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Two Concomitant Cases with Febrile Infection-Related Epilepsy Syndrome (FIRES) treated with "3-Dimensional Combination Treatment Protocol"

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Abstract

Objective: Febrile Infection-Related Epilepsy Syndrome (FIRES) is an immun-mediated epileptic encephalopathy presents as a febrile infection related super refractory status epilepticus with mortality rate of up to 30% in intensive care unit in spite of pharmacologically induced coma and immunotherapies. Early interventional ketogenic diet and cannabinoids are suggested for treatment with unknown mechanisms.

Case presentation: Here we report two concomitant FIRES cases treated with a "3 dimensional combined treatment protocol" for FIRES including (1); super refractory status epilepticus treatment protocol with intravenous infusion of antiepileptic and anesthetic drugs, (2) immunomodulatory therapies and (3) early interventional anti-epileptogenic therapy (ketogenic diet plus cannabinoids). The therapeutic intensity of the treatment protocol was monitored with serial EEG monitoring and Functional Independence Scores-WeeFIM. Two previously healthy school children manifesting super refractory status epilepticus were treated with moderate success. Both patients recovered with drug refractory epilepsy and neurocognitive impairments (patient 1; WeeFIM Scores were: self-care: 17, motor: 24, cognition: 10 and patient 2; WeeFIM score remained totally dependent: self-care: 8, motor: 5, cognition: 5) at the 12 months of follow-up.

Conclusion: Febrile infection-related epilepsy syndrome is a devasting catastrophic epileptic encephalopathy. Early interventional treatment protocols should be applied in the early period of super refractory status epilepticus.

Keywords: FIRES • Super refractory status epilepticus • Therapy • Ketogenic diet • Cannabinoids

Abbreviations: FIRES: Febrile Infection-Related Epilepsy Syndrome; PICU: Pediatric Intensive Care Unit; RSE: Refractory Status Epilepticus; WeeFIM: Functional Independence Scores; MRI: Magnetic Resonance Imaging; CSF: Cerebro Spinal Fluid; EPSEP: Ege Paediatric Status Epilepticus Protocol

Introduction

Febrile Infection-Related Epilepsy Syndrome (FIRES) is a recently defined catastrophic epileptic encephalopathy manifesting with focal seizures resistant to antiepileptic drugs, requiring pharmacologically induced coma and advanced supportive therapies [1,2]. The mortality is reported as 10-30% in Pediatric Intensive Care Unit (PICU) [2,3]. In the acute phase of FIRES, the response of immunotherapies with steroids and immunoglobulins are limited by the fact that small case series demonstrating that no one is superior. Early interventional ketogenic diet and cannabinoids are suggested for treatment with unknown mechanisms. In the chronic phase, after weeks or months, super Refractory Status Epilepticus (RSE) disappear but most cases survive with severe neurologic sequela and drug-refractory epilepsy [2,3]. Here we report two concomitant cases of FIRES treated with a "3 dimensional combined treatment protocol "including; (1) antiepileptic and anesthetic drugs infusions (2) immunomodulatory therapies and (3) early interventional anti-epileptogenic treatment with ketogenic diet plus cannabinoids. The therapeutic intensity of treatment protocol was monitored with serial EEG monitoring and Functional Independence Scores (WeeFIM).

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Case Report

Demographics

Patient 1: Eleven-year-old healthy school boy presented to PICU with focal motor seizures and encephalopathic state. Viral serological analysis of blood and Cerebro Spinal Fluid (CSF) showed no abnormalities. A panel for auto-immune antibodies was negative (Table 1). Magnetic Resonance Imaging (MRI) of brain revealed no abnormalities (Figure 1A). The diagnosis of FIRES was established as exclusion diagnosis with febrile-triggered status episodes.

Patient 2: Eight-year-old healthy school girl admitted to PICU with focal motor seizures. The brain MRI revealed hyperintensity in the bilateral inferior hypothalamic region and parahippocampal arae (Figure 1C). Burst suppresion coma was achieved with thiopentale sodium infusion. The panel of autoimmune antibodies was negative (Table 1). No viral polymerase chain reaction/cultures or serologic evidence of pathogens was detected.

Treatment protocols

After obtaining informed consent from both concomitant patients, treatment initiated with an early interventional " 3 dimensional combined treatment protocol " for FIRES including; (1) Intravenous antiepileptic drug and anesthetic drug infusion for treatment of super RSE (2) Immunomodulatory therapies and (3) Early interventional anti-epileptogenic treatment with ketogenic diet plus cannabinoids in the period of super-RSE.

