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The short-term and long-term outcome of febrile infection-related epilepsy syndrome in children

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ABSTRACT

Background: The febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy which developed the refractory status epilepticus following or during a nonspecific febrile illness. To analyze the short-term and long-term outcome of FIRES in the children, we retrospectively analyzed the related data.
Methods: The motor outcome was evaluated by modified Rankin scale (mRS). Poor motor outcome was defined as a mRS score of 4 or higher at discharge. Significant motor decline was defined as the mRS difference more than 2 before hospital admission and at discharge.
Results: We totally enrolled 25 patients for analysis. Four patients were expired during hospitalization, and one patient was lost to follow-up after discharge. Therefore, a total 20 patients were finally analyzed. The age of disease onset ranged from 1.6 to 17.2 years (mean: 9.6 ± 4.4 years). Newly acquired epilepsy and cognitive deficit occurred in 100% and 61%, respectively. The duration of the anesthetic agents ranged from 7 to 149 days (mean: 34.2 ± 36.1 days). The duration of anesthetic agent usage ($p = 0.011$), refractory epilepsy ($p = 0.003$), and the use of ketogenic diet ($p = 0.004$) were significantly associated with the poor long-term motor outcome, and the number of anesthetic agents tended to be associated with the poor long-term motor outcome ($p = 0.050$). In-hospital mortality was 16%. Significant functional decline at discharge occurred in 100%. However, there was improvement in long-term follow-up.
Conclusion: The outcome of FIRES is poor with significant mortality and morbidities. Refractory epilepsy with cognitive deficit in survived cases is common, but improvement is possible.

1. Introduction

The febrile infection-related epilepsy syndrome (FIRES) is a catastrophic epileptic encephalopathy which developed the refractory status epilepticus following or during a nonspecific febrile illness without evidence of CNS infection in previously healthy children.

The first cases of FIRES were reported by Awaya and Fukuyama in 1986 [1]. Since then, various case series were reported for refractory status epilepsy related to encephalitis-like diseases of an unknown etiology. In the past studies, the FIRES has been variably called acute encephalopathy with inflammation-mediated status epilepticus devastating epilepsy in school-aged children (DESC) [2], acute encephalitis with refractory, repetitive partial seizures (AERRPS) [3], idiopathic hemiconvulsion-hemiplegia and epilepsy syndrome (IHHE), fever-induced refractory epileptic encephalopathy in school-aged children, new-onset refractory status epilepticus (NORSE) [4], severe refractory status epilepticus owing to presumed encephalitis [5], and FIRES [6]. However, the new definition defined FIRES as a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 h prior to the onset of refractory status epilepticus, with or without fever at onset of status epilepticus [7].

The FIRES is difficult to be treated with antiepileptic drugs (AEDs) and often requires deep sedation with anesthetic drugs for the control of seizures. The etiology of FIRES remains unknown. The infection, immune-mediated [8], inflammation-mediated mechanisms [9] or genetic predisposition have been hypothesized. However, patients with FIRES usually show the absence of any identified infectious agents, and the cerebrospinal fluid (CSF) only reveals mild inflammatory changes without evidence of an infection or a specific autoimmune antibody. No known genetic mutation was also noted, including Sodium Voltage-Gated Channel Alpha Subunit 1 (SCN1A), Protocadherin19 (PCDH19), and DNA polymerase subunit gamma (POLG1) [10]. The elevated autoimmune antibodies such as antivoltage-gated potassium channel (anti-VGKC), antiglutamic acid decarboxylase (anti-GAD), and antiglutamate receptor 3 (anti-

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GluR3) antibodies have been hypothesized to be the pathogenic mechanisms of FIRES in recent reports [11,12], but the potential pathogenic role in FIRES is doubtful [13].

The epileptiform activity of electroencephalography (EEG) in FIRES may be focal, multifocal, or generalized, and the brain Magnetic Resonance Imaging (MRI) usually reveals hyperintensities in some patients, predominantly in the temporal regions, but also in the insula and the basal ganglia. The seizures in FIRES are always resistant to multiple AEDs, anesthetic agents, ketogenic diet, or immunosuppressive agents. After remission, the chronic refractory epilepsy, the high mortality rate, cognitive function decline, or severe neurological sequelae were reported in most cases [12]. The mortality rate ranged from 11% to 30% [6,14]. The mental retardation was noted in 66%–100% of survivors in previous studies [2,12,14].

