OUTCOMES OF REFRACTORY STATUS EPILEPTICUS IN CHILDREN

Javeria Raza Alvi, Areeba Wasim, Mohsin Ali, Muhammad Athar Khalily, Zia-Ur-Rehman, Tipu Sultan

The Children's Hospital and Institute of Child Health, Lahore Pakistan

ABSTRACT

Objective: To determine the outcome of Refractory Status Epilepticus (RSE) in children and the factors affecting the outcome.
Study Design: Cross-sectional study.
Place and Duration of Study: High Dependency Unit of Pediatrics Neurology Department at the Children's Hospital and Institute of Child Health, from Aug 2019 to Mar 2020.
Methodology: This study was conducted on the children presenting with refractory status epilepticus. Structured proforma was used for recording predictive factors. Modified Rankin scale prior to the presentation and Glasgow Coma Scale at presentation were documented and compared with the discharge scores.
Results: Out of 75 children, 46 (61.4%) were males with mean age of 4.43 ± 3.47 years. Common etiologies were acute symptomatic in 37 (49.3%), progressive encephalopathy in 19 (25.3%), static encephalopathy in 9 (11.9%), remote symptomatic in 4 (5.3%), acute on remote symptomatic in 3 (4.0%), idiopathic and unclassified in remaining patients. Mean time between seizures onset and first benzodiazepine injection was 44 ± 36 minutes. Duration of RSE was <24 hours in 17 (22.7%), 24-48 hours in 15 (20.0%), 48-72 hours in 14 (18.6%), 72-96 hours in 12 (16%) and >96 hours in 17 (22.7%). At discharge 33 (44%) returned to baseline, 31 (41%) developed neurological disability while 11 (15%) expired during the stay. Etiology and duration of status epilepticus had significant impact on outcome with *p*-value of 0.021 and 0.041, respectively.
Conclusion: Acute etiology was associated with higher mortality whereas return to baseline was also fair among survivors. This poses implications for emergency management to significantly improve the treatment outcomes.

Keywords: Etiology, Outcome, Pediatrics, Status epilepticus.

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INTRODUCTION

Status Epilepticus (SE) is one of the most frequent childhood neurological emergency, characterised by diverse etiology and if prolonged, associated with unfavourable outcome particularly in case of refractory status epilepticus.[1] A study done in Thailand estimated that 5.10 children per 100,000 population suffered from SE every year and incidence in the developing countries is even higher.[2,3] Another study quoted incidence of 20/100,000 children.[4]

SE is a life threatening problem where there are continuous seizures for 5 minutes or more, or repetitive seizures without regaining consciousness.[3] It results from failure of mechanisms to terminate seizures resulting in injury to neurons and cell death.[5] Duration of seizure activity from time point t-1 to time point t -2 is important in interpreting the short and long-term consequences.[6] RSE is defined as continuous seizures that fails to respond to minimum of 2 anti-epileptic drugs including one benzodiazepine (BZD) group. It is estimated that 23-48% of status epilepticus children progressed to RSE.[3] Etiology may vary and acute infection of central nervous system is among the most common causes followed by stroke, resistant epilepsy (genetic or acquired), degenerative brain disease or intoxication.[7,8] However, at times, it is challenging to identify the underlying cause instantly, resulting in prolonged duration of seizures.[8] RSE occurrence is more common with acute etiology as compared to the chronic epilepsy.[3] RSE is difficult to treat, requiring high doses of antiepileptic medications, continuous infusions of benzodiazepine (midazolam or diazepam) or anaesthetic agents along with intensive monitoring of vital signs.[7]

Patients suffering from RSE may develop recurrent status epilepticus, acute hippocampal injury, poor quality of life, intellectual or behavioural impairment or even death.[9] Mortality is associated with potentially acute etiology and impaired consciousness level at presentation but there is no significant association with gender, seizure type or history.[10]

Prognosis of RSE is not well characterised, particularly in local setting of Pakistan. The rationale of the study was to assess the early outcome of RSE patients, while keeping in mind the impact of outcome

Correspondence: Dr Javeria Raza Alvi, Pediatric Neurology, The Children's Hospital and Institute of Child Health, Lahore Pakistan
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predictive factors that significantly influence the prognosis.

METHODOLOGY

It was a hospital based study conducted at the High Dependency Unit of Pediatrics Neurology Department at the Children's Hospital and Institute of Child Health, Lahore from August 2019 to March 2020 after obtaining the ethical approval from the institutional review board (ltr no. 2019-50-CHICH). Sample size was taken as 75 patients calculated by taking incidence of refractory status epilepticus as 5.10/100,000 population with 95% confidence interval and 5% margin of error using Open-Epi calculator. Sampling technique was non-probability consecutive.

