Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2024 Jun 15; 12(2):304-308.
https://doi.org/10.3889/oamjms.2024.11895
eISSN: 1857-9655
Category: *C - Case Reports*
Section: *Case Report in Pediatrics*

Febrile Infection-Related Epilepsy Syndrome (FIRES), a Possible Cause of Super-Refractory Status Epilepticus: A Case Report

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Edited by: Sasho Stoleski
Citation: Sahraoui HE, Danaoui K, Sihami A, Mouaffak Y, Younous S. Febrile Infection-Related Epilepsy Syndrome (FIRES), A Possible Cause of Super-Refractory Status Epilepticus: A Case Report. Open Access Maced J Med Sci. 2024 Jun 15; 12(2):304-308. https://doi.org/10.3889/oamjms.2024.11895
Keywords: Antiepileptic drugs; Fever; Immunoglobulin; Ketogenic diet; New-onset super refractory status epilepticus; Febrile infection-related epilepsy syndrome; Seizures
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Received: 15-Mar-2024
Revised: 08-Mar-2024
Accepted: 18-Apr-2024
Ahead of print: 25-Apr-2024

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Febrile infection-related epilepsy syndrome (FIRES) is a subset of NORSE that requires a febrile infection between 24 h and 2 weeks before the onset of refractory status epilepticus (SE), with or without fever at the onset of SE, and with no restriction to the age of the patient. The literature on FIRES is scarce.

CASE PRESENTATION: This article reports a case of a patient of 8 years old without relevant family, psychosocial, prenatal or perinatal, or pathological history and normal neurodevelopment. The child consulted on a pediatric emergency with convulsive SE preceded 8 days before by otitis with acute fever managed with cephalosporin. Subsequently, seizures appeared in the following 48 h, characterized by generalized tonic-clonic seizures lasting 5–6 min. The seizures became more frequent until consciousness deteriorated, and motor SE appeared. In consequence, a coma was initiated, and the patient was hospitalized for emergency pediatric reanimation, where multifocal clonic and myoclonic seizures continued. A lumbar puncture with polymerase chain reaction was done twice and returned negative. Two magnetic resonance imaging scans were performed: the first was normal and the second, after 20 days in the hospital, showed cortical damage with SE. Different anticonvulsant treatments were used for 4 weeks: Valproic acid, clobazam, ketamine, levetiracetam for 24 days, and relay to, brivaracetam used in the treatment of epilepsy to control focal seizures; propofol, midazolam, and some antiepileptic drugs were used simultaneously and at maximum recommended doses, achieving a poor initial response, but eventually leading to total crisis control. The patient receives immunoglobulin for 2 days 1 g/kg/J. A ketogenic diet aimed at therapy and known antiepileptic properties, rich in lipids, and low in sugars, causing ketonemia in non-surgical drug-resistant epilepsies, was used for our patient with an efficacy that proved to be remarkable on the frequency of undergoing seizures, his tolerance was good. The diet can be maintained for 20 days without incident, in particular, with no episode of hypoglycemia. Electroconvulsive therapy (formerly called sismotherapy, electronarcosis, or shock therapy) is a therapeutic tool used in several psychiatric illnesses was also used with different frequencies for our patients twice a week with no favorable response. The evolution was marked by the aggravation of the patient following diffuse cerebral edema resulting in cardiac arrest and non-response to resuscitation measures, the patient declared at 07 AM on February 27, 2023.

CONCLUSION: FIRES is a rare epilepsy syndrome of unclear aetiology in which children, usually of school age, suddenly develop very frequent seizures after a mild febrile illness. Seizures in FIRES are typically difficult to treat, and the prognosis is poor.

Introduction

Febrile infection-related epilepsy syndrome (FIRES) is considered a severe epileptic encephalopathy with multifocal refractory status epilepticus (SE) [1] In 1986 Awaya and Fukuyama first described encephalitis such as an entity occurring in previously normal children [2]. Since then, the syndrome has been variably called severe super refractory SE due to presumed encephalitis, [3] idiopathic catastrophic epileptic encephalopathy, new-onset refractory SE, devastating epileptic encephalopathy in school-aged children, acute encephalitis with refractory repetitive partial seizures FIRES, and fever-induced refractory epileptic encephalopathy in school-age children.

FIRES in previously healthy children is characterized by three phases: An initial phase with a simple febrile infection, a few days later followed by an acute phase with highly recurrent focal seizures that evolve rapidly into super refractory SE often with no more fever and generally without additional neurological features, and finally a chronic phase consisting of drug-resistant epilepsy and neuropsychological impairment.

