FULL-LENGTH ORIGINAL RESEARCH

Early ictal and interictal patterns in FIRES: The sparks before the blaze

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Summary

Objective: Febrile infection–related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy described as explosive onset of super refractory status epilepticus (SRSE) in previously healthy children. We describe electroencephalography (EEG) abnormalities in the hyperacute phase of FIRES, with the aim of contributing to the diagnostic characterization of a syndrome otherwise lacking specific biomarkers.

Methods: This is a retrospective single-center, case series of seven children with FIRES. Cases were identified from a Neurocritical Care database. Patient characteristics and clinical course were obtained from electronic medical records. Electroencephalography recordings were reviewed in two segments: the initial 12 h of recording and the 12 h prior to initiation of a medically induced burst suppression (BS).

Results: Fourteen 12-h segments of video–electroencephalography (EEG) recordings were analyzed for commonalities. A beta–delta complex resembling extreme delta brush (EDB) occurred in at least one 12-h segment for all patients. In six patients, seizures were brief and relatively infrequent during the first recording, with a gradual evolution to status epilepticus by the second. We observed a characteristic electrographic seizure pattern in six of seven patients with prolonged focal fast activity at onset. Shifting seizures were seen in four of seven patients.

Significance: The diagnosis of FIRES is typically assigned late in a patient's clinical course, which has broad implications for clinical care and research. We retrospectively analyzed acute EEG features in seven patients with FIRES and discovered three common features: gradual increase in seizure burden, presence of a recurrent EDB, and a typical seizure pattern. Recognition of this pattern may facilitate early diagnosis and treatment.

KEY WORDS: Febrile infection–related epilepsy syndrome, Super refractory status epilepticus, Extreme delta brush, Status epilepticus.

Febrile infection–related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy that is described as an explosive onset of super refractory status epilepticus (SRSE), defined as status epilepticus (SE) that continues >24 h after the onset of general anesthesia, or recurs after its withdrawal.[1] The onset of SRSE is typically preceded by a seemingly benign, nonspecific febrile illness in a previously healthy school-aged child. The diagnosis is one of exclusion made after the infectious, metabolic, genetic, and autoimmune evaluation yields negative results.[2–4] The etiology of FIRES remains unknown, although there is suspicion for inappropriate activation of the innate immune system.[2,5–7] Most centers trial a combination of antiepileptic and immune-modulating therapies with disappointing results.[2,8,9] Outcomes in children with FIRES are poor, with 10–30% of cases resulting in death, refractory epilepsy in 90% of survivors, and severe intellectual disability in a third.[2,5,9]

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Key points

- Extreme delta brush (EDB) is common in the EEG background of patients with FIRES during the acute presentation
- Electrographic seizures in patients with FIRES have characteristic features of prolonged focal fast activity and hemispheric shifting ictal activity
- EEG can be used as an early biomarker in patients with FIRES

Despite the unrelenting quality of SRSE in patients with FIRES, the syndrome is not widely recognized.[4] The lack of specific clinical criteria and/or confirmatory tests leads to a broad and expensive diagnostic evaluation for most patients. The course for patients with FIRES is often protracted, with the diagnosis applied late in the course, if at all. Patients are frequently placed in pharmacologic coma for prolonged periods and have associated medical complications further obscuring our understanding of the natural course of disease. Recent reports suggest that early introduction of cannabidiol, human recombinant interleukin (IL)-1 receptor antagonist (Anakinra), or ketogenic diet (KD) may be associated with reduced seizure burden in the acute period.[8,10,11]

It is crucial to develop early diagnostic tools to aid in prompt diagnosis. With that purpose, we aim to investigate the role of electroencephalography (EEG) prior to pharmacologic burst suppression (BS) as a potential early biomarker for the diagnosis of FIRES. We retrospectively describe the acute clinical features of seizures and EEG patterns in seven children with FIRES. We seek to identify early signs of FIRES to promote timely recognition and aid in selection of optimal therapies.

Methods

We performed a retrospective analysis on seven patients with a diagnosis of FIRES from 2007 to 2017. Patients were identified from a prospective Neurocritical Care database, and this study was approved by our center's institutional review board. The electronic medical record (EMR) was used to supplement patient demographics and clinical course.

