Predictive Factors for Refractory Convulsive Status Epilepticus: a 7-year Retrospective Study

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ABSTRACT

Background. Status epilepticus (SE) is defined as continuous seizure activity lasting for more than 30 minutes without full recovery of consciousness. Refractory convulsive status epilepticus (RCSE) is defined as convulsive seizures lasting more than 60 minutes despite treatment using first- and second-line intravenous anti-epileptic drugs (AEDs) and anesthetic agents.

Objectives. To determine the incidence of RCSE among patients with status epilepticus (SE) within a 7-year period in the Philippine General Hospital. Specifically, this study aims to identify risk factors associated with the progression of SE into RCSE.

Methods. This is a retrospective study of Filipino adults admitted at the Philippine General Hospital from January 2003 to September 2010 for SE.

Results. One hundred eight (108) patients were identified to have SE. Of these, only 66 had available hospital records. Among patients with SE, 16% (n=11) were identified to have RCSE. Only two variables were significantly associated with RCSE, namely, first-onset seizures (p=0.0214), and abnormal cranial imaging (p=0.131). Sensitivity of first onset seizures and abnormal cranial imaging as predictive factors for developing RCSE is 81.82%, and the specificity of the two variables is 52.7% and 63.4%, respectively. The presence of both factors predicts RCSE with a high sensitivity rate of 82%.

Conclusion. The incidence of RCSE among patients with SE is 16%. The significant risk factors for developing RCSE are abnormal cranial imaging and first-onset seizures. Presence of both variables can predict occurrence of RCSE with a relatively high sensitivity rate.

Key Words: status epilepticus, refractory convulsions, seizures

Abstract presented at the 29th International Epilepsy Congress, 2011, Rome, Italy.

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Introduction

Status epilepticus (SE) is a clinical condition warranting emergent neurologic intensive care management. It is characterized as onset of epileptic seizure or series of seizure attacks lasting for 30 minutes without regaining consciousness.[1] Generalized convulsive SE (GCSE) is described as continuous, convulsive epileptic episodes lasting more than 5 minutes, or two or more seizures, with impairment of consciousness in between seizures.[2,3] On the other hand, non-convulsive SE (NCSE) is defined as change in mental status from baseline for at least 30 minutes, with associated ictal discharges on electroencephalographic (EEG) studies.[2]

Etiologies of SE are variable. Studies reveal that at least one-third of the SE cases are due to an exacerbation of a previously existing seizure disorder, while another one-third of the cases are first onset or de novo seizure episodes. Previous or new onset cerebrovascular disease, subarachnoid hemorrhage, CNS infections, hypoxic injury, isoniazid toxicity, and alcohol withdrawal are known precipitating factors for SE.[2]

Worldwide, the incidence of SE ranges from 10 to 50 per 100,000 persons.[2] SE-related mortalities range from 7 to 20%.

About 31% to 43% of patients with SE proceed to become refractory SE (RSE), further classified into convulsive RSE (RCSE) and the non-convulsive type (RNCSE).[3,7] RCSE is defined as convulsive seizure activity lasting more than 60 minutes that fails to respond after first- and second-line anti-epileptic drugs (AEDs) are instituted.[4] The development of RCSE may be due to delays in recognition and management, and by the severity of other underlying conditions. In the Veteran Administrative (VA) cooperative study, about 56% of the SE cases responded to first-line treatment regimen, while about 7% resolve after subsequent administration of second-line regimen, and 3% after the third-line agent.[2,5] The pathophysiology behind the failure of epileptic seizures to respond to the treatment regimens in RCSE is still being studied.

In general, RSE is associated with a poor prognosis, as only one-third of the cases would return to their pre-morbid states. Patients with RSE usually develop systemic complications such as rhabdomyolysis, pulmonary edema, cerebral edema, hyperglycemia, and multi-organ failure

resulting in a longer hospital stay.[2] It is also associated with higher mortality rates (68%) on 30-day outcome studies, especially if associated with severe pre-morbid conditions.[2,6]

This study aims to determine the incidence of RCSE among patients with SE within a 7-year period in a tertiary hospital. Specifically, this study would also identify risk factors associated with the progression of SE into RCSE.

