. On admission, the patient was febrile (38.8 °C) with otherwise normal vitals.

Brain MRI, head CT and toxicology screening within the first 24 h of admission were normal. CSF analysis was notable for 10/μl white cells and 600 mg/L protein suggesting an inflammatory process. The possibility of an infectious etiology had been considered and empiric therapy with vancomycin, ceftriaxone, and acyclovir was initiated.

The viral and autoimmune encephalitis and paraneoplastic panels include but were not limited to ANA, ANCA, IgA, total complement, anti-ds DNA, anti-Smith, anti-SSA/SSB, anti-Scl, anti-centromere, anti-cardiolipin, anti-CCP, HHV-6, CMV, VZV, West Nile virus, enterovirus PCR, HSV-1 PCR, HSV-2 PCR in CSF and/or serum were negative. CSF NMDA receptor antibody level was <1:1, negative. Liver enzyme levels were insignificant.

Two days after admission, he had clinical progression to focal to bilateral tonic-clonic seizures. The patient was placed on continuous long-term monitoring VEEG.

The patient was initially in focal non-convulsive status epilepticus with independent left>>right temporal onsets. The patient subsequently became resistant to anticonvulsant polytherapy regimens (lorazepam, levetiracetam, phenytoin, lacosamide, clobazam). Intravenous (IV) methylprednisolone treatment initiated for presumed autoimmune etiology [Fig. 1].

The hospital course continued with non-convulsive status, multifocal, often without obvious clinical correlate. The patient was intubated, and subsequently, anesthetics (propofol, midazolam, ketamine, pentobarbital, isoflurane) were added for super-refractory status epilepticus. In the subsequent days propofol, midazolam, ketamine continued while pentobarbital was weaned off due to the development of severe hypokalemia. The patient remained refractory to the usual intravenous anesthetics with variable suppression and breakthrough near continuous ictal state. Hence, ketamine, midazolam, and propofol were gradually weaned off while isoflurane was initiated. There was eventual progression to multifocal ictal onsets and eventually a pharmacologic burst-suppressed pattern with prominent multifocal epileptiform discharges within bursts. Both breakthrough electrographic and

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electro-clinical seizures were noted with inhalational anesthetic wean.

CSF and serum analysis with extensive work-up for infectious, autoimmune, and paraneoplastic syndromes were unrevealing. Repeat brain MRI and malignancy screening, including chest, abdomino-pelvic CT, and testicular ultrasound were unremarkable.

Antiseizure polytherapy trials (phenobarbital, topiramate, zonisamide, pregabalin, perampanel) were continued with ineffective results [Fig. 1].

Electroconvulsive therapy (ECT) was applied with a total of 6 sessions along with a ketogenic diet.

Immunomodulatory therapy with plasmapheresis, intravenous immunoglobulin (IVIG), rituximab, and cyclophosphamide were applied with a limited response at the 3-month mark.

A week and a month later, after admission, repeat LP and serum analysis with extensive work-up for autoimmune/infectious encephalitis, paraneoplastic syndromes were unrevealing.

The patient remained in status epilepticus with independent left-hemispheric and right frontal onsets. Bi-frontal epileptiform discharges and right greater than left hemispheric slowing was noted. Seizures were largely subclinical/electrographic. Repeat brain MRI nearly after 3 months of admission showed mild diffuse parenchymal volume loss.

Cannabidiol (CBD) was initiated in a liquid form at a concentration of 100 mg/ml administered through PEG at a dose of 15 mg/kg/day. Following CBD treatment, status epilepticus was aborted. The EEG in one week improved with sustained continuous awake background with stage II sleep and mild diffuse dysfunction [Fig. 2].

In a 1 week after the initiation of CBD, the patient started following simple one-step verbal commands. Neurologic status continued to improve, and 2 weeks later, the patient was fully conversant with a gradual return of motor functions.

