PAPER

Prognosis of status epilepticus: role of aetiology, age, and consciousness impairment at presentation

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J Neurol Neurosurg Psychiatry 2006;**77**:611–615. doi: 10.1136/jnnp.2005.080887

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Received 21 September 2005
In revised form 10 November 2005
Accepted 17 November 2005

Background: Identification of outcome-predictive factors could lower risk of under- or over-treatment in status epilepticus (SE). Older age and acute symptomatic aetiology have been shown to predict mortality, but other variables are controversial and level of consciousness has received relatively little attention. The objective of this study was to assess variables predictive of mortality, particularly those available at presentation.
Methods: The discharge database (1997–2004) of two university hospitals was screened for adult patients with EEG confirmed SE, excluding cerebral anoxia. Outcome at discharge (mortality, return to baseline clinical conditions) was analysed in relation to demographics, clinical features, and aetiology. Aetiologies were also classified based on whether or not they were potentially fatal independently of SE.
Results: Mortality was 15.6% among 96 patients with a first SE episode, 10 of whom also experienced recurrent SE during the study period. Eleven other patients had only recurrent SE. Mortality was 4.8% among these 21 patients with recurrent SE. Return to baseline condition was more frequent after recurrent than incident SE ($p = 0.02$). For the first SE episode, death was associated with potentially fatal aetiology ($p = 0.01$), age ≥ 65 ($p = 0.02$), and stupor or coma at presentation ($p = 0.04$), but not with gender, history of epilepsy, SE type, or time to treatment ≥ 1 h.
Conclusions: At initial evaluation, older age and marked impairment of consciousness are predictive of death. Surviving a first SE episode could lower the mortality and morbidity of subsequent episodes, suggesting that underlying aetiology, rather than SE per se, is the major determinant of outcome.

Status epilepticus (SE) is a neurological emergency, with a short term mortality of 7–39%.[1–5] An aggressive therapeutic approach to SE has been recommended, including induction of general anaesthesia in SE resistant to first and second line antiepileptic drugs, since refractory SE carries a high risk of deleterious sequelae if treatment is delayed.[6 7] This, however, is best documented for generalised convulsive (GC) SE; there is no consensus about the best strategy for treating the two most common forms of non-convulsive (NC) SE, which are complex partial (CP) SE and non-convulsive SE with coma (NCSEC). Furthermore, there is evidence that underlying neurological damage, rather than the duration of SE, is the best predictor of outcome.[2 8–10]

Because of doubts regarding the risk of permanent neurological damage in NC SE, some authors advocate a more conservative strategy[9 11–15]; NC SE in critically ill elderly patients has been shown to have a high mortality (52%) that may in part be associated with extensive benzodiazepine use.[16] Others have reported an overall poor outcome in patients with NC SE,[10 17–19] especially if related to refractory SE.[20 21] Better understanding of the prognostic factors of SE could have an important impact on treatment strategy, helping to select the population most likely to benefit from aggressive treatment, and potentially decreasing the risks of over-treatment to others.

Previous studies showed that older age and acute symptomatic aetiology are related to poor outcome.[22] Results are less consistent for other variables: time to treatment or to seizure control,[2 8 23] gender,[2 8] and ethnicity.[1 8] Consciousness impairment has received little attention, and no study has considered the role of a history of prior episodes of SE. With particular attention to the latter two variables, we aim to describe a hospital based, adult population with SE, and identify prognostic factors. Because of the poor prognosis of SE following anoxic-ischaemic insults, we excluded this group from analysis.

METHODS

Patients

We screened the common computerised database of two tertiary referral hospitals (Brigham and Women's Hospital and Massachusetts General Hospital) for patients with SE in the period May 1997 to April 2004. The search strategy was: [status epilepticus OR grand mal status OR epilepsia partialis continua OR petit mal status] AND [EEG]. SE was defined as ongoing seizures, or repetitive seizures without intercurrent normalisation of consciousness or return to baseline for at least 30 min. EEG was defined as positive if showing an ictal or periodic pattern or, if performed postictally, showing focal slowing (with or without interictal discharges) unexplained by other causes, or generalised slowing with interictal epileptiform activity. Patients with periodic EEG patterns unassociated with any clinical seizure activity apart from coma were not identified by our search. Subjects with anoxia-ischaemia, insufficient data regarding clinical diagnosis or EEG, incorrect diagnosis (isolated seizures, non-epileptic seizures), and patients <16 years were excluded.