Methods

This is a retrospective, descriptive study of adult patients admitted for SE. All patients, with a diagnosis of status epilepticus managed by the adult neurology service of the Philippine General Hospital from January 2003 to September 2010 were included in the study. Patients were identified using manual screening of patient records, annual census, and computerized search. A total of 108 patients with SE were identified; however, only 66 records were available. Of these, patients who had uncontrolled generalized tonic clonic seizures lasting more than 60 minutes and had been given two or more intravenous anti-epileptic loading doses, drips, or anesthetic agents were classified as RCSE.

The following variables were obtained: age, sex, etiology of SE, presence of co-morbidities, time of first-onset of seizure, compliance to SE protocol upon admission, AEDs, EEG, cranial imaging, blood chemistry (serum Na), CSF studies, length of hospital stay, and outcomes. Retrievable records of EEG tracings and digital records were reviewed using the Neurofax μ EEG-9100 software (Nihon Kohden, Japan).

Univariate analysis using Pearson's correlation coefficient (chi square test) was used to determine the association of the different variables with patient outcomes. Significant variables on univariate analysis (p-value<0.05) were included in the multivariate analysis using logistic regression analysis. Significant correlation is defined by a p value of <0.05. Stepwise logistic regression was performed on the variables to further limit the number of significantly correlated variables. Sensitivity and specificity of the variables most significantly associated with the dependent variable would be computed. Data were analyzed using Stata 9.2 (Stata Corp, LP) software.

Results

Sixty six (66) patients clinically diagnosed as SE were included in the study. Of these, 11 patients (16%) were identified to have RCSE. The mean age of patients with RCSE is 33.18±20.1 years. Eight of the RCSE cases (73%) developed from first-onset seizures. About 55% of the RCSE cases (n=6) were caused by acute viral meningoencephalitis. The diagnosis of viral CNS infection was based on clinical symptomatology, CSF pleocytosis, electroencephalographic and neuro-imaging findings. However, only 1 case of viral encephalitis was confirmed using herpes simplex virological test. Other notable etiologies for RCSE are previously uncontrolled seizure disorder (27%, n=3) and brain tumors (18%, n=2).

EEG was performed in 34 out of the 66 SE patients. Ten of these EEGs had normal results but these tests were performed after seizure control. Of the 11 RCSE patients, only 9 patients had EEG studies (Table 1). The presence of generalized slowing, intermittent rhythmic delta activity, periodic lateralized epileptiform discharges, and generalized spike and wave complexes were observed in all of the RCSE EEG studies.

Table 1. Factors associated with the development of RCSE among patients with SE

Risk factor	SE n=66	RCSE n =10	p-value
Sex			
Male	34	3	0.078 (NS)
female	32	8	
Co-morbidities			
none	33	6	0.741 (NS)
at least 1 systemic illness	33	5	
Etiology of SE			
neurologic	52	10	0.281 (NS)
systemic	14	1	
Onset of seizures			
first-onset	35	9	0.036 (S)
childhood onset	31	2	
Compliance to medications			
good	31	5	0.912 (NS)
poor	35	6	
AEDs used			
oral	11	0	0.104 (NS)
IV	55	11	
EEG			
normal	10	0	0.109 (NS)
abnormal	24	9	
CSF studies			
abnormal	9	6	0.205 (NS)
normal	6	2	
Cranial imaging			
abnormal	24	9	0.008 (S)
normal	28	2	
Blood chemistry			
Na < 135	14	5	0.034 (S)
Na > 135	51	6	

Magnetic resonance imaging (MRI) and computed tomography (CT) scans were performed in 52 out of 66 SE patients (Table 1). Nine out of the 11 RCSE neuroimaging studies revealed abnormalities such as cerebral edema, white matter changes, and focal post-contrast enhancements (tumoral lesions).

Seizure control in 45% of the RCSE cases (n=5) was achieved using three or more IV AEDs. Midazolam drip (0.1 mg/kg/hr) was used as a second-line IV AED in six cases (60%) of RCSE, while Phenobarbital (20mg/kg) and Valproic Acid (20mg/kg) were used in four cases (40%). Levetiracetam (1 g IV loading dose) was used as an adjunct IV therapy in four cases (40%). Seizure control in a patient

with previously diagnosed epilepsy was achieved using Propofol (6 mg/kg/hr) in addition to four other IV AEDs.

Table 1 shows the risk factors associated with the development of RCSE among patients with SE. Using univariate analysis, only three variables were significantly correlated with RCSE among patients with SE. These risk factors are: first-onset seizures (p=0.036), abnormal cranial imaging (p=0.008), and serum sodium levels <135 (p=0.034).

