

Study of Refractory Status Epilepticus from a Tertiary Care Center

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Abstract

Objectives: To determine the proportion of refractory status epilepticus (RSE) and super-RSE (SRSE) among patients with status epilepticus (SE) and to analyze RSE and non-RSE (NRSE) in terms of etiology and predictors for RSE. **Materials and Methods:** Patients were identified from discharge summaries database with keywords of SE and records of the portable electroencephalogram (EEG) machine from January 2011 to March 2016. **Results:** Two hundred and eighteen events were included in the study with 114 (52.3%) males, bimodal age preponderance age <5 years 30%, and second peak in age 15–65 years 52.8%, preexisting seizures were present in 34.4% ($n = 75$). Nearly 77.1% had NRSE ($n = 168$) and 22.9% had RSE ($n = 50$). This included 17 patients with SRSE ($n = 17$, 7.8% of all SE). Central nervous system (CNS) infection was a single largest etiological group in SE (69/218, 31.7%). In RSE, autoimmune encephalitis (17/50) and CNS infection (13/50) were the largest groups. *De novo* seizures ($P = 0.007$), low sensorium at admission ($P = 0.001$), low albumin at admission ($P = 0.002$), and first EEG being abnormal ($P = 0.001$) were risk factors on bivariate analysis. An unfavorable status epilepticus severity score (STESS) was predictive for RSE ($P = 0.001$). On multivariate analysis, *de novo* seizures ($P = 0.009$) and abnormal EEG at admission ($P = 0.03$) were predictive for RSE. **Conclusions:** Fifty patients had RSE (22.9%), of which 17 went on to become SRSE (7.8%). Unfavorable STESS score was predictive for RSE on bivariate analysis. On multivariate analysis, *de novo* seizures and abnormal initial EEG were predictors of RSE.

Keywords: Nonrefractory status epilepticus, refractory status epilepticus, status epilepticus, status epilepticus severity score, super-refractory status epilepticus

INTRODUCTION

Status epilepticus (SE) is one of the common causes of neurological morbidity and mortality with annual incidence of around 10–41/100,000 individuals.^[1] The definition of SE has evolved over the past three decades, and currently, SE is defined as any seizure which continues for more than 5 min.^[2] The most recent ILAE classification recognizes that the duration would depend on the semiological type of SE.^[3] The task force has proposed two time points, t1 and t2, with t1 referring to point where treatment has to be initiated, and T2 as the point beyond which long-term consequences become more likely. SE being heterogeneous in terms of definition and causes; the management has evolved mostly from consensus rather than strong evidence from randomized controlled clinical trials.

Mortality rates in SE have been reported to be about 15%–20%.^[4] Refractory SE (RSE) had a mortality rate of about 35% in one pooled review, and super-RSE (SRSE) has a mortality of 30% to 50% in various studies.^[5] There is a paucity

of studies assessing etiology, frequency, early predictors, and outcome in SE, RSE, and SRSE in the Indian setting.

The objective of the present study was to analyze the proportion of RSE and SRSE among the patients presenting with SE to a tertiary care center and to identify the etiologies and predictors for RSE in these patients.

MATERIALS AND METHODS

The study was conducted in a 2800-bedded tertiary care hospital in South India. The study was approved by the Institutional review board. We included the data of children and adults with SE presenting to neurology ward and neurology intensive care unit, medical intensive care unit, pediatric

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How to cite this article: Kohli S, Pasangulapati SB, Yoganathan S, Rynjah GL, Prabhakar AT, Aaron S, *et al.* Study of refractory status epilepticus from a tertiary care center. *Ann Indian Acad Neurol* 2017;20:116-21.

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DOI:
10.4103/aian.AIAN_385_16

intensive care unit, and emergency room from January 2011 to March 2016.