Inclusion Criteria: Patients of both genders, between the ages of 1 month to 18 years presenting with convulsive refractory status epilepticus (including all seizure types irrespective of their etiology) were included in the study.

Exclusion Criteria: Patients with non-convulsive status epilepticus were excluded from this study because it was difficult to interpret the seizures and its time span and thus response to anti-epileptic drugs.

Refractory status epilepticus (RSE) was defined as continuous seizures that failed to respond to at least two anti-epileptic drugs including one from benzodiazepine (BZD) group (midazolam or diazepam) and one other antiepileptic drug either Phenytoin, Sodium Valproate or Levetiracetam. The study included children who presented with RSE in emergency or progressed to RSE after admission. Data was recorded on a pre-designed proforma including age, gender, consanguinity, any significant past history, etiology of SE, duration and time between the onset of seizure to first Benzodiazepine injection. Etiology was defined in the groups. Acute symptomatic etiology in which Status Epilepticus (SE) occurred in a previously normal child within 1 week of acute CNS injury (infection due to bacterial, viral or autoimmune causes), acute demyelinating disorders and prolonged febrile seizures. Prolonged febrile seizures were defined as SE in a normal child between the age of 6 months to 5 years during an episode of febrile illness in absence of CNS infection.[11] Remote symptomatic etiology was defined as SE in a patient where CNS injury had occurred at least a week before presentation. Acute on remote symptomatic etiology was defined as SE occurring within 1 week of acute neurological insult in a previous neurologically impaired child.[11] Progressive encephalopathy included neurodegenerative disorders, epileptic encephalopathies and neurometabolic disorders while static encephalopathy included cerebral palsy. Idiopathic epilepsy was defined as second unprovoked seizure leading to SE.[11] Unclassified when unable to place in other categories. In order to define the etiology, neuroimaging, cerebrospinal fluid analysis (when indicated), electroencephalography (EEG) and any other relevant investigations were also performed. In subjects with previous neurological diagnosis, previous clinical details, imaging, EEG results and prescriptions were reviewed. Outcome was defined by using modified Rankin score (0-6) and taken as either return to baseline (0-1 score), neurological disability (2-5 score) or mortality (6 score). Neurological disability was further divided into mild (2 score), moderate (3 score) and severe disability (4-5 score) based on the mRankin score. Baseline Glasgow coma scale was also taken with modified Rankin score to help define outcome in previously neurologically disabled children. Chi-square test was used for calculating association between outcome and different variables including etiology, duration of status epilepticus and association between etiology with seizure type & age. The *p*-value of ≤0.05 was considered significant.

RESULTS

Total of 75 children were enrolled in the study out of which 46 (61.4%) were males and 29 (38.6%) were females. The mean age of the patients was 4.43 ± 3.47 years. Distribution of age in various subgroups showed that 32 patients (42.7%) were between 1 month to 2 years of age, 25 patients (33.3%) were 2-6 years, 16 patients (21.3%) were 6-12 years and 2 patients (2.7%) were 12-18 years of age. Table-I represents patients characteristics and etiology. Among the enrolled patients, 33 (44%) returned to baseline while 31 (41%) developed neurological disability at discharge, and 11 (15%) expired during hospital stay. Neurological disability was mild in 3 (9%) cases, moderate in 12 (39%) cases and severe in 16 (52%) cases as shown in Figure-1. 7 (9%) patients had mild disability, 29 (39%) patients moderate disability and 39 (52%) severe disability shown in Figure-2. Acute symptomatic etiology was found in all age group but most common in early ages while progressive encephalopathy was almost equally divided in early infancy and late childhood (p<0.01). Generalized seizures had significant association with etiology (p<0.01) shown in Table-II. Etiology was associated with morbidity in terms of neurological disability and mortality with significant *p*-value (0.021). Acute symptomatic etiology was the most common cause of RSE with 37 patients (49.3%) followed by pro-

gressive encephalopathy in 19 patients. (25.3%). There were most commonly seen with acute etiology and the prolonged the duration of SE, the poorer was the outcome (p=0.041). There was no association across age groups, and time of onset of seizure and first benzodiazepine injection with the outcome (Table-III).

Table-I: Patient characteristics and etiology.

