IVIG Treatment in FIRES: Report of 3 cases from Southeastern Anatolia and a Brief Review of the Literature

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Abstract

Background: Febrile infection-related epilepsy syndrome (FIRES) is a severe epileptic encephalopathy with acute onset following a febrile disease in previously healthy children. Its etiology has not been elucidated yet. There is no treatment algorithm with a positive response. Here, we aimed to present the summary of literature in terms of our experience in FIRES management in a secondary care hospital in the Southeastern Anatolia and immunotherapy outcomes.

Cases: We report three FIRES-associated super-refractory status epilepticus cases followed up by the Pediatric Neurology Unit at Mardin State Hospital. The cases known to be healthy were hospitalized due to focal seizures and seizures with secondary generalization which started after a febrile disease which had developed 3-5 days before. Since seizures persisted for more than 24 hours despite the effective treatment, the super-refractory status epilepticus was accepted. No infectious agent was detected. Progression to chronic refractory epilepsy with cognitive impairment was observed. Two patients received intravenous immunoglobulin (IVIG) and steroids, other received only IVIG. IVIG was continued monthly. The time of the first administration of IVIG was days 2-4. Partial response was obtained within 2-7 days. Monthly IVIG was observed to be protective against status epilepticus attacks triggered by fever. Although all cases received similar treatments at similar times, different outcomes from each other developed. One of them died, the others developed sequelae.

Conclusion: FIRES is a condition that can cause super-refractory status epilepticus. Although IVIG treatment alone does not appear to be effective in the acute phase, regular IVIG treatment may prevent recurrent exacerbations.

Keywords: FIRES • IVIG • Steroid • Superrefractory status epilepticus

Introduction

The diagnosis of Febrile infection-related epilepsy syndrome (FIRES) is made clinically in healthy children with the onset of treatment-resistant seizures that develop 4 days (1-12 days) on average after a febrile disease with the absence of an infectious agent, and with the progression to chronic refractory epilepsy, with cognitive sequelae [1-4]. Super-refractory status epilepticus (SRSE) is a treatment-resistant condition that persists for more than 24 hours despite intravenous (i.v.) anesthetics and antiepileptics (AED) [5-7]. Version, tonic posturing, lateralized face jerking, focal motor limb movements with autonomic feature are frequently observed [8]. Clustered seizures are observed every 2-4 weeks on average, sometimes accompanied by status epilepticus (SE) during chronic phase [1,4]. Cranial magnetic resonance imaging (MRI) is usually normal on admission [9]. Then cerebral edema, leptomeningeal involvement, signal abnormalities in the hypothalamus, thalamus, frontotemporal regions are reported [9-12]. Global brain atrophy mostly occurs within a few weeks [3,9]. Electroencephalography (EEG) reveals diffuse background slowing and interictal discharges at the frontotemporal regions [3,4,11]. Although burst-suppression coma is induced with i.v. anesthetics, SE repeats during weaning in the acute phase [4]. Studies about immunotherapies such as corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PE) are very limited. Here, we aimed to share our experience in the treatment of SRSE that progressed on the basis of FIRES and to discuss the effects of immunotherapy in the acute and chronic periods by reviewing the literature.

Cases

Case 1: A previously healthy 4-year-old male was hospitalized with SE 4 days later his first complex febrile seizure. The seizures were observed to start in the form of the clonic spasm of the right arm, twitching of mouth, lip smacking, cyanosis, and become generalized. Laboratory investigations (including blood cell count, biochemical investigations, metabolic and infectious analyzes) were normal. Cerebrospinal fluid (CSF) analysis showed mildly increased protein. Cranial MRI revealed hyperintensity on T2 and FLAIR sequences in the left medial temporal lobe. Seizure activity continued despite treatments with diazepam, phenytoin, levetiracetam, midazolam infusion, valproic acid, oxcarbazepine, thiopental infusion, and ketamine infusion. IVIG was administered on the fourth day, followed by pulse steroid. The frequency of seizures decreased slightly one week after immunotherapy. In the second week, the patient's seizures became constant. He benefited from topiramate loading. On the 32nd day, febrile SE was observed again. IVIG was administered again. Seizure control was partially achieved on the 36th day. SE developed on the 64th day again. IVIG was administered for the third time. Seizure control was partially achieved within two days, and IVIG was continued to be administered every 28 days. The patient was discharged in the fourth month with topiramate, phenytoin, gabapentin, and clobazam. In cranial MRI, there was parenchymal loss and mesial temporal atrophy in the left hemisphere. In the follow-up, seizures, of which frequency increased with fever were observed. He did not experience SRSE during the IVIG period. After the monthly IVIG treatment was discontinued, there were recurrent hospitalizations because of seizures lasting for 20-30 minutes during infection periods. He benefited from phenytoin loading treatment in all of them. At the end of 1 year, short-term focal seizures are observed a few times a month in Table 1.

