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Risk Factors for Refractory Status Epilepticus – A Case Control Study

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ABSTRACT

Aim and objective: To study the risk factors for refractory status epilepticus. Materials and methods: 111 children between the age group of 1 month to 12 years admitted in the hospital with the diagnosis of refractory status epilepticus (RSE) were included in the case group and 100 children between the age group of 1 month and 12 years admitted in the hospital with status epilepticus(SE) were included in control group in the study. A thorough history was obtained from the parents after obtaining the consent for the study and the results were analysed for statistical significance. Result: Focal to secondary generalization was more associated with RSE than SE group with a significant p value of 0.018 and an odds ratio of 2.475 with 95% confidence interval being 1.152- 5.319 . Vast majority of the patients with RSE were brought to the hospital more than 60 min after onset of seizure, with the exact number being 51 in RSE group and 30 in SE group with a p value of 0.015. 19 cerebral palsy patients out of 30 in the RSE group had a prior history of neonatal seizure and 3 cerebral palsy patients out of 15 in the SE group had a prior history of neonatal seizure. History of neonatal seizure among cerebral palsy children had a significant association with RSE with a p value of 0.003 . 38 patients in the RSE group and 26 patients in NRSE group had seizure disorder. Drug withdrawal was a cause of RSE in 71% of the patients in RSE group with a significant p value of 0.001 . Inadequate drug dose as a cause of RSE was seen in 47.3% of patients in RSE group as against 19.2% in the SE group and this as a risk factor for RSE had a significant p value of 0.031 . Conclusion: Focal to secondary generalization of seizure, prolonged duration of seizure (> 60 min) prior to hospitalization, history of neonatal seizure among children with cerebral palsy, drug withdrawal and inadequate drug dosage among children with seizure disorder were found to be independent risk factors for refractory status epilepticus in our study.

KEYWORDS Refractory status epilepticus, status epilepticus, cerebral palsy

INTRODUCTION:

Status epilepticus is a frequent neurological emergency . The incidence of SE has a bimodal distribution with peaks in children aged less than a year and the elderly[1] Although conventional antiepileptic drugs can terminate status epilepticus in most cases, a substantial minority of patients develop medically refractory status epilepticus . Although the entity of refractory status epilepticus is widely recognized and discussed, a standard definition has not yet been evolved and is usually defined as seizure activity that continues after first and second line therapy has failed[2].Such patients are considered to be in refractory status epilepticus and escalation of therapy with administration of non-barbiturate anaesthetic agent is then recommended with the therapeutic endpoint of achieving seizure control, electrical silence or both[3] . These patients require management in pediatric intensive care unit, with continuous cardiorespiratory and electro-encephalographic monitoring along with the aggressive therapy to control seizures.The optimal management of such patients remains unclear and large controlled studies comparing the various agents are lacking. Very few studies have been done in India and abroad on refractory status epilepticus, so, the data on the clinical profile and treatment modalities and their effectiveness is also limited. Generalized status epilepticus is refractory to standard anticonvulsant therapy in at least 9% of patients and additional intervention is required [4 ,5]. Identification of predictors for refractory status epilepticus is crucial for detection of patients at risk early in the course of the disease.Refractory status epilepticus is a condition in search of improved clinical characterisation and more efficient treatment options. In contrast with status epilepticus in general, only a few studies have been reported on the subgroup of refractory status and moreover there are very few studies in childhood. So this study was conducted to identify those children at risk for refractory status epilepticus so that their parents can be counselled to prevent further episodes and to alert the medical care giver to know which patients will have refractory status epilepticus.

MATERIALS AND METHODS:

