Original Article

Clinical profile and treatment outcome of febrile infection-related epilepsy syndrome in South Indian children

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Abstract

Purpose: To describe the clinical features and outcome of febrile infection-related epilepsy syndrome (FIRES), a catastrophic epileptic encephalopathy, in a cohort of South Indian children. **Materials and Methods:** We performed a retrospective chart review of a cohort of children with previously normal development who presented with status epilepticus or encephalopathy with recurrent seizures following a nonspecific febrile illness during the period between January 2007 and January 2012. They were divided into two groups super refractory status epilepticus (SRSE) and refractory status epilepticus (RSE) depending on the duration and severity of the seizures. **Key Findings:** Fifteen children who met the inclusion criteria were included for the final analysis. The age of the children at presentation ranged 3-15 years (median 6.3 years). All the children presented with prolonged or recurrent seizures occurring 1-12 days (median 4 days) after the onset of fever. Eight children had SRSE while seven children had refractory seizures with encephalopathy. Cerebrospinal fluid (CSF) analysis was done in all the children in the acute phase, and the cell count ranged 0-12 cells/μL (median 2 cells/μL) with normal sugar and protein levels. Initial neuroimaging done in all children (MRI in 10 and CT in 5), and it was normal in 13 children. Treatment modalities included multiple antiepileptic drugs (AEDs) (4-9 drugs) (median 5 drugs). Midazolam (MDZ) infusion was administered in seven patients. Eight patients required barbiturate coma to suppress the seizure activity. The duration of the barbiturate coma ranged 2-90 days (median 3 days). Steroids were used in 14 children and intravenous immunoglobulin (2 g/kg) in 7 children. Three children died in the acute phase. All children were maintained on multiple AEDs till the last follow-up, the number of AEDs ranged 1-6 (median 5 AEDs). The patients with super refractory status in the acute phase were found to be more severely disabled at the follow-up; the median score of these patients on the Glasgow Outcome Scale (GOS) was 2 compared to 5 in the RSE group. **Significance:** This study reports one of the largest single center cohorts from India, with an adverse long-term developmental and seizure outcome. The duration and severity of seizures in the acute period correlated directly with the short-term and long-term clinical outcomes. There is an urgent need for developing new effective therapeutic strategies to treat this acute catastrophic epileptic syndrome.

Key Words

Encephalopathy, febrile infection, status epilepticus

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Ann Indian Acad Neurol 2016;19:188-194

Introduction

Febrile infection-related epilepsy syndrome (FIRES) is a recently described catastrophic epileptic encephalopathy seen in developmentally normal children.[1] It is characterized by an explosive onset of refractory seizures or status epilepticus following a minor febrile illness. Overall, the mortality and

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.173305

How to cite this article: Patil SB, Roy AG, Vinayan KP. Clinical profile and treatment outcome of febrile infection-related epilepsy syndrome in South Indian children. Ann Indian Acad Neurol 2016;19:188-94.
Received: 02-06-15, **Revised:** 21-06-15, **Accepted:** 01-09-15

long-term morbidity rates for this condition are very high and it is usually followed by both chronic drug-resistant epilepsy and neurodevelopmental disabilities in the survivors.[2,3] However, this entity has also been described under many other names emphasizing either the characteristics of acute refractory epilepsy or the presumed pathogenesis such as "acute encephalitis with refractory, repetitive partial seizures" (AERRPS),[4] "severe refractory status epilepticus due to presumed encephalitis,"[5] "idiopathic catastrophic epileptic encephalopathy,"[6] "new-onset refractory status epilepticus" (NORSE),[7] and "devastating epileptic encephalopathy in school-aged children" (DESC).[3]

Even though a recent literature review showed an apparent clustering of reported cases from Japan and Europe, this entity is thought to be seen all over the world. Here, we describe the clinical characteristics along with the long-term developmental and seizure outcomes of a cohort of children with FIRES from South India managed in a single center over a period of 5 years. Comparison is also attempted with the previously reported clinical series stressing on the homogeneity of this patient population.

Materials and Methods

A cohort of previously normal children who presented at the Amrita Institute of Medical Sciences, Kochi, Kerala, India, during the period 2007-2012 with status epilepticus or encephalopathy with refractory seizures following a minor febrile infection, which was treated on an outpatient basis and did not require major investigations, was included in this study. This study was approved by the Institutional Review Committee and Ethics Committee.

