ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 09 | September - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CLINICAL, ELECTROPHYSIOLOGICAL & RADIOLOGICAL PROFILES OF FIRES (FEBRILE INFECTION RELATED EPILEPSY SYNDROME) PATIENTS AND THEIR FOLLOW-UP, EXPERIENCE FROM TERTIARY CARE HOSPITAL OF EASTERN INDIA

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ABSTRACT

Febrile infection-related epilepsy syndrome (FIRES) is a subtype of new-onset refractory status epilepticus (NORSE), characterized by the onset of refractory seizures in previously healthy individuals following a febrile illness 2 weeks to 24 hours prior, without evidence of structural, toxic, metabolic, or infectious encephalitis. This prospective observational study at Dr. B.C. Roy Post Graduate Institute of Paediatric Sciences, Kolkata, eastern India, was conducted over 18 months (December 2022–May 2024) to describe the clinical, electrophysiological, and radiological profile of FIRES with one-year follow-up. Among 32 children (mean age 4.13 ± 1.65 years; 65.6% male); 84.4% patients presented with generalized tonic–clonic seizures. Fever at seizure onset occurred in 65.6% patients, 23 patients (71.9%) had no past medical history. All received midazolam infusion; 62.5% patients received intravenous immunoglobulin (IVIG) alone, 25% IVIG plus steroids, and 12.5% steroids only. Mortality was 18.8%(n=6). Mean ventilation, hospital stay, and intensive care stay durations were 9.37 ± 4.45, 38 ± 6.46, and 28 ± 2.63 days, respectively. At discharge, MRI (magnetic resonance imaging) and EEG (electroencephalography) were normal in 84.4% and 90.6% patients; but at one-year, abnormalities increased to 65.3% ($p = 0.0003$) and 46.2% ($p = 0.004$) respectively. Among 26 survivors, chronic epilepsy syndrome occurred in 46.2%, cognitive delay in 26.9%, behavioural disorders in 19.2%, and 7.7% patients had no disability. Ketogenic diet (n = 10) was associated with significantly lower rate of chronic epilepsy syndrome ($p = 0.015$) and EEG abnormalities ($p = 0.015$) versus non-ketogenic management. FIRES remains a rare but devastating paediatric encephalopathy with high morbidity and mortality, highlighting the need for early recognition, aggressive supportive care, and exploration of ketogenic therapy to improve outcomes.

KEYWORDS

FIRES, NORSE, EEG, ketogenic diet

INTRODUCTION

Febrile infection-related epilepsy syndrome (FIRES) is a rare, devastating epileptic encephalopathy in which refractory status epilepticus occurs within 24 hours to 2 weeks after a febrile infection, with or without fever at onset, in previously healthy children aged typically 5–13 years (Serino et al.,2019). It is a subcategory of new-onset refractory status epilepticus (NORSE), defined by sudden onset of RSE (refractory status epilepticus) without an identifiable structural, toxic, or metabolic cause. The incidence is ~1 per 1,000,000, with a male predominance (van Ballen et al.,2010; Sculier et al.,2019; Heilbig et al.,2020). FIRES has two phases; the acute phase lasts up to 12 weeks, beginning with increasing seizure frequency and duration, culminating in super-refractory SE, often unresponsive to standard antiseizure therapy. EEG may show extreme delta brush or shifting low-amplitude fast activity (Lam et al.,2019). Prognosis is poor, with mortality up to 30% and survivors frequently left with chronic intractable epilepsy and cognitive deficits; ranging from mild to severe disability or vegetative state (Fox et al.,2017; Lai et al.,2018). Chronic phase seizures recur every 2–4 weeks, accompanied by cognitive, language, and motor impairment (Wirell et al.,2022).

Pathogenesis

The exact pathophysiology of FIRES is unknown. It is a catastrophic epileptic encephalopathy where seizures are the visible tip of a deeper neuronal–glial dysfunction. EEG often shows global slowing and extreme delta brushes, indicating synaptic dysfunction, however neuronal autoantibodies are typically absent, and there's little response to first-line immunotherapy, making autoimmune encephalitis unlikely (Lee,2020; Kessi et al.,2020).

The syndrome appears infection-triggered, often following minor peripheral infections, but without clear infectious agents in most cases. Early MRI and CSF (cerebrospinal fluid) findings are often normal, suggesting no frank encephalitis, though elevated CNS (central nervous system) cytokines/chemokines, e.g. IL (interleukin)-1β, IL-6, TNF (tumour necrosis factor), IL-8; indicating a neuroinflammatory process. This immune activation likely involves glial and perivascular T-cells, creating a latent period between fever and seizures (Ritter et al.,2021).

A prevailing hypothesis is immune dysregulation (Pavone et al.,2022). It is proposed that overactivation of the IL-1 axis due to endogenous IL-1 receptor dysfunction, explaining positive responses to anakinra (IL-1 receptor antagonist). Overactive microglial inflammasomes and hyperinflammatory monocytic responses may perpetuate seizures. This creates a vicious cycle—seizures trigger neuroinflammation, which further lowers seizure threshold, causing sustained status epilepticus.