However, using multivariate analysis (Table 2), only two variables were significantly associated with RCSE: first onset seizures (p=0.0214) and abnormal cranial imaging (p=0.0131). Sensitivity of first onset seizures and abnormal cranial imaging as predictive factors for developing RCSE is 81.82%. On the other hand, the specificity of the two variables is 52.7 and 63.4%, respectively.

Table 2. Association of Significant Risk factors for RCSE by Multivariate Analysis

Variables	Odds Ratio	Confidence Interval	P value
Onset of seizures	18.0120	1.5345 – 211.4288	0.0214 (S)
Blood chemistry	6.999	0.6986 – 70.1388	0.0979 (NS)
Cranial imaging	35.7058	2.1219 – 600.8389	0.0131 (S)

*S= significant, *NS= not significant

If both variables are taken together, the probability of predicting progression to RCSE using the area under the receiver-operator characteristic (ROC) curve, which compares the true positive rate and false negative rates, is 0.8891. This translates to an 88.91% probability of an RCSE event occurring if the two variables, first-onset seizures and abnormal cranial imaging, are present at the time of the convulsive seizure attack.

The average length of hospital stay was 31.5±97.30 hours. The range of hospital stay was from 4 to 115 days. The mortality rate for RCSE was 3 in 11 cases (27%).

Discussion

RCSE is one of the most common neurologic emergencies with high rates of mortality and morbidity. There is paucity of comprehensive studies that analyze its underlying factors, therapeutic response, and management outcomes.[1,2] However, it is important to identify patients who are at risk of developing RCSE to prevent long-term deleterious complications.[1]

In this study, the prevalence of RCSE among patients with SE was 16%. This is lower than a previous German study where 43% of patients with SE developed into RSE.[4] The difference may be due to the heterogeneity of the populations under study.[8] Management of RSE also varied across different neurocritical care facilities.[4] The actual rate of RCSE in this study may be higher if patients had been monitored in a neurological intensive care unit, or if they had been referred immediately at the onset of the symptoms.

A recent related retrospective study revealed that de novo RCSEs generally have poorer prognosis, causing a mortality rate of 55%, and development of long-term neurologic sequelae such as post-SE symptomatic seizures in 29% of the patients.[7]

Abnormal cranial imaging was also strongly correlated with RCSE. Of the 24 patients with abnormal CT/MRI findings, a total of 10 (42%) had RCSE. Most of these abnormalities were consistent with CNS infections, brain metastasis, or encephalomalacia. These underlying structural pathologies cause variedly distributed epileptogenic foci which may predispose the patient to SE, and eventually RCSE.[9] A retrospective study on the predictors of RCSE in a German neurologic facility revealed 88.9% of the patients with RSE were secondarily caused by focal CNS diseases.[5]

All patients (n=6) with viral CNS infection initially presenting with uncontrolled first-onset seizures proceeded into RCSE. In a study by Misra et al. (2008), about 37 out of 93 patients (40%) with CNS infection develop into SE.[9] However, the proportion of patients progressing from SE to RSE was only 10.9%. This is comparable to our data (9.1%, n=6). Encephalitis is cited in several studies as an important etiologic predictor for developing SE and RCSE. A recent study in India also demonstrated that a large proportion of RCSE patients have CNS infections (44.4%), particularly viral encephalitis.[10] Furthermore, a subset of RCSE would further progress to a protracted course. The super refractory SE (SRSE) is defined as SE continuing for greater than 24 hours after initiation of anesthetic therapy, including cases of SE recurring upon withdrawal or reduction of the anesthesia.[11] A recent Chinese study indicated that a majority of SRSE is caused by viral encephalitis (67.7%).[12] Encephalitis usually has multiple focal epileptogenic foci which are cortically distributed. Other cases such as herpes virus encephalitis may also cause intractable seizures, as the virus has predilection for the temporal lobe, a region with a low seizure threshold.[5]

In summary, early determination and identification of risk factors for SE is important to prevent progression to RSE. However, this study did not determine whether discharged patients returned to their pre-morbid functional baseline or if these patients developed long-term neurologic complications. In addition, patients' Glasgow Outcome Scores (GOS) and APACHE II scores should be obtained on admission and compared to pre-discharge scores but were not in this study.

This study identified two predictive factors for developing RCSE: abnormal cranial imaging and first-onset seizures. The presence of both variables can predict occurrence of RCSE with a relatively high sensitivity rate. The study is limited by the small number of patients identified with RCSE, as well as limited information regarding the variables leading to RCSE.

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