Variables

Through analysis of discharge summaries, clinical notes, and laboratory results, we identified demographics, previous epilepsy history, SE aetiology (according to ILAE criteria,[24] classified as acute symptomatic, remote symptomatic, progressive symptomatic, and idiopathic/cryptogenic), seizure semiology, time to treatment (that is, latency between seizure onset and administration of the first AED), and outcome at hospital discharge (dead, alive but substantially impaired relative to baseline clinical condition, or returned to baseline).

Abbreviations: CP SE, complex partial SE; GC SE, generalised convulsive SE; NC SE, non-convulsive SE; NCSEC, non-convulsive SE with coma; PFE, potentially fatal aetiology; SE, status epilepticus; SP, simple partial

In parallel, the following aetiologies were further defined, in blinded fashion regarding the clinical outcome, as potentially fatal (PFE), that is, potentially leading to death independently of SE: acute ($\leqslant$7 days) large vessel ischaemic stroke, acute cerebral haemorrhage, acute central nervous system infection, severe systemic infection, malignant brain tumour, AIDS with CNS complications, chronic renal insufficiency requiring dialysis, systemic vasculitis, metabolic disturbance or acute intoxication sufficient to cause coma in the absence of SE, eclampsia, and intracranial tumour surgery. Conversely, AED withdrawal, an acute symptomatic aetiology, and such remote or progressive symptomatic conditions as previous trauma, stroke, CNS infection, dementia, multiple sclerosis, or meningioma were considered not potentially fatal. Ethnicity was categorised as Caucasian versus non-Caucasian, age as $<$65 years versus $\geqslant$65 years, and time to treatment initiation as $<$1 h versus $\geqslant$1 h. Seizure semiology and consciousness impairment were assessed according to the earliest medical or paramedical description, in every case prior to treatment initiation, and generally after cessation of the first witnessed convulsion in the case of convulsive SE. Seizures were classified as simple partial (SP), complex partial (CP), generalised convulsive (GC), and, if diagnosis in a comatose subject was only possible with EEG, as non-convulsive associated with coma (NCSEC). Level of consciousness was categorised as alert, somnolent (arousable and responsive), stuporous (arousable but non-responsive), and comatose (non-arousable).

Prospective validation

We assessed the quality of 33 medical records of patients with SE consecutively identified in our EEG laboratory. This showed that our search strategy would have been able to identify 25/33 (76%) patients. Eight subjects did not have complete data in their discharge summary, especially regarding diagnosis (for example, mention of seizures but not SE); demographics, clinical characteristics, and outcome did not differ from those of the other 25 patients.

Statistical methods

Comparisons of proportions were performed using Fisher's exact test. Logistic regression was used to develop a multiple variable model to predict death in patients with incident SE. Exact methods were used to estimate odds ratios and 95% confidence intervals (LogXact-6, Cytel Software, Cambridge, MA). Conditional maximum likelihood estimates were reported, except that the median unbiased point estimate was reported for ethnicity. All potential predictors were binary except that extent of consciousness impairment at presentation (alert, somnolent/confused, stuporous, comatose) and seizure type (SP, CP, GC, NCSEC) were ordinal. The full model had all potential predictors and the single least significant predictor was eliminated at each step. The final model retained all predictors with p values less than 0.10.

RESULTS

Of 240 patients identified, 133 were excluded due to insufficient clinical data (33 patients), incorrect diagnosis (that is: isolated seizures and non-epileptic seizures; 54 patients), paediatric age (33 patients, median age 4 years, range 1–13, all referred to the Massachusetts General Hospital), and anoxia (13 patients). Of the latter, nine had NCSEC, all of whom died, and two of the four remaining patients had convulsive SE and also died. Thus 107 patients were analysed, accounting for 127 SE episodes. EEG during the first 24 h showed ictal discharges in 55 episodes (43%, 12 deaths), periodic patterns in 15 (12%, two deaths), and postictal slowing and/or interictal epileptiform activity in 57 (45%, two deaths). The latter group all had clinically obvious seizures, including SP with motor phenomena (six episodes), CP (15), and GC (36).

