Factors predictive of outcome in patients with de novo status epilepticus

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Summary

Background: About 50% of status epilepticus (SE) patients have no previous history of epilepsy, but often have worse outcome. The aim of this study was to evaluate potential risk factors that are predictive of poor outcome in non-selected de novo status epilepticus patients.

Methods: Eighty-three adult status epilepticus patients without a pre-existing history of epilepsy that were admitted to hospital for treatment were enrolled in this 11-year retrospective study. The baseline prognostic variables were analyzed based on stepwise logistic regression analysis after a minimum of one-and-half years of follow-up.

Results: The overall fatality rate was 55.4% (46/83) during the study period. Poor outcome was associated with older age, presence of refractory status epilepticus, potential fatal etiologies, lower GCS score at presentation and level of consciousness on admission. The results of stepwise logistic regression demonstrated that age on presentation and potential fatal etiologies were independently associated with presence of poor outcome, and any increase in age by 1 year increases poor outcome by 7.5%.

Conclusions: The outcome for those with de novo status epilepticus is poor and this may be attributed to the older age at onset and the potential fatal underlying conditions such as infection and metabolic derangement.

Introduction

Despite the advent of modern monitoring techniques and new anti-epileptic drug (AED) therapy, status epilepticus (SE) remains a potentially fatal disease.1 A better delineation of potential prognostic factors and outcomes can help identify patients who may benefit from intensive care, avoid unnecessary treatment and improve further management strategies.

Several studies showed that 40–60% of SE patients have no previous history of epilepsy.2–4 In contrast to patients with a previous epilepsy history, who are related to better outcome, patients without previous epileptic history often have a poorer outcome.3 Very little information is available regarding the risk factors that are predictive of poor outcome in ‘de novo’ status epilepticus patients.5 The outcome for those with de novo status epilepticus is poor and this may be attributed to the older age at onset and the potential fatal underlying conditions.

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Materials and methods

We retrospectively reviewed the medical records, using pre-existing standardized evaluation forms, of patients with SE admitted to the Department of Neurology, Kaohsiung Chang Gung Memorial Hospital between January 1995 and December 2005. Chang Gung Memorial Hospital-Kaohsiung is a 2482-bed acute-care teaching hospital, which is the largest medical center in southern part of Taiwan and provides both primary and tertiary referral care to patients. There were 143 SE patients during the study period. Of these, only 60 had a previous diagnosis of epilepsy.

In this study, SE was defined as continuous or repetitive seizure activity persisting for at least 30 min without recovery of consciousness between attacks.\textsuperscript{1,6} Furthermore, de novo SE was slightly modified from a previous study\textsuperscript{7} and included both of the following: (i) SE patients without pre-existing history of epilepsy or SE; and (ii) SE developed in patients at the time of hospitalization. Non-convulsive status epilepticus (NCSE) was diagnosed when there was a change of consciousness or mental state associated with continuous epileptiform discharge lasting for at least 30 min on electroencephalography without clinical seizure activities.\textsuperscript{8,9} Refractory status epilepticus (RSE) was defined as generalized convulsive or non-convulsive SE that continued clinically or electrophysiologically despite first or second line therapy and required coma induction for seizure management.\textsuperscript{7} Patients were excluded from the study if: (i) their age was <16 years; and (ii) they had seizures or chronic epilepsy before this episode.

The etiologic classification was based on the International League Against Epilepsy Commission’s report.\textsuperscript{6} SE was considered to be caused by ‘acute symptomatic’ central nervous system (CNS) disease if it occurred within 1 week after an acute CNS insult. ‘Progressive symptomatic’ CNS disease was defined as the presence of a non-static CNS condition such as brain tumor, CNS lupus, or a neuro-degenerative disease. ‘Remote’ CNS disease was defined as the presence of a history of CNS insult, and the time between SE and the neurologic insult was >1 week. SE was classified as ‘idiopathic/cryptogenic’ in the absence of acute, progressive, or remote CNS disease, as well as the absence of any substance association.\textsuperscript{6}

