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Generalised convulsive status epilepticus in Singapore: Clinical outcomes and potential prognostic markers

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ABSTRACT

Purpose: To study the characteristics, outcomes and prognostic markers of convulsive status epilepticus (SE) in Singapore.
Methods: 62 adult admissions to the National University Hospital Singapore from 2002 to 2005 were studied. Ethnicity, history of epilepsy, educational subnormality, neuroimaging, seizure duration, length of stay, Modified Rankin Scale (MRS) pre and post discharge, blood glucose, creatine kinase, potassium, white cell and platelet count were recorded. An MRS ≥ 3 at discharge was defined as a poor outcome. ROCs of significant variables were plotted to identify the best test cut-offs.
Results: Mean age was 59.2 years (range 20–94). 75.9% patients had epilepsy. Mean length of stay was 14 days (range 1–75). Univariate analyses revealed age ($p = 0.01$, OR 1.075, 95% CI 1.030–1.122), length of stay in ICU ($p = 0.03$, OR 1.299, 95% CI 1.014–1.665) and hospital ($p = 0.014$, OR 1.203, 95% CI 1.038–1.393) and hyperglycemia ($p = 0.045$, OR 1.327, 95% CI 1.007–1.750) associated with poor outcome. Test cut-off values for prognostic markers were established: age ≥ 55 years (ROC 0.790, sensitivity 72.3, specificity 85.7, PPV9 4.4%, NPV 48.8%) and serum glucose ≥ 7 mmol/L (ROC 0.737, sensitivity 72.3, specificity 80.0, PPV 93.5%, NPV 36.4%). A discriminant model using these variables was then constructed with probability scores for poor outcome.
Discussion: Age, hyperglycemia and length of stay in hospital influenced outcome from convulsive SE in the local population with hyperglycemia being a novel prognostic marker. Some prognostic markers cited in the literature differed, highlighting the possibility that these indicators may vary across population groups.

1. Introduction

Status epilepticus (SE) carries a significant mortality, ranging from 7 to 40% based on reports predominantly from the United States and Europe.[1–4] Prolonged refractory SE can cause severe neurological morbidity.[3] The treatment strategies for SE are not without potentially life-threatening consequences leading to the inevitable dilemma as to how aggressively some cases should be managed.[2]

There has been a lack of data on SE in Singapore hence little is known of the demographic and clinical features within a predominantly Asian multi-ethnic population. We previously reported cases of severe new onset and highly refractory SE with dismal outcomes.[5] These cases were fortunately a rare occurrence but prompted us to examine all cases of SE admitted to our tertiary institution. Emerging literature has highlighted certain clinical features that identify patients with poor prognoses in the early stages of presentation that may guide management plans.[2,3,6,7] We aimed to identify prognostic features within our local population and compared these to other reports.

2. Materials and methods

This was a retrospective case-note study. Admissions to the National University Hospital, a tertiary referral center between January 2002 and December 2005 were examined. Patients were identified using an electronic hospital database. Patients discharged in the index period with an International Classification of Diseases (ICD)-9 code concerning epilepsy (345. X and all

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subsequent extensions) as part of either the primary or secondary discharge diagnosis were evaluated. Case-notes were individually reviewed. Adults over the age of 18 years were included. We excluded children because the differing causes and prognoses of SE in this population indicate that this is a largely heterogeneous group.[8,9] SE was defined as ongoing seizures and/or repetitive seizures without intercurrent normalization of consciousness or return to baseline for at least 30 min. Only patients who presented with convulsive (defined as witnessed generalized motor manifestations, within or outside hospital) SE were included since the time of onset and seizure duration could be more accurately determined. Patients with a non-convulsive, partial SE, 'subtle' SE and SE secondary to post-anoxic encephalopathy were excluded. We recorded age, gender, ethnicity, past history of epilepsy, educational sub normality (defined as incomplete primary school education as a direct consequence of mental disability), structural abnormality on neuroimaging, concurrent anticonvulsant regime, length of stay in the intensive care/high-dependency unit and etiology of the SE. Following careful review of the case-notes, etiology was grouped into several headings according to international recommendations[8]:

(1) Acute (provoked) symptomatic.
(2) Remote (unprovoked) symptomatic.
(3) Progressive (unprovoked) neurologic conditions.
(4) Cryptogenic.

White cell count, platelet count, serum potassium, creatine kinase and glucose at the time of presentation were recorded. A leukocytosis is often seen post-ictally.[9] Rhabdomyolsis (along with the hyperkalemia associated with it) and disruption in glucose homeostasis is recognized in convulsive status epilepticus.[10–12] We found that the above laboratory data were recorded in all SE patients at the time of presentation and hence we were curious if any were potential prognostic markers.

The Modified Rankin Scale (MRS)[15] was used as a functional outcome measure and an MRS score was given prior to admission (based on information from relatives and carers) and at the point of discharge.