Case 2: A previously healthy 5-year-old male patient was admitted with spasm of the left hand. It was learned that five days ago, he had started on antibiotics due to a febrile respiratory infection. His physical examination and laboratory investigations were normal. CSF analysis revealed mild pleocytosis. Within hours, his seizures were observed to start in the left arm and leg and to turn into secondarily generalized convulsions. Cranial MRI was normal. Seizure activity continued despite treatments with diazepam, phenytoin, levetiracetam, valproate, topiramate, phenobarbital, oxcarbazepine, midazolam, propofol, ketamine and thiopental. IVIG and steroid were administered on the third day. At the end of the first month, the SRSE developed again with high fever. The frequency of seizures regressed after the second dose of IVIG. Brain edema, and T2/FLAIR hyperintense lesions in the bilateral parietooccipital regions were observed on second MRI. However, one week later, despite multiple AEDs, he continued to have seizures 4-6 times a day. In table 1 he died in the second month of his hospitalization due to sepsis and multiple organ failure.

Case 3: A previously healthy 5-year-old female patient, applied with asymmetry in the right half of her face. It was learned that she had been started on oral antibiotics due to a febrile respiratory infection three days ago. During the follow-up, twitching in the right half of her face, the clonic spasm of the arm, and seizure displaying generalization were observed. It

was thought that facial palsy could be a postictal finding. Within hours, her seizures became frequent and generalized with SRSE. Cranial MRI revealed an increase in leptomeningeal contrast in bilateral frontotemporal areas. CSF analysis was normal. Her seizures continued despite diazepam, phenytoin, levetiracetam, midazolam infusion, valproic acid, and thiopental infusion. IVIG was administered on the second day. The frequency of seizures began to decrease after IVIG. However, at the end of the first month, mild fever and an increase in seizure frequency were observed again. IVIG was administered for the second time. Cranial MRI was normal. At the end of the second month, table 1 indicates she was discharged with partially provided seizure control.

Discussion

The disease course and outcomes of our patients who received similar treatments at a similar time and benefited from IVIG were different from each other. We cannot differentiate whether the treatment responses we observed based on the cases were the natural course of the disease or the IVIG effect. However, we think that the frequency of seizures, which increased with fever in the acute phase and the transition to the chronic phase, could be controlled by IVIG to some extent, and even we were able to prevent the patients from re-entering the SRSE picture. The FIRES diagnosis of our cases, who did not have any previous disease and were aged between 4-5 years, was made with their clinical picture which started with focal seizures 3-5 days after their upper respiratory tract infection and progressed rapidly to SRSE and continued with chronic refractory epilepsy. These seizures were characterized by autonomic findings, orofacial and extremity motor jerks with secondary generalization, and in which consciousness is affected as reported in the literature [3,4,8,13]. Similarly to the previous cases, we observed slowing in the diffuse ground rhythm and/or epileptiform discharges in the frontotemporal and/or frontocentral regions in EEG [3,4,11]. Similarly to the recently identified MRI findings, the MRI of one case was normal at the admission, and hippocampal, temporal signal changes and leptomeningeal contrasting were detected in the others as indicated in Table 1 and Table 2 [1,3,9,14]. The underlying mechanisms that cause FIRES have not been clearly explained. Although there had been a history of a previous febrile infection, due to the inability to detect an infectious agent, the non-infectious immune-mediated process was considered [3,12,13,15]. Thus, immunotherapies such as corticosteroids, IVIG, PE and rituximab have been tried. Although there are studies in which they were found to be ineffective in the acute phase, Alparslan et al. Table 3 shows presented that they received a response to IVIG within two days [1,16]. Table 1 stipulates we could not receive a response in one case, and in the other two patients, we observed a slight decrease in the frequency of seizures between 2-7 days . Table 1 specifies in some publications, IVIG was continued for a long time with better outcomes [3,11,17,18]. In our first case, we observed seizure clusters triggered by fever and the recurrence of SE during the clinical course. Furthermore, we realized that these periods coincided with 24-30 days which is the half-life of IVIG [19,20]. We observed that the frequency of seizures which increased during the exacerbation period decreased 2-4 days after regular IVIG and he was not hospitalized due to SE after IVIG courses. As denoted in Table 1 in the other case, we received a partial response to the first dose of IVIG within seven days and second IVIG dose prevented exacerbation of fever induced SE. In our first case who benefited regular IVIG, there was a mild protein increase in CSF. Thus FIRES cases with CSF protein increase may be a subgroup benefiting from immunotherapy [1,3,4,12,18]. The literature presented that ketogenic diet (KD), high-dose phenobarbital, plasma exchange, ketamine, lidocaine, and MgSO4 were partially effective in the acute phase [3,6,11,14,21-24]. With their anti-inflammatory effects and cytokine storm-

