

The etiologies and outcome of convulsive status epilepticus in children at tertiary care hospital Kashmir India



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ABSTRACT

Background: Convulsive status epilepticus (CSE) is a common neurological emergency, where immediate supportive and specific treatment determines the outcome of the patient. Therefore, immediate management and etiological workup of CSE should be done in tandem to decrease associated morbidity and mortality. **Aims and Objectives:** The study aimed to ascertain different etiologies and outcomes of CSE in children. **Materials and Methods:** The study was a prospective observational hospital-based study conducted in a tertiary care hospital from October 2020 to September 2022. **Results:** The most common type of seizure in CSE was GTCS, 154 cases (83.7%), followed by focal seizure 12 % (26 cases). Almost 35% of patients had CSE as a first presentation for PICU admission and the rest 65% of patients did have a previous history of seizures. The most common etiology of CSE was remote symptomatic, seen in 27.2%, followed by acute central nervous system infection in 19.5%, febrile status in 19.5%, and cryptogenic/idiopathic SD in 14.9%. Among the patients who had encephalitis, the common etiologies were enteroviruses and herpes simplex. We did not find any case of Japanese encephalitis, West Nile encephalitis, cerebral malaria, or dengue case in our study. Therefore, recommending cerebrospinal fluid panels for these vectors borne viral brain diseases is a waste of resources in Kashmir, India. Furthermore, we did not find any case of neurocysticercosis in our study as a cause of CSE. **Conclusion:** In our study, we had 16 cases of encephalitis, and most of them were caused by enteroviruses and herpes simplex virus. We did not find any case of Japanese encephalitis, West Nile encephalitis, cerebral malaria, or dengue case in our study. Vector-borne diseases transmitted by different mosquitoes do not occur in Kashmir.

Key words: Etiology; Outcomes; Status epilepticus; Children; Encephalitis; Meningitis

INTRODUCTION

Status epilepticus (SE) is one of the common neurological emergencies that require immediate management to prevent death and/or permanent damage to the nervous system.

The duration of continuous seizure activity used to define SE has varied over time. Historically, the International League Against Epilepsy (ILAE) and others defined SE as a single epileptic seizure of >30 min duration or a series of epileptic seizures during which function is not regained between ictal events in 30 min. For treatment

decisions, however, a shorter time window (e.g., >5–10 min of continuous seizures) has been favored and generally accepted in the clinical community, particularly for generalized convulsive seizures.¹

The ILAE revised its definition of SE in 2015, and the revised definition incorporates both time points. A condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures (after time point t1); and a condition that can have long-term consequences (after time point t2),

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including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.²

The estimated incidence of childhood SE is between 17 and 23 episodes/100,000/year.^{3,4}

The highest incidence is in the 1st year of life and febrile SE is the most common etiology. Approximately 60% of children are neurologically healthy before the first episode of SE.⁵

SE may occur in the setting of underlying, premorbid epilepsy or as the first manifestation of epilepsy. Virtually, any cause of epilepsy may have a first presentation with SE and may also be an acute symptom of medical or neurologic disease. The more common examples of the latter include:⁶

- Central nervous system (CNS) infections
- Acute hypoxic-ischemic insult
- Metabolic disease (e.g., hypoglycemia, inborn error of metabolism)
- Electrolyte imbalance
- Traumatic brain injury
- Drugs, intoxication, poisoning
- Cerebrovascular event.

Other risk factors for SE in children with symptomatic epilepsy include focal background electroencephalography (EEG) abnormalities, focal seizures with secondary generalization, the occurrence of SE as the first seizure, and generalized abnormalities on neuroimaging.⁷

Mortality associated with SE can result from the underlying condition or respiratory, cardiovascular, or metabolic complications of SE. In prospective studies, the mortality rate during hospitalization in high-income countries ranged from 2.7% to 5.2%. The reported longer-term mortality rates of SE in children vary between 3.8% and 17%. The underlying etiology is the main predictor of mortality.⁸

Aims and objectives

The aim is to study the etiologies and outcomes of convulsive SE (CSE) in children 1 month–18 years.