Ten patients with FIRES were identified from the database and all had the following: (1) SRSE preceded by a nonspecific febrile illness; (2) an extensive evaluation including infectious, metabolic, and immune studies that did not reveal an etiology for refractory seizures; and (3) no chronic medical disease. In keeping with previous FIRES studies,[4,9] patients were excluded if they had preexisting epilepsy, were younger than 2 years, or had known neurologic disease or a structural brain abnormality sufficiently severe to explain the clinical presentation. All patients were placed in pharmacologic BS at least once during their course. The agent of BS for all was pentobarbital, and it was initiated 17–156 h after admission (mean 98, standard deviation [SD] 49 h). Of the 10 patients with FIRES, 7 had sufficient EEG data prior to BS initiation available for review and thus were included.

Clinical features

All patients had thorough infectious, immune/autoimmune, metabolic, and genetic tests performed. All patients underwent magnetic resonance imaging (MRI) with Gadolinium within 4 days of admission. For a comprehensive list of specific tests performed in each patient, please refer to Table S1.

EEG features

All EEG studies were reviewed independently by a board-certified pediatric neurophysiologist and a board-certified pediatric epileptologist. The reviewers were not blinded. All EEG studies were in digital format with time-locked video and single-lead electrocardiography (ECG). Electrodes were placed according to the international 10–20 system. All seven patients were monitored with EEG shortly after arrival to the hospital. EEG was continued without significant interruption and continued throughout the entire BS period. Two segments of EEG recording were comprehensively reviewed; the first 12 h of recording and 12 h prior to pharmacologic induction of BS. Five patients had raw EEG in original format available for review, two patients had EEG available only in a clipped state (Table 2).

Interictal description

Interictal features analyzed included the presence and location of slowing, excessive beta frequency activity, sleep architecture, and epileptiform discharges. Epileptiform discharges were characterized as spikes (duration 20–70 msec), sharp waves (duration 70–200 msec), and spike-wave discharges or polyspikes. While analyzing the recordings we noted a recurrent pattern of 15–18 Hz activity superimposed over 1–3 Hz slowing in the frontal and central regions reminiscent of extreme delta brush (EDB), although with a slightly slower frequency.[12] When present, this pattern was characterized as EDB.

Ictal/Interictal continuum

The presence of rhythmic activity and periodic discharges was analyzed and characterized according to the American Clinical Neurophysiology Society 2012 guidelines.[13]

Ictal description

Ictal features analyzed included seizure origin, evolution, duration, and average burden during each 12 h segment. Clinical correlation was assessed when possible.