Although there were several reports describing the clinical manifestations and management of FIRES, the studies related to short-term and long-term outcome remained limited, especially in children. Therefore, in the present study, we described the short-term and long-term motor and cognitive outcome of FIRES in the children in Taiwan. We analyzed the potential risk factors correlated with the prognosis in our study. To our best knowledge, this is the first study describing the short-term motor outcome and long-term motor outcome of FIRES in children.

2. Methods and subjects

We performed a retrospective study in previously healthy children, who presented with refractory status epilepticus following or during a nonspecific febrile illness admitted to National Taiwan University Hospital during April 2001 and June 2017. The medical information, including the patient's past history, family histories, clinical features, diagnostic findings, therapeutic interventions, virologic and immunologic investigations, the neuropsychological assessments, and the management of the chronic epilepsy, were collected. The Institutional Review Board of National Taiwan University Hospital had approved this study.

The diagnosis of FIRES was made in a previously well child with the following: (1) acute onset of a refractory status epilepticus requiring intensive care treatment following or during a nonspecific febrile illness or encephalitis-like illness; (2) lacking evidence of infectious pathogen in CSF. The children with previously reported seizures, febrile seizures, known neurologic diseases, acute disseminated encephalomyelitis, structural brain abnormality, metabolic disorders, genetic disorders, subdural hemorrhage, or identification of an infectious pathogen in CSF were excluded from the present study. The CSF and blood tests were performed in all patients for infectious pathogens. The autoantibodies tests, brain Computed tomography (CT), or MRI were variably performed. The treatment protocol was standardized for the refractory status epilepticus. The intravenous AEDs such as phenytoin, phenobarbital, valproate acid, or the levetiracetam were used to the persistent seizures although the benzodiazepines were given. The patients had persistent seizure activity despite the two initial doses of benzodiazepine, and a second-line antiseizure drug, a continuous infusion of midazolam was used. The anesthetic drugs such as propofol or thiopental were administered if midazolam was ineffective, and the ketamine was added in those patients with persistent convulsive seizures or side effects of previous anesthetic agents. Serial electroencephalography (EEG) monitoring was applied in all the patients and the pediatric neurologist adjusted the AEDs according to the EEG results. The anesthetic medications would be tapered gradually after seizures were brought under control for 24 h.

The functional outcome was evaluated by modified Rankin scale (mRS), and it is a scale for measuring the degree of disability or dependence in the daily activities of people. The mRS was determined at admission, discharge, less than 6 months, and over 1 year after discharge by the neurologists. The mRS scores run from 0 to 6, running from perfect health without symptoms to death: no symptoms (score 0), no significant disability — able to carry out all usual duties and activities (score 1), slight disability — unable to carry out all previous activities but able to look after own affairs without assistance (score 2), moderate disability — requiring some help but able to walk without assistance (score 3), moderately severe disability — unable to walk without assistance and unable to attend to own bodily needs without assistance (score 4), severe disability — bedridden, incontinent, and requiring constant nursing care and attention (score 5), and dead (score 6). Poor motor outcome was defined as a mRS score of 4 or higher at discharge. Significant motor decline was defined as the mRS difference more than 2 before hospital admission and at discharge. The cognition measured by the neuropsychological assessments and the chats recorded by the neurologist are evaluated. The cognition was stratified into two groups for statistical analyses: (1) normal (with or without learning disabilities); (2) mild, moderate, severe intellectual disability, and vegetative state. After the discharged, the oral antiepileptic medicines for seizure control and the physical and the occupational therapy were prescribed, and the duration of the outpatient department for follow-up ranged from three months to 6 months. The neuropsychological assessments were performed after the acute phase in most patients, and the physical therapists and the pediatric neurologists assessed the motor and cognitive level.

The mixed model test and Fisher's exact test were used for the statistical analyses. Mixed effect models were used to analyze the effect of potential predictors to mRS score in long-term motor outcome. We divided the patients into two groups for the analysis of the potential predicting factors for mRS score. The Fisher's exact test was used to access the relationship of each category of risk factor between groups. Univariate analysis was done for the correlations of the mRS score and cognitive level at follow-up with the following variables: age at disease onset, sex, duration of hospitalization, number of AEDs during the hospitalization and discharge, duration and the number of anesthetic agents, CSF protein, CSF White Blood Cell (WBC) counts, and the presence of atrophy or increased signal on MRI or CT during the acute phase. The statistical analyses were performed using SPSS statistics, version 25, Software. The statistical significance was defined as a p-value <0.050.