Ninety six patients experienced their first SE episode during the study period (47 male, 49 female; median age 54.5 years, range 19–97). Ten of these (10.4%) had a recurrence during the study period, whereas 11 others had only recurrent episodes (their first SE episode was not recorded in the study period). Mortality in incident SE was 15/96 (16%). The difference in mortality between the 86 patients with incident only SE (15/86, 17.4%) and the 21 subjects with recurrent SE (1/21, 4.8%) was not significant ($p = 0.19$). The likelihood of return to baseline clinical condition at discharge, however, was higher in patients with recurrent SE (13/21, 61.9%) than in those with incident only SE (29/86, 33.7%; $p = 0.02$). Demographics, aetiological variables, and consciousness impairment did not differ significantly between these two groups, whereas patients with recurrent SE had a higher prevalence of SP SE (3/21 *v* 2/86, $p = 0.05$).

Further analysis was limited to the 96 patients with incident SE episodes. Figure 1 and table 1 show their demographic and clinical data. Older age was associated with higher mortality. No African-American or Hispanic patient died. Consciousness and SE semiology descriptions prior to treatment were derived from notes made by the ambulance crew in 25 patients (26%, four deaths), by outside hospital staff in 20 (21%, three deaths), and by staff at the study hospitals (emergency department or inpatient unit) in 51 (53%, eight deaths). Fourteen of 15 deaths occurred in patients who were stuporous or comatose at presentation. The prevalence of NCSEC was low, but its mortality was high (3/5; and 12/14 or 86% when considering the excluded anoxic patients). SE duration of 1 h or more prior to treatment was equally prevalent in surviving and deceased patients (table 1). Regarding semiology, there was no difference in mortality between CP SE (6/42) and GC SE (6/45), while fewer patients with SP SE (0/4) and more with NCSEC (3/5) died; numbers were too small to assess significance. Among NCSEC patients, 3/3 who were treated after 1 h died as opposed to 0/2 who were treated earlier.

Aetiological classification is shown in table 2. By chance, the prevalence of PFE and acute symptomatic aetiologies was the same (56 cases); however, the two groups were distinct, with 42 cases in both groups. PFE showed the highest association with poor outcome. Furthermore, PFE was recorded in 12/35 patients who returned to baseline clinical conditions and in 44/61 who did not ($p<0.01$), whereas for acute symptomatic aetiology the proportions were 18/35 and 38/61, respectively ($p = 0.39$). Of note, mortality did not differ significantly considering the acute symptomatic category as a whole, or acute symptomatic associated with an underlying chronic aetiology, although remote symptomatic aetiology had a slightly lower mortality than acute or progressive symptomatic aetiology. Only three subjects had an idiopathic-cryptogenic aetiology, none of whom died.

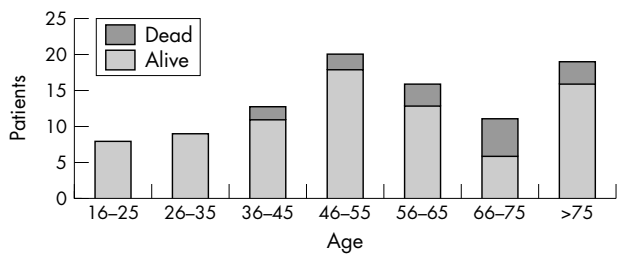

Figure 1 Age distribution in 96 patients with incident SE episodes.