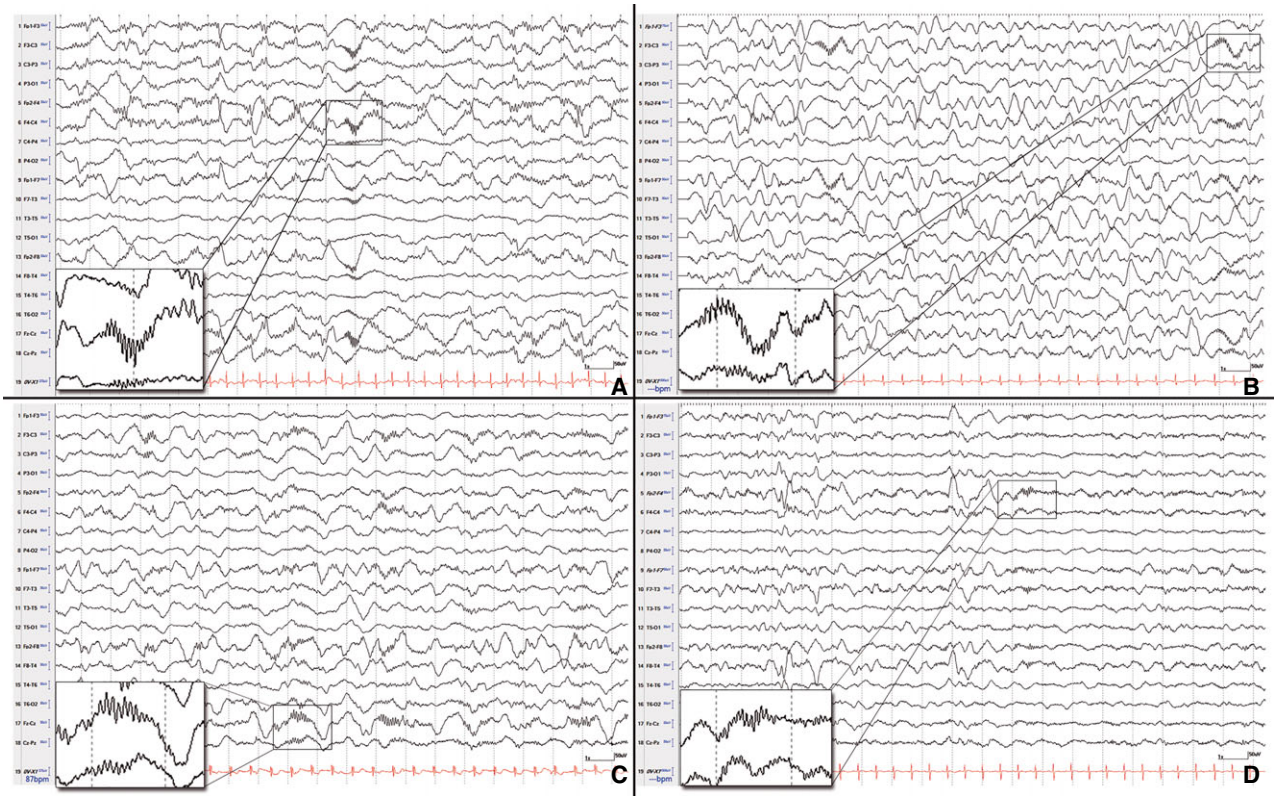

Figure 1.
Extreme delta brush on a bipolar montage demonstrated in four patients. (**A**) Patient 4, (**B**) patient 3, (**C**) patient 6, and (**D**) patient 2.

Results

Clinical features

Patient characteristics are summarized in Table 1. The mean age was 8 years (range 5–16 years). Male-to-female ratio was 4:3. All patients had a nonspecific febrile illness within 7 days from onset of seizures, described as either upper respiratory tract infection with odynophagia or, less often, a gastrointestinal illness. One patient had preexisting isolated speech delay and another Attention-Deficit/Hyperactivity Disorder (ADHD). All others were typically developing children.

All patients underwent a spinal tap within the first 24 h of hospitalization. Testing for infectious diseases yielded negative results in all patients. We detected paraneoplastic antibodies in the sera of two patients: Patient 1 had low positive titer to voltage-gated potassium channel (VGKC) at a level of 0.11 nmol/L (normal <0.02 nmol/L). Patient 2 had positive antibody to N-type calcium channel (CCN) at a level of 0.16 nmol/L (normal <0.03 nmol/L). Neither patient fit the clinical phenotype associated with the specific antibody that was identified. Cerebrospinal fluid (CSF) neopterin was 122 to >300 nmol/L (mean 255, SD 68 nmol/L; normal <27 nmol/L).[14] Metabolic and genetic tests were nondiagnostic. Patient 2 had a heterozygous missense substitution in *GRIN2A,* c.2357G>A (p.R846H) thought to be a variation of unknown clinical significance (VUS). Patient 3 had a heterozygous VUS in the *ALDH7A1* gene. Neither patients' genetic profile was thought to explain the clinical phenotype. Patients 1 and 4 had clinical whole exome sequencing (WES) that was nondiagnostic. Patient 5 had testing performed for mitochondrial depletion syndrome, which was negative. Two patients (3 and 5) had congenital structural brain abnormalities that were not thought to explain the clinical picture (see Table 1).

EEG features

Salient features are described below and summarized in Table 2.

Extreme delta brush (EDB)

The EEG background for all patients contained EDB consisting of a paroxysmal beta–delta complex consisting of 15–18 Hz beta activity superimposed over 1–3 Hz delta in the frontal and central regions. This EDB pattern was recurrent and frequent in all patients, and distinguished from presence of generalized excess in beta activity (Fig. 1). EDB was seen in five patients during both recordings; in one patient it was seen only in the first recording and in one patient only in the second.

