Refractory Convulsive Status Epilepticus in Children: Etiology, Associated Risk Factors and Outcome

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Abstract

Objective

Refractory status epilepticus (RSE) is a life-threatening disease in children wherein the patient’s convulsive seizures do not respond to adequate initial anticonvulsants. RSE is associated with high rate of mortality and morbidity. This study was aimed to survey the risk factors leading status epilepticus (SE) to RSE in children, and their early outcome.

Materials & Methods

Patients with SE hospitalized in Tabriz Children’s Hospital, Iran were studied during the years 2007 and 2008 with regard to their clinical profile, etiology, the treatment methods available to them and their outcome upon release from the hospital.

Results

Among 132 patients with SE, 53 patients (40.15%) suffered from RSE. Acute symptomatic etiology was a risk factor responsible for developing RSE in the patient (P=0.004). Encephalitis was the most common etiology of acute symptomatic SE. There was no significant relationship observed between RSE and the patients’ age, gender, date of initial drug intake and type of seizure. The mortality rate was 8.3% and a new neurological deficit occurred in 25.7% of cases. None of RSE with encephalitis returned to the baseline status. Mortality and morbidity rates were significantly higher in children with RSE than in those with SE (P=0.006).

Conclusion

Etiology of SE significantly influenced prognosis of it with significant incidence of RSE in acute symptomatic group. Because acute neurological insult such as encephalitis and meningitis are common causes of RSE in children, proper management of them is necessary to avoid permanent brain damage.

Keywords: Refractory status epilepticus; Etiology; Mortality; Morbidity; Children

Introduction

Status epilepticus (SE) is defined as any continuous convulsive seizure activity or intermittent convulsive seizure activity without regaining of consciousness between them lasting for more than 30 min. SE is the most common and the urgent life-threatening neurological emergency in children (1-3). Either convulsive or no convulsive SE affects both children and adults; it is sometimes associated with high morbidity and mortality, particularly in infants varying from 4% to 39% in...
different studies (4-6). SE is either terminated with anticonvulsant medications, i.e., non-refractory status epilepticus (NRSE) or refractory to medications, i.e., refractory status epilepticus (RSE), the SE that does not respond to initial therapy with adequate doses of two or three anticonvulsant medications, or status epilepticus lasting 60 min or longer (1, 2, 7, 8).

The annual incidence rate of SE is 41 per 100,000 people, of whom approximately 9% to 44% have RSE (9-10). RSE is accompanied by the higher rates of morbidity and mortality (11), with reported the total mortality of 16% (12). Risk factors associated with RSE are less clearly known in children. Risk factors for RSE include young age, delay in onset of treatment and being afflicted with focal motor seizure (13).

The aim of the present study was to identify etiology, associated risk factors and outcome of RSE in SE pediatric patients.

**Materials & Methods**

**Study population**

The study group included in this study met the following inclusion criteria: patients younger than 18 yr of age admitted with a diagnosis of status epilepticus at Children’s Hospital, Tabriz, Iran between 2007 and 2008. If patients experienced more than one episode of SE, only the first episode of SE would include in the study.

**Study design**

We did a hospital-based cross-sectional analytical study at Tabriz Children’s Hospital. It is a major regional tertiary care referral center that gives high-level healthcare services to the pediatric patients of northwest of Iran, mainly East Azerbaijan Province in all pediatric subspecialties. All 132 consecutive patients presented with SE initially (Figure 1), were stabilized by the trained staff of the emergency room (ER) service with establishment of an intravenous access and initiation of hospital SE treatment protocol; then, were admitted to the Pediatric Intensive Care Unit (PICU), and cared for with continuous blood pressure, pulse oximetry and cardiac monitoring. Some patients with cardiorespiratory compromise (particularly RSE cases) were intubated and underwent mechanical ventilation.