3. Results

3.1. General characteristics

A total of 25 patients (11 females, 14 males) were enrolled. One patient was lost to follow-up after discharge. Four patients (16%) were expired during the acute phase in hospitalization. The cause of death included sepsis in two, arrhythmia in one, and suspected propofol infusion syndrome in one. The other 20 patients were followed up for 9 months to 15 years after the initial presentations. We used the mixed model test and Fisher's exact test for univariate analysis of those 20 patients and to find out the potential predictors to the functional and cognitive outcome (Table 1). The female to male ratio was 1:1.5 in our study. The onset age of FIRES was 9.6 ± 4.4 years (range: 1.6–17.2 years). We included one patient with gross motor delay without past history of epilepsy. All other patients were healthy before FIRES without history of seizures or epilepsy. All patients presented with seizures during or following the febrile illness, with an interval of 1–7 days after the fever (mean: 3.7 ± 1.3 days, median: 4 days). The predisposing factors included upper respiratory tract infection ($n = 14$, 70%), fever with unknown focus ($n = 4$, 20%), and Gastrointestinal (GI) tract symptoms ($n = 2$, 10%). All patients had consciousness change ($n = 20$, 100%). The presenting symptoms included seizures in 20 (100%), headache in 7 (35%), general weakness in 3 (15%), lethargy in 3 (15%), and personality change in 2 (10%). The initial seizures were generalized tonic–clonic seizures in 15 (75%) and focal seizures with impaired awareness in 5 (25%).

Table 1
Clinical features and the discharge and long-term functional outcome in FIRES. Expressed in number (percentage) and mean ± SD.

Characteristics	Total (n = 20)	Mild (mRS 0–3)	Moderate (mRS 4–6)	Discharge outcome, p	Long-term outcome, p*
Gender (female/male)	8(40.0)/12(60.0)	4(50.0)/4(50.0)	4(33.3)/8(66.7)	0.504	0.304
Age (years)	9.6 ± 4.4	8.5 ± 4.7	10.3 ± 4.3	0.199	0.934
≦9.5 years old	10(50.0)	5(50.0)	5(50.0)		
>9.5 years old	10(50.0)	3(30.0)	7(70.0)		
Predisposing factor					
Fever, focus unknown	4(20.0)	2(50.0)	2(50.0)	0.525	0.923
URI	14(70.0)	6(42.9)	8(57.1)	0.607	0.597
GI symptoms	2(10.0)	0(0.0)	2(100.0)	0.188	0.615
Neurological sign					
Headache	7(35.0)	2(28.6)	5(71.4)	0.19	0.222
Weakness	3(15.0)	2(66.7)	1(33.3)	0.382	0.923
Consciousness change	20(100.0)	8(40.0)	12(60.0)	N	N
Personality change	2(10.0)	0(0.0)	2(100.0)	0.453	0.691
Lethargy	3(15.0)	2(66.7)	1(33.3)	0.231	0.691
Initial seizure type					
Focal with consciousness impairment	5(25.0)	1(20.0)	4(80.0)	0.349	0.342
GTC	15(75.0)	7(46.7)	8(53.3)	0.349	0.342
Brain MRI (N = 20)					
Negative finding	4(20.0)	3(75.0)	1(25.0)	0.435	0.308
Abnormal finding	16(80.0)	5(31.3)	11(68.8)		
Brain CT (N = 16)					
Negative finding	12(75.0)	5(41.7)	7(58.3)	0.594	N
Abnormal finding	4(25.0)	2(50.0)	2(50.0)		
EEG (interictal) (N = 19)					
Generalized epileptiform discharge	1(5.3)	0(0.0)	1(100.0)	0.636	N
Focal seizure with secondarily generalized	6(31.6)	2(33.3)	4(66.7)	0.490	0.275
Multifocal epileptiform discharge	15(78.9)	5(33.3)	10(66.7)	0.369	0.146
Diffuse cerebral dysfunction	19(100.0)	8(42.1)	11(57.9)	N	N

* p value analysis by mixed effect model test.