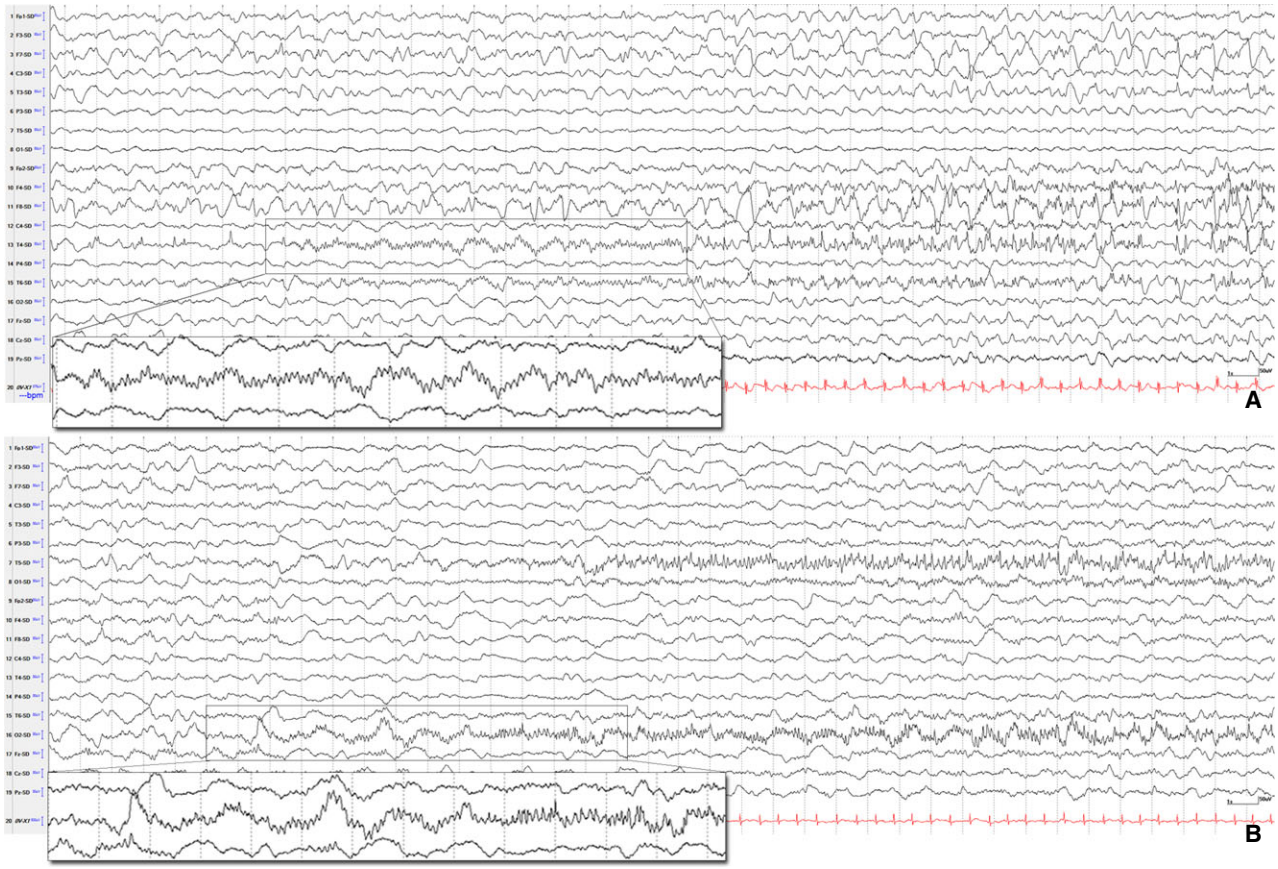

Figure 2.
Typical seizure pattern with focal fast activity preceding spikes or spike/wave complexes on a referential montage. (**A**) Patient 3 and (**B**) patient 6.
Epilepsia © ILAE

Gradual increase in seizure burden

A noteworthy feature of the EEG recordings during the first 12 h was the overall low electrographic seizure burden and paucity of epileptiform discharges. Two patients had no seizures in the first 12 h of recording. Four patients had four to eight brief seizures (average <1 min duration and <1 seizure/h). Most seizures were either subclinical or focal with impairment of consciousness. No patient had a generalized convulsive seizure in the first 12 h of monitoring. No patient had status epilepticus by either definition of seizure lasting >30 min or electrographic seizure activity present for >50% of a 1 h EEG epoch. All patients were described as encephalopathic between recurrent seizures, which was not explained by subclinical seizure.

On the second EEG recording analyzed (prior to initiation of medically induced BS) the typical seizure burden was higher at 1–5 seizures/h. Two patients (1 and 2) had continuous seizures lasting for >30 min. All patients had seizures comprising >50% of a 1 h EEG epoch (electrographic SE). Two patients had convulsive seizures and the rest had subclinical seizures. The timing between the first and second EEG recording was 12–144 h (mean 87, SD 47 h).

Characteristic seizure pattern

A specific seizure pattern was identified in six patients. This pattern consisted of focal activity >10 Hz of small to moderate amplitude evolving to well-formed rhythmic spike and spike-wave complexes (Fig. 2). In four of seven patients, ictal activity shifted from one hemisphere to the contralateral (Fig. 3). Most seizures in the first 12 h of recording arose from frontal, central, and temporal areas on either hemisphere. In the second EEG recording, seizures were noted to arise from occipital and parietal areas as well. Typically, the focal faster activity preceded the rhythmic spike and spike and wave complexes by 30–45 s, but occasionally was seen up to 90 s prior. The fast activity often remained, superimposed on the spike and spike wave complexes. Patient 3 had seizures that did not fit the characteristic seizure pattern noted in the others. Seizures in this patient lacked the focal fast activity at the initiation of the seizure. In contrast, the ictal onset was characterized by paroxysmal focal delta and theta range rhythmic slowing with a broad field.