Characteristics	Values
Mean age, years (SD)	4.43 ± 3.47
Gender, n (%)	
Male	46 (61.4%)
Female	29 (38.6%)
Seizure Type, n (%)	
Generalized	40 (53.3%)
Focal	14 (18.7%)
Focal with bilateral tonic clonic	18 (24%)
Mixed (clonic, tonic, myoclonic)	3 (4%)
Mean time between seizure onset and 1st Benzodiazepine (min)	44 ± 36
Duration of Refractory Status Epilepticus , n (%)	
<24 hours	19 (25.3%)
24-48 hours	14 (18.6%)
48-72 hours	14 (18.6%)
72-96 hours	11 (14.7%)
>96 hours	17 (22.8%)
Etiology, n (%)	
Acute symptomatic	37 (49.3%)
Central Nervous system infection	29 (38.6%)
Acute Demyelinating Encephalomyelitis	1 (1.33%)
Autoimmune encephalitis	3(4.0%)
Prolonged febrile status	4 (5.3%)
Progressive encephalopathy	19 (25.3%)
Neuro-degenerative disorder	9 (11.9%)
Epileptic Encephalopathy	8 (10.7%)
Metabolic disorder	2 (2.7%)
Static encephalopathy	9 (12%)
Remote symptomatic	4 (5.3%)
Structural epilepsy	3 (4.0%)
Post meningitic sequalae	1 (1.3%)
Acute on remote symptomatic	3 (4%)
Idiopathic epilepsy	2 (2.7%)
Unclassified	1 (1.4%)

DISCUSSION

Refractory status epilepticus (RSE) affects approximately one third of patients presenting with status epilepticus.[12,13] In this study of 75 enrolled children with convulsive RSE, we found that the outcome was guarded in terms of high mortality rate (15%) and neurological disability (40%) but with prompt management, return to baseline among survivors was also fair (45%). According to an international study regarding the outcome, 21% of status epilepticus patients progressed to RSE, neurological sequalae were reported in 22% cases, while case mortality rate was 11%, close to our study results but 67% returned to baseline, higher than our study.[14] Another systematic review of different studies on the outcome of convulsive status epilepticus (CSE) showed a better outcome in terms of short term mortality between 2.7-5.2% while morbidity of less than 15%.[13] A local study on convulsive SE correlated the etiology with the outcome and concluded acute etiology as a concerning cause for SE and poor outcome with 16% patients developing mental retardation, 22% mortality while only 22% recovered completely.[15]

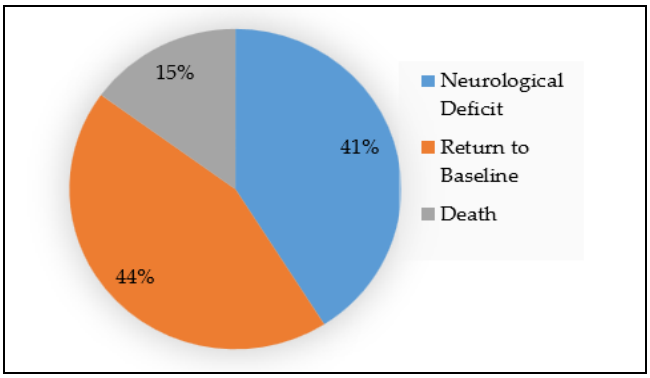

Figure-1: Percentage of patients according to outcomes of refractory status epilepticus.

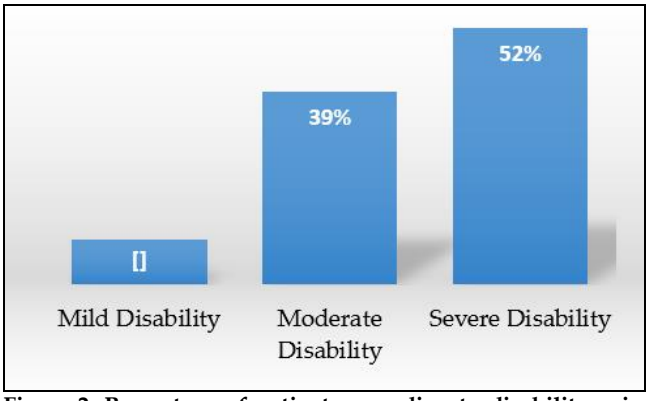

Figure-2: Percentage of patients according to disability using modified Rankin score.

Etiology is the major outcome predicting factor.[16] In a study on refractory status epilepticus, they found the occurrence of RSE more common in patients with new onset seizures rather than chronic epilepsy and central nervous system infections and head trauma being more dominant etiologies in developing countries.[3,17] In a study conducted on fifty children with CSE, 20 children progressed to RSE and CNS infection was the most common etiology found.[18] Another study emphasized on the substantial morbidity and mortality associated with CSE and etiology but not duration of

Table-II: Relationship of etiology with age and seizure type.

