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# Combination of intravenous immunoglobulin and steroid pulse therapy improves outcomes of febrile refractory status epilepticus

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ABSTRACT

*Background:* Febrile infections are an important cause of paediatric refractory status epilepticus, and immune-mediated mechanisms and inflammatory processes have been associated with neurological manifestations in such patients. The aim of this study was to investigate the effects of immunotherapy as adjuvant treatment for febrile refractory status epilepticus.

*Methods:* We retrospectively reviewed cases of febrile refractory status epilepticus in a paediatric intensive care unit between January 2000 and December 2013 and analysed their clinical characteristics. Patients positive for antineuronal antibodies against surface antigens were excluded.

*Results:* We enrolled 63 patients (38 boys), aged 1–18 years, all of whom received multiple antiepileptic drugs. Twenty-nine (46%) of the patients received intravenous immunoglobulin alone, 16 (25.4%) received a combination of intravenous immunoglobulin and methylprednisolone pulse therapy, and 18 (28.6%) did not receive immunotherapy treatment. Overall, 12 (19%) patients died within 1 month. After 6 months, 12 (20%) patients had good neurological outcomes, including two who returned to baseline and 13 (29.5%) who had favourable seizure outcomes. We compared the outcomes of the different treatments, and found that a combination of intravenous immunoglobulin and methylprednisolone pulse therapy had the best neurological and seizure outcomes at 6 months compared to intravenous immunoglobulin alone and no immunotherapy.

*Conclusions:* Our observational study showed that a combination of intravenous immunoglobulin and methylprednisolone pulse therapy as adjuvant treatment for febrile refractory status epilepticus was associated with better neurological and seizure outcomes. Further prospective studies are needed to confirm these findings.

## 1. Introduction

Refractory status epilepticus is a state of persistent seizures lasting more than 2 h despite optimal treatment with antiepileptic drugs (Shorvon and Ferlisi, 2011). It is a neurological emergency which can cause severe neurological sequelae, and even death. There are various causes of paediatric refractory status epilepticus, some of which are febrile related (Mizuguchi et al., 2007; Lin et al., 2009, 2010). Immune-mediated mechanisms and inflammatory processes may play a role in determining or contributing to neurological manifestations in such patients (Mizuguchi et al., 2007; Nabbout et al., 2011). Nevertheless, it is difficult to differentiate the aetiology in the first 1–2 days of refractory status epilepticus.

Regarding the pathogenesis, increasing evidence suggests that acute brain inflammation caused by fever and status epilepticus can lead to persistent brain excitability, which may then contribute to refractory status epilepticus (Mizuguchi et al., 2007; Vezzani et al., 2009). Subsequently, persistent refractory status epilepticus-induced chronic brain

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inflammation may contribute to further epileptogenesis (Vezzani et al., 2013). In addition, experimental evidence has shown that brain inflammation is caused by the activation of interleukin-1 receptor/toll-like receptor pathways (Vezzani et al., 2009; Vezzani et al., 2013). Preliminary clinical observations have also suggested a likely vicious cycle involving inflammation and seizure activity in status epilepticus, the so called "acute encephalopathy with inflammation-mediated status epilepticus" (Nabbout et al., 2011). Furthermore, encephalitis has been reported to be accompanied by different levels of inflammatory cytokines in the brain (Mizuguchi et al., 2007). Therefore, modulating immune disturbance and inflammatory processes may be important in managing febrile refractory status epilepticus.

Accumulating evidence supports the combined use of anti-inflammatory and antiepileptic drugs to reduce brain inflammation, which may then decrease seizure burden in refractory status epilepticus and subsequent epileptogenesis (Janigro et al., 2013; Holzer et al., 2014). However, studies on the use of intravenous immunoglobulin (IVIG) and methylprednisolone pulse therapy as adjuvant treatment of febrile status epilepticus are lacking, and only a few case reports have been published (Holzer et al., 2014; Gall et al., 2013; Khawaja et al., 2015; Kramer et al., 2005; Okanishi et al., 2007; Saito et al., 2007; Sakuma et al., 2010; Specchio et al., 2010). The early and aggressive application of immunotherapy in such patients may facilitate a faster recovery (Gall et al., 2013; Khawaja et al., 2015), however it remains unclear whether or not a combination of IVIG and methylprednisolone pulse therapy is superior to IVIG alone. The aim of this retrospective study was to investigate the effects of different immunotherapies for the management of children with febrile refractory status epilepticus in the acute stage. In order to include diverse aetiologies, we focused on previously healthy children who presented with febrile refractory status epilepticus, and excluded those positive for antineuronal antibodies against surface antigens which are well-known to be immunotherapy-responsive.