Electroencephalographic (EEG) monitoring was not used for the diagnosis of convulsive SE initially, but was performed when the seizures had been controlled to exclude any probable diagnosis of nonconvulsive SE. The study was approved by Ethics Committee of Tabriz University of Medical Sciences and informed consent was obtained from the parents of all the hospitalized children.

**Definitions and classifications**

**Status epilepticus**

SE is defined as any continuous convulsive seizure activity or intermittent convulsive seizure activity without regaining of consciousness between them lasting for more than 30 min (1, 2).

**Refractory status epilepticus**

There is no single definition for RSE. Definitions used in the literature are different based on the number of used medications and the duration of the seizure activity (7). However, we used following definition for RSE in this study: the status epilepticus that does not respond to initial therapy with adequate doses of two or three anticonvulsant medications, or status epilepticus lasting 60 min or longer despite of treatment with therapeutic doses of at least one first line medication, followed by one second line medication (1, 2, 10, 12).

**Non-refractory status epilepticus**

The term non-refractory status epilepticus (NRSE) was used to indicate those patients whose SE terminated with first and/or second line medications within less than 60 min after administration of the first drug according to the hospital treatment protocol.

**Hospital treatment protocol**

There is no consensus about the optimal therapy of SE and RSE in the literature (14). We used modified “Medical College of Virginia Status Epilepticus Treatment protocol for Children” (15) in order to standardize the pediatric SE care and treatment in the emergency room and PICU. The treatment objective was complete control of patients’ clinical convulsive epileptic activity. All patients were treated using the following protocol:

Line1: Children who presented with convulsive seizure...
activity for more than 5 minutes received three repeated doses of 0.3 mg/kg intravenous diazepam at the fifteen-min intervals along with a dose of 20 mg/kg of intravenous phenytoin (at a rate of 1 mg/kg per min).

Line 2: If the seizures resumed or continued, they received intravenous phenobarbital at the dose of 20 mg/kg during 10 to 30 minutes. If SE continued in children younger than 2 years 100 mg of pyridoxine was administered.

Line 3: If SE continued despite the first and second line medications, or seizures lasted 60 min or more, the condition was considered as the RSE and the patient received intravenous midazolam, a loading dose of 0.2 mg/kg followed by a conscious infusion of 1-5 μg/kg per min titrated every 15 min. Treatment is typically 24 h.

Line 4: If control is still not achieved, thiopental sodium with an initial intravenous loading dose 5 mg/kg and maintenance dose of 1-5 mg/kg/h in PICU is necessary.

**Etiology**

SE was classified into 4 categories based on previously published studies (16-19) as follows:

(a) Acute symptomatic: SE develops because of acute neurological insults such as trauma, CNS infection, metabolic disturbances or a systematic disorder.

(b) Remote symptomatic: This category includes patients with a particular neurological disorder (chronic encephalopathies) predisposing them to epileptic seizures, and this includes cases due to previous congenital or acquired epileptogenic brain damage. Some investigators separate a category of progressive encephalopathies that others include them with remote symptomatic (18).

(c) Idiopathic: The idiopathic category, which sometimes is also termed cryptogenic, includes epileptic patients who have SE because of their sudden discontinuation of anticonvulsant medication or in the absence of an underlying lesion in the central nervous system or any causal brain damage.

(d) Febrile: The febrile SE includes epileptic seizures accompanied by fever lasting more than 30 min while cerebrospinal fluid analysis does not indicate anything in favor of CNS infection.

**Demographic, clinical and paraclinical data**

The patients’ data was collected and documented in three categories using a structured data collection questionnaire and related chart review as follows:

(a) Demographic data including age and gender.

(b) Clinical data including medical history, neurological and other physical examinations, type of seizure, duration of SE, different types of treatments used and related side effects. Classification and type of seizures were conducted based on the criteria of International League against Epilepsy (ILAE) (1).