We further identified etiologies that are potentially fatal independent of SE as potentially fatal etiologies (PFE), including acute (7 days) large vessel ischemic stroke or cerebral venous sinus thrombosis, acute bacterial or viral encephalitis, malignant brain tumor, end-stage renal disease requiring dialysis, severe systemic infection and metabolic disturbances sufficient to cause coma in the absence of SE.\textsuperscript{10} Conversely, remote or progressive symptomatic conditions like previous trauma, old stroke, previous CNS infection, aseptic meningitis and dementia were considered not potentially fatal. ‘Aseptic meningitis’ was defined as: (i) clinical evidence of acute meningitis such as fever, headache or other signs of meningeal irritation, absence of any microorganism on Gram stain or bacterial culture of cerebrospinal fluid (CSF), (ii) CSF parameters of mild pleocytosis, a small and variable increase in protein and glucose content of the CSF is normal, and (iii) there is no clinical and magnetic resonance imaging evidence of encephalitis.\textsuperscript{11,12} If SE could be assigned etiologically to more than one of the sub-groups described above, it was assigned to the most probable group after considering the overall clinical picture.

Demographic data, including SE etiology, Glasgow coma scale, status seizure type, interval between seizure onset to AED therapy and outcome at hospital discharge were obtained. The interval between seizure onset and treatment was categorized as <1 h vs. >1 h,\textsuperscript{10} level of consciousness as alert, confused (arousable and responsive), stuporous (arousable but non-responsive) and comatose (non-arousable).\textsuperscript{10}

All of the patients were immediately treated according to the suggested management protocol of SE. In our institution, status epilepticus was initially treated with intravenous lorazepam bolus, followed by intravenous phenytoin loading if seizure persisted. If SE persisted, intravenous infusion of midazolam, valproate, propofol or phenobarbital was started, depending on the physician’s preference.

Outcome was measured by the condition on discharge and mortality during follow-up period, which was terminated by death or by the end of the study itself (June 2007). The outpatient department followed most surviving patients after discharge, with others interviewed by telephone to identify neurological outcomes. For the purposes of analysis, clinical outcomes were determined by the Glasgow outcome scale (GOS), with favorable outcome being GOS 4–5 (moderate disability or good recovery) and poor outcome being GOS 1–3 (death, vegetative state or severe disability).\textsuperscript{13}

Two separate statistical analyses were performed. First, we attempted to find out the risk factors for poor outcome after a minimum of 1.5 year follow-up. The effects of individual variables including gender, status seizure type, etiology classification, the interval from seizure onset to treatment, duration of hospitalization, Glasgow Coma Score (GCS) on
presentation and mean ages on outcome were analyzed by univariate logistic regression. Second, stepwise logistic regression was used to evaluate the relationship between significant variables and outcomes, with adjustments made for other potential confounding factors. Only variables with a strong association with poor outcome ($P < 0.05$) were included in the stepwise logistic regression model. All statistical analyses were conducted using the SAS software package, version 9.1 (2002, SAS Statistical Institute, Cary, NC, USA).

**Results**

The 83 patients with *de novo* status epilepticus included 42 males (mean age: 60.1 years; range: 16–87 years) and 41 females (mean age: 62.8 years; range: 16–88 years) (Figure 1). *De novo* SE was predominant in adults aged >50 years, which peaked in the eighth decade. Among them, 20.5% (17/83) belonged to RSE, including CNS infection in six, metabolic derangement or infection in four, remote strokes in three, hypoxia in two, brain tumor in one and one was cryptogenic.

The underlying etiologies of patients are listed in Table 1. Stroke (37.4%), CNS infection (20.5%) and systemic infection or metabolic problems (13.3%) were the three most common three etiologies, followed by head injury, alcohol or drug intoxication, hypoxia, brain tumor, CNS lupus and idiopathic/cryptogenic. Among the cases of CNS infection, eight were acute bacterial meningitis, two were viral encephalitis and six were aseptic meningitis. In etiologic classification, 45 were acute symptomatic, 29 remote symptomatic, three progressive symptomatic and six idiopathic or cryptogenic. Potentially fatal causes were identified in 28 patients and are listed in Table 2. Regarding status seizure sub-types, 71 (85.6%, 71/83) patients presented as convulsive SE, seven (8.4%, 7/83) as non-convulsive SE and five (6%, 5/83) as simple partial SE.