Inclusion criteria

All children aged between 1 month and 18 years who, at presentation or during the hospital stay, had CSE.

Exclusion criteria

Patients in whom the information regarding seizure duration was incomplete or unclear, non-CSE, poisoning, and trauma.

Sample size

The sample size was 184 cases.

MATERIALS AND METHODS

Hospital-based prospective observational study performed in the Department of Pediatrics in Children Hospital Government Medical College, Srinagar, Kashmir, India, from October 2020 to September 2022.

Ethical approval for this study was obtained from the hospital ethics committee, order number F (Minutes-BOPGS) Accad/KU/Dated: 02-02-2022. During this period, a total number of 184 cases who were presented to the emergency with SE were included in the study.

Procedure

Every sick child with CSE had been assessed and triaged on arrival and a rapid cardiopulmonary assessment was made with immediate monitoring of heart rate, blood pressure, SPO₂, signs of shock, pupil size, and reaction to light. Before starting IV resuscitation, a blood sample was taken for baseline investigations. Then, the cases were managed according to the protocol followed in our emergency room/pediatric intensive care unit. After early management and stabilization of the patient, a detailed history was obtained, including duration of seizure, distance from the hospital where the fits started, mode of transport, any prehospital and/or treatment during transportation, precipitating factors, prior seizures/SE, drug history and compliance, any chronic medical or neurological illness, developmental milestones, and prior neurological status. Demographic and baseline data were recorded with the help of a performed pro forma. Variables included age, sex, type of SE, cause, duration of convulsions, duration of unconsciousness, precipitating factors, EEG, and number of antiepileptic drugs required to control the seizures, history of convulsions and fever, any complications that occurred and ultimate survival or death. Baseline investigations were also carried out, including complete blood count, blood glucose levels, serum electrolytes, serum calcium and magnesium, blood urea and creatinine, urinalysis, lumbar puncture, magnetic resonance imaging, and EEG were performed. Comprehensive cerebrospinal fluid (CSF) analysis depending upon clinical settings such as CSF count, chemistry, culture, viral PCR or ELISA, monoclonal bands, and NMDA receptor antibodies were done in a few patients to reach the etiological diagnosis of CSE. In a few patients' clinical exome or whole genome sequencing for epileptic disorders or syndromes was done to fix etiology and subsequent specific antiepileptic drug (AED) management.

Data thus collected were subjected to statistical analysis with the help of computer software SPSS version 23. A Chi-square test was applied and a P≤0.005 was considered significant. The relationship of various demographic,

clinical characteristics and etiology with outcome was evaluated employing the Chi-square test, Fisher's exact test for categorical data, and independent t-test for continuous data with normal distribution.

The primary outcomes were:

- Complete recovery without neurological sequela
- Recovery with neurological sequela
- Death.

RESULTS

The study was a hospital-based prospective observational study conducted in the age group 1 month–18 years. The diagnosis of SE was established in 184 patients (male: n=102; 55.4%). Most patients were <10 years of age and the median age was 4.9±0.9 years. Of the 184 cases of CSE, previous history of seizures was present in 32.8% (24) of the children. The range of distance traveled from the onset of seizures to the hospital was 0.5–60 km (Mean 23 km) and the mean of the time from the onset of seizure to the hospital was 44.9±20.4 min. The 48 (26.1%) children had received some treatment before they arrived at the hospital (Table 1).

Generalized tonic–clonic seizures were the most common presentation of CSE observed in 83.7% (154) of the patients, followed by partial seizures with secondary generalization in 14.1% (26). The other less common seizures observed were complex partial seizures 1.1% (2), and multifocal seizures (Table 2).