(c) Paraclinical data including patients’ collected blood sample for the CBC and serum electrolytes levels such as sodium, calcium, phosphorus, magnesium, glucose, creatinine and lactate. Laboratory data recorded during the first 24 h after the onset of SE. In order to perform certain metabolic and toxicology tests, blood and urine samples of some patients were also collected according to their history, clinical examination and the initial test results. If meningitis or encephalitis were suspected (as was the case in all febrile patients), the cerebrospinal fluid was tapped for examinations (analysis, culture and PCR for herpes simplex). Presumed encephalitis was defined as presence of symptoms of an acute febrile illness prior to, or at the time of the onset of SE, with CSF pleocytosis and no positive findings in cerebrospinal fluid culture (12).

**Outcome**

The patients’ outcome was evaluated during hospitalization and on discharge. It was categorized into three distinct groups based on short-term prognosis including mortality (death), morbidity (development of a new neurological deficit) and recovery (return to baseline condition, i.e., the same neurological condition as prior to RSE or NRSE) (Figure 1). Outcome considered “poor” if mortality and/or morbidity occurred and “good” if patient recovered (7).

**Statistical analysis**

Univariate analysis was used to determine factors associated with the development of RSE in patients presented with SE. Chi-square and Fisher’s exact tests were used to compare determined short-term outcome between RSE and NRSE groups. The t test was used for analysis of continuous data with normal distribution and Mann Whitney U test for data with non-normal distribution.
distribution. Statistical analysis was performed using
SPSS 17.0 (Chicago, IL, USA). Differences were
considered significant at P<0.05.

Results
Age, gender and patients
There were 73 (55.30%) boys and 59 (44.70%) girls
presented with SE to the hospital. From 132 patients, 79
(59.85%) had NRSE and 53 (40.15%) had RSE, with
the mean age 38.44±0.61 months (ranging from 2 to 204
months) for NRSE group and 40.11±0.78 months (ranging
from 1 – 156 months) for RSE group, respectively
(P=0.82). With regard to the gender, 46 (58.22%) in
NRSE group and 27 (50.94%) in RSE group were
boys (P=0.28). The time interval between the initiation
of seizure and the administration of anticonvulsant
medications was 20.83±17.48 min (ranging from 3 to
75 min) in NRSE group and 15.02±13.56 min (ranging
from 2 to 45 min) in RSE group (P=0.15).

Etiology
Table 1 compares the etiologic factors associated with
the two groups of patients.
There was a rather significant etiologic variation between
the two groups. Acute symptomatic etiology was an
associated risk factor with RSE (OR=3.35; 95% CI 1.47-
7.61, P=0.001). Febrile seizure was against development
of RSE (P=0.001). The etiologies of acute and remote
symptomatic SE are shown in Table 2.

Hospital treatment protocol
All 53 patients with RSE received anticonvulsants, i.e.
diazepam, phenytoin and phenobarbital, and midazolam
infusion as well. In 42 (79.24%) patients, SE resumed
and in 11 (20.76%) thiopental infused since they did not
respond to the midazolam.

Outcome
Regarding the patients’ short-term outcome, there were
11 (8.33%) deaths, 9 and 2 of them were from the RSE and
SE groups, respectively (OR=7.34; 95% CI: 1.52-35/46;
P=0.008). The risk of death was 7 times higher in the
RSE group compared to SE group. A new neurological
deficit occurred in 21 (38.18%) RSE patients and in
13 (16.88%) SE patients (OR=3.04; 95% CI: 1.36-6.82;
P=0.006). None of RSE with encephalitis returned to
the baseline status. Dividing the patients’ outcome into
the two categories of good and poor (poor outcome
means death or development of a new neurological
deficit) indicated that there was a significant relationship
between the patients’ outcome and their etiology. In
overall, poor outcome was more prevalent in the acute
symptomatic etiology in SE patients (P=0.04). There was
no significant relationship between a poor outcome and
the patients’ age, gender and initiation of anticonvulsant
medications.