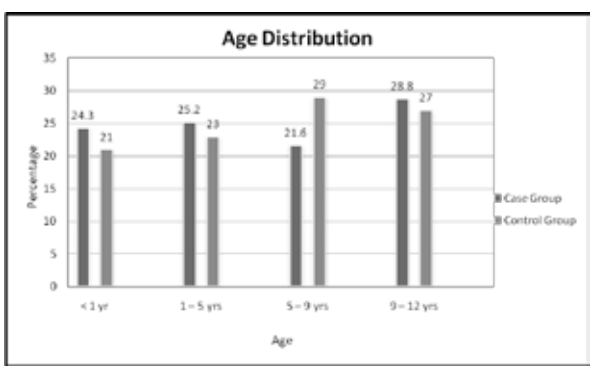
A case-control study was conducted at Institute of child health, Egmore between September 2007 and October 2009. The study population were those with continuous seizure activity lasting for more than 30 minutes or intermittent seizure activity without recovery of consciousness in between the episode[6] in children aged between 1 month to 12 years. Children less than 1 month and more than 12 years, those with seizure only at home, those with history of head injury were excluded from the study. A case was defined as those with seizures lasting beyond treatment with a benzodiazepine and second line intravenous anticonvulsant drug(phenytoin and phenobarbitone). Control was defined as those with seizures responding to benzodiazepine and a second line intravenous anticonvulsant drug (phenytoin or phenobarbitone). 111 children between the age group of 1 month to 12 years admitted in the hospital with the diagnosis of refractory status epilepticus were included in the study group and 100 children between the age group of 1 month and 12 years admitted in the hospital with status epilepticus were included in control group in our study.Status epilepticus was diagnosed when child had continuous seizure lasting more than 30 minutes or several seizures occurring without regaining consciousness between the seizure activity. These children were treated with 0.1 mg/kg of lorazepam 2 doses, 20mg/kg loading dose of phenytoin followed by 10 mg/kg half loading dose of phenytoin and 20 mg/kg loading dose of phenobarbitone at predetermined time interval in succession after stabilizing the

airway, breathing and circulation. Intubation was done prior to phenobarbitone administration. Refractory status epilepticus was the diagnosis if the child continued to have seizure activity despite adequate doses of medications mentioned above.A thorough history was obtained from the parents regarding name, age, sex,area, duration of seizure prior to reaching hospital, type of seizure , presence or absence of fever. Past history of seizure / status epilepticus and the anticonvulsant drug and dose (whether adequate) and any history of drug default or any recent change in anticonvulsant drug was enquired and noted down. Any history of drug or toxin ingestion , family history of status epilepticus or febrile seizure was enquired. Presence of any neurological co morbidity and its type if present , was enquired in detail.

RESULT:
A total of 111 children in case group with refractory status epilepticus and 100 children in control group with non refractory status epilepticus were studied.

The age distribution is as follows:

Figure – 1
Age distribution



The percentage of RSE cases was comparable in all the age groups (figure 1).The number of RSE cases in children <1 year was 27(24.3%) with an insignificant p value of 0.565 and Odds ratio of 1.209 . This is in contrast to the previous studies which concluded <1 year as a risk factor for RSE. The youngest child in the study group was 2 months and the child with maximum age in study group was 12 yrs. The commonest age group in this study was 9 – 12 yrs with 32 cases (28.8%).

The sex distribution is as follows:

TABLE- 1
SEX DISTRIBUTION

SEX	CASES	CONTROL	TOTAL
MALE	61(55%)	57(57%)	118(55%)
FEMALE	50(45%)	43(43%)	93(45%)

The total number of male patients in the study was 118(55%), with 61 in the RSE group and 57 in the control group(table 1). The total number of female patients in the study was 93(45%), with 50 in the RSE group and 43 in the SE group. Not either of the sex had a significant p value and so neither were found to be a risk factor for RSE.

TABLE – 2
Duration of seizure prior to reaching hospital

Duration	Cases	Control	X2	p value	OR	95% confidence limit
<30 min	19(17%)	21(21%)	0.516	0.08	0.77	0.31-1.78
30-60 min	41(37%)	49(49%)	3.13	0.38	0.6	0.32-1.34
>60 min	51(46%)	30(30%)	5.656	0.015	2.1	1.1-4.2
Total	111	100				

Vast majority of the patients with RSE were brought to the hospital more than 60 min after onset of seizure, with the exact number being 51 in RSE group and 30 in SE group with a p value of 0.015 which is significant and an odds ratio of 2.1 (table 2) . The median duration of seizures before reaching the hospital was 40 minutes and standard deviation was 38.12 minutes. Minimum time of seizures before reaching hospital was 10 minutes while the maximum time was 90 minutes. Long duration of seizure prior to reaching hospital was found to be a risk factor for RSE.