All EEG reports were reviewed in the EMR, and results were consistent with the independent analysis of the EEG

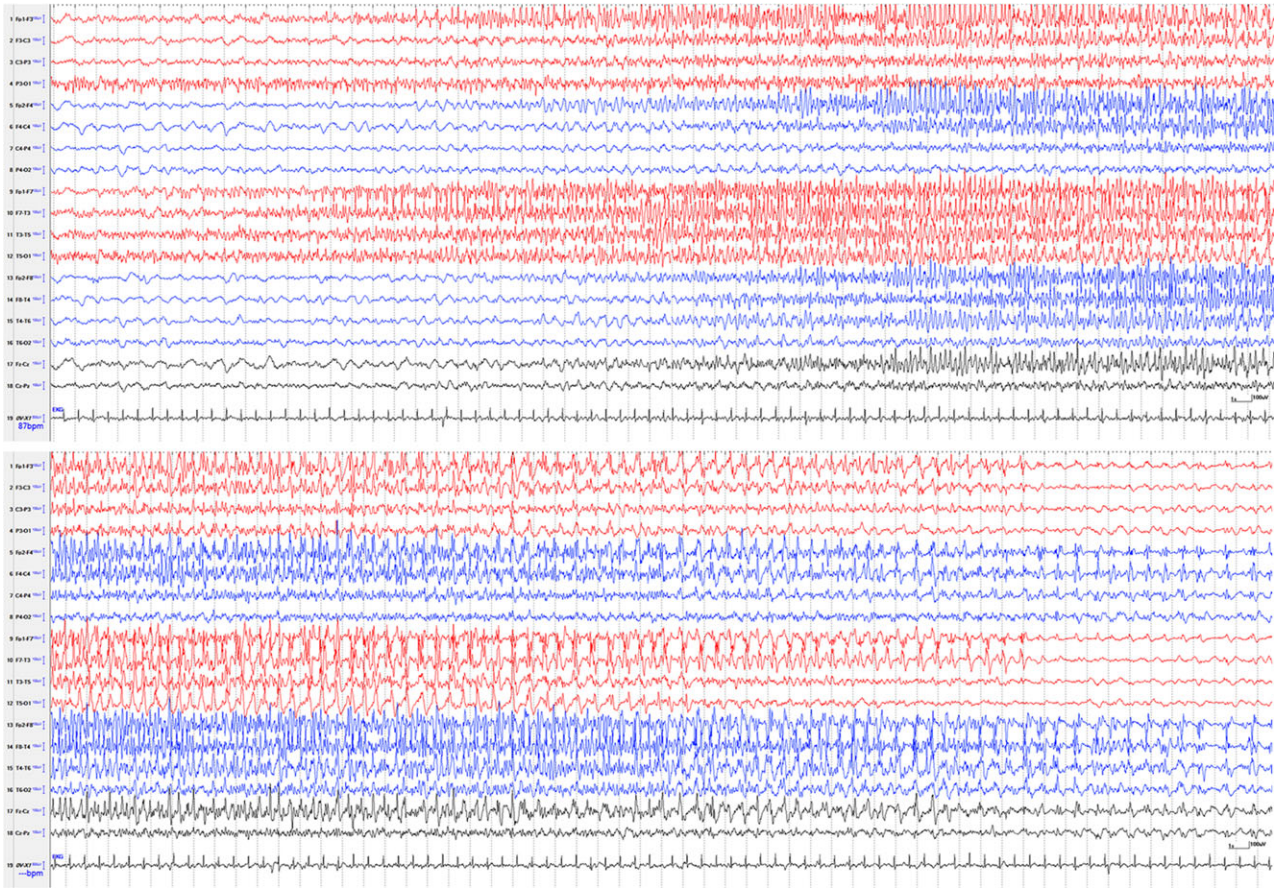

Figure 3.
EEG recording on a bipolar montage on patient 6 showing ictal shifting. The seizure begins in the left occipital region with spread to the left hemisphere. Twenty seconds later, there is ictal activity in the right frontal region with subsequent spread to the entire right hemisphere. The seizure continues to the right hemisphere after the left-hemisphere seizure ends. Red: Left-sided electrodes, Blue: Right-sided electrodes, Black: vertex electrodes, and electrocardiogram.

recordings except for the presence of EDB, which was either not mentioned or described as paroxysmal bursts of fast activity.