The anticonvulsant regimen was gradually consolidated, and perampanel and clobazam were weaned off; cannabidiol increased to 20 mg/kg/day two weeks after initiation. The patient was discharged on phenytoin, zonisamide, phenobarbital, levetiracetam, lacosamide, and cannabidiol 100 mg/ml oral liquid at a dose 7.5 ml/12qH. Given the patient's complex in-hospital stay and super refractory seizures, the AEDs and cannabidiol were planned to be given indefinitely as tolerated.

The patient remains seizure-free 2 months post-discharge and is independent with daily activities resuming rehabilitation. Gradually, the patient returned to his baseline and was able to resume prior school coursework.

3. Discussion

Despite exhaustive workup, most NORSE/FIRES cases (52%) remain unidentified (cryptogenic), while of those identified etiologies most were autoimmune (19%), paraneoplastic encephalitis (18%) or infection-related (8%) [2]. Unfortunately, currently, there is no specific treatment for cryptogenic NORSE. The role of conventional antiepileptic drugs and immunotherapies with regard to treatment are limited [1,2]. Outcomes are generally poor, and mortality is high, around 20% [2].

Several experimental models suggest that CBD reduces seizure frequency and duration with conventional and unconventional antiepileptic effects, along with a neuroprotective role [3]. Additionally, CBD's anti-inflammatory effect may explain the potential therapeutic value in this case, given the highly probable inflammatory process in the pathogenesis in NORSE. However, our search remains inconclusive [2,4]. Gofshteyn et al. reported the potential therapeutic effect of cannabidiol for FIRES in a series of 7 pediatric patients with improved response and timeline similar to our report [3].

We cannot infer that CBD was the only effective drug in the patient's clinical improvement, given the complexity of the case and the confounding factor of polytherapy. However, at the time CBD was administered, the conventional antiseizure drugs were consolidated. Additionally, quick clinical improvement of the patient after CBD administration was another clue that CBD may be effective in NORSE.

To our knowledge, this case is the first adult NORSE/FIRES case that a patient showed significant improvement (independent with activities of daily living) after cannabidiol treatment.