Table 1: Summary of Clinical Features of our Patients

Case	Case I	Case II	Case III
Gender	M	M	F
Age	4	5	5
Lag from febrile illness onset to SE	4	5	3
Lag from fever control to SE	1	2	-
Laboratory	Elevated CSF protein (50mg/ dL)	Mild pleocyctosis 8/mm3	UR
EEG	Left frontotemporal and frontocentral epileptiform discharges	Generalized slowing Right frontotemporal epileptiform discharges	Bilateral frontotemporal epileptiform discharges
MRI	A: Hypersignal left temporal lobe FU: Brain atrophy of left hemisphere	A: Normal FU: Brain edema, parietal-occipital hypersignal	A: Bilateral frontotemporal leptomeningeal enhancement FU: Hypersignal periventricular region
Treatment	DZP, PHT, LEV, MDZ, VPA, OXC, Thiopental, Ketamine, TPM, LTG, CLOB, GABA	DZP, PHT, PHB, LEV, MDZ, PROP, VPA, TPM, Thiopental, Ketamine, OXC	DZP, PHT, LEV, MDZ, VPA, Thiopental
IVIG	(2gr/ kg in 2 days) (monthly IVIG)	(2 gr/kg in 2 days) (2 times)	(2 gr/ kg in 2 days) (2 times)
Steroid	30 gr/ kg 3 days (tapering in 2 weeks)	30 gr/ kg 3 days (tapering in 2 weeks)	-
Responsive to treatment	Partially responsive to IVIG and phenytoin and clobazam	Nonresponsive	Responsive to IVIG
IVIG initiation day / Time for effectiveness	1st course: 4th day / 7 days 2nd course: 32th day / 4 days 3rd course: 64th day / 2 days 4th course: 3th month / 2 days 5th course: 4th month / good response 6th course: 5th month / good response 7 th course: 6th month / good response	1st course: 3rd day / - 2nd course: 30th day / -	1st course: 2nd day / 7 days 2nd course: 1st month / 7 days
AED at discharge	TPM, PHT, CLOB, GABA	OXC, LEV, TPM, PHT	LEV, VPA
Outcome	Refractory epilepsy Loss of ambulation Feeding via nasogastric tube FU (1 year later): Epilepsy, ambulation with help, oral feding achieved	Exitus	Mild facial palsy sequele Epilepsy

(M: Male, F: Female, CSF: Cerebrospinal fluid, UR: Unremarkable, A: Admission, FU: Follow-up, IVIG: Intravenous immunoglobulin, DZP: Diazepam, MDZ: Midazolam, PROP: Propofol, PHT: Phenytoin, PHB: Phenobarbital, CLOB: Clobazam, CLON: Clonazepam, VPA: Valproic acid, LEV: Levetiracetam, TPM: Topiramate, LTG: Lamotrigine, OXC: Oxcarbazepine, GABA: Gabapentine).

Table 2: Summary of Clinical Features of Cases Published in the Literature.

	Study	n of patients	M:F	Age (years)	Lag from febrileillness onset to SE (days)	Seizure type	Laboratory (n)	MRI (n)	EEG(n)	Outcome
1	Agarwal et al. [29]	1	NA	4	3 weeks	Secondary generalized	UR	A: Hypersignal hippocampus FU: Hippocampal atrophy	A:Multifocal epileptiform discharges	Epilepsy Cognitive decline
2	Alpaslan et al. [16]	1	1:0	8	6	Secondary generalized	UR	A: Normal FU: Normal	A:Generalized slowing FU: Focal temporal epileptiform discharges	Epilepsy Cognitive decline
3	Byler et al. [17]	1	1:0	5	7	Secondary generalized	Leukopenia Thrombocytopenia Transaminase elevation Pleocytosis	A: Hypersignal hippocampi FU: Bilateral hippocampal atrophy	A: Frontal, occipital or centrotemporal epileptiform discharges	Epilepsy
4	Caputo et al. [6]	1	0:1	13	6	Focal seizures Secondary generalized	UR	A: Normal FU: Normal	A: Diffuse slowing Bilateral temporal focal discharges FU: Bilateral temporal slowing	Cognitive decline Anxiety Depression
5	Carabolla et al. [11]	12	8:4	Mean 8.5 (2-13.5)	2-10	Focal seizures Secondary generalized	Pleocytosis(7) Elevated CSF protein(1)	A: Normal(5) Hypersignal hippocampi/ periinsula/ basal ganglia(7) FU: Diffuse atrophy(5), Mesial temporal sclerosis(4)	A: Diffuse slowing(12), Temporal(4), frontotemporal(4), frontal(2), frontoparietal(2) seizure onset FU: Backround slowing(12) Frontal, temporal or frontotemporal focalspikes(12)	Epilepsy Mental retardation Behavioral disturbances
6	Chou et al. [30]	1	0:1	12	7	Generelized	UR	A: Hypersignal hippocampi, medial temporal, posteromedial thalamus, external capsules	A: Diffuse slowing Frequent ictal fast activity FU: Normal	Impaired short term memory
7	Fen Lee et al. [10]	29	12:17	Mean 8.9 (1.2-17.8)	Mean 6 (2-14)	Secondary generalized(25) Generalized(4)	Pleocytosis(9)	A:Normal(18) Leptomeningeal enhancement, Hypersignal hypocampi, temporal, thalamus(11) FU: Diffuse brain atrophy, Temporal, preiventricular hyperintensity (20)	Focal spike(15) Generalized polyspike(3) Generalized spike and wave(1) BS(4) PLED(1)	Exitus (3 during acute phase, 3 during follow-up) Epilepsy(20) Learning disability(6) Vegetative state, severe mental retardation(11)
8	Fox et al. [4]	1	0:1	6	7	Secondary generalized	UR	Normal	Left foci Generalized periodic epileptic discharges PLED	Epilepsy Cognitive decline
9	Gofstheyn et al. [26]	7	5:2	Mean 7 (3-8)	NA	Focal seizures Secondary generalized	Pleocytosis(6) Elevated CSF protein(1)	A: Normal(4), restricted diffusion in the lentiform nuclei(1), bleeding along the corpus callosum(1), signal abnormality of temporalsulcus(1), volume loss, gliotic change, hippocampal sclerosis(1)	Diffuse background slowing Focal epileptifom discharges	Epilepsy Cognitive decline Ataxia Exitus(1)