To ensure the identification of all the cases, computer-based search was done on discharge summaries available on the clinical workstation. The portable electroencephalogram (EEG) of the department was also screened for cases from January 2011 to 2016. Based on previous studies, the sample size was derived as 272 for finding the prevalence of RSE in SE, with a precision of 5% and 95% confidence interval (CI).^[6] A total of 218 patients with SE were included in the study. SE was defined as any seizure which lasted more than 5 min. RSE was defined as any SE which required more than two antiepileptic drugs for the control of seizures. SRSE was defined as SE continuing for 24 h or more with the use of anesthetic agents or recurrence of seizures on weaning off the anesthetic agents following a 24 h seizure-free period.^[7]

Baseline demographic data, seizure semiology at onset, duration of seizures, preexisting seizures, type of SE, etiology, status epilepticus severity score (STESS), serum albumin, and outcome were recorded from database on Clinical Workstation, and EEG was reviewed from EEG database. We reviewed the first EEG taken after admission, usually done within 24 h of admission over a period of 30–45 min. The episodes were classified as acute symptomatic, remote symptomatic, and cryptogenic.^[8] All patients were managed per protocol given in Figure 1.

The data was analyzed using SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA). The patients were analyzed in terms of frequency, etiology, and outcome. The positive variables or predictors of RSE were further analyzed by logistic bivariate analysis for the odds ratio for the prediction of RSE. The variables which were significant on bivariate logistic regression were further analyzed by multivariate logistic regression.

RESULTS

Two hundred and eighteen events of SE were included in the analysis. No patient had recurrent events. There were 114 males. Nearly 43.5% were aged <15 years. The onset of SE was *de novo* in 143 patients (65.6%). One hundred and sixty-eight (77.1%) were non-RSE (NRSE) and fifty (22.9%) were RSE. Of these, 50 with RSE and 17 had SRSE (7.8% of total). Overall, central nervous system (CNS) infection was a single largest etiological group (31.7%) with metabolic derangement in 12.8% and cerebrovascular accidents (CVAs) in 9.6%. Cryptogenic seizures accounted for one-fifth of the patients. Demographic and Baseline characteristics are depicted in Table 1. Etiological distribution of SE among NRSE, RSE, and SRSE is shown in Table 2.

Bivariate analysis for predictors of RSE in the study population showed that *de novo* seizures ($P = 0.007$), level of consciousness ($P = 0.001$), low serum albumin ($P = 0.002$), and abnormal EEG ($P = 0.001$) were significant factors as shown in Table 3. Age more than 15 years was

Table 1: Demographic and baseline characteristics

Baseline characteristics	Values (%)
Gender	
Male	114 (52.3)
Female	104 (47.7)
Age (years)	
<15	95 (43.5)
>15	123 (56.5)
Preexisting epilepsy	
Yes	75 (34.4)
No	143 (65.6)
Type of SE	
NRSE	168 (77.1)
RSE	33 (15.1)
SRSE	17 (7.8)
Classification of SE based on etiology	
Acute symptomatic	164 (75.2)
Remote symptomatic	42 (19.3)
Cryptogenic	12 (5.5)
Classification of SE based on type of seizure at presentation	
CPS	6 (2.8)
GTCS	166 (76.1)
NCSE	14 (6.4)
Myoclonic status	12 (5.5)
Focal with secondary generalization	18 (8.3)
Tonic seizures	2 (0.9)
STESS score	
Favorable	65 (29.8)
Unfavorable	153 (70.2)
Outcome at discharge mRS	
1	53 (24.3)
2	58 (26.6)
3	32 (14.6)
4	24 (11)
5	15 (6.8)
6	27 (12.4)
Data not available	9 (4.1)
Serum albumin level	
Normal	93 (42.7)
Low	84 (38.5)
Data not available	41 (18.8)

NRSE = Nonrefractory status epilepticus, RSE = Refractory status epilepticus, SRSE = Super-refractory status epilepticus, SE = Status epilepticus, CPS = Complex partial seizures, GTCS = Generalized tonic-clonic seizures, NCSE = Nonconvulsive status epilepticus, STESS = Status epilepticus severity score, mRS = Modified Rankin Scale

associated with a higher risk of RSE though this was not statistically significant ($P = 0.062$). There were 27 deaths (12.4%) during hospitalization. Cause of death was central herniation due to raised intracranial pressure in one and septicemia in other 26.