The baseline clinical data and the details of the investigations and treatment were recorded by chart review. The seizures were classified according to the scheme proposed by the International League Against Epilepsy.[8] The resistant seizures were further divided into refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) according to the existing literature.[9] RSE is defined as continuous seizures for more than 2 h despite the treatment with intravenous antiepileptic drugs (AEDs) such as benzodiazepines, phenytoin, phenobarbitone, and valproate. SRSE is defined as status epilepticus that continued or recurred despite using general anesthesia for 24 h. Surviving children were followed up until the last contact. Seizure frequency, number of AEDs and neurodevelopmental outcomes, and the findings on the follow-up electroencephalography (EEG) and magnetic resonance imaging (MRI) of the brain were recorded.

Results

A total of 15 children who met the inclusion criteria were identified during the study period. All the children were aged between 3 years and 15 years with median age of 6.3 years at presentation. Male-to-female ratio was 4:1. All the children were developmentally normal and had no prior history of febrile or afebrile seizures. One child among them had a family history of epilepsy, and two had a family history of febrile seizure.

The preceding febrile infection was a nonspecific respiratory infection that occurred in 12 children, and 2 children had acute diarrheal disease. One child had fever with nonspecific lymphadenopathy before the onset of seizures. The interval between febrile illness and onset of seizure was variable between 1 day and 12 days with a median of 4 days. On presentation, eight children had SRSE while seven children had refractory seizures with encephalopathy. Seizures manifested as tonic seizures, facial twitching, opercular seizures, and generalized tonic–clonic convulsions.

Prolonged intensive care unit (ICU) EEG monitoring lasting for 24-48 h was done in the acute stage in all the children. The interictal record showed diffuse slowing consisting of high amplitude polymorphic delta waves in all the children. Repetitive focal clinical seizures with electrographical correlation were noted in 12 children. One child had a nonconvulsive status epilepticus intermixed with recurrent convulsions at presentation.

Initial neuroimaging done in all the children (MRI in 10 and CT in 5), and the report was normal in 13 patients. One patient showed T2 hyperintensities in the left hippocampus after prolonged seizures. Another child had nonspecific left temporal lobe hyperintensities.

Cerebrospinal fluid (CSF) analysis was done in all the children in the acute phase and the cell count ranged 0-12 cells/μL (median 2 cells/μL) with normal sugars and protein levels. Four patients had their CSF lactate measured that ranged 1.4-1.9 mmol/L (median 1.5 mmol/L). CSF culture for infective agents was negative in all the patients. Further investigations were performed according to the clinical situation at the time of the treatment. CSF polymerase chain reaction (PCR) results for herpes simplex and Japanese encephalitis were negative in four patients in whom the test was carried out, including the child who had choreoathetoid movements and left putaminal hyperintensity. Similarly, PCR result for *Mycobacterium tuberculosis* (Sequence IS 6110, Amrita Labs, Kochi, Kerala, India) in four patients was negative. Chikungunya PCR and rabies PCR were done in one patient each, based on clinical suspicions that also turned out to be negative. Further etiological analysis was based on clinical judgment in individual cases. Three patients underwent analysis for antinuclear antibodies with negative results. Urinary porphobilinogen was not detected in all the six patients tested. CT scans of the chest and abdomen were performed as part of a paraneoplastic workup in four patients that did not show any abnormality. *N*-methyl-D-aspartate (NMDA) receptor antibody (immunofluorescence assay, Metropolis Lab, Mumbai, Maharashtra, India) in two patients was negative. Thyroid antibodies tested in five patients (immunochemiluminescent assay, Amrita Labs, Kochi, Kerala, India) were found to be negative. Positron emission tomography (PET) scan was not performed in any of the children as most of them had recurrent seizures or status. Molecular genetic studies and investigations for mitochondrial mutations were not performed due to financial constraints.