10	Howell et al. [8]	7	7:0	Mean 10.8 (6.7-14)	3-6	Focal seizure Secondary generalized	Pleocytosis(2) Elevated CSF protein(2)	A: Temporal, hippocampal, insular hyperintensity FU: Normal (3) Diffuse cortical atrophy(2) Hippocampal atrophy±sclerosis(2)	Diffuse background slowing Focal epileptifom discharges BiPLED BS	Epilepsy Cognitive decline Exitus(1)
11	Kenney Jung et al. [28]	1	0:1	32 months	7	Generalized	UR	A: Normal FU: Diffuse cortical volume loss	Multifocal discharges	Epilepsy
12	Kramer et al*[3]	77	4:3	Mean 8 (2-17)	Mean 4 (1-14)	Generalized (5) Secondary generalized (19) Opercular (9) Focal seizure (58)	Pleocytosis(44) OCB(4)	A:Normal(35) Leptomeningeal enhancement(4) Hippocampal, periinsular hyperintensity(12), diffuse atrophy(2) FU: Diffuse brain atrophy(28) Hippocampal hyperintensity(17)	Generalized polyspike(5) Temporal(16), frontotemporal(16), frontal(13), central, parietal, occipital(15) seizure onset	Exitus(9) Epilepsy(63) Normal(12) Borderline cognitive decline(11) Mild MR(10) Moderate MR(16) Severe MR(8) Vegetative state(11)
13	Lin et al. [7]	2	1:1	4-10	1-6	Generalized	Pleocytosis	Cerebral edema Rhombencephalitis	Bilateral temporal epileptiform discharge	Cognitive decline Motor deficit Epilepsy
14	Nabbout et al. [21]	9	4:5	Mean 74 months (54-98 months)	1-6	Focal seizure Generalized	Pleocytosis	A: Hypersignal mesial temporal	A: Diffuse delta/ teta activity with spikes FU: Perisylvian discharges	Exitus(1) Epilepsy
15	Nozaki et al. [14]	1	1:0	7	3	Secondary generalized	Pleocytosis	A: Hypersignal splenium of corpus callosum FU: Brain atrophy	A: Diffuse slowing	Hyperactive behaviour
16	Patil et al. [2]	15	4:1	Mean 6.3	Mean 4 (1-12)	Generalized Opercular Facial twitching	UR	A: Normal (13) Hyperintensity in temporal, hippocampi (2) FU: Normal(6) Diffuse atrophy (1) Hiperintensity in hippocampi, temporal, putaminal (3) Dilate ventricule(1)	A: Diffuse slowing FU: Diffuse slowing(6), Focal discharge(2), Multifocal spikes(2)	Exitus(3) Epilepsy Motor deficit
17	Rivas Coppola et al. [9]	7	6:1	Mean 4.7 (3 months-9 years)	Mean 5.5 (1-14)	Focal seizure Secondary generalized	Pleocytosis(3) Elevated CSF protein(3)	A:Normal(4), Cytotoxic edema in hippocampi(1) FU: Cerebral atrophy and cerebellar volume loss(7)	A: Multifocal epileptiform discharges, Temporal lobe epileptifrom discharges	Non-ambulatory and non-verbal(4) Cognitive decline(1) Epilpesy(7)
18	Sa et al. [25]	2	2:0	9 and 5 years respectively	4	*Secondary generalized *Generalized respectively	NA	A: *Abnormal signal in basal ganglia, external capsule, cortex / *Brain edema respectively	NA	1st patient: Epilepsy 2nd patient: Epilepsy and vegetative state