Multivariate analysis for the variables which was statistically significant on bivariate analysis showed a significant association with *de novo* seizures ($P = 0.009$) and abnormal EEG ($P = 0.03$) [Table 4].

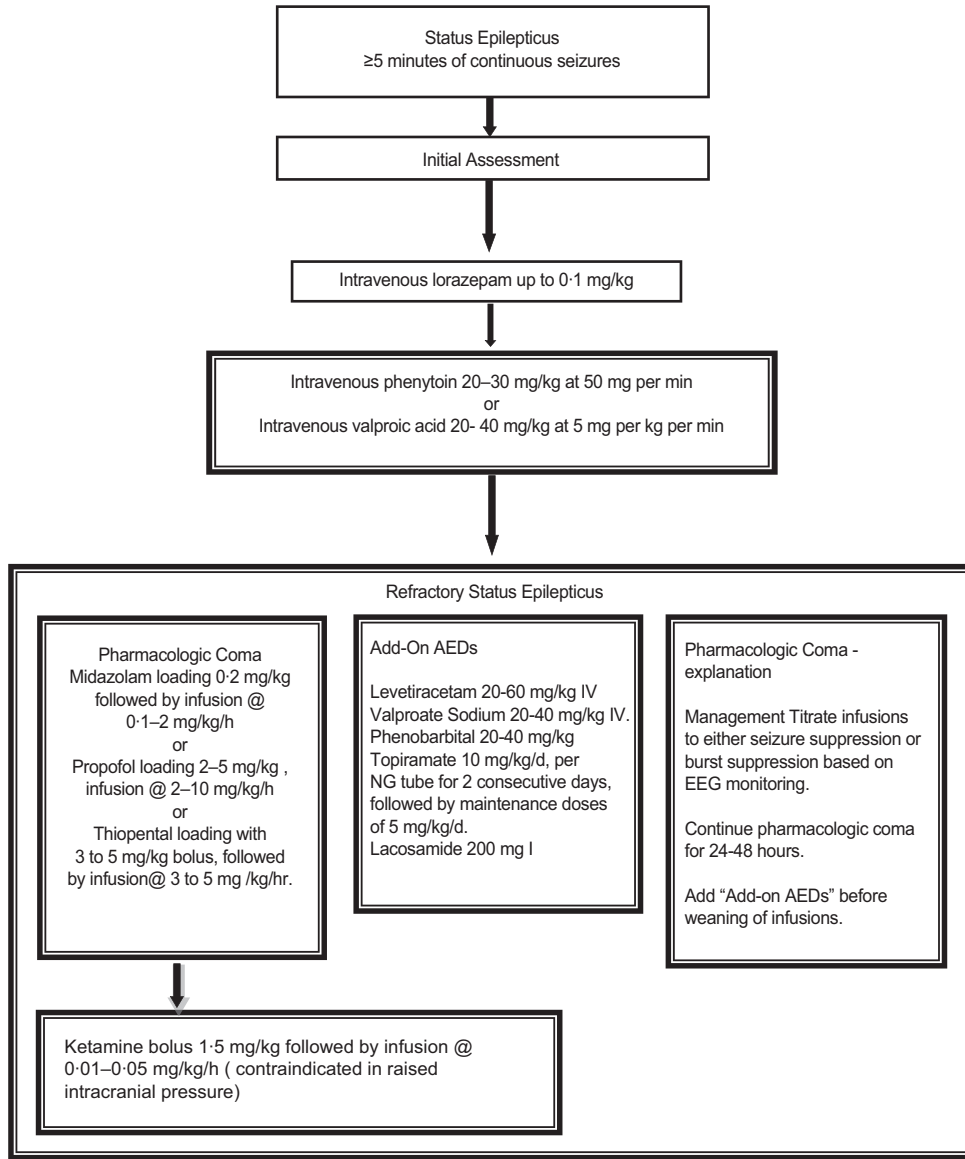


Figure 1: Our protocol for management of status epilepticus

Table 2: Etiological distribution in patients with status epilepticus

Etiology	NRSE	RSE	SRSE
Autoimmune	Nil	6	11
AED withdrawal	13	1	Nil
Metabolic	19	7	2
CVA	18	3	Nil
Unknown	24	1	Nil
Others	38	6	Nil
CNS infection	56	9	4
Total	168	33	17