Discussion
Convulsive SE is the most common form of SE and
accounts for about 90% of all pediatric SE cases
(4). In the present study, RSE occurred in 40.15%
of patients with convulsive SE. In a study of 193
pediatric SE patients, 26% had RSE (16). Different
studies have reported the prevalence of RSE among
SE patients from 11% to 43% (4, 8-12, 20-22). The
differences among different studies can be attributed
to sociological, economical and geographical diversity
of the study populations and the referral bias existing
in their selection and the lack of a standard definition
for RSE. Tabriz Children’s Hospital is a tertiary -level
referral center and almost all children with critical
conditions (such as SE) referred to this center solely.
An acute symptomatic etiology was the most prevalent
cause of RSE (41.51%), and SE due to an acute
symptomatic etiology increased the risk of RSE by
3.35 times. In various studies, an acute symptomatic
etiology was proved the major associated risk factor
for RSE in SE patients. In a study on 22 children with
RSE, an acute symptomatic etiology was presented
as a risk factor for RSE and mortality was related to
etiology and EEG finding (12). In a review article on
outcome and mortality of SE in children, adolescents
and adults, sequel and risk of recurrence of SE were
primarily related to the underlying cause; RSE was most
often consequence of an acute neurologic condition or
neurodegenerative disease (2).
In the present study, the type of epileptic seizure was
not revealed as a associated risk factor for RSE, but
in several studies, the focal seizure at the onset of the
epileptic seizure was considered a risk factor related to
RSE (20, 22).

Similar to other studies, no significant relationship was found between the occurrence of RSE in children and their age and gender (2, 4, 13, 19, 21-22); however, some studies indicate that age is an associated risk factor for RSE (6, 23).

Like other studies, we did not observe a significant relationship between the initiation of anticonvulsant medications and occurrence of RSE; however, one study indicated a correlation between delay in the start of treatment and transformation of SE to RSE (8).

The main risk factor related to RSE is acute symptomatic etiology, which leads to structural-functional damage and the inability to respond to anticonvulsant medications. Although efforts are made to control seizures, it is vital that the therapy is directed to the underlying condition whenever possible. Indeed, when it is not done, there will be a significant risk for prolongation of the SE and rendering it harder to control (8-12).

According to the present study, midazolam infusion terminated epileptic seizures in 43 (78.19%) of patients with RSE. The rate of midazolam success in controlling seizure varied from 73% to 95% (20, 24-25). In a comparative study between thiopental, midazolam and propofol for controlling RSE, the rate of success was the same for all three medications; nevertheless, rate of recurrence was higher in midazolam group even though they suffered less systematic side effects (26). The management of refractory status epilepticus is heterogeneous in many aspects, even among clinicians who are most familiar with this severe condition (27). It appears that under conditions where a favorable PICU is lacking and by considering costs of treatment, midazolam is the least costly drug for refractory generalized convulsive SE in children (29).

In the present study, 45 (34.09%) of patients suffered from the poor outcome (death and a new neurologic deficit) that was significantly higher in the RSE group compared to NRSE group; this result was similar to that obtained by several studies in which there was a systematic relationship between SE patients’ neurological outcome and their etiology (4, 12, 16, 22).

In a study of 122 children with SE, no death was directly attributable to generalized convulsive SE (29). Therefore, in order to decrease mortality and morbidity rates, controlling the SE is not the only contributing factor; rather, the early and proper diagnosis of the underlying acute disease greatly contributes to improving the patients’ outcome.

In our study, none of RSE due to encephalitis returned to the baseline condition. In a study of 46 children with SE secondary to presumed encephalitis, 20 were diagnosed with RSE, 6 were died and 13 developed a new neurologic deficit. In the follow-up examinations, none of the patients recovered to their previous neurological conditions (30).

