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Recurrence of status epilepticus: prognostic role and outcome predictors

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Abstract

Objective: Predictors of morbidity and mortality after Status Epilepticus (SE) have been extensively studied in hospital- and population based cohorts. However, little attention has been directed towards SE recurrence after an incident episode. We investigated clinical and demographic characteristics of patients presenting SE recurrence, and its specific prognostic role.

Methods: In this observational cohort study, we screened our prospective registry of consecutive adults with SE between April 2006 and February 2014. Demographic and clinical data were compared between incident and recurrent SE episodes; risk of SE recurrence was assessed through survival analysis, and the prognostic role of SE recurrence with multivariable logistic regressions.

Results: Of the incident cohort (509 patients), 68 (13%) experienced recurrent SE. The cumulative recurrence rate over 4 years was 32 %. Recurrence risk was significantly reduced after an acute SE etiology (HR: 0.5; 95% CI: 0.31-0.82, p=0.005), and was borderline increased in women (HR: 1.59; 95% CI 0.97-2.65, p=0.06). While recurrent SE episodes showed lower morbidity and mortality, prognosis was independently related to SE severity (STESS score) and potentially fatal etiology, but not to SE recurrence.

Significance: This study provides class III evidence that SE recurrence involves a significant proportion of patients, and that recurrence risk is independently associated with chronic etiology and to a lesser extent with female gender. However, contrary to underlying cause and SE severity, SE recurrence per se does not independently correlate with outcome. Early identification of patients at higher risk of SE recurrence may influence their management during follow-up.

Status epilepticus (SE) represents a neurological condition with considerable risk of morbidity and mortality[1-3]; etiology, increasing age, severe impairment of consciousness prior to treatment, and de novo presentation, have been independently associated with an unfavorable outcome[4-7]. It has also been shown that a consistent proportion of patients surviving a refractory SE episode will subsequently develop epilepsy[8, 9], suggesting that SE can be considered, at least in some situations, as the hallmark of a major epileptogenic insult. However, relatively little is known about SE recurrence in survivors after an incident SE; to the best of our knowledge, only one population-based study specifically addressed the risk of recurrence after a first afebrile SE episode[10]. The population-based studies conducted in Richmond in 1996 and in Germany in 2001 mentioned SE recurrence rate[2, 11] without further analyses. Furthermore while pre-existing epilepsy has been reported to be a factor of relatively good prognosis in patients with incident SE[6, 11], it is still not clear if SE recurrence also independently portends a better prognosis as compared to incident episodes. Moreover, identifying subjects at high risk of recurrent SE would be potentially useful in order to adapt their clinical follow-up.

To address these issues, we investigated clinical and demographic characteristics of patients presenting recurrent SE, factors related to SE recurrence and their specific prognostic role.

Methods

Patients and SE definition

We analyzed our prospective registry of consecutive adult patients with SE[12] treated in our center between April 1st 2006 and February 28 2014 (94 months). SE was defined as continuous seizures for longer than 30 (until 2008), or five minutes (since

2008, in line with the operational definition[13, 14]). Patients younger than 16 years old (pediatric age with potentially different epidemiological implications), or with post-anoxic coma (in view of the almost invariable dismal outcome), were not included in this registry. After reviewing the computerized medical records of our hospital, subjects with incident SE prior to the study period (treated either inside or outside our institution) or with incomplete clinical data were excluded. The population covered by our hospital represents about 250'000 habitants as first-line, and up to 1'000'000 as a third-line center. In the context of the SE registry, this observational cohort study was fully approved by our Ethic Commission.

Definition of Variables

During each admission, demographic and clinical data were prospectively collected using the best available source, as previously outlined[12]. The STESS (Status Epilepticus Severity Score), a validated clinical score[15, 16], was calculated before treatment initiation (0-2: favorable, 3-6: unfavorable outcome). Etiology was classified according to criteria of the International League Against Epilepsy[13]; as previously reported by us and others[17, 18], we further classified etiologies as "potentially fatal" if potentially leading to death independently of SE (e. g., acute large vessel ischemic stroke, acute cerebral hemorrhage, acute central nervous system infection, severe systemic infection, malignant brain tumor, acquired immunodeficiency syndrome with central nervous system complications, chronic renal failure requiring dialysis, systemic vasculitis, metabolic disturbance or acute intoxication sufficient to cause coma in the absence of SE). Conversely, antiepileptic drug (AED) withdrawal, an acute etiology, and remote or progressive symptomatic

causes such as brain trauma, stroke, slow evolving dementia, multiple sclerosis or meningioma, were not considered as potentially fatal.

The worst seizure type for each incident SE episode was classified in increasing order of severity as absence, generalized myoclonic (in genetic generalized epilepsy), simple partial (focal without consciousness impairment), complex partial (focal with consciousness impairment), generalized convulsive (GC), and non-convulsive associated with coma (NCSEC); EEG was required to diagnose non-convulsive episodes. Refractory SE was defined in episodes after failure of the first and second treatment lines[12]. At hospital discharge, outcome was prospectively categorized into return to baseline clinical conditions, survival with neurologic sequelae, or death. Status Epilepticus recurrence during the study period was assessed through screening of our prospective SE registry.

