

Febrile infection-related epilepsy syndrome (FIRES) treated with immunomodulation in an 8-year-old boy and review of the literature

Caner Alparslan¹, Fulya Kamit-Can², Ayşe Berna Anıl³, Nihal Olgaç-Dündar⁴, Dilek Çavuşoğlu⁵, Zeynep Göç¹

¹Department of Pediatrics, ²Department of Pediatric Intensive Care Unit, ³Department of Pediatric Neurology, University of Health Sciences, Tepecik Training and Research Hospital; ⁴Department of Pediatric Intensive Care Unit, ⁵Department of Pediatric Neurology, Katip Çelebi University, Izmir, Turkey. E-mail: caneralparslan@gmail.com

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Febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epilepsy syndrome which is characterized by acute onset of refractory status epilepticus following a febrile infection occurring in previously normal children. Despite the various treatment options that have been tried, exact treatment strategy is still undetermined. This is the first pediatric case of FIRES from Turkey which was successfully treated with intravenous immunoglobulin (IVIG).

A previously healthy 8-year-old boy was referred to our hospital with a pre-diagnosis of status epilepticus and encephalitis. He presented with acute onset of convulsions and unconsciousness following fever and malaise lasting 7 days. On physical examination Glasgow coma scale was 12, his pupils were miotic. He had café-au-lait spots on his body. His fundus examination, cerebrospinal fluid findings and cranial magnetic resonance imaging did not reveal any abnormality. Results of comprehensive search for metabolic, toxicological, infectious and autoimmune etiologies were all negative. Generalized slowing was seen on the electroencephalography (EEG) of the patient indicating possible encephalopathy. The patient developed convulsive status epilepticus and was intubated on day 5. His seizures were controlled by continuous infusion of midazolam, thiopental and used for 4 days. Phenytoin, levetiracetam, topiramate were used simultaneously. IVIG was administered as an immunomodulator for refractory seizures on day-9. The patient was extubated on day 11. The diagnosis was made after a comprehensive negative search for central nervous system infection, autoimmune and metabolic diseases. At follow up it was learnt that he had had only two seizures in two years. Status epilepticus did not recur.

Clinicians should keep in mind FIRES which is a diagnosis of exclusion especially in refractory status epilepticus. IVIG treatment could have a benefit in these patients.

Key words: child, febrile, infection, epilepsy, syndrome, intravenous immunoglobulin.

Febrile infection-related epilepsy syndrome (FIRES) is a devastating multi-drug resistant epilepsy syndrome following a febrile infection in previously healthy patients.¹ The exact mechanism of FIRES is still unknown.¹⁻³ A majority of patients have normal cerebrospinal fluid (CSF) examination, brain imaging and metabolic tests^{1,2,4-6}. Diagnosis of FIRES is

based on exclusion.¹⁻¹⁰ Despite the various treatment options that have been attempted, the exact treatment strategy is still undetermined. Modulation of the immune system have been tried due to the possibility of inflammatory pathways in FIRES. Preliminary evidence suggests that treatments such as steroids, intravenous immunoglobulins (IVIG) and

Table I. Comparison of Characteristic Features of FIRES Cases in Literature.

Authors	Patient number (n)	Male: Female	Average age (years)	Days of fever (day)	Main seizure type	EEG abnormality (%)	MRI abnormality (%)	CSF abnormality (%)	Anti-epileptic drug number	IVIG	Ketogenic diet	Other	Outcome		
													Normal	Exitus	Epilepsy
Kramer et al. ¹	77	4:3	8	4	Secondary generalized	59	42	44	6	30	4	-	5	9	63
Van Baalen et al. ²	22	8:3	6.5	5	Secondary generalized	100	59	-	5	10	0	-	?	?	?
Caraballo et al. ⁴	12	2:1	8.5	2-10	Secondary generalized	100	58	75	?	10	2	-	2	0	10
Byler et al. ⁸	1	1:0	5	6	Generalized	100	0	0	4	1	1	-	0	0	1
Singh et al. ⁵	2	1:1	7 and 10	7	Generalized	100	0	0	5-7	1	2	-	0	0	2
Lin et al. ⁶	2	1:1	4 and 10	1	Generalized	100	100	?	4	1	0	Hypothermia in 2	2	0	0
Our case	1	1:0	8	7	Secondary generalized	100	0	0	4	1	0	-	0	0	1

EEG: electroencephalography; MRI: magnetic resonance imaging; CSF: cerebro-spinal fluid; IVIG: intravenous immunoglobulin.

plasma exchanges might be helpful, but they have not been systematically studied.^{1,2} Ketogenic diet is an alternative treatment option which has dramatic response defined in the literature, but there is still debate concerning efficiency in FIRES due to lack of controlled studies.^{5,6} Therefore, a majority of patients have survived with major neurologic co-morbidities.^{1,5-10}

In the present case, we aim to emphasize the importance of FIRES as an etiology of refractory status epilepticus. Also, we want to share our experience about successful immunomodulation treatment with IVIG in an 8-year-old boy diagnosed with FIRES. As far as we know, this is the first reported pediatric case of FIRES from Turkey.