The most common underlying etiology of CSE was Remote symptomatic (n=50; 28.7%). Among the patients of remote CSE twelve patients (24%) died. The second major cause of CSE was febrile SE (n=32; 18.3%), followed by CNS infections 18.3% (32). Whereas none of the patients died due to febrile SE, the mortality in patients with CNS infections was 21.8%. The other less common causes of CSE were neurocutaneous syndromes, neurometabolic disorder, noncompliance to drugs and cerebrovascular accidents. Instead of extensive investigations, the underlying etiology was not found in 26 patients (14.9%).

The highest mortality was observed in patients with neurometabolic disorders (50%), followed by remote symptomatic and CNS infections, and observed in 24% and 23.5% of patients, respectively. There was no mortality in patients with febrile SE (Table 3).

The CNS infections such as encephalitis and meningitis were common underlying etiologies of CSE observed in

Table 1: Sociodemographic profile of patients presented with convulsive status epilepticus

Variable	Value
Median age	4.9 years
Males, n 90(%)	102 (55.4%)
Prior history of seizures, n (%)	24 (32.8%)
Distance traveled between the onset of seizures and hospital presentation, km	0.5–60 km
Mean time to reach to hospital	Mean: 23 km
Prehospital treatment, n (%)	44.9±20.4 min
	48 (26.1%)

Table 2: Frequency and pattern of seizures in patients admitted with convulsive status epilepticus

Type of seizures	Frequency
Partial with secondary generalization	26 (14.1%)
GTCS*	154 (83.7%)
Complex partial epilepsy	02 (1.1%)
Multifocal seizures	02 (1.1%)

*GTCS: Generalized tonic–clonic seizure

Table 3: Etiological spectrum and outcome of pediatric convulsive status epilepticus

Etiology	Number of cases n=174	Recovered (%)	Died
Febrile status epilepticus	36 (20.6)	36 (100)	0 (0)
CNS infections	32 (18.3)	25 (78.12)	07 (21.8)
Remote symptomatic	50 (28.7)	38 (76)	12 (24)
Idiopathic	26 (14.9)	24 (92.3)	02 (7.7)
Neurocutaneous syndrome	04 (2.29)	04 (100)	0 (0)
Neurometabolic disorder	04 (2.29)	02 (50)	02 (50)
Noncompliance	10 (5.7)	08 (80)	02 (20)
CNS Hemorrhage	04 (2.29)	04 (100)	0 (0)
Systemic illness	06 (3.4)	06 (100)	0 (0)
Tumor	02 (1.14)	02 (100)	0 (0)

CNS: Central nervous system

(n=16; 38.09%) and (n=12; 28.5%) patients, respectively. There were 4 (9.5%) cases of CNS tuberculosis and 2 (4.7%) cases of brain abscesses, who presented with CSE. The other less common underlying etiologies of CSE were hypoglycemia, hyponatremia, ICH, and ADEM, suggesting the critical importance of neuroimaging, CSF analysis and metabolic testing in patients presenting with CSE (Table 4).

Twenty-six patients (14.0%) died during the study period, irrespective of etiology and 75% (n=138) of patients recovered without any sequel. Mortality was related to the age of the patients, cause of SE, distance from the hospital and prior treatment received at rural health. The majority of the patients, 75% (138), recovered without any disability, and 10 patients developed permanent disability in different Sensory-motor combinations (Table 5).

Table 4: Etiological spectrum of acute symptomatic pediatric convulsive status epilepticus

Etiology	Number of cases	Percent
Encephalitis	16	38.09%
Pyogenic meningitis	12	28.5%
CNS Tuberculosis	4	9.5%
Brain abscess	2	4.7%
Hypoglycemia	1	2.3%
Hypernatremia	1	2.3%
Hyponatremia	0	0.0%
ICH*	4	9.5%
ADEM#	2	4.7%
Total	42	

*Intracranial hemorrhage, #Acute demyelinating encephalomyelitis.

Table 5: The outcome of pediatric convulsive status epilepticus

Outcome	No of cases n=184	Percentage
Recovered without sequelae	138	75.0
Recovered with sequelae	10	5.5
Death	26	14.0
LAMA	10	5.5
Total	184	100

DISCUSSION

CSE, also known as convulsive status epilepticus, is an important and life-threatening form of epilepsy. This study is the first in our region to summarize the demography, etiology, and outcome of CSE.