Table 1 Clinical data for 96 incident SE episodes

First SE episode	Total (96)	Dead (15)	Alive (81)
Gender			
Male	47	9 (60%)	38 (47%)
Age			
⩾65	31	9 (60%)	22 (27%)
Ethnicity			
White	71	14 (93%)	57 (70%)
Black	17	0	17 (21%)
Hispanic	5	0	5 (6%)
Unknown	3	1 (7%)	2 (3%)
No history of seizures	45	10 (67%)	35 (43%)
Time to treatment			
⩾1 h	45	7 (47%)	38 (47%)
PFE	56	14 (93%)	42 (52%)
Seizure type			
SP	4	0	4 (5%)
CP	42	6 (40%)	36 (44%)
GC	45	6 (40%)	39 (48%)
NCSEC	5	3 (20%)	2 (2%)
Consciousness			
Alert	4	0	4 (5%)
Somnolent/confused	20	1 (7%)	19 (23%)
- and CP	19	1 (7%)	18 (22%)
- and GC	1	0	1 (1%)
- and NCSEC	0	0	0
Stuporous	28	4 (27%)	24 (30%)
- and CP	20	4 (27%)	16 (20%)
- and GC	8	0	8 (10%)
- and NCSEC	0	0	0
Comatose	44	10 (67%)	34 (42%)
- and CP	3	1 (7%)	2 (2%)
- and GC	36	6 (40%)	30 (37%)
- and NCSEC	5	3 (20%)	2 (2%)

CP, complex partial status epilepticus; GC, generalised convulsive status epilepticus; NCSEC, non-convulsive status epilepticus with coma; PFE, potentially fatal aetiology; SP, simple partial status epilepticus.

Analysis of potential predictors of death at discharge is given in table 3. In univariate analysis, Caucasian ethnicity, age ⩾65 years, PFE, and extent of consciousness impairment were significantly related to mortality. However, only the latter three remained significant in multiple logistic regression; PFE was highly predictive (OR 11.69, p = 0.01). Patients of Caucasian ethnicity, indeed, had a significantly higher prevalence of subjects over 65 years of age as compared to non-Caucasians (28/71 *v* 3/25, p = 0.01), whereas association with PFE or stupor/coma did not differ.

Specific aetiologies related to mortality were stroke, CNS tumour, CNS infection, and alcohol/drug toxicity (table 4). Deaths associated with the latter aetiological group were mainly due to drug toxicity (two patients), whereas only one patient died after a SE caused by alcohol withdrawal. Among specific aetiologies related to death, patients older than 65 years of age had a non-significantly higher prevalence of stroke (26% *v* 12% in younger patients; p = 0.14) and CNS tumour (19% *v* 12%; p = 0.37), and a lower prevalence of CNS infection (6% *v* 15%, p = 0.33); systemic infection and intoxication were encountered with similar frequency in both age groups.

Table 2 Aetiology for 96 incident SE episodes

First SE episode	Total (96)	Dead (15)	Alive (81)
Acute symptomatic	56	10 (67%)	46 (57%)
Acute on chronic	37	7 (47%)	30 (37%)
Remote symptomatic	19	2 (13%)	17 (21%)
Progressive symptomatic	18	3 (20%)	15 (19%)
Idiopathic/cryptogenic	3	0	3 (4%)
Potentially fatal	56	14 (93%)	42 (52%)

Table 3 Potential predictors of death at discharge

Variable	OR	95% CI	p
A: Single variable potential predictors of death in 96 incident SE episodes*			
Age ⩾65 years	3.97	(1.11 to 15.23)	0.03
Male gender	1.69	(0.48 to 6.33)	0.52
Caucasian ethnicity	7.33	(1.15 to ∞)	0.03
History of epilepsy	0.38	(0.09 to 1.37)	0.16
Acute symptomatic aetiology	1.52	(0.42 to 6.18)	0.68
Potentially fatal aetiology	12.75	(1.78 to 563.5)	0.004
Extent of consciousness impairment	2.23	(1 to 6.13)	0.05
Extent of seizure severity	2.11	(0.82 to 5.86)	0.13
Time to treatment <1 h	1.01	(0.29 to 3.61)	1.00
B: Final multiple variable model to predict death in 96 incident SE episodes			
Potentially fatal aetiology	11.69	(1.52 to 540.8)	0.01
Age ⩾65 years	5.41	(1.30 to 25.5)	0.02
Extent of consciousness impairment	3.03	(1.05 to 11.3)	0.04

*Since no non-Caucasian patient died, the upper limit of the confidence interval for ethnicity could not be estimated.

