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# Combined immunoglobulin and plasmapheresis treatment for Febrile Infection-Related Epilepsy Syndrome (FIRES)☆

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ABSTRACT

Febrile infection-related epilepsy syndrome (FIRES) is a rarely observed and destructive syndrome progressing with resistant seizures or refractory status epilepticus. In this report we present in a treatment procedure with plasmapheresis of a pediatric patient with FIRES and currently unknown etiology in order to contribute to the literature.

## 1. Introduction

Febrile infection-related epilepsy syndrome (FIRES), which is a subcategory of New-Onset Refractory Status Epilepticus (NORSE), is a destructive syndrome progressing with resistant seizures or refractory status epilepticus occurring a short time after a non-specific fever infection [1]. NORSE is a clinical presentation in which new onset refractory status epilepticus is observed without a clear structural, metabolic or toxic cause in a patient without preexisting active epilepsy or other neurological disease [1]. FIRES is relevant for all ages but generally occurs in previously-healthy children aged from 3 to 15 years [1–3]. It is a rare syndrome with estimated incidence of 1/1,000,000 [4]. The clinical tableau occurs 1–14 days after a non-specific fever infection developing in fully healthy pediatric patients [5]. At the onset of status epilepticus, the patient may or may not have fever [1].

This syndrome generally does not respond to antiseizure medications, so high-dose steroids, intravenous immunoglobulin and plasmapheresis, cannabidiol, tacrolimus, rituximab and cyclophosphamide may be used. But the efficacy of these treatments is still uncertain [6].

In this article, the progression in the clinical tableau of a FIRES patient with seizures stopped by intravenous immunoglobulin and plasmapheresis combined treatment and electroencephalography (EEG) investigations during admission were investigated.

## 2. Case

A four-year old female patient attended the emergency service with fever, confusion and seizure. After emergency intervention for the patient, physical examination found Glasgow coma score of 7, eyes closed, bilateral light reflexes present, localized painful stimuli and occasional meaningful sounds. Pupils were isochoric, on the midline and bilateral light reflexes were present. Deep tendon reflexes for lower and upper extremities were symmetrically increased.

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**Table 1**
Daily follow-up form.

| Day of hospitalization | Clinical findings | Treatment administered | EEG finding | Performed Imaging and laboratory tests |
|---|---|---|---|---|
| 0. day | Fever | Midazolam, phenytoin, antibiotic, | | LP |
| | | | | Brain CT |
| | Focal to bilateral tonic-clonic seizure | Midazolam infusion | | Viral panel |
| | | Keppra loading and maintenance | | |
| 1st day | Generalized SE | Midazolam 1 mg/kg/h | | |
| | No fever | Intubation | | |
| | GCS: 8 | Carbamazepine | | |
| | | Carnitine | | |
| | | Coenzyme q | | |
| | | Benvida | | |
| | | Valproic acid | | |
| | | Thiopental | | |
| 2nd day | Hypotension, | Thiopental loading + maintenance | | Contrast and non-contrast brain MRI |
| | Electrographic seizure activity | | | |
| | | Adrenalin infusion | | Diffusion MRI |
| 3rd day | | Ketamine infusion, | Seizure activity | CSF culture: negative |
| | | Pulse steroid treatment | | |
| 5th day | Intubated, DTR hypoactive, | IVIG 500 mg/kg | Electrical seizure, burst suppression | Check-up brain MRI and diffusion MRI taken. |
| | PLR + /+ | planned for 4 days | | |
| | | | | No involvement |
| 8th day | IVIG 4th day, | Plasmapheresis 1:1.5 with | Seizure present | |
| | Plasmapheresis planned | IVIG 400 mg/kg | | |
| 10th day | | Plasmapheresis 3rd dose, | Reduction in seizure activity | |
| | | Other treatments continued | | |
| 12th day | Every other day decision about plasmapheresis. | 5th dose of plasmapheresis | Sleep spindles present | |
| | One day IVIG, the next day plasmapheresis | | | |
| 20th day | | 9th dose of plasmapheresis | Normal | |
| | | Thiopental infusion reduction began | | |
| 30th day | | Patient firstly had thiopental then midazolam and finally ketamine infusion reduced and stopped | | |
| | | Patient extubated. | | |
| | | Physiotherapy began | | |
| 40th day | Patient could not speak | Valproic acid loading administered | | Valproic acid and carbamazepine levels were low |
| | Oral intake began | | | |
| | Began walking again | Midazolam infusion began when seizure continued | | |
| | IVIG 500 mg/kg with 4 doses planned | IVIG 1st day | | LP performed |
| | | | | Limbic panel examined. |
| 50th day | Patient discharged when fully recovered. | | | |

EEG: electroencephalogram, LP: lumbar puncture, CT: computed tomography, MR:magnetic resonance imaging, DTR: deep tendon reflex, PLR: pupillary light reflex

In her history, the patient was learned to be previously healthy, with a mild cold and fever 3–4 days previously.

Laboratory findings, hemogram, biochemistry, C-reactive protein, procalcitonin and cerebrospinal fluid (CSF) examination were within normal intervals. Contrast and non-contrast brain tomography found no features.

Viral panel was negative. The patient's lactate and ammonia level were in normal range.

Initial treatment for the patient was organized as ceftriaxone, vancomycin, acyclovir and oseltamivir. For fever, the patient was administered routine paracetamol.