All children received empirical treatment with injectable antibiotics and injection acyclovir for a minimum period of 14

days. All patients were treated according to our departmental status epilepticus protocol. They were initially given intravenous (IV) lorazepam at the dose of 0.1 mg/kg followed by a loading dose of IV phenytoin of 20 mg/kg. If the seizures continued despite the administration of phenytoin, the children were given IV phenobarbitone (20 mg/kg). This was followed by midazolam infusion (MDZ) infusion 200 μg/kg using IV bolus injection slowly followed by infusion at the rate of 1-10 μg/kg/min. If the seizures continued despite MDZ infusion, the children were treated with barbiturate anesthesia. Thiopentone was used at 3-5 mg/kg bolus dose to produce burst suppression pattern followed by maintenance dose started at 1 mg/kg/h. The dosage was titrated depending upon the EEG response to a maximum dose of 5 mg/kg/h. Multiple AEDs were used as polytherapy to control the seizures. The number of AEDs used per patient ranged 4-9 with a median of 5 AEDs. The major drugs used were as follows (with the number of patients in parentheses): Phenytoin (11), phenobarbitone (11), sodium valproate (13), levetiracetam (14), topiramate (12), clobazam (12), and clonazepam (9). MDZ infusion was administered in seven patients. Eight patients required barbiturate coma to suppress the seizure activity. Duration of barbiturate coma ranged 2-90 days with a median of 3 days. In patients who remained refractory despite the use of barbiturate coma, other modalities were tried. One child received ketamine infusion (1-4 μm/kg/hr). Ketogenic diet (KD) was tried in two children up to maximum ratio of 4:1.

All the eight children with SRSE received immunotherapies. Six children received IV immunoglobulin while all received a trial of steroids. IV immunoglobulin was given at a dose of 2 g/kg infusion over a period of 5 days. Steroids were administered as an initial pulse IV methylprednisolone at a dose of 30 mg/kg (maximum 1 g) for 5 days followed by 2 mg/kg oral steroids as per the departmental protocol. Steroids were tapered slowly over 4-6 weeks. Out of seven children with resistant seizures (RSE), six children received some kind of immunotherapy (six steroids/one IV immunoglobulin).

Three children with SRSE died in the acute phase of the disease with multiple complications related to prolonged seizures and ICU stay. These children received barbiturate coma for seizure control; out of them, one died during the barbiturate coma stage due to refractory hypotension and septicemia. Another child died due to septicemia during the ICU stay, and the third child died due to aspiration pnuemonia. There was no mortality in the group with RSE.

Outcome at discharge was measured on the Glasgow Outcome Scale (GOS). Children with SRSE had a poor outcome with a median GOS of two, on other hand median GOS was four in children with RSE.

The duration of the follow-up period was variable ranging from 4 months to 5 years (median 6 months). Twelve children who survived the acute phase had a follow-up phase characterized by refractory epilepsy. In seven children, there was no seizure-free period after the acute phase. The remaining children were seizure-free at the last follow-up with a seizure free period ranging from 6 months to 13 months, however on polytherapy. At the time of the last follow-up, seizures were noted in seven children. Five children had multiple seizures per month, out of whom two had a seizure frequency of 2-3/week. Two children had intermittent seizures with a frequency range of around 2-4 in 6 months. One child had status epilepticus after 6 months of follow-up. All the five children with SRSE on follow-up continued to have refractory epilepsy and required 3-6 AEDs (median 5) to control the seizures. Children with RSE required a relatively lesser number of AEDs (1-6, median 5).

Interictal EEGs were performed in all children after a variable period of follow-up. Six children had excessive slowing of background rhythm without any epileptiform abnormality. Two had focal slowing predominantly from the left hemisphere. Two children had multifocal epileptiform abnormality. Normal EEG was seen in two patients.

Eleven children had repeat MRI of the brain following a variable period after the disease onset (2 weeks to 16 months). It was normal in six children, with one child showing diffuse atrophy. One child had left temporal lobe hyperintensities that decreased in subsequent scans. One child had significantly dilated ventricles and the other had left putaminal hyperintensity in repeat scans. Two children showed progression of MRI changes as mentioned in Table 2.

Neurodevelopmental, behavior, and memory assessments were done by age-appropriate tests during the follow-up. Behavior and cognition were also assessed by parental interview and in some children based on school performance. At the time of the last follow-up, only 3 out of 12 children were going to normal school and all of them had an average scholastic performance. Vineland Social Maturity Scale (VSMS) was used for one child during the follow-up that showed a score of 86 with a social age less than his chronological age. Three children were found to be severely disabled on the last follow-up requiring support for walking and daily needs. Three children were significantly hyperactive. Patients with super refractory status in the acute phase were found to be more severely disabled on the follow-up, the median GOS being 2 compared to 5 in the RSE group.