Discussion

FIRES is a catastrophic epileptic encephalopathy with an unsatisfactory response to conventional management for SRSE. Development of an early biomarker for identification of FIRES is needed, as patients present with relatively nonspecific symptoms. While exploring infectious, genetic, metabolic, toxic, and autoimmune etiologies in a child presenting with recurrent seizures and encephalopathy, a suspicion for FIRES should also be maintained, especially if workup is unrevealing and SRSE ensues. In this retrospective analysis, we present EEG features that may facilitate early recognition of FIRES. Three commonalities were noted in our series: a relative paucity of electrographic seizures gradually evolving to status epilepticus, a recurrent EDB in the EEG background, and a characteristic electrographic seizure pattern.

SE in patients with FIRES is usually described as being explosive in onset.[2,4,8] Although all our patients developed SRSE over a few days, the initial seizure burden was relatively low. A profound clinical encephalopathy was present between seizures, out of proportion to what would be expected for a postictal state and not explained by subclinical seizures. To our knowledge, this has not been described previously. The optimal strategy to prevent or mitigate epileptogenesis during this important period is yet to be determined. Further studies analyzing the byproducts of innate immune activation during the hyperacute stage could shed light on potential targeted therapies early in the course.

An additional common element was a stereotypical complex resembling EDB, which was observed in all our patients in at least one of the EEG recordings, and frequently in both. Schmitt et al.[12] described a characteristic EEG pattern observed in patients with N-methyl-D-aspartate

Table 1. Patient demographics and clinical characteristics

Patient ID	Age (years)/sex	Infectious studies/CSF WBC in nmol/L	Serum antibodies in nmol/L/CSF neopterin in nmol/L[a]	Metabolic/genetic testing	MRI/day obtained	Functional outcome 3 months after FIRES diagnosis
1	8/M	ND/0	VGKC 0.11[b]/ >300	ND/ND	T_2 hyperintensities in BG, RT, EC, and DWI signal in hippocampus/day 2	Severe encephalopathy, dependent for all ADLs, tracheostomy with ventilator support & GT Death 4 months after presentation.
2	6/F	ND/47[d]	CCN 0.16 [e]/ Not done	ND/GRIN2A [c]	Normal/day 4	Moderate cognitive impairment, required moderate assistance with ADLs, tracheostomy without ventilator support & GT
3	5/F	ND/0	Negative/ 260	ND/ALDH7A1[c]	Congenital fenestration of midportion of septum pellucidum/day 2	Mild cognitive impairment, required minimal assistance with ADLs
4	5/M	ND/17	Negative/ >300	ND/ND	T_2 hyperintensities in hippocampus, increased temporal perfusion/day 1	Severe cognitive impairment, dependent for all ADLs, tracheostomy without ventilator support & GT
5	7/M	ND/7	Negative/ 122	ND/ND	T_2 hyperintensities in R insula, R ventricular heterotopia/ day 2	Severe cognitive impairment, dependent for all ADLs, tracheostomy with ventilator support & GT
6	9/M	ND/8	Negative/ 255	ND/ND	T_2 hyperintensities in hippocampus and R amygdala/ day 1	Mild cognitive impairment, required moderate assistance with ADLs.
7	16/F	ND/5	Negative/ 295	ND/ND	T_2 hyperintensities in BG, insular cortex and hippocampus/day 1	Severe encephalopathy, dependent for all ADLs tracheostomy with ventilator support & GT

CSF, cerebrospinal fluid; WBC, white blood [cell] count; MRI, magnetic resonance imaging; FIRES, febrile infection–related epilepsy syndrome; ND, nondiagnostic; BG, basal ganglia; RT, right thalamus; EC, external capsule; DWI, diffusion-weighted imaging; ADLs, activities of daily living; GT, gastrostomy tube; VGKC, voltage-gated potassium channel; CCN, calcium channel.

[a]Normal value <27 nmol/L.

[b]Normal value <0.02 nmol/L.

[c]Heterozygous variant of uncertain clinical significance.

[d]Traumatic spinal tap.