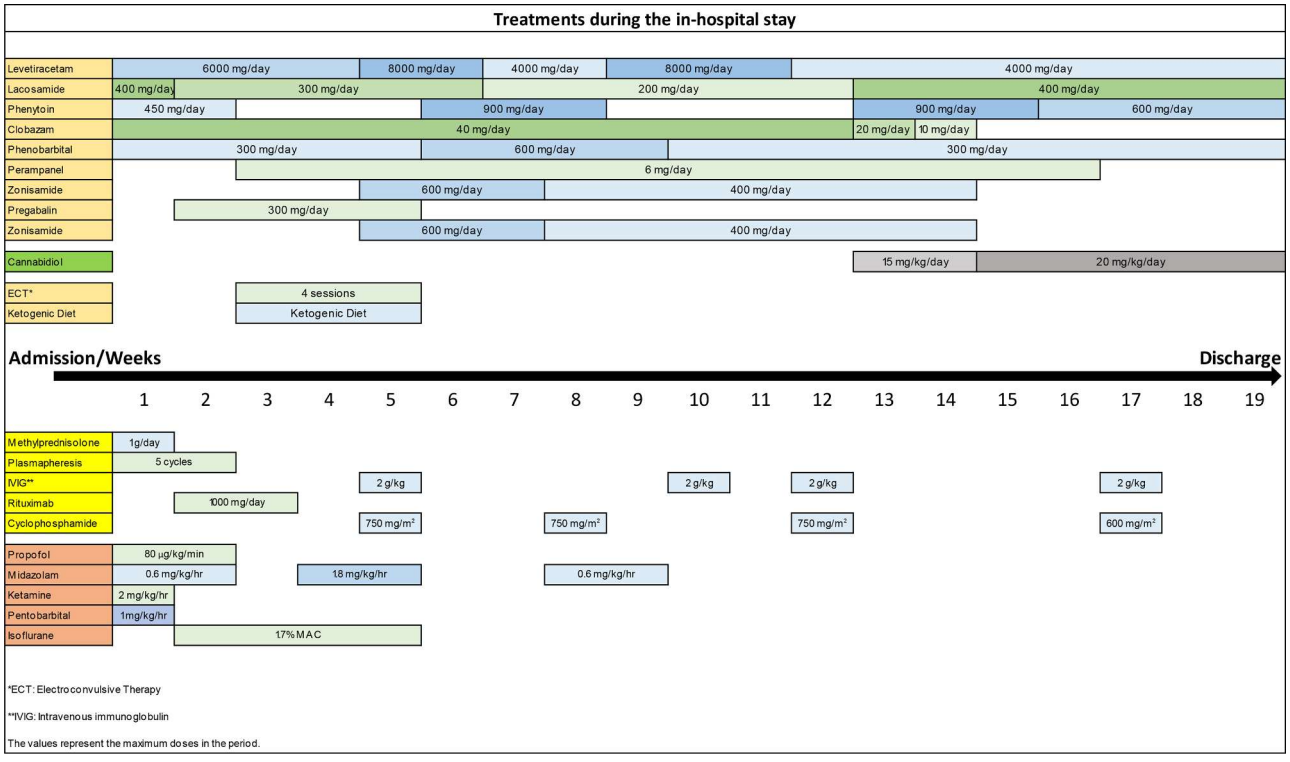

Fig. 1. Medications and Treatments over the Hospital Course.

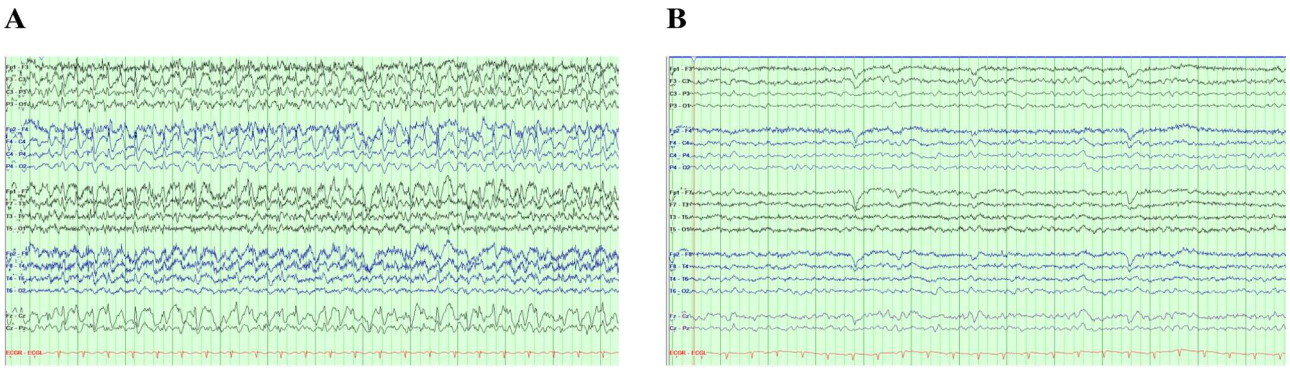

Fig. 2. Electroencephalography (EEG)
(A) EEG performed pretreatment with cannabidiol shows generalized seizure activity.
(B) EEG performed post-cannabidiol treatment shows eye-blinking activity and patient out of coma.

4. Conclusion

Cryptogenic NORSE/FIRES can be devastating for the patient, family, and healthcare professionals. High-dose cannabidiol treatment can be a promising treatment in selected patients with NORSE/FIRES.

Disclosure

None of the authors has any conflicts of interest to disclose.

The case was presented at poster session of American Clinical Neurophysiology Society (ACNS) Annual meeting February 5–9, 2020.

Declaration of Competing Interest

The authors of this article have no conflicts of interest.

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