The clinical characteristics and investigations in the acute phase are given in detail in Table 1. The long-term clinical outcome is described in Table 2.

Discussion

FIRES represents an acute severe epileptic disorder occurring in relation to a febrile episode, in previously normal children around early school years, with the majority of the children (73%) presenting between the ages of 4 and 9 years. Our case series of this catastrophic febrile infection-related epileptic encephalopathy is one of the largest reported clinical series from India.

The baseline clinical features of this cohort are similar to the previously reported studies from other geographic regions.[1,2,10] Krammer *et al*. described the pathogenesis, treatment, and outcome in 77 patients with FIRES in a multicenter retrospective case series.[11] The median age of onset in this series was 8 years compared to 6.3 years in our cohort. Median duration of the onset of seizures after febrile

Table 1: Details of the follow-up and outcome

Follow up					Follow up EEG	Follow up Neuroimaging/MRI			GOS on follow up
Period	Seizures	AED	Cognition	Behavior abnormalities		No	Timing	Findings	
4 Months	No	5	Good	Hyperactivity	Normal EEG				5
5 Months	No	4	Good	Hyperactivity	Background slowing	1	4 week	Normal study	5
19 Months	3/ Mo	6	Impaired	Absent	Temporal (Lt)				2
Death						2	2 week/6 week	T2 Hyerintensities in bilateral periventricular white matter, caudate nuclei and posterior midbrain	1
4 Months	2 / 4 Month	5	Impaired	Hyperactivity	Background slowing				5
5 years	No	3	Impaired	Absent	Background slowing	4	2 wk/4k/5 wk/4 Mo	1. Normal study (2 wk) 2. Abnormal Hyperintense areas involving bilateral ganglio thalamo capsular regions and bilateral cerebral and cerebellar hemisphere (4 wk) 3. Complete resolution of parenchymal changes	2
36 Months	2-3/6 Mo	3	Impaired	Present	Background slowing	1	12 days	Normal study	2
13 Months	2-3/wk	5	Impaired	Present	Multifocal spike and waves	1	8 Months	Normal study	5
12 months	14/month	5	Impaired	Absent	Background slowing	1	16 Months	Normal study	4
5 years	1-2/wk	5	Impaired	Present	Left Hemispheric spike and waves	1	25 days	Decrease in Lt temporal Hyperintensities compared to previous MRI	4
13 Months	No	1	Good	No	Normal EEG	1	4 week	Normal study	5
6 Months	Status after 1 Month	6	Good	Hyperactivity	Background slowing				5
Death						1	4 week	Original findings with Hydrocephalus ex vacuo	1
Death						1	3 Months	Diffuse atrophy	1
6 months	2-3 /day	6	Impaired	Choreoathetoid movements	Multifocal spike and waves	2	9 days/34 days	Lt putamen hyperintensity	2