In this prospective hospital-based observational study, the data of 184 cases of CSE in the age group 1 month–18 years were analyzed to develop standard operating procedures to decrease morbidity and mortality associated with CSE in developing nations. In our study, the mean age of the children was 4.9 years and 55.4% were male patients. The increased prevalence of CSE in children <5 years of age has been reported in various studies conducted across India (Chin,⁸ Bergamo et al.,⁹ and Admuthe et al.,¹⁰ in their study have also observed the mean age for the CSE 4.5 years and findings are consistent with our study.

In our study, the minimum distance travelled by the patients to reach the tertiary care hospital was 0.5 km and the maximum distance was 60 km (Mean of 23 km). The prehospital therapy with first-line AED was received by 48 patients (26.1%) and the rest 136 (73.9%) patients did not receive any type of therapy, although some of them had been referred to rural care health delivery system. Further, of 48 patients who had received prehospital therapy, only 32 were given the right drug in the right dose and 16 children had received improper medication or

drug dosage. All those patients who had received delayed or wrong treatment had adverse outcomes and therefore, there is great scope to improve outcomes in CSE, if the right treatment at the right time is given at doorsteps. Therefore, one of the important findings in our study was that to improve the immediate and long-term outcome of patients with CSE a common neurological emergency, the rural health-care delivery system must be upgraded and strengthened. A study conducted by Eriksson et al.,¹¹ found a very significant association between treatment delay of more than 30 min and response to AED (P=0.003). Hence, our research also eluded that CSE should be managed with internationally acclaimed protocol as early as possible and preferably within 5–10 min. To achieve such an overambitious goal, the emergency departments of the rural health-care system deserve to be strengthened and manned by critical care specialists.

The most common type of seizures in patients, who presented with CSE were generalized Tonic–Clonic seizures, observed in 154 (83.7%) cases, followed by partial seizures with secondary generalizations in 12% (26 cases). Meanwhile, CSE was the first presentation, without any significant past neurological history in 35% of patients and the remaining 65% of patients did have a previous history of seizures. The study conducted by Gulati et al. also found that in 53.3% 4patients, the status epilepticus was their first presentation to tertiary care hospital without any prior history of seizures.¹² The study was done by Garzon et al.,¹³ depicted that 40.6% of patients with CSE did not have any history of seizures, and CSE was their first presentation to the hospital. Therefore, SE can happen in any child without previous history of seizures or neurodevelopmental disorder and contingency plans should be always in place to decrease morbidity and mortality.

After doing a comprehensive workup of patients of CSE, our study revealed that the most common etiologies of CSE were remote symptomatic observed in 27.2%, acute CNS infection in 19.5%, febrile status in 19.5% and cryptogenic/idiopathic SD in 14.9% as is depicted in Table 3. The most common underlying cause for remote symptomatic seizures was posthypoxic ischemic encephalopathy and/or cerebral palsy. This was an important finding of our study, which indicates that although we have decreased the neonatal mortality rate to significant levels, not neonatal morbidity which has rather increased due to increased birth of premature babies, and advanced ventilatory management which save the life and not the intact neonate. Henceforth, our research findings suggest that although in the last decade, we have been successful in decreasing the neonatal mortality rate and our goal should be the survival of intact neonates, without long-term morbidity, which is still an unfinished agenda of neonatal care. We

need to upgrade and expand comprehensive neonatal services, neonatal resuscitation programs, and early child development programs.

Second, CNS infections were the second-most common cause of symptomatic CSE, ballooning around 19.6% of all cases. Although the expanded coverage of vaccination has decreased, the frequency and/or severity of bacterial causes of meningitis significantly extend in India, not the viral causes of CNS infection. Third, our study found that viral encephalitis was one of the common underlying infective causes of CSE and most of them were caused by enteroviruses and herpes simplex virus. In our study, interestingly, we did not find any case of Japanese encephalitis, West Nile encephalitis, cerebral malaria, or Dengue as the cause of CSE. These abovementioned diseases are mosquito (vector) borne diseases and do not occur in Kashmir, India. Because mosquitoes which act as vectors for these diseases do not thrive in the climatic conditions of Kashmir, India and as such should not be included in the differential diagnosis of acute CNS infections, encephalitis and altered mental status or CSE. Therefore, recommending a CSF panel for these viral-borne diseases is a waste of resources in Kashmir, India.