3.2. EEG, neuroimaging, and laboratory findings

All patients had ictal and electrographic seizures on EEG. The interictal EEG showing multifocal epileptic discharges was recorded in 15 (78.9%), focal epileptic discharges with secondarily generalized epileptiform discharges in 6 (31.6%), and generalized epileptiform discharges in one (5.3%). All patients had diffuse cerebral dysfunction in EEG, including mild diffuse cerebral dysfunction in one (5.3%), moderate diffuse cerebral dysfunction in 5 (26.3%), and severe diffuse cerebral dysfunction in 16 (84.2%).

The neuroimages were performed in all patients at disease onset. Brain CT were normal in 12 of 16 patients (75%), and 4 patients (25%) had abnormal brain CT finding, including two (50%) with brain edema and two (50%) with suspected diffuse white matter lesions. A total of 20 patients had MRI examinations, including four (20%) with normal MRI. Of 16 (80%) patients with abnormal brain MRI findings, the major findings included focal or multiple focal temporal lobe hypersignal lesions in 10 (50%), multiple focal extratemporal hypersignal lesions in eight (40%), single focal extratemporal hypersignal change in four (20%), brain edema in one (5%), brain atrophy in two (10%), diffuse white matter in two (10%), subdural fluid collection in one (5%), and leptomeningeal enhancement in one (5%). No one had cerebral hemorrhage.

Pleocytosis in CSF was noted in 7 (35%). Cerebrospinal fluid cell count varied from 0 to 112 cells/μl (mean: 12.6 ± 27.4 cells/μl). Cerebrospinal fluid protein varied from 2 to 181.2 mg/dl (mean: 43.8 ± 40.1 mg/dl), and the results were normal in 6 (30%) patients.

3.3. Treatment

All patients were admitted to the intensive care units for treatment and ventilator support. The seizures in two patients were controlled by AEDs. The anesthetic agents were given in 18 patients. The anesthetic agents included midazolam (n = 18), propofol (n = 7), thiopental (n = 7), ketamine (n = 4), cytosol (n = 1), lidocaine (n = 1), and fentanyl (n = 1). The duration of anesthetic agents ranged from 7 to 149 days (mean: 34.2 ± 36.1 days). The mean number of anesthetic agents for each patient was 2.2 ± 0.9 (range: 1–4). Multiple AEDs (3–10 drugs, mean: 5.4 ± 2) were given during hospitalization. At discharge, the average number of AEDs was 3.2 ± 1.7 (range: 1–7). Five (25%) patients received steroid pulse therapy, and 12 (60%) patients received Intravenous Immunoglobulin (IVIG) treatment. Adrenocorticotropic Hormone (ACTH) treatment was given in one patient and four patients received the ketogenic diet.

3.4. Prognosis

The duration of hospitalization ranged from 14 to 208 days (mean: 75 ± 56.2 days). A total of 20 patients were followed up for 9 months up to 15 years after the initial presentation.

All patients had subsequent epilepsy after discharge. A total of 17 (85%) patients had refractory epilepsy, and 3 (15%) patients were seizure-free under AED control. A total of 18 (90%) patients were evaluated for the outcome of cognition (Table 2), which showed mild intellectual disability in 7 (38.9%), moderate intellectual disability in two (11.1%), and severe intellectual disability in two (11.1%). Seven (38.9%) patients had normal cognition. The other neurological sequelae in the normal cognition group included attention deficit hyperactivity disorder (ADHD) in one (5.6%), emotion liability in one (5.6%), and poor memory in two (11.1%).

Significant functional decline occurred in 100% at discharge. Vegetative state was noted in one. The mRS in short-term outcome (less than 6 months) revealed no disability in 15%, mild disability (score 1–3) in 50%, and moderate disability (score 4–6) in 35%. In contrast, the long-term outcome revealed no disability in 27.8%, mild disability (score 1–3) in 44.4%, and moderate disability (score 4–6) in 27.8%, indicating the improvement in long-term follow-up (Fig. 1).

We used the mixed model test (Fig. 2) and Fisher's exact test for univariate analysis of the potential predictors to the functional outcome. We divided the patients into two groups for the correlation of the potential predictors with mRS scores. There was no significant difference in outcome based on the age, sex, the number of AED during discharge, the duration of hospitalization, initial neuroimage findings,

Table 2
Treatment and the outcome at discharge and the long-term motor outcome of FIRES. Expressed in number (percentage) and mean ± SD.