Intensive care monitoring first observed generalized seizure with

tonic clonic form and the patient was first given two single doses of midazolam respectively, with added phenytoin and levetiracetam and oxygen supply. When the seizure continued, midazolam infusion began. With clinical seizure continuing, the patient had valproic acid, carbamazepine, clonazepam, phenobarbital, lacosamide, and topiramate added to anticonvulsant treatments. In terms of mitochondrial pathology, pyridoxine, biotin and carnitine were begun.

In spite of midazolam infusion rate reaching maximum dose, seizures did not stop and thiopental was begun.

On the 5th day of admission, the patient's contrast and non-contrast brain magnetic resonance imaging (MRI) and diffusion MRI had no features identified.

With no seizures observed clinically, EEG of the patient found encephalopathy and seizure activity so the patient was considered to perhaps have autoimmune encephalitis. A limbic panel, antinuclear antibody, thyroid function tests, antimicrosomal antibody and antithyroglobulin were examined. The limbic encephalitis panel tests were negative both in serum and CSF.

Then pulse-steroid treatment was administered for 3 days, and was not observed to regulate the patient's electrical seizure activity, then was begun on ketamine infusion.

The patient's electrographic seizure activity sometimes began in the left hemisphere and was secondarily generalized, then immediately seizure activity began in the right hemisphere and was secondarily generalized. Due to electrical seizure activity migrating between hemispheres and laboratory and imaging tests to explain the etiology returning to normal, the patient was evaluated as FIRES and the decision was made to begin other immunotherapies. Intravenous immunoglobulin (IVIG) of 0.5 g/kg/dose was planned for 4 days administration and begun.

On the 9th day of admission, with no change in the patient's clinical status, the patient was given 0.4 g/kg IVIG infusion for 12 h and then plasmapheresis administration began.

On the 12th day of admission, after the 3rd session of plasmapheresis, EEG found electrographic seizure activity had stopped with suppression numbers and duration clearly reduced and bursts ameliorated. For 5 days consecutively and 4 days every other day, 9 sessions of plasmapheresis were administered.

After plasmapheresis treatment ended, EEG showed no electrical seizure activity and the patient had anticonvulsant infusion medications reduced. On the 40th day in intensive care, the patient had only mild slurred speech and ataxia and was discharged home with epilepsy using antiseizure drugs (Table 1).

## 3. Discussion

FIRES was first described by van Baalen in 2010. With the introduction of this disease definition, initial fever with lack of CSF findings indicating encephalitis and normal brain imaging are required [3].

For etiology, the focus is that an immunologic factor may play a role or there may be ion channel defects; however, there is no recommendation for treatment. Most of these patients had immunotherapy trialed (dexamethasone and IVIG), but only 1 patient had plasmapheresis and anti-IL2 receptor antibodies used, apart from these treatments [3].

Plasmapheresis is a method used for refractory status epilepticus (RSE) or super refractory status epilepticus (SRSE) in pediatric age groups. A study screening RSE or SRSE patients which administered plasmapheresis identified the etiology as FIRES in 27 of these 38 patients. A study by Zeiler generally administered plasmapheresis 5 times; however, they stated the administration regimes or administration with other immunosuppressives were unknown [7].

However, in the case described here, the patient was initially administered pulse-steroid treatment for 4 days, but IVIG was administered when seizures did not reduce. With the continuation of seizures in spite of thiopental and ketamine infusion, plasmapheresis with 1.5 times total plasma volume of fresh frozen plasma was administered every day in 5 sessions and then IVIG infusion was administered on 12 h before plasmapheresis.

EEG taken on the 3rd day of plasmapheresis observed seizure activity had reduced by a clear degree and from the 5th day, IVIG one day and plasmapheresis the next were used to complete 9 sessions. EEG taken after the 9th session observed only background rhythm slowing.

When the literature is screened, only 3 of 27 patients with FIRES treated with plasmapheresis saw any benefit and apart from these, one patient was observed to begin seizures again after plasmapheresis [7].

Our patient benefitted from plasmapheresis and this is considered to possibly be due to administering it with IVIG treatment. However, our patient had prolonged seizures again around one month after the completion of the combined plasmapheresis/IVIG treatment protocol. These seizures were treated quickly with midazolam infusion and IVIG (1 g/kg/day, two days).

Plasmapheresis and IVIG combined treatment is administered especially for acute immunoglobulin-associated organ rejection treatment, severe Guillain-Barré syndrome, and chorea in a pediatric-onset systemic lupus erythematosus patients and good outcomes were obtained [8–10]. In FIRES cases, the acute onset after fever infection leads to consideration that it is an immunoglobulin-mediated event. In our study, the success in seizure reduction with both plasmapheresis and IVIG concurrently may be related to a dramatic reduction in serum immunoglobulins available to affect cortical excitability. We think this patient benefited from plasmapheresis and IVIG combined treatment. However, there is a need for more studies related to this.

There are publications reporting that the combined use of plasmapheresis and IVIG may be beneficial in the outcome of some immune-mediated diseases with a synergistic effect [9]. The purpose of this method, if there are autoantibodies in the plasma, is to bind these antibodies with IVIG and remove them by plasmapheresis. In patients considered to have FIRES, we think plasmapheresis and IVIG treatment could be attempted together in the early period.

## CRediT authorship contribution statement

**Yasemin Coban:** Conceptualization, Methodology, Software. **Yilmaz Akbas:** Conceptualization, Methodology, Software. **Yasemin Coban:** Data curation, Writing - original draft. **Gokcen Oz Tuncer:** Visualization, Investigation. **Sultan Aydin Koker:** Software, Validation. **Yasemin Coban:** Writing – review & editing.

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