Meanwhile, Hui et al.,¹⁴ in their study, have observed that acute CNS infection was an independent adverse predictor of poor outcomes in CSE.

In our study, 10 patients left the study and 174 patients completed the study. Among 174 patients, 148 (85.1%) patients recovered and 26 (14.9%) patients died. The mortality rate in the present study was 14.9% and the mortality rate in children with CSE ranged from 14 to 33% in different other Indian studies, whereas the studies from developed countries report mortality of 9–11%.^{9,15-18} The risk factors that were significantly associated with mortality in this study, included longer duration of status, acute symptomatic etiology, the requirement of ventilatory support, and circulatory impairment at the time of admission to the hospital. Similar risk factors were found in other studies.^{10,15-17}

In our study, the outcome was good among cases who had traveled <10 km and was very high among 24 children who had traveled more than 40 km. The study revealed that the lower the distance to the treating hospital, the better the outcome and vice versa. This association was statistically significant ($P < 0.05$) and this mandates that all the patients of CSE should get priority treatment at their doorsteps which is possible only by strengthening the rural health-care delivery system.

Results of our study suggest that different etiologies, distance from the hospital, and past neurological insults

are directly affecting the outcomes of SE. Previously, in a systemic review of different studies, the observation was made that outcome of CSE was affected by the underlying causative factor of CSE.

Furthermore, our study concluded that etiologies of pediatric CSE differ from the causes resulting in CSE in adult patients. As far as the etiological spectrum was considered, febrile status comprised the highest number, followed by acute CNS infections and remote causes of CSE.

Results of our study suggest that etiologies are directly affecting the outcomes of SE. Previously, a systemic review of different studies was performed in which observation was made that outcome of CSE was affected by the causative factor of SE. It was also suggested in that systemic review that current data were insufficient to demonstrate the relation of the age of onset of SE, treatment provided and duration of the seizures with the possible outcome.¹⁸

Acute symptomatic seizures and increased length of hospital stay after admission are also associated with higher rates of mortality. The most adverse outcome, i.e., mortality was related to the age of the patients, cause of SE, distance from the hospital and prior treatment received at rural health care as suggested by a previous analysis.¹⁹

Our study adds that CNS infections are a common cause of pediatric CSE in this part of the world, but we did not find any case of vector-borne disease in our study. The different mosquitoes which act as vectors for above mentioned CNS infections do not thrive in the climate of Kashmir, India. Therefore, vector-borne viral diseases should be considered as a rare possibility in the differential diagnosis of acute CNS infections, encephalitis and altered mental status in Kashmir, India. Therefore, in our part of the world patients with febrile pediatric CSE should be empirically treated with acyclovir and CSF analysis done for all viruses other than arboviruses and vector-borne CNS encephalitis.

Limitations of the study

Some patients in our study have travelled a long distance without receiving any prehospital treatment and presented to emergency in a moribund condition with hemodynamic instability and severe acidosis and that might have confounded the outcome of the study.

CONCLUSION

The finding of our study depicts that although we have decreased neonatal mortality rate to significant levels, long-

term morbidity is still an unfinished agenda of neonatal care. We need to upgrade and expand comprehensive neonatal services, neonatal resuscitation programs and early child development programs.

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SMM- Definition of intellectual content, literature survey, prepared first draft of manuscript, data collection, data analysis, manuscript preparation; **SAN**- Concept, design, clinical protocol, manuscript preparation, editing, submitting manuscript and revision; **ST**- Design of study, statistical analysis, and interpretation; coordination and manuscript revision.

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