Case Report

A previously healthy 8-year-old boy was referred to our pediatric intensive care unit (PICU) due to status epilepticus. His medical history revealed a febrile upper respiratory tract infection lasting for 7 days. On admission, his Glasgow coma scale was 12, pupils were miotic and fundus examination were normal with respiratory rate 34/min, heart rate 120/bpm, body temperature 38.7°C, blood pressure 118/87 mmHg and oxygen saturation 100% (room air). He had two café-au-lait spots (2x1 cm and 1x1 cm) on his chest wall. The rest of the physical examination was unremarkable. Complete blood count, basic biochemical laboratory tests and also acute phase reactants were in normal range. CSF analysis was normal. Brain magnetic resonance imaging (MRI) did not detect abnormality. Cephalexin (200 mg/kg/day), vancomycin (60 mg/kg/day) and acyclovir (30 mg/kg/day) treatment were started. Generalized slowing was seen on the electroencephalography (EEG) of the patient indicating possible encephalopathy. At the PICU admission he had frequent seizure activity. Phenytoin (20 mg/kg loading, 5 mg/kg/day maintenance), midazolam (0.1-0.4 mg/kg/hour infusion) and finally levetiracetam (1gr/day) were started. On day-5, he had convulsive status epilepticus. He was intubated and barbiturate induced coma was achieved with thiopental (2 mg/kg/dose loading, 10-120 mcg/kg per minute maintenance 4 days). Topiramate (5 mg/kg/day) treatment was added on 7th day. IVIG (1g/kg/dose-for 2 days) was administered as an

immunomodulation with refractory seizures on the 9th day. Neurofibromatosis was ruled out with normal central nervous system imaging, normal ophthalmologic examination, normal height, normal skeletal system examination and also no neurofibromas and no family history. The results of CSF polymerase chain reaction analyses were negative for viral agents. Lymbic panel was negative for resulted NMDAR Ab, Glu1&Glu2, ANTI-CASPR2, ANTI LGI, GABABAR1/B2. Serum lead level was in normal range. Blood and urinary metabolic (organic acids, Tandem-mass spectroscopy) screening were all negative. His antibiotic treatment was stopped on 14th day due to negative cultures. The patient responded to IVIG after two days of administration and he was extubated on day-11. He was discharged with mild cognitive impairment. In the following two years, he had two complex partial seizures under levetiracetam treatment. EEG showed epileptiform discharges in right temporal head region. There were no structural brain changes in control brain MRI. Phenytoin and topiramate were stopped and levetiracetam treatment has been continued at the doses of 2 g daily.

Informed consent was taken from his parents for presenting this case.

Discussion

Febrile infection-related syndrome is a catastrophic epilepsy form which should be kept in mind in an acute multi-antiepileptic drug resistant seizures. Our case is the first pediatric case of FIRES from Turkey in the literature. In prediction of FIRES, the clinician should be ready to use alternative treatment options such as IVIG, rituximab, nervus vagus stimulation, plasma exchange, ketogenic diet, cannabidiol, anakinra or hypothermia without losing time.^{1,4-12}

The age of onset is mostly clustered about 8 years with a clear male gender predominance. Nearly all of the patients got febrile infection mostly upper respiratory tract infection before the onset. Duration of febrile infection just before the seizures about 1-14 days. Biphasic clinic which is described febrile course followed by seizure and cessation of fever thereafter is nearly universal.^{1-6,8} In our patient age, gender and initial course are completely consisted with the literature (Table I).

Except mild pleocytosis, CSF are negative in nearly all patients. Inflammatory markers of the brain are generally negative.^{1-4,7} In consistence with the literature, in our patient, all screening tests of CSF was negative. Most of the patients had normal initial MRI. In follow-up, atrophic changes especially occur in the temporal regions of the brain.¹⁻³ Byler et al.¹⁰ reported rapid onset of hippocampal atrophy in FIRES. Our patients first brain MRI was normal and there were no MRI changes in the two years follow-up. Electrical studies of the brain do not show specific pattern in FIRES, but temporal region originated spikes in EEG are detected in most of the patients.¹⁻³ We detected the same pattern of EEG in our patient.

Febrile infection-related syndrome is characterized by multi-drug resistant seizures. Most of the patients underwent barbiturate induced come due to status epilepticus despite receiving more than 4-5 anti-epileptic drugs.^{1-4,8} IVIG as an immunomodulatory agent can be an effective treatment alternative in FIRES. Response time to IVIG was very different.¹⁻³ In our case, IVIG treatment was given at 9th day of PICU follow-up. Cessation of his seizures occurred two days after IVIG administration. Kenney-Jung et al.¹² associated FIRES to neuroinflammation by treatment success of Anakinra (IL-1 β receptor antagonist) which is used to treat autoinflammatory disease in childhood and reduction in IL-1 β . Although both our case and the one reported by Kenney-Jung et al.¹² is insufficient to advocate inflammation as the mechanism of FIRES, treatment success is encouraging to further studies on that topic in FIRES treatment. Exact mechanism of ketogenic diet in treatment resistant epilepsy is still unknown. In the literature, Kramer et al.¹ and Nabbout et al.⁶ successfully managed more than half of the patients with FIRES by ketogenic diet. In our patient, given achievement of good response with IVIG, we did not consider ketogenic diet. We believe that the main concern here is the early diagnosis of the syndrome and quick response.

In conclusion, FIRES should be keep in mind in refractory status epilepticus which has serious morbidity and mortality in children. Diagnosis of FIRES is still based on exclusion and treatment approach still needs to be clarified.

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