These symptoms occur mostly in children between 3 and 15 years of age, but adult patients have also been described. A series of patients with this particular epileptic encephalopathy have been published in Japan, the UK, France, Germany, Italy, the US, Austria, Singapore, and Taiwan. The etiology and the mechanisms underlying FIRES are still unknown, and an immunologic source, a genetic predisposition, and an inflammation-mediated process have been hypothesized. At present, the ketogenic diet (KD) may be considered an efficacious treatment. Here, we report an atypical presentation of a case of a child of 8 years old admitted with motor SE.

Case Presentation

An 8-year-old male patient from Morocco, without relevant family, psychosocial, prenatal or perinatal, or pathological history, and normal neurodevelopment. The child consulted on a pediatric emergency with convulsive SE preceded 8 days before by otitis with acute fever managed with cephalosporin. Subsequently, seizures appeared in the following 48 h, characterized by generalized tonic-clonic seizures lasting 5–6 min.

The seizures became more frequent until consciousness deteriorated and motor SE appeared. In consequence, a coma was initiated and the patient was hospitalized for emergency pediatric reanimation, where multifocal clonic and myoclonic seizures continued.

A lumbar puncture with polymerase chain reaction was done twice and returned negative.

Two magnetic resonance imaging (MRI) scans were performed: The first was normal and the second, after 20 days in the hospital, showed cortical damage with SE.

Different anticonvulsant treatments were used for 4 weeks: Valproic acid, clobazam, ketamine, levetiracetam for 24 days, and relay to brivaracetam used in the treatment of epilepsy to control focal seizures; propofol, midazolam, and some antiepileptic drugs were used simultaneously and at maximum recommended doses, achieving a poor initial response, but eventually leading to total crisis control.

A KD aimed at therapy and known antiepileptic properties, rich in lipids, and low in sugars, causing ketonemia in non-surgical drug-resistant epilepsies was used for our patient with an efficacy that proved to be remarkable on the frequency of undergoing seizures, his tolerance was good. The diet can be maintained for 20 days without incident, in particular no episode of hypoglycemia.

The patient receives immunoglobulin for 2 days 1 g/kg/J.

Possible infectious, inflammatory, metabolic, autoimmune, and toxicological etiologies were discarded, while initial and second neuroimages did not show any alteration (Table 1).

Table 1: Paraclinical tests of the patient

Infectious	C-reactive protein and procalcitonin: Negative
	the serological tests were negative: TPHA VDRL, HIV, hepatitis, CMV, toxoplasma-specific IgM, and IgG, rubella
Autoimmune	P ANCA C ANCA negative
	Normal protein electrophoresis
	Anti-Sm negative
	Anti-RNP negative
	Anti-DNA negative
	RF negative
Metabolic	No problems with the urea cycle
	Lactate: 2.5
	Normal ammonia level in blood: 35

CMV: Cytomegalovirus, IgM: Immunoglobulin M, IgG: Immunoglobulin G.

The patient was intubated for 14 days then tracheotomies and put under inhalation anesthesia (isoflurane) for 20 days with a progressive regression and monitoring of seizures and biological balance regularly. The patient received seismotherapy sessions with frequencies from 20 joules to 48 joules without any satisfactory response to an epileptogenic threshold of <15 s.

The evolution was marked by the aggravation of the patient following diffuse cerebral edema, resulting in cardiac arrest and non-response to resuscitation measures, the patient declared at 07:00 in the morning on February 27, 2023.

Discussion

The temporary correlation between fever and the onset of SE has led to consider an autoimmune origin for this syndrome, although current evidence does not confirm this suspicion. In autoimmune epilepsies, epileptic seizures relate to the production of autoantibodies against central nervous system molecules, which is confirmed when some patients respond to immunomodulatory therapy [4], [5] and when some autoimmune diseases have a higher crisis incidence [6].

Innate and adaptive immunity has been observed in patients with autoimmune epilepsies, which increases inflammatory mediators, macrophages, and neutrophils, activating glial cells and stimulating neuronal death. Mediators seem to act as excitatory agonists, generating a postictal state [7], [8], [9], [10]. Autoantibodies have been proposed as the etiology of FIRES, without finding a direct causal association in all cases or being clear whether autoimmune inflammatory processes arise first or if the inflammatory activity is the result of the epileptic event [3], [10]. However, the evidence does not support this hypothesis completely given the variability of antineuronal antibody findings in FIRES patients and inconstant response to immunotherapy [11].

Likewise, FIRES is associated with monogenic mutations in PCDH19, SNC1A, and POLG1, which are in turn associated with epileptic encephalopathies of similar characteristics: Temporary association to infection, rapid onset of refractoriness, absence of encephalitis, and cognitive impairment markers in previously healthy patients [12], [13], [14]. The presence of prolonged SE can be related to mitochondrial disorders etiologies and affect the reserve of energy and, therefore, neuronal function [10], [15].