## 2. Material and methods

Refractory status epilepticus is defined as seizures lasting more than 2 h despite optimal treatment, including initial therapy with benzodiazepine followed by intravenous antiepileptic drugs such as phenytoin, phenobarbital, valproate or levetiracetam (Shorvon and Ferlisi, 2011; Lin et al., 2009, 2010). Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 h or more after the initiation of anaesthetic therapy, including cases where status epilepticus recurs with the reduction or withdrawal of anaesthesia[1]. Febrile refractory status is defined as fever and refractory status epilepticus. Encephalitis is defined as the presence of encephalopathy plus at least two of the following: 1) fever; 2) cerebrospinal fluid evidence of neuroinflammation; 3) abnormal electroencephalography findings; and 4) abnormal radiologic evidence (Lin et al., 2009, 2010).

We retrospectively reviewed paediatric patients admitted to the paediatric intensive care unit at our institution with a diagnosis of refractory status epilepticus between January 2000 and December 2013. The inclusion criteria for case ascertainment were previously healthy children and a diagnosis of febrile refractory status epilepticus. We excluded patients aged over 18 years, those without fever, and those with bacterial meningitis, a history of progressive neurological disorders and prior seizures or neurological insults, electrolyte imbalance, and hypoglycaemia. We also excluded patients positive for antineuronal antibodies against surface antigens (antibody to N-methyl-D-aspartate receptor, antibody to complex of voltage-gated potassium channels), and those who received other immunotherapies (such as methylprednisolone alone, a combination of IVIG and dexamethasone, rituximab and plasmapheresis).

A regular immunomodulation protocol for febrile refractory status epilepticus was established in our hospital in 2004. Between 2004 and 2009, IVIG was added to the patients' antiepileptic drugs within 48 h after hospitalization for febrile refractory status epilepticus, with a dosage of 400 mg/kg every day for 5 days (total 2 g/kg). After 2009, a combination of IVIG and methylprednisolone pulse therapy was used within 48 h after hospitalization. Methylprednisolone was given as high-dose pulse therapy (30 mg/kg/day with a maximum of 1000 mg/day) for the initial 3 days, followed by a maintenance dose of 1 mg/kg every 6 h for 4 days, and then tapered down in 1 week.

The clinical features, treatment and outcomes were recorded. We then divided the patients into three groups: those who received a combination of IVIG and methylprednisolone pulse therapy, those who received IVIG alone, and those who did not receive immunotherapy. The primary outcomes were neurological and seizure outcomes after 6 months of evaluation. The secondary outcome was the hospital course, including paediatric intensive care unit stay, duration of hospitalization, and 1-month mortality rate. The neurological and seizure outcomes were determined at 6 months after the first episode of status epilepticus. Neurological outcomes were evaluated according to the Pediatric Cerebral Performance Score. We defined a Pediatric Cerebral Performance Score of less than or equal to 2 as a good outcome, and greater than or equal to 3 as a bad outcome (Topjian et al., 2013). All of the patients were treated with antiepileptic drugs at discharge. Seizure outcomes were categorized into two groups after 6 months of follow-up: (1) intractable epilepsy, defined as more than two seizures per month in patients taking two or more antiepileptic drugs; and (2) favourable outcome, defined as being either seizure free or having fewer than two seizures per month after treatment (Lin et al., 2010). The hospital's Institutional Review Board approved this study (104-2573B, 201701354B0).

### 2.1. Statistical analysis

The primary and secondary outcomes were analyzed and compared between those who received a combination of IVIG and methylprednisolone pulse therapy, those who received IVIG alone, and those who did not receive immunotherapy. All statistical analyses were performed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation (SD) or percentage. The Mann-Whitney *U* test and Kruskal-Wallis test were used for continuous variables, and the chi-square or Fisher's exact test was used for categorical variables. A $p$ value of less than 0.05 was considered to be statistically significant. All statistical tests were two-tailed.

## 3. Results

In total, 68 previously healthy children diagnosed with febrile refractory status epilepticus were admitted to our paediatric intensive care unit during the study period. Of these 68 patients, 63 were included in this study, including 25 girls (39.7%) and 38 boys (60.3%), with a mean ( ± SD) age at presentation of 8.88 ± 5.11 years (range 2 months to 18 years). Five of the 68 patients were excluded, including two who received methylprednisolone pulse therapy alone, two who received a combination of IVIG and dexamethasone, and one with an uncertain history of immunotherapy (Fig. 1). The mean time of prior febrile infections in our study was 3.06 + / − 2.0 days (range 1–7 days). In the combination of IVIG and methylprednisolone pulse therapy group (n = 16), the initial seizure types were generalized tonic-clonic seizures (5/16; 31.2%), and focal and primary focal with secondary generalized seizures (11/16; 68.8%). Six of these 16 children (37.5%) developed super-refractory status epilepticus which required high-dose suppression coma therapy. In the IVIG group (n = 29), the initial seizure types were generalized tonic-clonic seizures (6/29; 20.7%), and focal and primary focal with secondary generalized seizures (23/29; 79.3%). Fourteen of these 29 children (48.2%) developed super-refractory status epilepticus. In the group who did not receive immunotherapy (n = 18), the initial seizure types were generalized tonic-