Genetic and metabolic causes are largely excluded in previously healthy children; genetic testing yield is near zero. FIRES is best understood as an inflammatory but not autoimmune-mediated encephalopathy, possibly a cerebral cytokine release syndrome, requiring both an immune trigger and an intrinsic susceptibility for self-sustaining epileptogenesis.

Management Strategy

Management remains challenging, with treatments including multiple antiseizure drugs, immunomodulators (IVIG, steroids, anakinra, tocilizumab, canakinumab, rituximab), ketogenic diet, and occasionally therapeutic hypothermia (Ritter et al.,2021; Kaur et al.,2022; Wong et al.,2023). Evidence for efficacy is limited. In a multicentre retrospective study, Kramer et al.2011 found no clear benefit from most treatments, though isolated responses to IVIG, ketogenic diet, and prolonged barbiturate coma were noted. Ketogenic diet and barbiturates were the most consistently reported treatments with partial benefit, and IL-targeted therapies such as anakinra and tocilizumab emerged as potential interventions.

Historically, FIRES was often misclassified - hindering epidemiological clarity. Epidemiological data remain scarce due to their rarity and inconsistent recognition. The outcome is generally poor; up to 30% die, and 66–100% of survivors experience cognitive delay (Sculier et al.,2019). Learning disabilities are common, and only a small fraction survives without neurologic sequelae.

Purpose Of The Study

Literature consistently emphasizes the importance of early diagnosis, supportive intensive care, and trial of therapies to reduce seizure burden and improve long-term outcomes. Despite decades of case reports and series, FIRES remains a catastrophic condition with no universally effective treatment, demanding further research into immune-mediated mechanisms and personalised therapeutic strategies.

METHODS

Aim And Objectives

1) To identify risk factors, Prognosis, and outcome of FIRES patients,
2) To identify treatment modality and its effect on long-term sequelae in FIRES patients.

Study Population

Age group of 6 months to 12 years, over a period of 18 Months (December 2022 to May 2024); 32 patients were included.

Study Design

Prospective, longitudinal, and observational study.

Inclusion Criteria

History of fever without focus, having new onset refractory seizure in a previously normal child (not controlled by 2 anticonvulsants) of age group of 6 months to 12 years.

Exclusion Criteria

Previous history of seizure, neurodevelopmental delay or drug withdrawal.

Data Collection And Statistical Analysis

After obtaining informed consent; demography, past clinical history and initial presentation of all patients were noted in a preformed proforma. MRI and EEG were done at initial presentation and follow-up at 1-year. CSF was sent for routine examination, JE (Japanese encephalitis) virus and autoimmune profile. Clinical course, treatment given and outcomes were noted. The survivors were followed-up at 1-year for any sequelae. The data were analysed using Statistical packages for the social sciences (SSPS)v26.0 software. Significant differences between groups were determined using the chi-square test or Fischer's exact test where appropriate. The p-value less than or equal to 0.05 was considered statistically significant.

RESULTS

Among 32 patients, the mean age was 4.13 ±1.65 years, among which male and female were 21 (65.6 %) and 11 (34.4 %) respectively. Initially 5(15.6 %) patients presented with focal onset clonic type with impaired awareness and 27(84.4 %) patients presented with generalized tonic clonic seizure. 11 patients (34.3 %) had no fever at the time of presentation. 2 (6.2%) had a history of diarrhoea, 2 (6.2%) had upper respiratory tract infection, 2 (6.2%) had pneumonia, 3 (9.4%) had simple febrile seizure, and 23 patients (71.9%) had no past medical history. The average no of antiepileptics was 4(3-6); all received midazolam infusion, only IVIG (2gm/kg) was in 20 patients (62.5%), IVIG and steroid for 8 patients (25 %), only steroid for 4 patients (12.5%). Mean duration of of hospital stay, intensive care stay, and mechanical ventilation were 38 ±6.46 days, 28 ± 2.63 days, and 9.37±4.45 days respectively. 6 (18.8 %) patients were dead and 26 (81.2 %) children were discharged. MRI and EEG abnormalities were present in only 5 (15.6%) and 3 patients (9.4%) respectively, which increased at 1-year follow-up (n = 26) to 17 (65.3%; p = 0.0003) and 12 patients (46.2%; p = 0.0040), respectively; depicting in table 1.

Among 26 FIRES patient survivors,12(46.2%) patients exhibited chronic epilepsy syndrome, 7(26.9%) had cognitive delay, 5(19.2%) displayed behavioural disorders, and 2(7.7%) experienced no disability after 1-year follow-up.

Among the survivors, 10 (38.4%) patients were put on ketogenic diet. Table 2 and Figure 1 described effect of ketogenic diet on neurological outcome. ketogenic diet was found to be effective in making significant differences in chronic epilepsy syndrome (p=0.015) and EEG changes (p=0.015) at 1-year follow-up, but not in other outcomes.