On discharge, 30 patients died and the other 53 survived. The 30 fatal cases included infection or metabolic derangement (22), underlying SE (4), sudden death of unknown etiology (2), arrhythmia (1) and cerebral sinus venous thrombosis (1). Of the 53 patients that survived after discharge, 12 had moderate to severe functional disabilities with GOS < 4 and 25 patients remained mild or good function state with GOS ≥ 4. After a minimum 1.5 year of follow-up, 24 patients had recurrent seizures, 7 developed recurrent SE and 16 patients died. For the 16 patients that expired, 7 died of sepsis, 3 recurrent SE, 2 cancers, 1 cardiac arrest, 1 aortic aneurysm rupture and 2 due to sudden death of unknown causes. The mean follow-up interval for the remaining survivors was 20.3 months (range: 2–146 months). The overall mortality rates on discharge and at the end of the study were 36.1% (30/83) and 55.4% (46/83), respectively.

The sex, mean age at onset, GCS score and consciousness level at presentation, seizure type,
etologies, refractory status epilepticus, the interval between seizure onset and treatment and mean hospital stay between the two patient (good and poor outcome) groups are listed in Table 3. Statistical analysis of the baseline clinical manifestations on outcome revealed the following important factors: age ($P = 0.0001$), presence of refractory status epilepticus ($P = 0.037$), potential fatal etiologies ($P = 0.011$) and mean GCS score at presentation ($P = 0.004$). Variables used in stepwise logistic regression analysis included mean age at presentation, potential fatal etiologies, mean GCS score at presentation and presence of refractory status epilepticus. After analysis of all the aforementioned variables, only potential fatal etiology ($P = 0.01$, OR = 12.763, 95% CI = 1.861–87.551) and mean age at presentation ($P = 0.0001$, OR = 0.915, 95% CI = 0.879–0.952) were independently associated with poor outcome, and any increase of 1 year in age had a corresponding increase in poor outcome by 7.5%.

**Table 3** Prognostic factors of patients with de novo status epilepticus

<table>
<thead>
<tr>
<th>Poor outcome N=58</th>
<th>Good outcome N=25</th>
<th>Total N=83</th>
<th>$P$-value</th>
<th>ORa</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>27/31</td>
<td>15/10</td>
<td>42/41</td>
<td>0.263</td>
<td>0.58</td>
</tr>
<tr>
<td>Mean age at onset</td>
<td>69.2 ± 14.4</td>
<td>43.6 ± 18.8</td>
<td>61.5 ± 19.7</td>
<td>0.0001</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean GCS on presentation</td>
<td>5.6 ± 2.1</td>
<td>7.6 ± 3.4</td>
<td>6.2 ± 2.7</td>
<td>0.004</td>
<td>1.33</td>
</tr>
</tbody>
</table>

**Seizure type**
- Convulsive: 49/22/71 ($P = 0.693$, OR = 1.19, 95% CI = 0.51–2.77)
- Non-convulsive: 7/0/7 ($P = 0.90$, OR = 1.17, 95% CI = 0.10–13.49)
- Simple partial: 2/3/5 ($P = 0.47$, OR = 0.44, 95% CI = 0.05–3.99)
- Refractory status epilepticus: 16/1/17 ($P = 0.037$, OR = 9.14, 95% CI = 1.14–73.30)

**Etiology**
- Acute symptomatic: 30/15/45 ($P = 0.48$, OR = 1.4, 95% CI = 0.54–3.63)
- Remote symptomatic: 21/8/29 ($P = 0.712$, OR = 0.83, 95% CI = 0.31–2.25)
- Progressive symptomatic: 2/1/3 ($P = 0.90$, OR = 1.17, 95% CI = 0.10–13.49)
- Idiopathic/cryptogenic: 5/1/6 ($P = 0.47$, OR = 0.44, 95% CI = 0.05–3.99)
- Potential fatal: 25/3/28 ($P = 0.011$, OR = 5.06, 95% CI = 1.49–20.66)

**Duration of status epilepticus**
- <1 h: 11/5/16 ($P = 0.91$, OR = 0.94, 95% CI = 0.29–3.05)
- ≥1 h: 47/20/67 ($P = 0.29$, OR = 0.99, 95% CI = 0.98–1.01)

**Mean Hospitalization days**
- 35.7 ± 38.3/26.1 ± 34.9/32.8 ± 37.4 ($P = 0.29$, OR = 0.99, 95% CI = 0.98–1.01)

*aThe odds ratio was calculated by univariate logistic regression.
OR, odds ratio; CI, confidence interval.