AED = Antiepileptic drugs, CVA = Cerebrovascular accident, CNS = Central nervous system, Others = Structural abnormalities, toxins, trauma and breakthrough seizures, NRSE = Nonrefractory status epilepticus, RSE = Refractory status epilepticus, STESS = Status epilepticus severity score

The EEG recordings of patients in the study are shown in Table 5. In bivariate analysis using normal and “abnormal” EEGs as variables, an abnormal EEG was significant. This remained so on multivariate analysis.

DISCUSSION

The incidence of SE was more common in age groups <5 years and between 40 and 60 years corresponding to a U-shaped age distribution previously noted by others.^[9-11]

Two previous retrospective studies found the incidence of RSE among SE to be 43% and 31%.^[12,13] A previous prospective observational study^[6] found the incidence of RSE among patients with SE to be 22.6% which is closer to our study (22.9%). There have been only a few studies on SRSE.

Table 3: Prediction of refractory status epilepticus in study group by bivariate analysis

Risk variables	Group		OR	95% CI	P
	NRSE, n (%)	RSE, n (%)			
Age					
<15	79 (83.2)	16 (16.8)	1.00	0.968-3.675	0.062
>15	89 (72.4)	34 (27.7)	1.886		
Sex					
Male	91 (79.8)	23 (20.2)	1.00	0.736-2.614	0.311
Female	77 (74.0)	27 (26.0)	1.387		
Preexisting seizures					
Yes	66 (88.0)	9 (12.0)	1.00	1.344-6.463	0.007
No	102 (71.3)	41 (50.0)	2.948		
Level of consciousness					
Alert/drowsy	63 (91.3)	91.3 (8.7)	1.00	1.774-10.93	0.001
Stupor/coma	105 (70.5)	70.5 (29.5)	4.400		
Seizure type at onset					
Convulsive	160 (78.4)	44 (21.6)	1.00	0.121-1.112	0.76
Nonconvulsive	8 (57.1)	6 (42.9)	0.367		
Seizure classification					
Symptomatic	156 (75.7)	50 (24.3)	NA	NA	0.52
Cryptogenic	12 (100)	0			
Albumin					
Normal	78 (83.9)	15 (16.1)	1.00	1.498-6.176	0.002
Abnormal/low	53 (63.1)	31 (36.9)	3.042		
EEG					
Normal	70 (90.9)	7 (9.1)	1.00	1.886-10.528	0.001
Abnormal	92 (69.2)	41 (31.8)	4.457		
STESS					
Favorable	60 (92.3)	5 (7.7)	1.00	1.883-13.274	0.001
Unfavorable	108 (70.6)	45 (29.4)	5.000		

NRSE = Nonrefractory status epilepticus, RSE = Refractory status epilepticus, EEG = Electroencephalogram, OR = Odds ratio, STESS = Status epilepticus severity score, CI = Confidence interval, NA = Not available

Table 4: Multivariate analysis for variables which were significant in bivariate model

Risk variable	OR	95% CI	P
Age			
<15	0.61	0.35-1.85	0.80
>15	1.00		
Albumin levels			
Normal	1.00	0.79-4.22	0.16
Low	1.83		
Level of consciousness			
Alert/drowsy	1.00	0.87-8.68	0.84
Stupor/coma	2.75		
EEG			
Normal	1.00	1.13-8.45	0.03
Abnormal	3.1		
Preexisting seizures			
Yes	1.00	1.38-10.43	0.009
No	3.8		

EEG = Electroencephalogram, CI = Confidence interval, OR = Odds ratio

A review by Ferlisi and Shorvon *et al.* on SRSE reported 15% of all cases of SE admitted to hospital were likely to become