Characteristics	Total N = 20	Mild disability (mRS 0–3) N = 8	Moderate disability (mRS 4–6) N = 12	Outcome at discharge, p value	Long-term outcome (N = 20), p value*
Immunotherapy					
Steroid pulse	5(25.0)	2(40.0)	3(60.0)	0.651	0.637
IVIG	12(60.0)	6(50.0)	6(50.0)	0.19	0.212
Ketogenic diet	4(20.0)	1(25.0)	3(75.0)	0.475	0.004
ACTH	1(4.0)	1(100.0)	0	0.32	0.099
Hospital stay length (days)	75 ± 56.2 (range:14–208)			0.125	0.099
≦41 days	10(50.0)	4(40.0)	6(60.0)		
>41 days	10(50.0)	2(20.0)	8(80.0)		
AED during hospitalization	5.4 ± 2.0 (range: 3–10)			0.077	0.142
≦3 number of AED	7(35.0)	5(71.4)	2(28.6)		
>3 number of AED	13(65.0)	3(23.1)	10(76.9)		
Number of anesthetic agents (N = 18)	2.2 ± 0.9 (range: 1–4)			0.119	0.050
≦2 number	13(72.2)	5(38.5)	8(61.5)		
>2 number	5(27.8)	1(20.0)	4(80.0)		
Duration of anesthetic agents (N = 18)	34.2 ± 36.1 (range: 7–149)			0.119	0.011
≦21 days	13(72.2)	5(38.5)	8(61.5)		
>21 days	5(27.8)	1(20.0)	4(80.0)		
Outcome (N = 20)					
Subsequent epilepsy	20(100.0)	7(35.0)	13(65.0)	N	N
Seizure-free	3(15.0)	2(66.7)	1(33.3)	0.376	0.066
AED during discharge	3.2 ± 1.7			0.058	0.728
≦3number of AED	11(55.0)	4(36.6)	7(63.6)	0.108	0.381
>3 number of AED	9(45.0)	5(55.6)	4(44.4)		
Refractory epilepsy	17(85.0)	5(29.4)	12(70.6)	0.049	0.003
Cognition (N = 18)					
Mild MR	7(38.9)	1(14.3)	6(85.7)	0.157	0.600
Moderate MR	2(11.1)	1(50.0)	1(50.0)	0.556	0.431
Severe MR	2(11.1)	0	2(100.0)	0.294	0.301

Note: MR: mental retardation;
* p value analysis by mixed effect model test.

CSF WBC counts, CSF protein, and the use of immunotherapy (IVIG and steroid pulse therapy). Although not significant, the number of AED during hospitalization ($p = 0.077$) tended to be associated with the motor outcome (Table 2). In contrast, the duration of anesthetic agent usage ($p = 0.011$), the refractory epilepsy ($p = 0.003$), and the use of ketogenic diet ($p = 0.004$) were significantly associated with the poor motor outcome (Fig. 2). Longer duration of anesthetic agent usage (>21 days) had a mRS score of 1.56 higher than those with shorter duration of usage (≤21 days). The mRS score of ketogenic diet group was also 2.19 higher than that without the use of ketogenic diet. The mRS score of more anesthetic agent groups (>2) also had 1.39 higher than the other group (≦2) ($p = 0.050$). Therefore, the longer duration of anesthetic agent usage, the refractory epilepsy, and the use of ketogenic diet were significantly associated with the higher mRS score, indicating poor motor outcome. The number of anesthetic agents ($p = 0.050$) also tended to be associated with higher mRS score, indicating poor motor outcome.

For analysis of predictors for cognition outcome, the cognition was stratified into two groups for statistical analyses: (1) normal (with or without learning disabilities); (2) mild, moderate, severe intellectual