DISCUSSION

FIRES is a catastrophic epileptic encephalopathy affecting developmentally normal children, characterised by an explosive onset of refractory seizures or status epilepticus following a minor febrile illness, and associated with high mortality and long-term neurological sequelae (Kramer et al., 2005). This study was conducted at dr BC Roy PGIPS. Among 32 patients, males comprised of 65.6%, similar to the marked male predominance of 4:1(Patil et al.,2016). Most patients (68.8%) were between 1–4 years of age, with a mean age of 4.13 ± 1.65 years, younger than the onset age reported by other studies (Lam et al.,2019; Lee et al.,2018), where mean ages were 9 years.

In this study, the average duration of hospitalisation and intensive care stay was 24.16 ± 9.94 and 15.62 ± 7.28 days, respectively, shorter than the 87-day median hospitalisation in other study (Lee et al.,2018).

Mortality occurred in 18.8% patients, higher than the 12% reported in another study (Specchio et al.,2020) but comparable to the 16% in-hospital mortality observed in other studies (Lam et al.,2019). All deaths occurred in children aged 1–4 years, with a male predominance (66.7%), though no statistically significant.

At one-year follow-up in this study, 46.2% of survivors had chronic epilepsy, 26.9% had cognitive delay, and 19.2% had behavioural disorders, while only 7.7% were disability-free.

A study reported higher rates of epilepsy (100%) and cognitive deficits (61%) in follow-up (Lam et al.,2019); whereas another study found epilepsy in 87% cases (Lee et al.,2018). MRI and EEG abnormalities in this study were initially present in 15.6% and 9.4% patients, respectively, but significantly increased at one-year to 65.3% (p = 0.0003) and 46.2% (p = 0.0040) respectively. This pattern is comparable to other studies (Lee et al.,2018); where MRI abnormalities rose from 38% to 87%, indicating progressive neurostructural injury beyond the acute phase.

It is postulated that ketogenic diet may exert not only an anticonvulsant effect—partly through the production of decanoic acid, which directly inhibits post-synaptic excitatory AMPA receptors—but also an anti-inflammatory action, promising some efficacy in FIRES patients (Appavu et al., 2016).

In this study, the ketogenic diet was found to be significantly significant in reducing the incidence of chronic epilepsy syndrome (p = 0.015) and EEG abnormalities (p = 0.015) at one-year follow-up, though not found statistically significant in other outcomes. Other studies also explored the relationship between different treatment modalities and disease parameters in FIRES patients (Kramer et al.,2011), concluding that the overall prognosis remained poor and no therapy reliably shortened the acute phase, except for a possible benefit from ketogenic diet.

CONCLUSION

FIRES in children were associated with high mortality and significant long-term morbidity, including chronic epilepsy, cognitive delay, and behavioural disorders. Neuroimaging and EEG abnormalities frequently progressed over the first-year. Early initiation of ketogenic diet significantly reduced chronic epilepsy syndrome and EEG abnormalities, though other outcomes remained unaffected.

These findings highlight the urgent need for early recognition, intensive supportive care, and targeted interventions such as ketogenic therapy to improve prognosis.

Limitation

Limited time period, small sample size, single-centred study, and lack of use of biologics, barbiturate coma make this study difficult to generalise to the entire population.

Table -1 Distribution of FIRES patients according to MRI, EEG changes at 1-year follow-up

	At the time of presentation n=32		At 1 year of follow up n=26		P value
Changes in MRI	abnormal	5(15.6 %)	abnormal	17(65.3%)	0.0003
	normal	27(84.4%)	normal	9 (34.7%)	
Changes in EEG	abnormal	3(9.4 %)	abnormal	12(46.2%)	0.0040
	normal	29(90.6 %)	normal	14 (53.8%)	

Table 2 Effect of ketogenic diet on neurological outcome of FIRES patients at 1-year follow-up

neurological outcome	Ketogenic diet (n=10)	Not on ketogenic diet (n=16)	P value
No disability after 1-year	2	0	0.20
Chronic epilepsy syndrome	2	10	0.015
Behavioural disorder	3	2	0.65
Cognitive delay	3	4	0.50
MRI changes at 1-year follow-up	5	17	0.20
EEG changes at 1-year follow-up	2	10	0.015

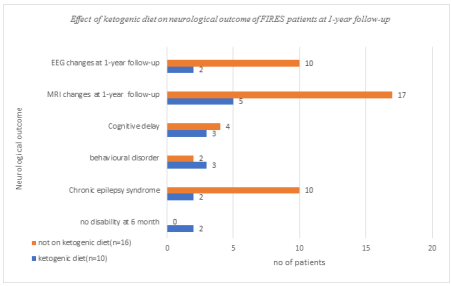

Figure 1: Effect of ketogenic diet on neurological outcome of FIRES patients at 1-year follow-up

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