A limitation of this study was that due to unavailability of EEG monitoring facility we did not use this valuable instrument for detecting subclinical seizure and detecting burst suppression pattern for evaluating effect of thiopental infusion.

In conclusion, Etiology of SE significantly influenced prognosis of it with significant incidence of RSE in acute symptomatic group. Because acute neurological insult such as encephalitis and meningitis are common causes of RSE in children, properly management of them is necessary to avoid permanent brain damage.

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Conflict of Interest
No conflict of interest.

Authors’ contribution
Mohammad Barzegar: Study design, coordinator of project, literature review, manuscript review
Mohammad Mahdavi: Study design, Data gathering, data analysis
Afshin Ghalehgolab Behbahani: Editing and revising the manuscript
Aidin Tabrizi: Literature review, preparing the manuscript
### Table 1. Etiological Factors Associated with SE and RSE

| Groups                      | Etiology                                      | RSE  | NRSE  | P. value |
|-----------------------------|-----------------------------------------------|------|-------|----------|
| Febrile                     |                                               | 6 (11.32) | 34 (43.4) | 0.001 |
| Acute Symptomatic           |                                               | 22 (41.51) | 12 (15.19) | 0.001 |
| Remote Symptomatic          |                                               | 20 (37.73) | 22 (27.84) | 0.27 |
| Idiopathic                  |                                               | 5 (9.43) | 11 (13.92) | 0.28 |

NRSE: non refractory status epilepticus; RSE: refractory status epilepticus

### Table 2: Etiologies of 76 cases with acute or remote symptomatic status epilepticus examined in this study

| 1. Acute symptomatic | 2. Remote symptomatic |
|----------------------|-----------------------|
| Encephalitis         | Cerebral palsy, Global developmental delay and Mental retardation |
| Meningitis           | Hydrocephaly          |
| Hyponatremia         | Anjelman syndrome     |
| Hypermartremia       | Rett syndrome         |
| Intracranial hemorrhage | Sturge-weber    |
| Drug induced         | Tuberosis sclerosis  |
| Cerebral infarction  | Suspected Alper disease |
| Hypoglycemia         | Organic aciduria      |
| Hypoxic –ischemic enceph induced | Brain malformation |

Brain Tumor 2
Fig 1. Study design: population, groups and outcome

References
1. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines on epidemiologic studies on epilepsy. Epilepsia1993; 34(4): 592-596.
2. Mitchell WG. Status epilepticus and acute repetitive seizures in children, adolescent, and young adults: etiology, outcome, and treatment. Epilepsia1996; 37(11):74-80.
3. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006; 368:222-229.
4. Saz EU, Karapinar B, Ozvetin M, Polat M, Tosun A, Serdaroglu G, et al Convulsive status epilepticus in children: Etiology, treatment protocol and outcome. Seizure 2011;20:115-118.
5. Raspall-Chaure M, Chin RFM, Neville BG, Scott RC. Outcome of pediatric convulsive status epilepticus: a systematic review. Lancet Neurol. 2006; 5: 769-79.
6. Hussain N, Appleton R, Thorburn K, Etiology, course and outcome of children admitted to pediatric intensive care with convulsive status epilepticus: A retrospective 5-year review. Seizure 2007; 16: 305-312.
7. Lambrechtsen F, Buchhalter J. Aborted and refractory status epilepticus in children:A comparative analysis. Epilepsia 2008;49(4):615-625.
8. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. J Neurol Neurosurg Psychiatr 2005; 76:534-539.
9. Chin RF, Neville BG, Scott RC. A systematic review of epidemiology of status epilepticus. Eur J Neurol 2004;11:800-810.
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10. Mayer SA, Claesen J, Lokin J, Mendelson F, Dennis LJ, Fitzsimmons BF. Refractory status epilepticus: frequency, risk factor and impact on outcome. Arch Neurol 2002;59:205-210.