Table 2: Baseline clinical characteristics and details of therapy

Age	Sex	Preceding Febrile Infection	Interval between Onset of seizure and preceding Infection	Seizure Type	EEG – Interictal	Initial Neuroimaging		AED			Immunotherapy		Barbitutrate Coma
						Type	Report	Drugs	Maximum Number	Midazolam Drip	Steroids	IVIG	Drug
7 yr	M	Acute Gastroenteritis	3 days	GTCS	Frontal(Right), Anterior Temporal (Right), Occipital (Left) spike and waves	CT	Normal study	VPA,DPH, LEV, PB, TPM	5	No	Y	N	Thio
3Y 10 M	M	Fever Nonspecific	7 days	TS, FDS	Frontocentral (Right) spike and waves	CT	Normal study	VPA,CLZ, LEV, CLB	4	NO	Y	N	No
6Y 3 M	M	Fever Nonspecific	4 days	GTCS	Parieto-temporo-occipital (Left) spike and waves	MRI	Normal study	VPA, LEV,DPH,PB, TPM,CLB, CLZ	7	NO	N	Y	Thio
5Y 7M	M	Upper respiratory tract infection, Acute Gastroenteritis	2 days	TS, FDS	Multifocal spike and waves; NCS	CT	Normal study	VPA,DPH, LEV, CBZ, TPM,CLB,PB	7	Y	Y	Y	Thio
5Y 12 D	M	Acute Gastroenteritis	7 days	TS,FDS	Bilateral Temporal spike and waves	MRI	Normal study	VPA, CLB, LEV,TPM, PB	5	Y	Y	Y	Thio
6 Y 8 M	M	Fever Nonspecific	1 day	FDS, GTCS	Occipital (Right) spike and waves	MRI	Normal study	TPM, PB, CLZ,LEV,DPH	5	Y	Y	Y	Thio
3 Y 1 M	M	Fever Nonspecific	4 days	FDS	Non specific Slow	CT Brain	Normal study	VPA, TPM, CLB, CLZ, LEV, PB,	6	Y	Y	N	No
11 Y 1M	M	Fever, Nonspecific	2 days	GTCS	Multifocal Spike and wave	CT	Normal study	LEV, LCM, VPA, CLZ	4	N	Y	N	No
3 Y 7 M	M	Fever, Nonspecific	12 days	TS,FDS	Multifocal and generalised spike and waves	MRI	Normal study	VPA, LEV, CLB, TPM, DPH	5	N	Y	N	No
12 Y	M	Fever, Nonspecific	6 days	GTCS, FDS	PLED, Frontotemporal (Left) spike and waves	MRI	Left Temporal lobe Hyperintensities	DPH,PB,CLB, CLZ	4	N	N	N	No
7 Y 25 D	F	Fever Nonspecific	7 days	FDS	Frontal (Left) spike and waves	MRI	Normal study	DPH, CBZ, PB, VPA, CLB, TPM, LEV	7	N	Y	N	No
3 Y 4 M	M	Fever with Lymphadenopathy	7 days	GTCS,FDS	Frontal (Right) spike and waves	MRI	Normal study	VPA, LEV, CLB, TPM, DPH	5	N	Y	Y	No
8 Y 6 M	M	Fever Nonspecific	3 DAYS	GTCS	Fronto temporal (Left) spike and waves	MRI	T2- Flaior HI in Lt Hippocampus	VPA, LEV, PB , DPH, TPM, CLB, CLZ	7	Y	Y	N	Thio
15 Y	F	Fever, flu like symptoms, Headache, Nausea	3 days	GTCS	Multifocal spike and waves	MRI	Normal study	PB,DPH, VPA, LEV, TPM,CLB, CLZ, CBZ, LCM	9	Y	Y	Y	Thio
6 Y	F	Fever Nonspecific	3 days	FDS	Multifocal spike and waves	MRI	Normal study	PB, DPH, VPA, LEV, TPM,CLB, CLZ, ESC, LCM	9	Y	Y	Y	Thio

DPH = Phenytoin, PB = Phenobarbitone, VPA = Valproate, LEV = Levetiracetam, TPM = Topiramate, CLB = Clobazam, CLZ = Clonazepam, LCM = Lacosamide, CBZ = Carbamazepine, ESC = Eslicarbazepine, Thio = Thiopentone, NCS = Nonconvulsive status, TS = Tonic seizures, FDS = Complex partial seizures/focal dyscognitive seizures

illness was 4 days for both the studies. The sex ratio in the present study is more inclined toward males (4:1), in contrast to their group (4:3). Despite extensive investigations, both the studies did not find any causative agents. The number of AEDs used (median 6) in the acute stage was also similar to the current series (median 5). Barbiturate coma was used for variable periods with a median period of 3 days in our study compared to 7 days in the other cohort. The overall outcome is also comparable with 93% of this largest series having refractory seizures on follow-up.

In another case series from Japan, Sakuma *et al*. described eight children with acute onset of refractory repetitive partial seizures following febrile illness.[4] The median onset was 6.8 years and the time taken for the first reported seizure was 4.3 days after the febrile illness, both of which are almost identical to our cohort. All of the 27 patients followed up in this series had residual epilepsy. Most of the children in this case series had residual cognitive impairments also with intelligence quotients measured using the Wisconsin Intelligence Scale for Children (III) which was less than 70 in 16 patients and below 20 in 10 patients. Though intelligence quotient (IQ) tests were not done routinely in our cohort on follow-up, the VSMS score was 86 in one child, with a social age less than his chronological age.