[e]Normal value <0.03 nmol/L.

receptor (NMDAR) encephalitis and coined the term "extreme delta brush" (EDB). EDB resembles the beta–delta complexes seen in premature neonates, which are characterized by delta frequency transients with superimposed 8–22 Hz fast activity.[15] EDB differs from a neonatal delta brush in that the overriding fast activity has a high frequency (20–30 Hz) and thus is designated "extreme." In the NMDAR cohort, the presence of EDB was associated with a more severe disease process, and the pattern resolved when the patient had a positive response to treatment. The cause of EDB remains unknown but is speculated to involve altered modulation of NMDAR-mediated currents.[12] All our patients were negative for NMDAR antibodies, but interestingly they also shared the pronounced encephalopathy and autonomic dysregulation of NMDAR encephalitis. These findings may suggest some overlap in the mechanisms of immune dysfunction in both disorders.

Another feature noted in our cohort was a characteristic electrographic seizure pattern. In all but one, the seizures typically began with focal faster waveforms, "sparks," followed by the gradual appearance of well-formed rhythmic spike or spike and wave complexes. We observed shifting seizures with contralateral hemisphere spread in four patients. One patient (3) did not have this characteristic electrographic seizure pattern. This patient's clinical course was distinct from the others in two ways. The seizure burden in the first 12 h of monitoring was higher than most, and on hospital day 25 a workup for multi-organ system dysfunction revealed hemophagocytic lymphohistiocytosis (HLH) with central nervous system (CNS) involvement. She was treated with high-dose steroids, Etoposide and intrathecal Methotrexate, resulting in an almost immediate seizure cessation followed by a more gradual improvement in encephalopathy. The genetic screening for primary causes

Table 2. Ictal and interictal features

Patient ID/ time between recordings	Recording	Medications received 24 h prior to EEG recording/immune modulating medications	PBR/sleep architecture/ excess beta/ slowing	Ictal–interictal continuum	Extreme delta brush	Seizure origin/average seizure duration/average seizure burden	Seizure >30 min/ seizure >50% epoch	Shifting seizures	Clinical seizure description	Characteristic seizure pattern
1/12 h	#1 recording[a]	PHT, PB, MDZ/none	No/Yes/No/Yes	GPD	Yes	BT/<1 min/<1/h	No/no	No	Subclinical	Yes
	#2 recording[a]	PHT, PB, MDZ/none	No/No/No/Yes	GPD ->BS	No	RT/>30 min /<1/h[b]	Yes/yes	No	Convulsion	Yes
2/60 h	#1 recording	PHT, LEV, PB, MDZ/none	No/No/Yes/Yes	No	Yes	BF, RC/<1 min/<1/h	No/no	Yes	Drooling	Yes
	#2 recording	PHT, LEV, PB, TPM, MDZ/IVIG	No/No/Yes/Yes	No	Yes	BF, RO, LT/1–5 min/5/h	No/yes	Yes	Subclinical	Yes
3/96 h	#1 recording	PHT, MDZ[c]/none	No/No/Yes/Yes	GPD, LPD[d]	Yes	LF, LT/<1 min/1/h	No/no	No	Eye deviation	No
	#2 recording	PHT, LEV, PB, MDZ, PRO[c]/none	No/No/Yes/Yes	GPD	Yes	LF, BT/>30 min/1/h	Yes/yes	No	Subclinical	No
4/84 h	#1 recording	PHT, LEV/none	No/No/No/Yes	No	Yes	BT, LO/1–5 min/<1/h	No/no	No	Subclinical	Yes
	#2 recording	PHT, PB, VPA, LCM, MDZ/IVIG, MP	No/No/Yes/Yes	GPD	Yes	BT, RC, LP/1–5 min/3/h	No/yes	Yes	Subclinical	Yes
5/144 h	#1 recording	PHT, LEV, MDZ[c], PRO[c]/none	No/No/No/Yes	RDA, LPD[d]	No	No seizures	N/A	N/A	N/A	N/A
	#2 recording	PHT, LEV, PB, VPA, KET[c]/IVIG, MP	No/No/No/Yes	GPD, LPD[d]	Yes	LF, LT, LC/1–5 min/5/h	No/yes	Yes	Subclinical	Yes
6/144 h	#1 recording	PHT, LEV, MDZ/none	No/Yes/Yes/Yes	No	Yes	BF, RC, LT/1–5 min/<1/h	No/no	Yes	Apnea	Yes
	#2 recording	PHT, LEV, PB, VPA, MDZ/IVIG, MP	No/No/No/Yes	RDA, GPD	Yes	BF, BT, LO/1–5 min/4/h	No/yes	Yes	Subclinical	Yes
7/72 h	#1 recording[a]	LEV, PRO[c]/none	No/No/Yes/Yes	RDA, GPD	Yes	No seizures	N/A	N/A	N/A	N/A
	#2 recording[a]	LEV, PHT, PB, MDZ, PRO/IVIG, MP	No/No/No/Yes	LPD[d]	Yes	LT, BC/5–15 min/1/h	No/yes	No	Convulsion	Yes