- Departmental protocol for convulsive status epilepticus (Ege Pediatric Status Epilepticus Protocol-EPSEP, previously reported) was performed for the initial treatment of super-RSE with anti-epileptic drugs [Phenobarbital: infusion >10 mg/kg/h with serum levels, phenytoin : loading dose: 30-40 mg/kg, midazolam: bolus 0.03-

Table 1. Comparison of clinical aspects of two cases treated with early interventional "3-dimensional combined treatment protocol" for FIRES.

Parameters	Patient 1	Patient 2
Age, (F/M)	11 years-old-boy	8 years-old-girl
Febrile infection	Pneumonia	Flu-like infection
Prodromal phase (day)	4 days	2 days
Seizure semiology at initial presentation	Focal motor seizures (clonic and mycolonic), focal to bilaterally	Focal motor seizures (clonic and mycolonic), focal to bilaterally
Super RSE (day)	33 days in PICU	57 days in PICU
CSF Analysis: Evidence for infectious encephalitis and metabolic disorders	None	None
Autoantibodies	CASPR2, NMDAR, AMPAR, LGI 1, GABABR : Negative	CASPR2, NMDAR, AMPAR, LGI 1, GABABR: Negative
MRI Acute phase Chronic phase (at the 12 months of follow-up)	Normal Moderate diffuse cortical atrophy	Involvement of the bilateral hypothalamic area and cortical edema Severe diffuse cortical atrophy
"3 dimensional combined treatment protocol"		
1. Super-RSE protocol AEDs	EPSEP plus levetiracetam, sodyum valproat, topiramate, clonazepam	EPSEP plus levetiracetam, topiramate, valproate, clonazepam
Anestethic drugs	Ketamine, sodium thiopentale, propofol	Propofol, sodium thiopentale, ketamine
2. First-line immunotherapy Second-line immunotherapy	Intravenous immunoglobulin pulse methyl prednisolone	Intravenous immunoglobulin pulse methyl prednisolone plasma exhange Rituximab
3. Ketogenic diet plus cannabionoids	Started 24th day of disease continued 12 months	Started 38th day of disease continued 6 months
Seizure outcomes		
Acute phase:	Febrile-related convulsive SE periods (1-2/day) in clinic on the 37th day frequency and duration of focal clonic and myoclonic seizures decreased	Febrile-related convulsive SE periods (4-5 days) in clinic on the 97th day frequency and duration of focal clonic and myoclonic seizures decreased
Chronic phase: (at 18 months of follow-up)	1-2 focal motor seizures in a month 1 convulsive status epilepticus in a year	4-5 focal motor seizures in a month 3 convulsive status epilepticus in a year
EEG outcomes		
Burst supression duration at 12 months of follow-up	No Antiepileptic dualterapy with multifocal epileptic activity on EEG examination	2 days Antiepileptic drug polytherapy with multifocal epileptic activity on EEG examination
ICU staying time (Day)	37 days	90 days
Overall neurological outcomes		
Functional Independence Measure for children (WeeFIM) at the discharge:	Self-care: 8	Self-care: 8
	Motor: 5	Motor: 5
	Cognition: 7	Cognition: 5
One year of follow up:	Self-care: 17	Self-care: 8
	Motor: 24	Motor: 5
	Cognition: 10	Cognition: 5

PICU: Pediatric Intensive Care Unit; EPSEP: Ege Pediatric Status Epilepticus Protocol; AMPAR: α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor; CASPR2: Contactin-Associated Protein-like 2; GABABR: γ-Amino Butyric Acid B Receptor; LGI 1: Leucine-Rich Glioma-Inactivated 1; NMDAR: N-Methyl-D-Aspartate (NMDA) Receptor

0.5 mg/kg with infusion rate: 0.02-0.6 mg/kg/h (up to 1.2 mg/kg/h), levetiracetam: 50-60 mg/kg/d)] followed with intravenous anesthetic drug infusion with maximum dosage [4].

- Immunotherapies were given to both patients; intravenous methylprednisolone 10-30 mg/kg/day for 3-5 days continued with oral prednisone 1 mg/kg/day and intravenous immunoglobulin 0.4 g/kg/day for 5 days. Plasmapheresis with 3-5 exchanges, one every other day. Rituximab (immunoglobulin G1 monoclonal antibody targeting CD20, 375 mg/m^2 per week for four weeks) were performed in patient 2.
- Anti-epileptogenic therapy was initiated in the early phase ketogenic diet with 1: 1 to 4: 1 ketogenic ratio and Cannabidiols (CBD) with the dosage of 10-25 mg/kg. A purified oil-based liquid CBD preparation (15% CBD +CBDa-Raw Hemp Oil) was started with an initial dose 10 mg/kg, up-titrated to maximum dose 25 mg/kg.