The exact etiopathogenesis of this clinical syndrome remains unclear. An infective etiology was initially presumed in view of the close temporal association of the seizures with the febrile illness.[5,10] None of the following pathogens were so far detected even after extensive search for infectious agents by available methods: Herpes simplex virus, *Enterovirus*, *Human herpesvirus 6*, Epstein–Barr virus, *Cytomegalovirus*, *Adenovirus*, *Measles virus*, influenza and parainfluenza viruses, and *Mycoplasma*.[4,11] We were also not able to find any infectious etiology in the present cohort.

The clinical course of this disorder is typically biphasic with an initial acute catastrophic phase followed by a chronic refractory epilepsy phase. The acute catastrophic phase is characterized either by an explosive onset of recurrent focal seizures or frank status epilepticus. We tried to classify the acute phase into SRSE or resistant status epilepticus depending on the duration and severity of seizures and the need for anesthetic drugs for seizure control. As expected, the super refractory status group had a higher mortality and immediate and long-term morbidity compared to children with less severe seizures. They also required higher number of AEDs during the acute and chronic phases.

The biphasic nature of the illness suggests a possible infection-triggered process rather than an infectious disease. Van Baalen *et al*. suggested an immune mechanism as a possible etiology in these patients.[1] Search for autoimmune mechanisms was attempted in many reported case series aimed at antibodies against voltage-gated potassium channels (VGKCs),[12,13] NMDA receptors,[14] and glutamate receptors.[14,15] Nabbout *et al*. found no evidence for antibodies against VGKC, NMDA receptors, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate A (AMPA) receptors, or GABAa receptors.[16] The response to immunotherapy is not that favorable in FIRES compared to many classical postinfectious immune neurological diseases such as acute disseminated encephalomyelitis (ADEM). In this cohort, immunotherapy had only very limited success. However, an immune mechanism mainly targeting the cell-mediated immunity or as an yet unidentified antibody may still be etiopathologically possible. Antibody-mediated processes classically need more time than the usual interval between the initial febrile episode and the characteristic explosive onset of seizures seen in patients with FIRES. Moreover, the acute explosive phase is immediately followed by a phase of chronic epilepsy without an interval for epileptogenesis, which is a strong pointer against a purely acquired disorder. This may favor the possibility of unmasking an epileptogenic trait by the febrile illness as the main neurobiological mechanism for the initiation of FIRES. The onset, refractoriness to currently available treatment, and the natural course of FIRES are somewhat reminiscent of the features of catastrophic genetic epileptic syndromes of infancy such as Dravet syndrome. However, a pathogenic mutation has so far not been identified in this population even after extensive research.[16] We have not done any of the genetic evaluation in this cohort. Idiopathic hemiconvulsion-hemiplegia (HH/HHE) syndrome is another acute catastrophic epilepsy syndrome, which has been thought to have an association with FIRES because of similarities in clinical presentation. The concept of "acute encephalopathy with inflammation-mediated status epilepticus" has been put forward considering vicious association of inflammation and seizure activity facilitated by the brain maturation process.[17]

The treatment of FIRES, which is a very resistant acute catastrophic epileptic syndrome, had very limited success with the traditional antiseizure management. The outcome remains uniformly poor; all children in the SRSE group are severely disabled both in the acute and chronic phases. In this cohort, children with super refractory status had a worse outcome that may indicate a greater severity of the disease. KD was found to be a better option in some cases to control the seizures.[18] The dramatic response to KD that is seen in some children may indicate a shared pathogenesis to some of the genetic epileptic syndromes such as myoclonic atonic epilepsy (MAE). In this cohort, KD was tried in two patients in the later phases of the illness with minimal response.

This retrospective clinical series shares the experiences of managing one of the largest cohorts of FIRES from a single center in South India. The baseline clinical features, the treatment response, and the long-term outcome of this cohort are comparable to the cases reported from other geographic regions. The outcome remains uniformly poor and it mainly depends on the duration and severity of the seizures. This study did not demonstrate any other clinical characteristics, significantly contributing to the final outcome. Being a retrospective study, it was difficult to make assumptions about the efficacy of different treatment modalities from this clinical series. Further multicentric prospective studies with larger patient numbers are needed to make firm conclusions about the safety and efficacy of the current treatment protocols. There is also an urgent need for developing better therapeutic options for this highly resistant epileptic syndrome.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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