19	Sakuma et al. [13]	29	19:10	Mean 6.8 (1-14)	Mean 4.9 (2-109)	Generalized(8) Secondary generalized(24) Focal seizure (26)	Pleocytosis(19) Elevated CSF protein(5)	A:Brain edema(2) Hippocampal, amygdaloid, periventricular, claustrum hyperintensity(12) FU: Diffuse brain atrophy, Hippocampal, amygdaloid hyperintensity	A: high voltage slow background(7), Multiple independent foci(15)	Exitus(1) Epilepsy(29) Cognitive decline, Memory impairment, Autistic tendency, Hyperkinetism, Learning disability, Personality change, Emotional instability
20	Singh et al. [22]	2	1:1	7 and 10 years	7	Generalized	UR	A: 1st patient: Hypersignal medial temporal lobe 2nd patient:Normal FU: 1st patient: Mesial temporal sclerosis	1st patient: Generalized periodic epileptiform discharges 2nd patient: SE arising fromleft frontal and temporal regions	Epilepsy Cognitive decline
21	Sort et al. [23]	1	1:0	11	7	Focal seizure Generalized	Pleocytosis	A: Normal FU: Diffuse brain atrophy	NA	Epilepsy Cognitive decline Hemiplegia
22	Specchio et al. [32]	8	5:3	Mean 7.4 (8months-17 years)	NA	Focal seizure	Elevated CSF protein(2) OCB(+)(2)	A: Normal(3), lateral ventricule enlargement(1), hypersignal periinsular, mesial temporal(4)	A: Diffuse slowing(7), BiPLEDs(1), frontal,central or temporal discharges	Epilepsy(7) Cognitive decline(8)
23	Tan et al. [24]	2	2:0	2 and 16 years	5	Focal seizure Generalized	UR	A: Normal/ Leptomeningeal enhancement/ Hypersignal thalami FU: Frontoparietal microinfarcts/ diffuse brain atrophy	A: Frontal and central bisysnchromous discharges	Exitus(1) Epilepsy(1)
24	Van Baalen et al. [12]	12	1:1	Mean 6 (2-12)	Mean 4 weeks (2 week-4 months)	NA	Pleocytosis	A: Basal gangliaand temporal signal changes	NA	NA
25	Veiga et al. [31]	1	1:0	4	7	Secondary generalized	Pleocytosis	A: Normal(CT) FU: Diffuse brain atrophy	A: Multifocal epileptiform discharges FU: Rare discharges, backroud slowing	Mental retardation Motor deficite Gastrostomy tube

(n: Number, M: Male, F: Female, SE: Status epilepticus, MRI: Magnetic resonance imaging, EEG: Electroencephalogarphy, NA: Not available, UR: Unremarkable, A: Admission, FU: Follow-up, CSF: Cerebral-spinal fluid, OCB: Oligoclonal band, CT: Computed tomography, BS: Burst-supression, PLED: Periodic lateralized epileptiform discharges, BiPLED: Bilateral independent periodic lateralized epileptiform discharges, MR: Mental retardation).

Table 3: Summary of Treatment Options and Treatment Responses of Cases Published in the Literature.

	Study	Acute treament(n)	IVIG (n, dose, duration, administration day)	Steroid (n, dose, duration, administration day)	KD (n, dose, duration, administration day)	Other	AED/Treatment after discharge	Effective treatments (n)	Lag from SE onset to effective treatment administration	Lag to responsive of effective treatment
1	Agarwal et al. [29]	LRZ PHT	-	-	-	-	NA	acute treatment		3 hours
2	Alpaslan et al. [16]	MDZ Thiopental PHT LEV TPM	2gr/kg (2 days)	-	-	-	LVT	IVIG	9 days	2 days
3	Byler et al. [17]	LRZ Barbiturate PHB PHT VPA LEV	2gr/kg (5 days) Monthly IVIG for 9 months	-	4:1 lipid/nonlipid	-	KD PHB PHT LVT	IVIG	42 days	Extubation at the 56th day
4	Caputo et al. [6]	MDZ PROP PHT PHB LEV LAC Ketamine	IVIG + (dose NA)	Methylprednisolone (1 gr for 5 days) 10th day	-	PE (5 days)	Prednisone LAC PHB LEV LRZ	*ketamine + steroid infusion *PE	*10 days (steroid) *12 days (PE)	A few hours (ketamin and methylprednisolone) Discahrge at 21th day (after PE)
5	Carabolla et al. [11]	PHB(12) PHT(12) BZD(12) LVT(12) VPA(6) Thiopental(6) CZP (5) OXC(4) TPM(6) Barbiturates(8)	IVIG 1.2 gr 3 times(10) IVIG every 21 days over 4,6 and 8 months(3)	Steroid(9) (30mg/kg/d over 5 days folowed by oral prednisolone at 1 mg/kg/day)	KD(2)	PE(1) RTX(1)	2-3 AEDs(10) IVIG(3) KD(2) Surgery(1) VNS(1)	Barbiturates(5) IVIG(2), Steroid(1), KD(1)	NA	NA
6	Chou et al. [30]	PHB LEV VPA MDZ Pyridoxine Pentobarbital PROP Thiopental Lidocaine	IVIG 1g/kg 3 times	Dexamethasone 7 days	KD (gastrointestinal bleeding side effect)	MgSO4 (20mg/kg/h)	PHB TPM LEV LRZ Pyridoxine	Lidocaine MgSO4	27 days (lidocaine) 30 days (MgSO4)	2 days (lidocaine) 1 day (MgSO4)
7	Fen Lee et al. [10]	AEDs(29) (NA) MDZ and/or Ketamin(29) Lidocain(3)	IVIG(4)	Steroid(3)	KD(7)	Hypothermia(2)	3 (1-5) AEDs (NA)	NA	NA	NA
8	Fox et al. [4]	PHB LEV MDZ Pentopbarbital LRZ PHT Pyridoxine Folinic acid ZNS CZP VPA	IVIG	Methylprednisolone	KD	PE Biotin L-carnitine	NA	NA	NA	NA
9	Gofstheyn et al. [26]	PHB(7) VPA(7) LEV(7) PHT(5) TPM(4) LAC(4) CRB(2) OXC(1) CLOB(4) CLON(1) Felbamate(2) RUF(1) ZNS(2) Perampanel(1) LTG(2) MDZ(4) Isoflurane(3) Pentobarbital(3) PROP(3) Ketamine(4)	IVIG(6)	Steroid(6)	KD(6)	PE(1) Hypothermia(3) RTX(1) CYC(1) VNS(2) Cannabidiol(7)(15-25 mg/kg/d))	2.8 AEDs KD(3) Cannabidiol	Cannabidiol(6)	NA	%90.94 mean change of seizure frequency at 4th week (Cannabidiol)