Etiology	Age in groups (n=75)				*p*-value
	1 month - 2 years	>2 - 6 years	>6 - 12 years	>12 - 18 years	
Acute symptomatic	13 (17.4%)	16 (21.3%)	8 (10.7%)	-	
Remote symptomatic	1 (1.3%)	1 (1.3%)	-	2 (2.7%)	
Acute on remote	1 (1.3%)	1 (1.3%)	1 (1.3%)	-	
Progressive encephalopathy	8 (10.7%)	4 (5.4%)	7 (9.3%)	-	
Static encephalopathy	6 (8%)	3 (4%)	-	-	
Idiopathic epilepsy	2 (2.7%)	-	-	-	
Unclassified	1 (1.3%)	-	-	-	
	Seizure type (n=75)				
	Generalized	Focal	Mixed	Focal with bilateral tonic clonic	0.000
Acute symptomatic	27 (36%)	3 (4%)	-	7 (9.3%)	
Remote symptomatic	-	4 (5.3%)	-	-	
Acute on remote	-	-	-	3 (4%)	
Progressive encephalopathy	8 (10.7%)	6 (8%)	2 (2.7%)	3 (4%)	
Static encephalopathy	5 (6.8%)	-	1 (1.3%)	3 (4%)	
Idiopathic epilepsy	-	1 (1.3%)	-	1 (1.3%)	
Unclassified	-	-	-	1 (1.3%)	

Table-III: Relationship between outcome and predictive factors.

Variable	Outcome			*p*-value
	Return to Baseline	Neurological Disability	Death	
	n=33 (44%)	n=31 (41%)	n=11 (15%)	
Etiology: n (%)				
Acute symptomatic	13 (17.3)	18 (23.8)	6 (8.2)	
Remote symptomatic	4 (5.3)	-	-	
Acute on remote symptomatic	-	1 (1.3)	2 (2.8)	0.021
Progressive encephalopathy	10 (13.4)	7 (9.3)	2 (2.8)	
Static encephalopathy	4 (5.3)	5 (6.6)	-	
Idiopathic epilepsy	2 (2.7)	-	-	
Unclassified	-	-	1(1.2)	
Duration of Refractory Status Epilepticus: n (%)				
< 24 hours	13 (17.3)	4 (5.3)	2 (2.7)	
24-48 hours	8 (10.7)	5 (6.7)	1 (1.4)	0.041
48-72 hours	5 (6.7)	8 (10.5)	1 (1.4)	
72-96 hours	4 (5.3)	6 (8.0)	1 (1.4)	
96 hours	3 (4.0)	8 (10.5)	6 (8.1)	
Mean time between onset of seizures to 1st Benzodiazepine injection: n (%)				
< 10 minutes	7 (9.4)	4 (5.4)	-	0.530
10-30 minutes	13 (17.3)	13 (17.1)	5 (6.8)	
>30 minutes	13 (17.3)	14 (18.5)	6 (8.2)	

status epilepticus was the main determinant.[19] 53.3% children in our study also had acute etiology including both acute symptomatic and acute on remote symptomatic but about 47% patients were previously diagnosed with epilepsy and their etiology included progressive and static encephalopathy, remote symptomatic and genetic epilepsy. This is close to the western data on RSE that showed forty percent of the children presenting with SE had previous neurological abnormality and fifteen percent had history of epilepsy.[17] It was reported in another study that etiology was the most important factor of outcome of status epilepticus but they found remote symptomatic etiology secondary to gliosis being the most common.[14]

Younger age along with central nervous system infection was an important factor for refractory status epilepticus which became malignant status epilepticus as reported by a study. These children had a longer duration of status epilepticus and thus a prolonged hospital stay and neurological disability.[20] It was described in another study that likewise etiology, age is also a significant predictive factor for convulsive status epilepticus with remarkable difference across various age groups, being more common in extremes of age.[17]

Contrary to this study, another study concluded that there was no significant relationship observed between RSE and the patients' age, gender and type of seizure.[10] Though our study also concluded that there was a significant association between younger age, etiology and seizure type. The proportion of generalized seizures was 73.6% in a retrospective study on 189 children with status epilepticus and concluded that neurologic outcomes and recurrence of SE were found to be strongly associated with etiology and seizure type but age and seizure duration had no effect on outcome.[21,22] In our study, generalized seizure type was also the most common seizure type (53.3%). It was stated in a study that prolonged duration of status epilepticus before recovery had a significant impact and was associated with worse outcome. Quoted in another study, the longer duration of seizure activity, the greater the risk of morbidity and mortality and the same was reported in our study as well.[23]

LIMITATION OF STUDY

We did not identify the long-term consequences that a single episode of refractory seizures could cause in terms of cognitive, behavioural and sensory impairments.

CONCLUSION

Acute etiology and longer duration of refractory status epilepticus were associated with higher morbidity and mortality; however, return to baseline was also fair in the survivors. This poses implications for emergency management to focus on reducing the duration of status epilepticus for better outcomes.

Conflict of Interest: None.

Authors' Contribution

JRA: Concept, design, data collection, data analysis, manuscript writing, AW: Data collection, MA: Data collection, MAK: Data collection, ZUR: Manuscript review and editing, TS: Manuscript review, editing and final approval.

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