Outcomes

Patient 1: On the day 24th standard ketogenic diet was initiated with a commercial preparation via gastric tube. On the 33rd day frequency and duration of focal myoclonic seizures decreased. Thiopentale sodium, midazolam and propofol infusions were weaned off gradually. Continuous EEG monitorization revealed sequential rhytmic, periodic focal spikes, sharp waves, spike-and-wave complexes erasing from parieto-occipital lobes and gradual spread into both hemisphere. Frequent electrographic seizures were recorded in the first three weeks of staying in PICU. Daily clustered focal myoclonic seizures remained one or two times a week at the discharge from PICU. On day 107, he responded with eyes and head movements to basic verbal commands from his parents, and he was discharged on day 114 with Functional Independence (WeeFIM) Scores: self-care: 8, motor: 5, cognition: 7. At one year of follow-up he was on dual antiepileptic therapy with multifocal epileptic activity on EEG examination and moderate diffuse cortical atrophy on MRI (Figure 1B). His

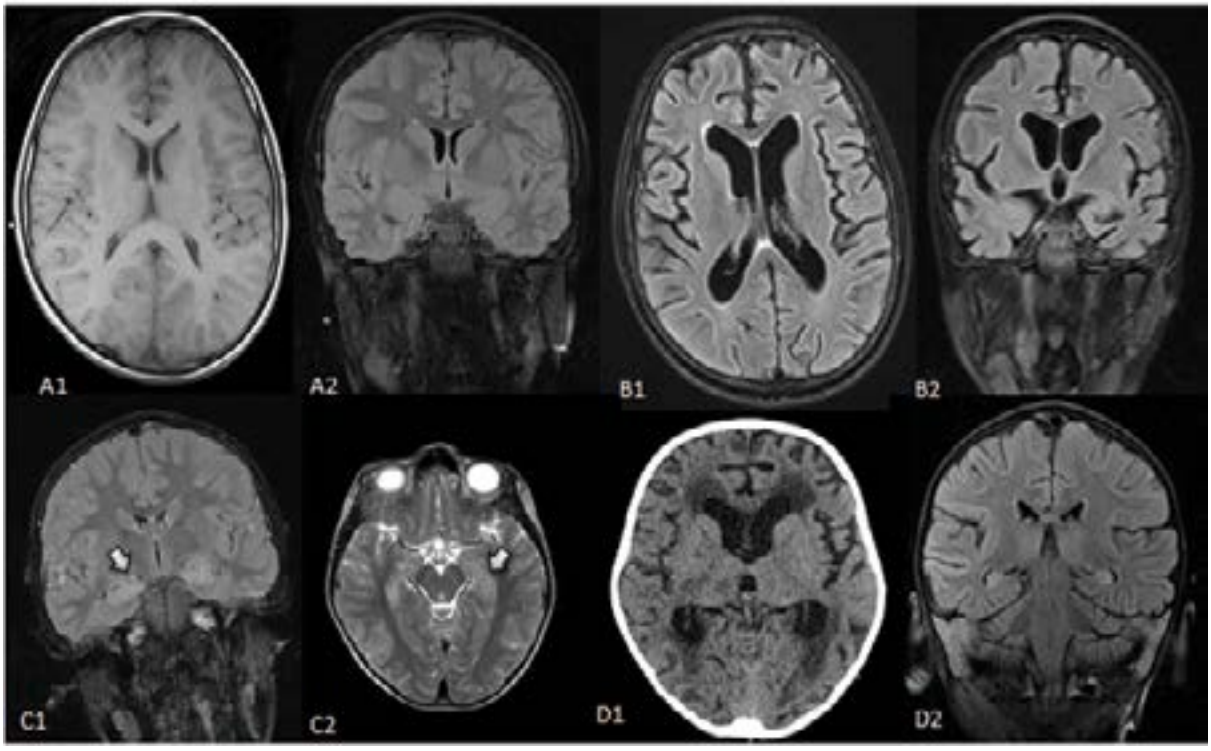

Figure 1. Patient 1: A (A1-axial image, A2-coronal image) Normal MRI in the acute phase of FIRES, B (B1-axial image, B2-coronal image) Moderate diffuse cortical atrophy at the 12 months of follow-up. Patient 2: C (C1-coronal image, C2-axial image) MRI revealed a hyperintensity (arrows) in the bilateral posterior hypothalamic region on a fluid-attenuated inversion recovery (FLAIR) sequence in acute phase, D (D1-axial image, D2-coronal) severe diffuse cortical atrophy at the 12 months of follow-up.

follow up WeeFIM Scores were: self-care: 17, motor: 24, cognition: 10 at the end of one year.