The MRS scoring system is shown below:

0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability, bedridden, incontinent and requiring constant nursing care and attention
6	Dead

2.1. Statistical analysis

Data was collected and statistical calculations were performed using SPSS v11.0. Frequency distributions of potential predictive features were studied. We defined patients with an MRS at the time of discharge of $\geq$3 as having a poor outcome. The association of individual factors with a poor outcome was analysed using the Fisher exact test. The receiver operating characteristic curves (ROCs) were performed on the significant variables from the univariate analysis to obtain the best test cut-off value that identified patients with a poor outcome. Using these predetermined cut-offs, the multivariate logistic regression was applied to create a discriminant model with probability scores for poor outcome.

Table 1
Demographic features of patients included in the study.

	Number of patients (%)
Male	34 (58.6)
Ethnicity–Chinese	36 (62.1)
Malay	11 (19)
Indian	6 (10.3)
Others	5 (8.6)
Known epilepsy (from any etiology) prior to admission	44 (75.9)
Educationally subnormal	6 (10.3)
Mortality	7 (12.1)

3. Results

A total of 61 admissions of 58 patients were included. Mean age of the patients was 58.4 years (standard deviation 18.5, range 20–94 years). Demographic data is presented in Table 1.

The mean duration of seizures using clinical correlation (defined as cessation of convulsive motor activity) prior to termination of SE was 98.7 min (30–540). 50 (82%) cases had clinical evidence of ongoing seizures upon arrival in the Emergency Department. Mean length of stay in the intensive care or high-dependency setting was 5 days (range 0–55 days) and hospital was 14 days (range 0–75 days).

43 (74.1%) patients underwent neuroimaging of which 24.1% had MRI scans. Structural brain abnormalities were detected in 93% of these patients. 37 cases (60%) underwent EEG during the admission with a median time to EEG of 24 h.

In 42 cases (68.9%), patients were on anticonvulsants prior to SE. Etiology of the SE is displayed in Table 2. Univariate analysis revealed etiology had no significant effect on outcome in our study ($p = 0.419$). Table 3 displays the Modified Rankin Scale (MRS) pre-admission (Pre-MRS) and at the time of discharge (Post-MRS).

Using our definition of poor outcome as those patients who had a MRS at the time of discharge of $\geq$3, 18 (29.5%) cases deteriorated in functional status. Univariate analyses of the demographic, clinical and laboratory features were performed (Table 4). Multi variate analysis and ROC curves of the significant variables that

Table 2
Distribution of etiology of SE in order of frequency.

Etiology of status epilepticus	Post-MRS $\leq$ 2	Post-MRS $\geq$ 3	Total
Acute	2	7	9
Remote	7	30	37
Cryptogenic	3	3	6
Progressive	2	7	9

Table 3
Modified Rankin Scale (MRS) pre-admission (Pre-MRS) and at the time of discharge (Post-MRS) categorized with a cut-off of 3.

Modified Rankin Scale	Pre-MRS (number of cases)	Post-MRS (number of cases)
$\leq$2	29	14
$\geq$3	32	47

Table 4
Univariate analysis of demographical, clinical and laboratory data in patients with a poor outcome.

	p value	Odds ratio (95% confidence interval)
Age	**0.01**	**1.075 (1.030–1.122)**
Males	0.871	1.105 (0.330–3.70)
Chinese	0.203	2.488 (0.612–10.122)
Educational disability	0.529	0.558 (0.091–3.424)
Known epilepsy	0.387	0.486 (0.095–2.492)
Seizure duration(>60minutes)	0.262	1.009 (0.994–1.024)
Structural abnormality	0.251	4.625 (0.339–63.06)
LOS ICU	**0.03**	**1.299(1.014–1.665)**
LOS hospital	**0.014**	**1.203 (1.038–1.393)**
Glucose	**0.045**	**1.327 (1.007–1.750)**
Creatine kinase	0.508	1.000 (0.998–1.007)
Potassium	0.145	1.904 (0.800–4.530)
White cell count	0.208	1.103 (0.947–1.284)
Platelet count	0.190	1.004 (0.998–1.011)

Values in bold indicate variables with p value <0.05.

Table 5
Multivariate analysis of the significant variables that might be applied as early indicators of poor outcome.

	p value	Odds ratio (95% confidence interval)
Age	0.020	1.097 (1.015–1.185)
Glucose	0.047	1.551 (1.003–2.394)

might allow us to prognosticate at the time of presentation was performed (Tables 5 and 6).

Applying these to a discriminant model, probability scores ranging from 0 to 1 were calculated. A value closer to one indicated a higher probability of a poor outcome. As all patients with a Pre-MRS ≥ 3 remained with Post-MRS of ≥ 3, this variable was excluded from the model (Table 7). ROC of the constructed model was 0.817.

4. Discussion

We aimed to study SE in the Singapore population to answer these questions:

- Are the clinical and demographic features similar to other reports in the international literature?
- Are there clinically useful prognostic markers?

In this study, gender and ethnicity of patients were not significant risk factors for the development of SE and did not influence the prognosis. The ethnic distribution of the study population was comparable to the composition of the population nationally and emphasizes the advantage of population studies in a multi-ethnic society such as that in Singapore.