DISCUSSION

In addition to older age and more severe aetiology, this study identifies extent of consciousness impairment at presentation as a prognostic factor for SE mortality, and suggests that a history of prior SE could be associated with better outcome.

Mortality among our 96 patients with first SE episode was 15.6%. Previous studies found SE short term mortality to be between 7.6% and 39%. This wide range is likely due to different study designs (retrospective[2 5] *v* prospective,[1 3 4] unclear inclusion of recurrent SE episodes[3]), demographics (high percentage of non-Caucasian patients[1]), and clinical features (that is, exclusion[3] or inclusion of anoxic patients,[1 2 4 5] having a poor prognosis; exclusion[4 5] or inclusion[1–3] of paediatric subjects having a better prognosis). Since anoxic patients were excluded, our series is most similar to the population based EPISTAR study,[3] but has roughly double the mortality (15.6% *v* 7.6%). Exclusion of paediatric patients and recurrent SE episodes, as well as referral bias in our hospital based series as compared to a population based study, probably account for this difference.

In our study period, the recurrence rate was 10.4% over 7 years. This value seems lower than previously found (13% over 2 years in two population based studies[1 4]), again probably because of the referral bias of our hospital based assessment. The same reason, in particular the fact that our clinics are tertiary referral centers, may account for the lack

Table 4 Specific causes of SE compared to outcome in 96 incident SE episodes

Aetiology	Total (96)	Dead (15) (16%)	Alive (81) (84%)
Stroke	16	3 (20%)	13 (16%)
CNS tumour	14	3 (20%)	11 (14%)
CNS infection	12	2 (13%)	10 (12%)
Low AED (confirmed)	10		10 (12%)
Systemic infection	9	2 (13%)	7 (9%)
Metabolic	7		7 (9%)
Alcohol/toxic	6	3 (20%)	3 (4%)
Brain surgery	4		4 (5%)
Congenital encephalopathy	3		3 (4%)
Vascular malformation	3		3 (4%)
Multiple sclerosis	1		1 (1%)
Idiopathic/cryptogenic	3		3 (4%)
Other	8	2 (13%)	6 (7%)

of a clear peak over 65 years in the age distribution of our cohort, as opposed to population based studies[1 3 4 25] (fig 1): a very similar distribution was found in a hospital based series of patients with first ever seizures.[26]

A previously unrecognised finding is the higher likelihood of return to baseline clinical condition, and trend toward lower mortality, in patients with recurrent SE than in patients experiencing only one SE episode. Patients with recurrent SE had a higher prevalence of SP SE; however, only five subjects had this seizure type in our series, and other demographic, aetiological, and clinical variables were equally distributed. If recurrent SE were less ominous than incident SE, this would provide further evidence that prognosis is more strongly related to the underlying clinical situation than to SE itself.

Multiple logistic regression identified three outcome-predictive factors. Underlying SE aetiology was the most powerful, as has been reported before.[7] Many studies found ''acute symptomatic aetiology'', or ''acute, life threatening aetiology'' to be a strong predictor.[2 10 16 27] The classic definition of acute symptomatic aetiology[24] may be misleading, however, since it comprises a very heterogeneous group, including, for example, patients with antiepileptic drug withdrawal (who generally have an excellent prognosis), and patients with a newly discovered CNS tumour or with encephalitis (who often have a poor outcome). Indeed, in the present analysis this category did not significantly predict outcome, while PFE was the most predictive factor for mortality and for not returning to baseline clinical condition. The definition of this entity appears straightforward from a clinical point of view, and allows consideration of progressive symptomatic aetiologies, such as malignant CNS tumours or chronic infections, which are excluded by the current acute symptomatic classification, and exclusion of AED withdrawal. Another interesting point in this context is that purely acute aetiologies and acute on chronic causes show similar mortality, suggesting that in the presence of an acute aetiology, an additional chronic process does not modify the outcome.