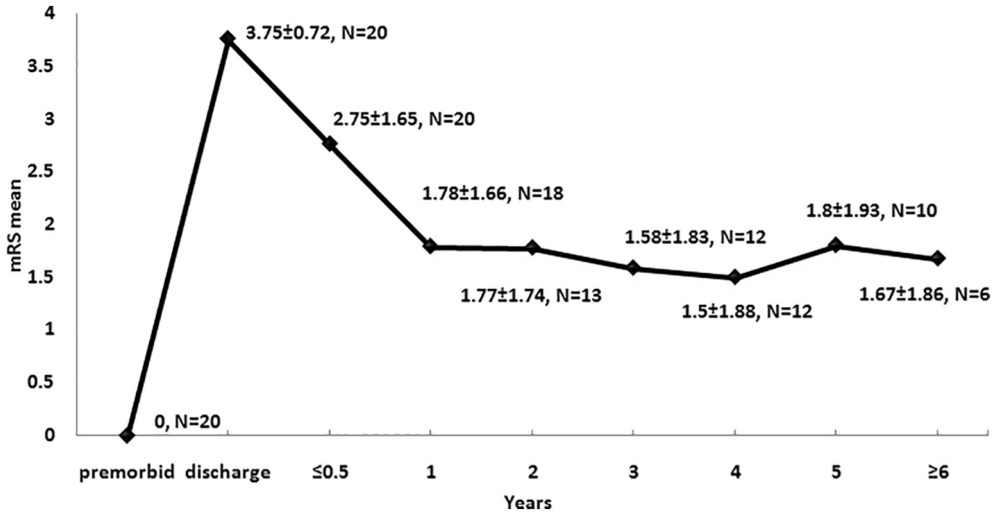

Fig. 1. Serial changes of mRS in follow-up showing the improvement of mRS in follow-up.