10	Howe Howell et al. [8]	PHB(5) Thiopental(3) PROP(2) BZD(7) CBZ(2) Gabapentin(1) LTG(1) LEV(2) PHT(7) OXC(2) VPA(3) TPM(4)	IVIG(2) (2gr/kg in 2 days)	Methylprednisolone(4) (15-30 mg/kg/day 5 days)	-	PE(1) (3 days) RTX(1) VNS(2)	2-3 AEDs (NA) VNS Oral steroid	VNS Oral steroid	NA	%30-40 reduction in seizure frequency (VNS)
11	Kenney Jung et al. [28]	MDZ PHB LAC TPM PROP Felbamate Ketamin CLON Fosphenytoin	-	Methylprednisolone (30mg/kg/day 3 days)	KD (4:1)	Anakinra (5mg/kg)	Anakinra Felbamate LEV	Anakinra	1st epoch 6 days 2nd epoch 54 days 3rd epoch 191 days	NA
12	Kramer et al+ [3]	MDZ PROP Lidocaine Ketamine MgSO4 Pyridoxine Folinic acid PHB Thiopental AEDs 6 (2-16)	IVIG(30)	Steroid(29)	KD(4)	Verapamil Biotin Dextrametorphan PE Paraldehyde Chloralhydrate Lignocaine	NA	IVIG(2) (2 gr/kg once per month for 8-9 months) KD(1) Barbiturate(1)	NA	2 days(KD)
13	Lin et al. [7]	MDZ LRZ DZP PHT PHB VPA VPA VGB CZP	IVIG 2gr/kg (5 days)	Steroid (30 mg/kg/day 3 days and 4 mg/kg/day 4 days)	-	Hypothermia (8days and 3 days respectively)	NA	Hypothermia	8 hours and 12 hours respectively	Extubation at the 25th and 9th day respectively
14	Nabbout et al. [21]	PHB PHT TPM LEV LTG BZD Thiopental	-	Steroid(2)	KD(9) (4:1 lipid:nonlipid)	-	NA	KD(7)	4-55 days	4-6 days
15	Nozaki et al. [14]	DZP MDZ CZP PHB PHT	-	-	-	-	NA	High dose phenobarbital	NA	NA
16	Patil et al. [2]	MDZ(7) PHT(11) PHB(11) VPA(13) LEV(14) TPM(12) CLOB(12) CLON(9) Barbiturate(8) Ketamine(1)	IVIG(6) (2gr/kg in 5 days)	Steroid(15) (30mg/kg/day 3 days, 2mg/kg/day and tapering in 4-6 weeks)	KD(2)	-	Mean 5 (3-6) AEDs	Poor response to immunotheraphy	NA	NA
17	Rivas Coppola et al. [9]	MDZ(5) LRZ(6) DZP(1) PHT/Fosphenytoin(6) PHB(6) VPA(4) LEV(7) TPM(2) CLOB(3) CLON(1) ZNS(4) RUF(1) LTG(1) OXC(2) Felbamate(3) LAC(5) VGB(1) Ketamine(1) Pentobarbital(6) Thiopental(1)	IVIG(5) (1-2gr/kg)	Methylprednisolone(4) (20-30mg/kg)	KD(4)	Hypothermia(3)		Poor response to KD(4) Transient improvement with hypothermia(1)	NA	NA

18	Sa et al. [25]	PHB(2) MDZ(2) Ketamine(2) Thiopental(2)	-	-	KD(2)	Cannabidiol(2) Anakinra(2) (5-10mg/kg/d) CMN-DBS(2)	NA	CMN-DBS(1) Anakinra(1) (responsive for the 1st patient)	27 and 37 days (CMN-DBS) 43 and 22 days (Anakinra) respectively	51th day (responsive for the 1st patient)
19	Sakuma et al. [13]	PHB(15) Thiopental(5) Thyamiral(4) DZP(5) MDZ (25) Lİdocaine PHT	IVIG(13)	Steroid(12)		PE(1)	NA	Steroid(2) MDZ(5)	NA	NA
20	Singh et al. [22]	PHT/fosphenytoine(2) PHB(2) LEV(2) VPA(2) TPM(2) MDZ(1) LRZ(1) Pentobarbital(2) LAC(1) CLOB(1)	-	Methylprednisolone(2) (5 days)	KD (4:1 lipid:nonlipid) KD (6:1 lipid:nonlipid)	-	1st patient: KD (3.25:1 lipid:nonlipid)) TPM PHB 2nd patient: KD (4:1 lipid:nonlipid) PHB TPM CLOB	KD(2)	1st patient: 13 days 2nd patient: 3 days	1st patient: 2 days 2nd patient: Ketosis achieved at the 20th day
21	Sort et al. [23]	DZP MDZ VPA PHT PROP VGB TPM LEV Pyridoxine Pentobarbital	-	Steroid (3 days) (2 courses)	KD	-	PHB TPM VGB	KD	48 days	61 days
22	Specchio et al. [32]	PHT(4) PHB(8) CBZ(6) OXC(1) VPA(3) TPM(3) CLOB(4) LEV(1)	IVIG(6)	Steroid(8)	-	-	Repeated IVIG(5)	IVIG	NA	25%-75% reduction in seizure frequency(IVIG)
23	Tan et al. [24]	MDZ(2) PHT(2) PHB(2) MDZ(2) LRZ(2) Thiopental(2) LEV(2) TPM(2) VPA(2) Pyridoxine(1) CBZ(1)	IVIG(2)	Steroid(1)	KD(1)	MgSO4(2) (50mg/kg loading; 10-30mg/kg/h maintenance)	NA	MgSO4(1)	35 days	37 days
24	Van Baalen et al. [12]	NA	IVIG	Steroid		PE	NA	No clear effect of immunotheraphy	NA	NA
25	Veiga et al. [31]	MDZ PHT PHB LEV VPA LAC TPM Thiopental Lidocaine Ketamine PROP Perampanel Pyridoxine Desflurane	IVIG (5 days)	Steroid	-	PE (4 times) Hypothermia (48 hours) ECT (Bifrontotemporal) (14 sessions over 12 days)	NA	ECT	NA	NA