EEG, electroencephalogram; PBR, posterior basic rhythm ; PHT, phenytoin ; PB, phenobarbital ; MDZ, midazolam ; LEV, levetiracetam; TPM, topiramate ; IVIG, intravenous immunoglobulin; PRO, propofol; LCM, lacosamide; MP, methylprednisolone; KET, ketamine; VPA, valproic acid; GPD, generalized periodic discharges; BS, burst suppression; LPD, lateralizing periodic discharges; RDA, rhythmic delta activity; BF, bilateral frontal; LF, left frontal; BT, bilateral temporal; RT, right temporal; LT, left temporal; BC, bilateral central; RC, right central; LC, left central; LP, left parietal; RO, right occipital; LO, left occipital.

[a]Clipped recording.

[b]Had two clinical seizures lasting 45 min and 3 h.

[c]Medication given for sedation not seizure.

[d]Periodic discharges were bilateral independent.

of HLH was negative and a diagnosis of secondary HLH with CNS involvement was ultimately assigned.

Prompt recognition of FIRES is needed to improve our understanding of the disease, particularly in the acute phase. To properly study the impact of early therapies (e.g., ketogenic diet, anakinra, CBD, and so on) we first need a diagnostic tool to identify patients in the early phase. We propose the use of EEG as a diagnostic tool to help identify the early stages of FIRES. Ictal shifting has been described previously in FIRES patients,[4,16] and our series supports this finding. In addition, we describe a focal fast activity at seizure onset and a pattern resembling EDB. We know patients with FIRES develop refractory epilepsy, but the acute seizures are likely the result of a process different from the chronic epilepsy.[4] The optimal strategy to mitigate the secondary epileptogenesis is unknown, but early implementation of seizure control and immune modulation may be important.

We acknowledge several limitations to this study including small sample size, retrospective nature of the analysis, and lack of controls with SRSE of alternative etiologies. The patients' treatment was not standardized and many of the medications received can alter the EEG tracing. In fact, many patients were administered anesthetic medications such as midazolam or propofol for sedation either in preparation for imaging studies or invasive procedures. These medications potentially contribute to seizure suppression as well as alteration of the background, including enhanced beta activity. For this reason, all medications received in the 24 h prior to EEG analysis are included in Table 2 for comparison. Nonetheless, what we describe is a "real life" environment in the intensive care unit (ICU), where most patients admitted for recurrent seizures and encephalopathy receive sedative medications as a component of their supportive care. Another limiting factor in this study is that two patients had clipped EEG recordings, and thus it is possible that characteristic features such as the presence of EDB, shifting seizures, prolonged continuous seizures, or interictal discharges were among the clipped data. Furthermore, although in the correct clinical context these features may enhance the diagnostic accuracy of FIRES, we cannot exclude their presence in other inflammatory/immune-mediated encephalitides.

FIRES is a rare disorder of uncertain etiology. Adoption of a unified nomenclature (i.e., FIRES),[17] has allowed for researchers to describe the clinical,[4,9] radiologic,[18–20] and electrophysiologic characteristics of this unique disorder in pediatrics.[4] Further work is being done to assess for overlap with the New Onset Refractory Status Epilepticus (NORSE) and other inflammatory/immune-mediated epilepsies.[21,22] Gaps remain in the diagnostic criteria, in part due to the lack of an understanding of the underlying etiology. Early diagnostic markers have the potential to advance our knowledge of disorder and enhance clinical care. Future directions for FIRES research should include analysis of early EEG features in larger cohorts and long-term follow-up to assess for alternative diagnoses applied outside of the acute phase.

Conclusion

Our series contributes to the understanding of early EEG features in FIRES. Three commonalities were found, an extreme delta brush within the EEG background, a gradual increase in seizure burden prior to onset of refractory status epilepticus, and a characteristic electrographic seizure pattern. These findings, if replicated, may help with early diagnosis and therapeutic decision-making. A potential approach to study disease biomarkers and enhance clinical care by developing consensus-driven therapies is to establish multicenter, multi-national collaborations, which we strongly encourage.

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Disclosure

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comprehensive list of laboratory workup performed in each patient.