TABLE- 3
TYPE OF SEIZURE

Type of seizure	Cases	Control	p value	Odds ratio	95% confidence interval
Focal to GTCS	26(23.4%)	11(11%)	0.018	2.475	1.152-5.319
GTCS	85(76.6%)	89(89%)			
Total	111	100			

Majority of the patients in both the groups had generalized tonic clonic seizures numbering 85 in RSE group and 89 in SE group. However focal to secondary generalization was more associated with RSE than SE with a Chi square value of 5.615 and a significant p value of 0.018 and an odds ratio of 2.475 with 95% confidence interval being 1.152- 5.319(table 3). This result goes hand in hand with the observation made by Stephan et al that focal onset of seizure was a major risk factor for RSE.

TABLE-4
Past history of status epilepticus

Past H/O Status epilepticus	Cases	Control
Yes	7(6.3%%)	6(6%)
No	104(93.7%)	94(94%)

7 patients among RSE group had previous history of status epilepticus as against 6 in SE group(table 4). Among this 7 in RSE group 2 patients had primary seizure disorder and 5 were cerebral palsy children with seizures. Among this 6 in SE group 1 patient had primary seizure disorder and 5 were cerebral palsy children with seizures. Past history of status epilepticus was not a risk factor for RSE and had an insignificant p value.

TABLE-5
Drug withdrawal

Withdrawal	Cases	Control	p value	Odds ratio	95% confidence interval
Yes	27(71%)	7(26%)	0.001	6.6	3.56-13.62
No	11(29%)	19(74%)			
Total	38	26			

38 patients in RSE group had seizure disorder out of which 5 had primary seizure disorder, 20 were cerebral palsy children with secondary seizure disorder and 3 were post meningitic/ encephalitic sequelae with secondary seizure disorder.7 patients in SE group had seizure disorder out of which 2 had primary seizure disorder,4 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with secondary seizure disorder.Drug withdrawal had a significant association with RSE with a p value of 0.001 and odds ratio of 6.6 and 95% confidence interval of 3.56-13.62(table 5)

TABLE-6
Inadequate drug dose

Dose inadequate	Case	Control	p value	Odds ratio	95% confidence interval
Yes	18(47.3%)	5(19.2%)	0.031	3.78	1.82-7.42
No	20(52.7%)	21(80.8%)			
Total	38	26			

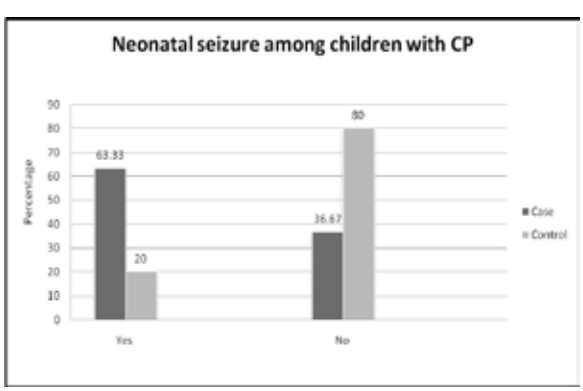
18 patients in RSE group had a history of drug withdrawal as against 5 in SE group. Among the 18 with history of drug withdrawal in RSE group 2 had primary seizure disorder,15 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with seizure disorder. Among the 5 with history of drug withdrawal in SE group 1 had primary seizure disorder,3 were cerebral palsy children with secondary seizure disorder and 1 was a post meningitic/encephalitic sequelae with seizure disorder. History of drug withdrawal was associated with RSE with a significant p value of 0.031(table 6) .

Table-7
Recent change in anti epileptic drug(AED)

Recent change in AED	Cases	Control	p value	Odds ratio	95% confidence interval
Yes	6(15.7%)	3(11.5%)	0.083	1.4	0.81-2.91
No	32(84.3%)	23(88.5%)			
Total	38	26			

6 patients in RSE group had a history of recent change in AED as against 3 in SE group (table 7). Among the 6 with history of drug withdrawal in RSE group 2 had primary seizure disorder,4 were cerebral palsy children with secondary seizure disorder and. Among the 3 with history of drug withdrawal in SE group 1 had primary seizure disorder,2were cerebral palsy children with secondary seizure disorder. History of recent change in AED was significantly associated with RSE with a p value of 0.031 .