(* Kramer et al; It include data from previously published eight studies; 14 patients from Mikaeloff et al 2006, 14 patients from Van balen et al 2010, 13 patients from Shyu et al 2008, 10 patients from Kramer et al 2005, 9 patients from Linet al 2008, 7 patients from Specchio et al 2010, 6 patients from Sahin et al 2001, 4 patients from Baxter et al 2004; So these eight studies did not added to our table) .

(n: Number, SE: Status epilepticus, NA: Not available, AED: Antiepileptic drug, IVIG: Intravenous immunoglobulin, KD: Ketogenic diet, PE: Plasma exchange, RTX: Rituximab, CYC: Cyclophosphamide, VNS: Vagal nerve stimulation, CMN-DBS: Centromedian thalamic nuclei deep brain stimulation, ECT: Electroconvulsive theraphy, BZD: benzodiazepine, DZP: Diazepam, MDZ: Midazolam, LRZ: Lorezepam, PROP: Propofol, PHT: Phenytoin, PHB: Phenobarbital, CLOB: Clobazam, CLON: Clonazepam, VPA: Valproic acid, LEV: Levetiracetam, TPM: Topiramate, LTG: Lamotrigine, LAC: Lacosamide, ZNS: Zonisamide, RUF: Rufinamide, CZP: Carbamazepine, OXC: Oxcarbazepine, VGB: Vigabatrine).

inhibiting effects, cannabidiol, anakinra, and hypothermia were presented as other options [9, 25-28]. The literature on the use of immunotherapies in the chronic phase is limited, and positive effects have been reported on a case basis [3,11,17]. Table 3 signifies although one study reported the IVIG first dose time, administration schedule, and time of effect, these details were not included in other studies [17]. While Van Baalen et al. recommended empirical immunotherapy in the acute phase, Kramer et al. suggested that long-term treatment could be continued if the effect of immunotherapy was observed [1,3] We also agree with these opinions. These cases may benefit from regular IVIG treatment. However, there is a need for prospective studies on this issue, which include the time of administration of agents and their duration of action and which use standard definitions required to say that they are effective [29-32].

Conlusion

Despite various difficulties in management of such critically ill patients, it is observed and evaluated these patients progression and experienced IVIG therapy in chronic phase of the disease. Although all cases received similar treatments at similar times, different outcomes from each other developed. There is no treatment scheme with a positive response yet. Although IVIG treatment alone does not appear to be effective in the acute phase, It is observed that regular IVIG treatment may prevent recurrent exacerbations. In this study, it is aimed to present the summary of literature in terms of our experience in FIRES and super-refractory status epilepticus management in a secondary care hospital in the Southeastern Anatolia region, immunotherapy outcomes, and other treatment options.