Autoimmunity plays an important role in epileptic disorders unrelated to infection or neoplasms [9], [16] and refractory epileptic encephalopathies with inconsistent findings of antibodies against neural surface antigens (antibodies anti-NMDA, anti-VGKC, and anti-GAD) [3], [9], [10], [17], [18], [19]. The presence of

antibodies and an excessive inflammatory response could justify the use of immunotherapy as a treatment for FIRES [3], [15]. VKKL-ab, anti-GAD, and GluR3 autoantibodies and oligoclonal bands in CSF are observed in a third of the patients [17]. However, the reason for their presence, as well as their consequences and correlation with the phenotypic variants of FIRES, is unknown.

FIRES usually develops in children under 15 years of age, who have fever between 2 and 14 days before the onset of symptoms, with a male–female ratio of 4:3. The febrile syndrome is attributed, mostly, to infections of the upper respiratory tract (more than 50%) and, in a smaller proportion, to gastroenteritis [17], [20]. Once epileptic seizures appear, a SE is established, and then an SRSE-like behavior is observed; this SE usually lasts from 1 to 12 weeks [17]. The seizures type at the beginning of the disease are mainly focal-motor, with clonic manifestations or segmental myoclonus that can compromise the face and other body segments [1], [21], sometimes reaching up to 100 daily crises [22], [23], Except for the presence of burst suppression in barbiturate coma, EEG shows multifocal activity with greater involvement of the temporal and frontal lobes [17].

With respect to neuroimaging, the variations observed in the MRI range between normal findings and different degrees of atrophy and hyperintensities in the temporal lobe, mainly in the hippocampal region [11], [24], [25], as well as in the insula and basal ganglia [10], perhaps secondary to prolonged neuronal activation [17].

Most of the medications indicated for this emergency, and even other non-usual medications such as carbamazepine or topiramate, have not shown a good response in the acute phase during SE [17], [21], [26], [27]. During this phase, barbiturates can be useful at high doses, achieving up to 50% of crisis control transiently; however, there are SE recurrences [26], [28].

Other series [19], [29] show that levetiracetam at regular doses for SE management could have a good response to control seizures in about half of FIRES patients. However, data are contradicted in another series of 12 patients [26], where control was not achieved with this medication. This treatment is effective in the long term to reduce seizures in more than 75% of patients at doses between 750 mg/d and 1500 mg/d, although adverse effects such as aggressiveness or impulsivity are frequent [30].

KD

Different series of FIRES patients have described the use of KD, finding a good response in terms of crisis control, thus turning this option into a promising therapy. A smaller proportion of patients did not respond and others presented recurrence when suspending it [1], [25], [26], [31], [32], [33]. Mikaeloff *et al*. [1] used KD in two FIRES patients; one of them had more than 100 seizures per day and achieved cessation of epileptic activity 2 days after initiating the treatment [1].

The use of KD in a study of nine patients showed that eight of them achieved ketonuria 2–4 days after initiating the diet, whereas seizures stopped in seven of them 2–4 days after achieving ketonuria. Patients who responded to the treatment regained consciousness 24–58 h after the cessation of seizures and motor functions in the following weeks. In one patient, KD was interrupted abruptly, which made the status recurrent in a short period and caused death 10 days later [32]. Vaccarezza *et al*. [33] reported the use of KD in three patients with possible FIRES who presented SE of 52, 30, and 18 days of evolution, in whom SE stopped after 24 h in the first two cases, and after 3 days, in the last. After establishing KD, the first patient remained free of crisis, the second had 10 partial seizures per month, and the third had a crisis per month, evidencing a good response to this therapeutic measure. During the chronic phase, one study assessed six patients treated with KD for a period between 6 months and 2 years, with a marked decrease in the frequency of seizures recurring once or twice a week [32].

Electroconvulsive therapy (ECT)

ECT (formerly called sismotherapy, electronarcosis, or shock therapy) is a therapeutic tool used in several psychiatric illnesses. It consists of the induction of a generalized convulsive seizure by a transcranial electric stimulation. ECT has numerous anticonvulsant effects, including elevated seizure threshold and decreased seizure duration, which make it a useful adjunctive therapy in epilepsy that is refractory or not amenable to treatment with medication.

The prognosis of FIRES is poor [33]. The seizures are recalcitrant, prolonged, and difficult to control [33]. There is no cure or known efficacious treatment for this condition. Mortality associated with FIRES is 10% during the acute phase and 13% during the chronic stage [13]. The presence of higher-grade periventricular white matter lesions is correlated with poorer neurological outcomes [13].

Conclusion

FIRES must be considered one of the possible etiologies of super-refractory SE, so early management strategies (such as KD) can be used to achieve control of the critically ill patient, control long-term seizures, and improve cognitive outcomes, having as the final result a positive impact on the quality of life of the patient.

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