Discussion

Although the outcomes of SE vary with case determination and inclusion criteria, length of follow-up, underlying diseases and complications, the mortality rate varies and is estimated at 10–30% in different series.4,10,14–20 This study demonstrates that the prognosis of de novo SE is poor. Our in-hospital mortality was 36% (30/83). However, if those with moderate to severe functional disability are taken into account, 69.88% (58/83) of patients can be considered as poor outcomes. The overall mortality rate was 55.42% (46/83) at the end of study, 29% (25/83) developed post-SE symptomatic epilepsy and 8.43% (7/83) had recurrent status epilepticus. Another retrospective study regarding patients hospitalized for reasons unrelated to epilepsy or prior seizures showed that the overall mortality rate is 61% (25/42), with only 20% (8/41) returning to baseline and leaving the hospital.5 Several articles have reported variables related to seizure outcomes after SE, including convulsive SE, age, etiology, duration before treatment and level of consciousness.1,2,7,10,14,15,18,20 Regarding underlying etiologies, acute symptomatic CNS diseases are the most common. Furthermore, our study demonstrates that potentially fatal etiologies are strongly associated with poor outcome. The development of de novo SE appears to be associated with an incidence of underlying brain lesions and metabolic derangement in other2,10,21 studies as well as ours. Regarding age distribution, one peak of incidence is in the 70th year of life. We also demonstrate that age is a significant prognostic factor of poor outcomes and any increase of 1 year in age will
increase the poor outcome by 7.5%. This is higher than another study regarding mortality after SE, which demonstrated that the odds ratio increased ~39% correlating with each increased decade of age. The level of consciousness at presentation is a well-known prognostic factor for outcome after SE, which is also a significant prognostic factor in this study.

The prognoses of NCSE vary throughout several studies. One recent study demonstrate that NCSE in patients who had pre-existing epilepsy has a substantially better prognosis than those who had acute neurological or systemic disorders. Accumulation of complications including underlying medical conditions, as well as the duration of seizure activity seems to be the basis of high mortality in other studies and in our study.

RSE is an important and serious clinical problem that requires prolonged and high-level intensive care, and is often associated with poor functional outcome. About one-fifth of patients in our study were refractory to first line anti-convulsants, which is significantly associated with poor outcome in de novo SE patients in our study. Acute symptomatic CNS disease, especially CNS infection, is the most common cause of RSE and has been associated with poor outcome and the development of post-SE symptomatic epilepsy in previous literature.

Whether or not the duration before treatment is a significant predictor for outcome remains controversial. In the Richmond study, duration >1 h is a predictor of poor outcome compared with duration <1 h, with an odds ratio of 9.79. However, the association is not found in other studies, including ours. This is probably because of different inclusion and exclusion criteria and underlying conditions of patients, which may influence statistical results. Furthermore, our study demonstrated that the underlying causes of these de novo SE, especially potential fatally etiologies, is the major determinant of outcome despite prompt treatment of the underlying condition and seizures.

Our study has several limitations. First, this was a retrospective analysis, the treatment protocol for SE would be different for each patient according to the preference of his/her doctor and underlying conditions, which may cause potential bias in statistical analysis. It was also not possible to assess the effect of prophylactic AEDs after the acute stage of de novo SE to prevent later epilepsy or draw conclusions. Second, most patients had an associated underlying acute symptomatic brain pathology or metabolic derangement. Thus, continued uncertainty was present in assessing the outcome. In addition, the assignment for potential fatal etiology may have some potential bias because it is not possible to conduct this in a blind manner in a retrospective design. Third, most patients in this study were treated with anti-convulsant medication after their first acute symptomatic SE, in accordance with our study protocol. Thus, our findings might have underestimated the ‘true’ frequency of seizure associated with the ‘natural history’ of untreated, unprovoked seizures. Fourth, our follow-up time was short, which might underestimate the incidence of late-onset seizures. Prolonged periods would be required for recurrent seizures in several individuals. Thus, there was also continued uncertainty in assessing the incidence of unprovoked seizures after de novo SE in non-selected patients. Although the sample size was not large, the number of variables considered for the multiple logistic regression analysis was small, i.e. only four variables were considered. Therefore, the maximum likelihood estimates of the coefficients are valid in the analysis.

In conclusion, de novo SE has become an important issue in the hospital setting. Our study has demonstrated that age on presentation is independently associated with poor outcome and any increase of 1 year in age will increase poor outcome by 7.5%. The outcome in those with de novo status epilepticus was poor, and this may be attributed to the older age at onset and the potential fatal underlying conditions such as infection and metabolic derangement.  

Conflict of interest: None declared.

References