SRSE.^[5] In our study, the incidence was 7.8%. In this study, 65.6% of SE were related to *de novo* seizures and were more likely to develop RSE (odds ratio 2.9). Similar findings were observed by Novy *et al.*^[6] One retrospective study found SE due to *de novo* seizures in 90%,^[14] whereas another prospective study reported about 58% of SE (70% among elderly) had *de novo* seizures.^[9]

Etiological analysis for SE in our study revealed that CNS infection was the most common cause constituting 32%. This was followed by metabolic derangements in 12.8%, unknown or idiopathic in 11.5%, CVAs in 9.6%, and autoimmune encephalitis in nearly 8%. Other etiologies included AED withdrawal, breakthrough seizures, poisoning, trauma, and congenital malformations. Cascino *et al.* described CNS infections in 17%, hypoxia in 20%, CVAs in 18%, unknown in 14%, and others less than 10%.^[14]

There were 164 (75.2%) patients with acute symptomatic seizures, 42 (19.3%) with remote symptomatic, and 12 (5.5%) with cryptogenic SE, respectively. In the prospective study in Richmond, Virginia, remote symptomatic etiology was observed in 39% of children and 24% of adults, whereas acute

Table 5: Initial electroencephalogram abnormalities in patients with status epilepticus

EEG findings	NRSE (n=168)	RSE (n=50)
Normal	63	7
Electrographic seizures	11	5
PLEDs	6	11
IEDs except PLEDs	34	10
Only background abnormalities	48	14
Data not available	6	3

EEG = Electroencephalogram, PLEDs = Periodic lateralized epileptiform discharges, IEDs = Interictal epileptiform discharges, NRSE = Nonrefractory status epilepticus, RSE = Refractory status epilepticus

symptomatic etiology was seen in 52% of children.^[9] Novy *et al.* described acute symptomatic, remote symptomatic, and cryptogenic seizures in 59%, 17%, and 8% of patients, respectively.^[6] An audit on SE from India had found 60% remote symptomatic and 16% acute symptomatic.^[15] The considerable variation in these reports could be related to referral bias or age groups studied.

STESS score was initially created for assessment of in-hospital mortality.^[16] However, subsequent studies showed a role for STESS for predicting RSE.^[17] In our study, STESS score of 0–2 was considered as favorable and 3–6 was considered as unfavorable. Of the fifty patients with RSE, 45 had unfavorable STESS. Of the 168 patients with NRSE, 108 had unfavorable STESS. On bivariate analysis, the odds ratio for unfavorable STESS leading to RSE was 5. While some have reported unfavorable STESS score was associated with poor outcome in RSE,^[18] the prospective study by Novy *et al.* did not find unfavorable STESS statistically significant in multivariate regression. However, in their study, impairment of consciousness at onset and *de novo* episodes were independent risk factors for RSE which were components in STESS.^[6] This study also showed that impaired consciousness and *de novo* seizures were independent risk factors for RSE. Further studies are likely to clarify the role of STESS in the prediction of RSE.

In our study, patients with low albumin were 3 times more likely to develop RSE ($P=0.002$, 95% CI: 1.498–6.176). Sutter *et al.* found low serum albumin to have 2.3 times the odds of developing RSE.^[19] Other acute phase reactant proteins have not been found significant.^[20]

The first EEG being “abnormal” was associated with RSE more than NRSE and was statistically significant, $P=0.001$ with 95% CI of 1.886–10.528. We attempted to further analyze the relation of admission level of consciousness (awake, drowsy, stupor, and coma) and first EEG. There was a significant association of abnormal EEG with RSE in the group which presented in coma ($P=0.003$). However, we could not get data on the sensorium at the exact time of recording first EEG as this was done within the first 24 h while the level of consciousness was recorded from initial

admission notes. Abnormal initial EEGs were seen in 15 out of 17 patients with autoimmune encephalitis, all of whom went on to develop RSE.

CONCLUSIONS

Nearly 22.9% patients with SE developed RSE, and 7.8% had SRSE. *De novo* seizures and an EEG on 1st day were statistically significant independent factors for developing RSE. Patients with acute symptomatic etiology, low serum albumin at admission, and low sensorium (stupor/coma) were also more likely to develop RSE on bivariate analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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