Age over 65 was also a significant predictor of death. Several studies agree on this point.[2 8 27] As would be expected, in our series older patients were somewhat more likely to suffer from SE associated with stroke and CNS tumours, conditions that have a high mortality.[1] Another possible explanation is that patients of more advanced age are less resistant to complications of SE and its treatment, such as pneumonia or venous thrombosis-pulmonary embolism, although we did not assess this aspect.

One recent study, limited to NC SE, analysed extent of consciousness impairment and found a relationship with poor outcome.[10] In our series, marked impairment of consciousness was associated with death in all subgroups of SE, whereas SE semiology was not, probably as a consequence of the low prevalence of NCSEC episodes after exclusion of anoxic patients. These data suggest that non-convulsive SE is not a precise definition: it encompasses NCSEC, CP SE, and absence SE (not seen in our series), categories that have markedly different prognoses, as reflected by the associated level of consciousness (which is ultimately related to the extent of the underlying CNS pathology). The possibility that some of the patients with less profound consciousness impairment were already in a postictal state is unlikely, as our cohort was selected by the presence of an ictal EEG or by a clear ictal semiology if EEG was not immediately available.

The Richmond group found that African-American patients had a higher incidence of SE but a better outcome; age distribution among different ethnic groups was not reported in that study.[1] In our cohort, ethnicity was predictive as a single variable, but lost predictive power after multivariate analysis, possibly due to its association with age: non-Caucasian patients, who had an excellent prognosis, were younger than Caucasians.

While some found a positive correlation between poor outcome and delay to treatment initiation,[23] others did not find this association.[2 8] Time to treatment was not predictive in our series, and analysis of the subgroup of patients with GC SE or NCSEC did not modify this result. This may be surprising, since previous studies have shown that untreated GC SE carries a high risk of deleterious neurological and systemic complications.[1 20 28–32] One possible explanation is that time to treatment is critical for extremely severe SE episodes, but not for all types of SE; in our series this is suggested by the outcome of the few patients with NCSEC. Thus, we cannot exclude that the low total number of patients in NCSEC diminished the impact of time to treatment. Of note, subjects studied here were managed with a non-uniform treatment protocol; this has been the object of a separate analysis limited to refractory SE, which showed that different treatment strategies had no obvious influence on prognosis.[33]

Although this was a retrospective study, a prospective validation procedure showed that more than 75% of the patients would have been identified by the search strategy, and the potentially missed patients did not differ from the others in terms of demographics, clinical characteristics, or outcome. To our knowledge, other retrospective hospital based SE series did not report any validation procedure. Less than 14% of the considered subjects had to be excluded due to insufficient clinical data. Emphasis on diagnostic specificity in data collection, including only patients with ictal, periodic, or plausibly postictal EEG abnormalities, likely reduced the risk of recruiting subjects with non-epileptic seizures or other conditions mimicking SE. The assessment of clinical variables previous to treatment by paramedical personnel in some of the cases reflects common clinical practice, since many subjects receive benzodiazepines before reaching hospital. Outcome assessment at discharge represents a limitation inherent to the retrospective design.

As compared to previous work, this study identifies extent of consciousness impairment as an important predictor of SE outcome. It is known that underlying aetiology is a more important determinant of outcome than SE itself; similar to epilepsy, SE should be considered as a symptom of the underlying clinical situation rather than a disease in itself. Though SE aetiology is often unknown at presentation, age and level of consciousness are immediately available to the treating clinician, and knowledge of these predictive variables may help to design a prospective study to investigate how to optimise treatment, specifically as regards directing aggressive strategies toward those most likely to be helped rather than harmed.[9 16]

ACKNOWLEDGEMENTS

The authors thank Drs Tracey Milligan and Barbara Dworetzky, who helped with the database searches and shared ideas on SE, Dr Dworetzky and Dr Shahram Khoshbin, who interpreted many of the EEGs and provided advice on patient treatment, and all the Partners Neurology residents and staff neurologists at BWH and MGH, as well as emergency physicians who cared for the patients.

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Dr Rossetti is supported by the Swiss National Science Foundation and the SICPA Foundation, Prilly, Switzerland. Statistical analyses were supported by the Biostatistics Consulting Service, Center for Clinical Investigation, Brigham and Women's Hospital.

Competing interests: none declared

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