11. Fernández IS, Abend NS, Agadi S, An S, Arya R, Carpenter JL et al. Gaps and opportunities in refractory status epilepticus research in children: A multi-center approach by the Pediatric Status Epilepticus Research Group (PSERG). Seizure 2014; 23: 87-97.

12. Sahin M, Menache CC, Holmes GL, Riviello JJ. Outcome of severe refractory status epilepticus in children. Epilepsia 2001; 42:1461-1467.

13. Kang DC, Lee YM, Lee JS, Kim HD, Coe CJ. Prognostic factors of status epilepticus in children. Yonsei Med J 2005; 46(1):27-33.

14. Claesen J, Hirsch LJ, Mayer SA. Treatment of status epilepticus: a survey of neurologists. J Neurol Sci 2003;211:37–41.

15. Pellock JM, Deorenzo RJ. Status epilepticu. In : Swaiman KF, Ashwal S, ferriero DM, Schor NF. Swaiman,s Pediatric Neurology Principles and Practice. 5th ed, New York; Elsevier, 2012, p:798-810.

16. Maytal J, Shinar S, Moshe SL, Alvarez LA. Low mortality and morbidity of status epilepticus in children. Pediatrics 1989;83:232-231.

17. Logroscino G, Hesdorffer DC, Cascino G, Annegers JF, Hauser WA. Time trends in incidence, mortality, and case-fatality after first episode of status epilepticus. Epilepsia 2001; 42:1031–1035.

18. Phillips SA, Shanahan RJ, Etiology and mortality of status epilepticus in children- a recent update. Arch Neurol 1989;46:74-76.

19. Shinnar S, Maytal J, Krasnoff L Moshe SL. Recurrent Status epilepticus in children. Ann Neurol 1992; 31:701-706.

20. Barzegar M, JafariRoohi AH. Refractory status epilepticus in children; risk factors, management and early outcome. Journal of Shaheed Sadoughi University of Medical Sciences and Health Services 2008; 15(4): 16-20.

21. Garzon E, Fernandes RM, Sakamoto AC. Analysis of clinical characteristics and risk factor for mortality in human status epilepticus Seizure 2003, 12:337-345

22. Komur M, Arslankoylu AE, Okuyaz C, Keceli M, Derici D. Management of Patients With Status Epilepticus Treated at a Pediatric Intensive Care Unit in Turkey. Pediatr Neurol 2012; 46: 382-386.

23. Kwong KL, Chang K, Lam sy. Features predicting advers outcomes of status epilepticus in childhood. Hong Kong Med 2004;10:156-159.

24. Ozdemir D, Gulez P, Uran N, Yendur G, Kavakli T, Aydin A. Efficacy of conious midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus. Seizure 2005; 14:129-32.

25. Morrison G1, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children Intensive Care Med 2006 Dec;32(12):2070-6. Epub 2006 Sep 15.

26. Claassen J, Hirsch L, Emerson R, Mayer S. Treatment of refractory status epilepticus with pentobarbital, propofol or midazolam. A systematic review. Epilepsia 2002, 43:146-153.

27. Holtkamp M, Masuhr F, Harms L, Einhäupl KM, Meierkord H, Buchheim K. The management of refractory generalised convulsive and complex partial status epilepticus in three European countries: a survey among epileptologists and critical care neurologists. J Neurol Neurosurg Psychiatr 2003; 74:1095-9.

28. Gilbert DL, glauser TA. Complications and costs of treatment of refractory generalized status epilepticus in children. J Child Neurol. 1999;14:597-602.

29. Brevood JC, Joosten KF, Arts WF, van Rooij RW, de Hoog M. Status epilepticus: clinical analysis of a treatment protocol based on midazolam and phenytoin. J Child Neurol 2005; 20:476-81.

30. Lin JJ, Lim KL, Wang HS, Hsia SH and Wu CT. Analysis of status epilepticus related presumed encephalitis in children. Eur J Ped Neurol 2008, 12:32-37.