In keeping with international reports, increasing age was significantly associated with poor functional outcome and higher mortality.[1,2,6,7,13,16] In addition, length of stay in the intensive care unit and hyperglycemia on arrival correlated with poorer prognoses. Elderly patients are more likely to spend a longer period in an intensive care setting although this may be due to the complications rather than a direct result of the SE per se. In an aging population, the data of epidemiological studies may be significantly biased by age and the time may come when elderly patients are categorized separately as a distinct subgroup.

Table 7
Probability scores of poor outcome in patients with the above characteristics at the time of presentation.

Glucose ≥ 7	Age ≥ 55	Probability of Post- MRS ≥ 3
No	No	0.2385
No	Yes	0.6182
Yes	No	0.6182
Yes	Yes	0.8933

The relationship between hyperglycemia and poor outcome has to our knowledge never been established in the literature. It is uncertain if this is a feature that may be unique to the Singapore population. The high catecholamine drive that is recognized in the early stages of SE pathophysiologically causes hyperglycemia.[14,20] In vitro studies confirm that hyperglycemia increases hippocampal neuronal excitability, propagating status epilepticus.[17] The neuronal toxicity of hyperglycemia is well established in the cerebrovascular disease model, accounting for increased mortality and poorer outcomes.[18] We postulate that the degree of serologically measurable hyperglycemia may be a reflection of these mechanisms at work and have a direct bearing on the poorer prognoses seen in such cases.

This study confirms that an established diagnosis of epilepsy is a risk factor for SE but is not associated with poor outcome.[7,14,19] Etiology has been cited as a significant predictor of outcome.[16,21] In our study, etiology did not appear to significantly affect outcome. The majority of the patients had a remote etiology indicating established central nervous system lesions.[8] The outcome was poor in the majority (77.8%) of patients who had an acute symptomatic etiology, consistent with other reports.[3,6] Etiology was not formally studied when we were assessing potential prognostic markers as it would have been difficult to determine etiology at an early enough stage in most cases for this to be useful. In our study, the etiology did not significantly predict outcome for several likely reasons: we employed the MRS score as a marker of outcome rather than mortality and included cases of convulsive SE only.

The high number of patients with underlying educational sub normality (all of whom had pre-existing epilepsy) represents a group of patients with underlying abnormal CNS function which is a predisposing factor in epileptogenesis.[21,22] A link between epilepsy and learning disability has been established yet it remains unclear whether mental disability represents an independent risk factor for the development of SE.[22] There was no evidence that this was a significant prognostic indicator in our study. It ought to however be noted that this cohort of patients does not include those who died as a result of SUDEP, a significant cause of mortality in learning disabled patients with epilepsy.[21]

The duration of seizures was not a reliable prognostic marker in our study. The literature has been inconsistent regarding this matter due to difficulty in establishing the definite effect of seizure duration independent of etiology.[4,16,19] Determination of the time of onset and abolition can be difficult. It is now well recognized that a number of patients continue to have electrographical evidence of seizures with no clear motor manifestations.[7,14] However establishing an accurate duration of SE electrographically

Table 6
Statistical analysis on the potential use of early prognostic markers.

	ROC	Sensitivity	Specificity	Positive predictive value (PPV) (%)	Negative predictive value (NPV) (%)
Glucose ≥ 7	0.737	72.3	80.0	93.5	36.4
Age ≥ 55	0.790	72.3	85.7	94.4	48.8

in a community-based population would be very difficult to achieve. To ensure uniformity in our clinical data, we defined the onset of convulsive SE as the time at which generalized motor manifestations began and termination as cessation of all motor activity of the limbs. The wide variation in the seizure duration was largely due to the delay in patients being brought to hospital, which also accounts for the high percentage of patients that were having on-going seizures upon arrival in the Emergency Department. Singapore has an extensive paramedical service with rapid response times and it is likely that a delay in the activation of emergency medical services was the cause although we were unable to determine this objectively. There remains a significant social stigma attached to the diagnosis of epilepsy with poor levels of patient education which needs to be addressed.[23] The high proportion of cases (75.9%) known to have epilepsy prior to the admission with SE would lend support to this. Furthermore, this figure is likely an underestimate as it was dependent on self-reporting.

The next phase of the study involved the application of the relevant demographic and clinical features that were significantly associated with a poor outcome into a predictive model. All patients who had a poor pre-morbid functional status prior to presentation were discharged in an equally poor if not worse state and this is not surprising when we consider the significant morbidity associated with convulsive SE. Indicators of prognosis at the time of presentation such as age and serum glucose were statistically applied in the group of patients with an MRS of $\leq$3. The high ROC of this discriminant model indicates its potential use as a predictor. We found that patients with normal or only mildly impaired functional status who are above the age of 55 years and are hyperglycemic at presentation have a significant probability of a poor outcome.

5. Conclusion

This study highlights similarities and differences with other reports on the epidemiological features of SE. In our Singaporean population we identified hyperglycemia as a novel prognostic marker and used in conjunction with age, may provide us with useful prognostic information at the time of presentation. This study also emphasizes the possibility of different populations showing different identifiers of poorer prognoses.

Conflicts of interest

None.

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