Patient 2: Ketogenic diet was initiated on day 38 for FIRES with a commercial preparation via nasogastric tube. By the 18th day of ketogenic diet ketosis was achieved with 4: 1 ratio. Super-RSE controlled on the 57th days in PICU. After treatment of status epilepticus in PICU, serial EEG examinations indicated sharp wave epileptiform discharges over bilateral frontal and temporal hemispheres with brief generalized burst activities. She was discharged with brief focal clonic seizures a day controlled with ketogenic diet (4: 1) plus cannabionids after 183rd day of her admission. At discharge her Functional Independence (WeeFIM) Scores were: self-care: 8, motor: 5, cognition: 5, totally dependent. At the follow-up of one year, she is still on antiepileptic drug polytherapy with multifocal epileptic activity on EEG. MRI examination at the first year of follow-up revealed markedly diffuse cortical atrophy (Figure 1D). End of the one year of follow up WeeFIM score remained totally dependent (self-care: 8, motor: 5, cognition: 5) the comparison of the demographic, treatment and outcome characteristics of cases were given in Table 1.

Discussion

FIRES is a catastrophic epileptic syndrome mainly effecting healthy school children [1,3]. Here we report two cases with FIRES presenting with super-RSE. Most cases of FIRES evolve to super RSE and have unfavorable outcome, with long-term severe neurologic sequela and epilepsy [3]. The proposed treatment flowcharts for FIRES include GABAergic therapy at highest doses, immunotherapy, mild hypothermia, ketogenic diet started as early as possible, avoiding (especially prolonged) burst-suppression coma, and to test cannabidiol [1,3]. Both cases were treated with an early interventional "3-dimensional combined treatment protocol "for FIRES in the period of super-RSE. The comparison of the demographic, treatment and outcome characteristics of cases were given in Table 1. Both patients received first-line immunotherapy (high-dose prednisolone and intravenous immunoglobulin) concomitantly to intravenous antiepileptic therapy and the anesthetic drugs infusions with highest tolerable doses. In the acute phase of FIRES, episodes of status epilepticus were controlled on the 33 and 57 days of ICU admission for patient 1 and 2. Additionally patient 2 had six episodes of status epilepticus while patient 1 had only two status epilepticus episodes in admission period. During the acute phase of disease patient 2 had also received plasmapheresis in PICU. Combined treatment of ketogenic diet and cannabinoids were initiated in the PICU as an early interventional anti-epileptogenic treatment. Patient 1 continued this combination therapy plus polytherapy with antiepileptic drugs for 12 months with a favorable outcome without recurrence of RSE. Patient 2 continued ketogenic diet plus cannabinoid therapy for 6 months. Patient 2 had four episodes of RSE treated with high dose GABAergic antiepileptic drugs during the 12 months follow-up. Then a second-line immunotherapy with rituximab was initiated for this patient. She had only single episode of RSE in the following 6 months.

The treatment intensity of the "3-dimensional treatment protocol" for FIRES was followed with continuous EEG monitoring in PICU and serial EEG examination in follow-up period (Table 1). Patient 2 had a burst suppression coma which is a standard care in super-RSE. There are concerns regarding its use in FIRES, since prolonged burst suppression coma has been significantly associated with a worse cognitive outcome. These results call for caution of inducing burst-suppression coma [2]. Pharmaco-resistant epilepsy and severe motor-cognitive impairment which is caused by super-RSE determines the prognosis [2]. Patient 2 had a more prolonged super-RSE 57 days in PICU. Additionally more frequent status epilepticus episodes in the chronic phase of FIRES has been identified in patient 2 who had worse motor and cognitive impairment. The presented combination therapy "3-dimensional treatment protocol" should be in tested in new case series with large-number patients. The exact pathogenesis is actually unknown albeit some authors hypothesized underlying mechanism of FIRES with immune-mediated non-autoimmune process in genetically predisposed patients. However only Caputo et al report a pediatric case of FIRES like syndrome which detects GABAAR antibodies and speculated ketamine (non-competitive NMDAR antagonist) treatment is a beneficial alternative combined with the steroides [5]. Despite lack of biomarkers for FIRES, early diagnosis is important to guide the treatment of status epilepticus and epileptic encephalopathy. The potential pathophysiologic role of cytokines and related effect of other molecules in FIRES-associated epileptogenesis should be investigated in animal models.

Conclusion

Febrile infection-related epilepsy syndrome is a devasting catastrophic epileptic encephalopathy. Early interventional treatment protocols should be applied in the early period of super refractory status epilepticus.

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