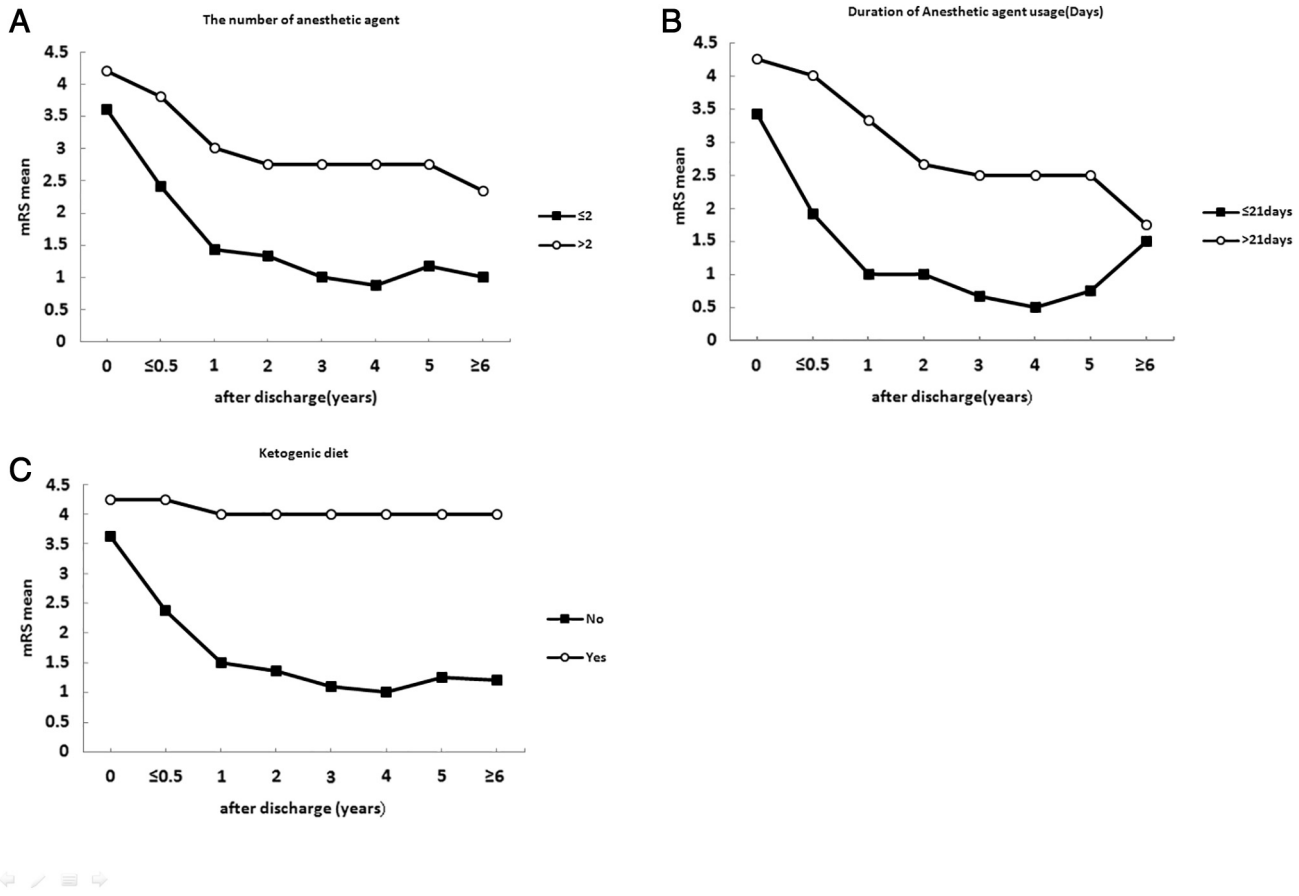

Fig. 2. We used the mixed model tests to analyze the potential factors associated with the mRS score. The X axis showed the duration of follow-up, and the Y axis showed the mRS score change. (A) showing the results in another two groups, ≤2 and >2 of number of anesthetic agents ($p = 0.050$). (B) showing the results of two groups, ≤21 days and >21 days of duration of anesthetic agent usage ($p = 0.011$); (C) showing the results of two groups, with and without ketogenic diet ($p = 0.004$).

disability, and vegetative state. We found that the number of anesthetic agents, age, sex, the number of AED at discharge and hospitalization, CSF protein level, and neuroimage findings were not correlated with poor cognition outcome (Table 3). However, the duration of anesthetic agents ($p = 0.010$), the duration of hospitalization ($p = 0.025$), and cognition at discharge ($p = 0.043$) were associated with the poor long-term cognition outcome.

4. Discussion

The FIRES is a catastrophic disease by intractable recurrent or prolonged seizures with unknown etiology. In our study, the age at onset of FIRES was in preschool or school years with male predominance, and upper respiratory tract infection was the most common preceding factor as previous studies [6,15,16]. However, the infectious pathogens and autoimmune investigation in our patients were all negative. Although the mortality rate in FIRES can be as high as 11%–30% and the intellectual disability was in 66%–100% of survivors in the past studies, the mortality rate in our series was 16%. Only 61% had intellectual disability, and mild intellectual disability was found in 39%. It indicated a better prognosis in the present study.

The intractable epilepsy in FIRES can lead to a decline of cognitive function and memory. The pervasive excitatory synaptic activity accompanying seizure may lead to neuronal injury and death with abnormal neuronal sprouting and thereby interfere with the normal pruning and complex rearrangement of neuronal connectivity that characterizes the developing nervous system. However, better seizure control during the acute stage of FIRES as in the present study may decrease the neuronal damage leading to lower rate of intellectual disability and better prognosis.

Poor cognitive outcome had been shown to be associated with longer duration of anesthesia in patients with FIRES as in the present study [12,17]. In one previous study, a longer period of therapeutically induced burst–suppression coma was also associated with a poorer cognitive level at long-term follow-up [12], similar to our study. Previous studies suggested that pentobarbital and other barbiturates may reduce the cerebral blood flow in animals and humans [18,19] and cerebral metabolic rate. These blood flow changes may induce insult to the vulnerable hippocampus [20]. Therefore, the longer duration of anesthesia and the use of multiple AEDs might be associated with the poorer cognition and motor outcome. We considered that a longer disease process needing longer burst–suppression coma state for therapy may reflect a more severe condition, leading to worse outcome.

The use of ketogenic diet in the acute phase was also associated with poor motor outcome in the present study. In previous retrospective studies, some described that the early ketogenic diet treatment was an alternative or adjunct therapeutic option for seizure control [21] and may improve cognitive outcome in FIRES [12,16,22,23]. The early ketogenic diet was also shown to decrease the severity of status epilepticus and mortality rate [21], and therefore, had better prognosis. However, in our patients, we started the ketogenic diet at the later stage of status epilepticus, and they still had refractory status epilepsy when ketogenic diet was used. We considered that these patients might have more severe condition leading to worse motor outcome.

Some patients in our series also used immunomodulating therapies in acute phase of FIRES, but the response to the treatment was poor, similar to previous studies [15,16]. Although immunomodulating

Table 3
The long-term cognition outcome of FIRES. Expressed in number (percentage).