Conflict of Interest

The authors declare no conflict of interest

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References

1. Van Baalen, A., et al. "Febrile infection-related epilepsy syndrome: Clinical review and Hypotheses of epileptogenesis." *Neuropediatrics* 48 (2017): 5-18.
2. Patil, S.B., et al. "Clinical profile and treatment outcome of febrile infection-related Epilepsy syndrome in South Indian children." *Ann Indian Acad Neurol* 19 (2016): 188-194.
3. Kramer, U., et al. "Febrile infection-related epilepsy syndrome (FIRES): Pathogenesis, treatment, and outcome: A multicenter study on 77 children." *Epilepsia* 52 (2011): 1956-1965.
4. Fox, K., et al. "Febrile Infection-Related Epilepsy Syndrome (FIRES): A Literature Review and Case Study. " *Neurodiagn J* 57 (2017): 224-233.
5. Marawar, R., et al. "Updates in Refractory Status Epilepticus." *Crit Care Res Pract* 2018 (2018): 936-949.
6. Caputo, D., et al. "Febrile infection-related epilepsy syndrome (FIRES) with super-refractory status epilepticus revealing autoimmune encephalitis due to GABAAR antibodies." *Eur J Paediatr Neurol* 22 (2018): 182-185.
7. Lin, J.J., et al. "Therapeutic hypothermia for febrile infection-related epilepsy syndrome in two patients." *Pediatr Neurol* 47 (2012): 448-450.
8. Howell, K.B., et al. "Scheffer IE, Freeman JL, et al. Long-term follow-up of febrile infection-related epilepsy syndrome." *Epilepsia* 53 (2012): 101-110.
9. Rivas Coppola, M.S., et al. "Chronological Evolution of Magnetic Resonance Imaging Findings in Children with Febrile Infection-Related Epilepsy Syndrome." *Pediatr Neurol* 55 (2016): 22-29.
10. Lee, H.F., & Chi, C.S. "Febrile infection-related epilepsy syndrome (FIRES): therapeutic complications, long-term neurological and neuroimaging follow-up." *Seizure* 56 (2018): 53-59.
11. Caraballo, R.H., et al. "Febrile infection-related epilepsy syndrome: A study of 12 patients." *Seizure* 22 (2013): 553-559.
12. Van Baalen, A., et al. "Febrile infection-related epilepsy syndrome without detectable autoantibodies and response to immunotherapy: A case series and discussion of epileptogenesis in FIRES." *Neuropediatrics* 43 (2012): 209-216.
13. Sakuma, H., et al. "Acute encephalitis with refractory, repetitive partial seizure (AERRPS): A peculiar form of childhood encephalitis." *Acta Neurol Scand* 121 (2010): 251-256.
14. 14. Nozaki, F., et al. "Reversible splenic lesion in a patient with febrile infection-related epilepsy syndrome (FIRES)." *Neuropediatrics* 44 (2013):291-294.
15. Nabbout, R., et al. "Acute encephalopathy with inflammation-mediated status epilepticus." *Lancet Neurol* 10 (2011): 99-108.
16. Alparslan, C., et al. "Febrile infection-related epilepsy syndrome (FIRES) treated with immunomodulation in an 8-year-old boy and review of the literature." *Turk J Pediatr* 59 (217): 463-466.
17. Byler, D.L., et al. "Rapid onset of hippocampal atrophy in febrile-infection related epilepsy syndrome (FIRES)." J *Child Neurol* 29 (2014): 545-549.
18. Specchio, N., et al. "Childhood refractory focal epilepsy following acute febrile encephalopathy." *Eur J Neurol* 18 (2011): 952-961.
19. Björkander, J., et al. "Prospective open-label study of pharmacokinetics, efficacy and safety of a new 10% liquid intravenous immunoglobulin in patients with hypo- or agammaglobulinemia." *Vox Sang* 90 (2006): 286-293.
20. Rojavin, M.A., et al. "Quantitative Evidence of Wear-Off Effect at the End of the Intravenous IgG (IVIG) Dosing Cycle in Primary Immunodeficiency." *J Clin Immunol* 36 (2016): 210-219.
21. Nabbout, R., et al. "Efficacy of ketogenic diet in severe refractory status epilepticus initiating fever induced refractory epileptic encephalopathy in school age children (FIRES)." *Epilepsia* 51 (2010): 2033-2037.
22. Singh, R.K., et al. "Cognitive outcomes in febrile infection-related epilepsy syndrome treated with the ketogenic diet." *Pediatrics* 134 (2014): e1431-1435.
23. Sort, R., et al. "Ketogenic diet in 3 cases of childhood refractory status epilepticus." *Eur J Paediatr Neurol* 17 (2013): 531-536.
24. Tan, W.W., et al. "Use of Magnesium Sulfate Infusion for the Management of Febrile Illness-Related Epilepsy Syndrome." *Child Neurol Open* 2 (2015): 2329048X14550067.
25. Sa, M., et al. "Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES - Two different outcomes." *Eur J Paediatr Neurol* 23 (2019): 749-754.
26. Gofshteyn, J.S., et al. "Cannabidiol as a Potential Treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES) in the Acute and Chronic Phases." *J Child Neurol* 32 (2017): 35-40.
27. Zhu, Y., et al. "Abnormal neurogenesis in the dentate gyrus of adult mice lacking 1,25-dihydroxy vitamin D3(1,25-(OH)2D3)." *Hippocampus* 22 (2012): 421-433.
28. Kenney-jung, D.L., et al. "Febrile infection-related epilepsy syndrome treated with anakinra." *Ann Neurol* 80 (2016): 939-945.
29. Agarwal, A., et al. "Hippocampal changes in febrile infection-related epilepsy syndrome (FIRES)." *Polish J Radiol* 80 (2015): 391-394.
30. Chou, I.C., et al. "Marked improvement in febrile infection-related epilepsy syndrome after lidocaine plus MgSO4 treatment in a 12-year-old girl." *Epilepsy Behav Case Reports* 6 (2016): 6-9.
31. Veiga, A.M., et al. "Effectiveness of electroconvulsive therapy for refractory status epilepticus in febrile infection-related epilepsy syndrome." *Neuropediatrics* 48 (2017): 45-48.
32. Specchio, N., et al. "Epileptic encephalopathy in children possibly related to immune-mediated pathogenesis." *Brain Dev* 32 (2010): 51-56.

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