Figure-2
Neonatal seizure among children with CP



19 cerebral palsy patients out of 30 in the RSE group had a prior history of neonatal seizure and 3 cerebral palsy patients out of 15 in the SE group had a prior history of neonatal seizure. History of neonatal seizure among cerebral palsy children had a significant association with RSE with a p value of 0.003(figure 2).

DISCUSSION:
This case-control study was conducted to study the risk factors for refractory status epilepticus and its impact on outcome of the patient.

Table-8
Comparison of age and sex distribution with other studies

	Mean age	Range	M:F
Present study	5.91yrs	2mo-12yrs	1.06:1
Roshan la et al.,	4.07yrs	2mo-13ytr	3:1
Ramon rivera et al.,	2.2yrs	2mo-12yrs	1:1.4
John Igartua et al.,	4.25yrs	17days-16yrs	-
Minagawa K,at al.,	3.5yrs	1mo-18yrs	-

The mean age of children in our study was 5.91years, while in the study by Roshan Lal et al was 4.07 years and2.2 years in study by Ramon Rivera et al. The mean age was 3.5 years and 4.25 years in studies by Minagawa K et al.,and John Igartua et al. Less than 1 year as a risk factor for RSE as made out in the study by Col.M.K.Behera et al was not a risk factor in this present study.There was no clustering of cases in any age group. So age was not a risk factor for refractory status epilepticus. The ratio of male to female in the present study was 1.06:1 which is comparable to the study done by Ramon rivera et al ., in which it was 1:1.4. higher incidence in males (3 times more) was noticed in study by Roshan Lal et al (table 8).

Table-9
Comparison of seizure type with other studies

Seizure type	Present study	Stephen et al	Roshan Lal et al	Ramon Rivera et al	John Igartua et al
GTCS	76.6%	23%	65%	755	62.55
Partial to GTCS	23.4%	73%	20%	4.2%	25%

Though 76.6% of the patients had GTCS in the present study, focal to secondary generalization was more associated with RSE with a p value of 0.018(table 9). A similar observation has already been made in the study by Stephen et al.

6.3% of patients in the present study with RSE had prior history of status epilepticus as against 6% in the SE group with an insignificant p value. No previous studies are available to compare this as a risk factor.

Duration of seizure prior to hospitalization was >60 minutes in 46% of patients in RSE group compared to 30% in SE group with a significant p valueof 0.015 . Prolonged duration of seizure prior to hospitalization was a risk factor for RSE , similar to the observation made by Ramon Rivera et al ., where the mean time was 0.75 hours.

38 patients in the RSE group and 26 patients in SE group had seizure disorder. Drug withdrawal was a cause of RSE in 71% of the patients in RSE group with a significant p value of 0.001 . Inadequate drug dose as a cause of RSE was seen in 47.3% of patients in RSE group as against 19.2% in the SE group and this as a risk factor for RSE had a significant p value of 0.031 .

History of neonatal seizure among children with CP was observed in 63.3% of RSE group compared to 20% in SE group with a significant p value of 0.003. This result is similar to the observation made by Yoko Ohtsuka et al where 100% of refractory cases with CP had a history of neonatal seizure.

CONCLUSION:
In this study the following factors were found to be significantly associated with refractory status epilepticus

- Focal to secondary generalisation of seizure
- Withdrawal of antiepileptic drugs in patients with seizure disorder
- inadequate drug dosage in patients with seizure disorder
- Past history of neonatal seizure among patients with cerebral palsy
- Prolonged duration of seizure(>60 min) prior to treatment

REFERENCES:

1. Chin RF, Neville BG, Scott RC. A systematic review of the epidemiology of status epilepticus. Eur J Neurol 2004; 11: 800-10
2. Shorvon SD , Status epilepticus : Its clinical features and treatment in children and adults : Cambridge University Press : England ; 1994 p 201
3. Hanhan UA, Fiallos MR : Status Epilepticus. Ped Clinics of North America 2001 June ; 48 : 683-94
4. David JJ , Tasker RC : The management of acute epileptic seizures and status epilepticus. Recent advances in pediatrics 2001 ; 19 : 1-16
5. Hanhan VA ,Fiallos MR: Status Epilepticus. Ped clinic of North America2001 ; 48 : 683-94
6. Kleigman , Behrman , Jenson , Stanton : Nelson Textbook of Pediatrics; 18; 2473-75