Characteristics	Total N = 18	Good cognition N = 7	Poor cognition N = 11	p value
Duration of hospitalization				0.025
≤41 days	9	6(85.7)	3(27.3)	
>41 days	9	1(14.3)	8(72.7)	
Duration of anesthetic agent				0.010
≤21 days	11	7(100.0)	4(36.4)	
>21 days	7	0(0.0)	7(63.6)	
Number of anesthetic agent (N = 16)				0.511
≤2	12	5(71.4)	7(63.6)	
>2	4	1(14.3)	3(27.3)	
Age				0.648
≤9.5 years old	8	3(42.9)	5(45.5)	
>9.5 years old	10	4(57.1)	6(54.6)	
Sex				
Female	7	3(42.9)	4(36.4)	0.583
Male	11	4(57.1)	7(63.6)	
AED number in hospitalization				0.326
≤3	3	2(28.6)	1(9.1)	
>3	15	5(71.4)	10(90.9)	
AED number in discharge				0.167
≤3	9	5(71.4)	4(36.4)	
>3	9	2(28.6)	7(63.6)	
CSF protein				0.676
Normal	5	2(28.6)	3(27.3)	
Abnormal	13	5(71.4)	8(72.7)	
Neuroimage finding				0.220
Normal	5	4(57.1)	3(27.3)	
Abnormal	13	3(42.9)	8(72.7)	
Cognition at discharge				0.043
Good	3	3(42.9)	0(0.0)	
Poor	15	4(57.1)	11(100.0)	

therapies had been shown to decrease seizure frequency in previous studies [8], it did not change the frequency of seizures in the present study. Therefore, whether immunomodulating therapies play a role in seizure control also remains to be investigated.

In the present study, the longer duration of hospitalization and the poorer cognition level at discharge were correlated with poorer long-term cognition outcome in our patients. We considered that the more severe condition may need more time to become stabilized during the hospitalization, and the poorer cognitive level at discharge may also reflect a more severe condition. Therefore, both factors may lead to worse long-term outcome in the patients.

In our study, all patients had subsequent epilepsy after discharge, but 15% became seizure-free under AED control in long-term follow-up. It is different from some studies that none of the patients had a seizure-free period [12,16] but is similar to some previous studies [15,16]. In our result, refractory epilepsy was associated with higher mRS score at discharge. Although previous studies showed that death may occur after 4–8 months of ongoing seizures in the most refractory cases, none of our patients was found to be dead after discharge.

In previous studies, no long-term motor outcome analysis was done before. One previous multicenter study showed that the younger age onset of FIRES and higher log of burst–suppression coma duration were significantly associated with the worse cognitive outcome. However, the degree of cognitive insult was not correlated with the number of foci in EEG during the acute phase, MRI abnormalities, and duration of mechanical ventilation [12], which was different from the present study. In our patients, the duration of anesthetic agents and the duration of hospitalization were significantly associated with the poor long-term cognition outcome. Another study reported that the survivors with FIRES had moderate to severe intellectual impairments in 66.7% and borderline intellectual disabilities in 33.3% in long-term follow-up [15], which was also different from the present series. In our study, only two (11.1%) had severe intellectual disability, and seven (38.9%) had normal cognition, indicating better prognosis in the present study.

To our knowledge, this is the first series to analyze the potential risk factors possibly associated with the motor outcome in short-term and long-term follow-up. In our present study, all the survivors had the significant functional decline that occurred at discharge. However, the short-term and long-term outcome revealed decline of mRS values gradually with time, indicating the improvement in long-term follow-up. In our present series, some patients also had a good outcome with freedom of seizure.

Our study had some limitations. We lacked follow-up data in a minority of our survivors; some of these cases were discharged with poor functional outcome but might have improved over time. Because FIRES was not very common in Taiwan, the case number in the present study was limited, although our hospital is the major leading University hospital in Taiwan. Further multicenter study with long-term follow-up may solve this problem.

In conclusion, FIRES is a catastrophic epileptic encephalopathy. The longer duration and more anesthetic agents or AEDs, longer duration of hospitalization, and poor cognition during discharge suggested possibly correlated with poorer long-term motor and cognition outcome. Although some of these cases were discharged with poor functional outcome, they have improved over time. Chronic or refractory epilepsy in survived cases are common, but freedom of seizures is possible.

5. Key points

- The FIRES is a catastrophic epileptic encephalopathy that has the significant mortality and morbidities.
- Febrile infection-related epilepsy syndrome is difficult to be treated with antiepileptic drugs and often requires deep sedation with anesthetic drugs for the control of seizures. The early use of ketogenic diet can improve the neurological outcome, which needs further investigation.
- The longer duration and more anesthetic agents or antiepileptic drugs, longer duration of hospitalization, and poor cognition during discharge suggested a possible correlation with poorer long-term motor and cognition outcome.
- Chronic or refractory epilepsy in survived cases is common, but freedom of seizures is possible.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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