Statistical analysis

Comparisons of clinical variables between incident and recurrent SE episodes were performed using two-sided Fischer, t, and χ^2 tests, as needed. The SE recurrence rate was estimated using a survival analysis (considering the number of patients and not of SE episodes), where patients lost to follow-up were censored at their last visit at our hospital (regardless of the department; assessed though the computerized chart review), and deceased subjects at their date of death; the effect of different clinical factors was examined through univariable and multivariable Cox regression analyses. Outcome predictors (mortality, return to baseline clinical conditions) were investigated with stepwise multivariable logistic regressions; goodness of fit of the models was assessed with the Hosmer-Lemeshow test. Calculations were performed

with the Stata Software, version 12 (College station, TX) and SPSS version 20 (SPSS Inc. Chicago, Illinois); significance was set as p<0.05.

Results

Cohort characteristics

Of the 650 SE episodes prospectively recorded in the database during the study period, 41 had to be excluded: 34 (5%) were found to have presented an incident SE prior to the study period, and 7 (1%) had incomplete data available. Among the remaining 609 SE episodes, 509 (84%) incident and 100 recurrent SE episodes were studied; 562 (93%) episodes (470 incident and 92 recurrent) lasted more than 30 minutes.

Table 1 illustrates demographic and clinical variables of the studied cohort. While 441 patients had only incident events (203 women, 238 men), 68 patients of the incident group of 509 patients (13%) experienced SE relapses during the 8-years study period; 53 had only one recurrence (26 women, 27 men), while 15 had two or more relapses (13 women, 2 men: 8 with 2 relapses, 3 with 3 relapses, 3 with 5 relapses, and 1 with 7 relapses). Among the 470 incident SE that lasted more than 30 minutes, there were 61 that recurred (13%), whereas 18% (7 / 39) of incident SE that lasted between 5 and 29 minutes experienced relapses. Within recurrent SE episodes, there was a higher prevalence of women with a lower STESS (median score of 2, suggesting a favorable outcome), and a smaller proportion of subjects with GCSE/NCSEC and potentially fatal etiologies.

Risk and predictors of SE recurrence

To investigate the variables associated with a SE recurrence risk, we conducted a survival analysis (**Figure 1A**): the overall cumulative SE recurrence rate was 32% at 4 years, with a median follow-up of 0.32 years (range: 1 day - 8.2 years). **Table 2** illustrates demographical and clinical variables related to the risk of SE recurrence in the survival analysis: an acute symptomatic etiology (HR 0.5, 95%CI 0.31-0.82, p=0.005), and, to a lesser extent, female gender (borderline significant, HR: 1.6, 95% CI: 0.97-2.65, p=0.06) were independently related to SE recurrence. To highlight the role of etiology, **Figure 1B** shows the cumulative survival rate without recurrence, depending on the acuteness of the underlying cause. Among recurrent SE episodes, the three leading causes were AED withdrawal (33%), previous stroke (18%), and brain tumor (14%); the distribution of etiologies among genders was not significantly different, in analogy with the prevalence of acute or potentially fatal causes.

Outcome

Mortality rates in incident and recurrent SE episodes are shown in **Figure 2**. Seventy-four patients (12% of all patients; 15% of those with only incident SE: 39 men and 35 women) and 6 (2% of all patients; 11% of subjects with one recurrent SE: 5 women, 1 man) died, while no fatality was noted in the group with 2 or more recurrences. Following incident SE, a return to baseline clinical condition was recorded in 254 (50%) patients, as compared to 63 (63%) of subjects experiencing recurrent SE episodes (p=0.017, X^2). A stepwise multivariable logistic regression, considering variables associated with lack of return to baseline, identified potentially fatal etiology (OR: 3.05; 95% CI: 2.14-4.34) and a higher STESS (OR: 1.63; 95% CI: 1.43-1.87), but not SE recurrence (OR: 0.9; 95% CI: 0.55-1.47); the model had an

acceptable goodness of fit (P=0.123, Hosmer-Lemeshow). Analysis of mortality, considering only the last SE episodes for each patient, identified the same variables: potential fatal etiology (OR: 3.03; 95% CI: 1.74-5.30) and increasing STESS (OR: 1.60; 95% CI: 1.31-1.93), with an acceptable goodness of fit (p=0.551, Hosmer-Lemeshow), while incident as compared to recurrent SE episodes was, again, not significant.

Discussion

This study, based on a hospital-based cohort and using a conservative assessment of follow-up, provides Class III evidence [19] that SE recurrences involve 32% of patients at 4 years, and that the lack of an acute symptomatic etiology for the incident SE episode, and to a lesser extent a female gender, independently correlate with a higher risk of SE recurrence. While survival was higher among patients with recurrent SE episodes, mortality and morbidity following SE are related to the underlying clinical profile of the patient, but not SE recurrence itself.

The crude recurrence rate over 8 years was 13% (68 of 509 patients); nevertheless, in order to account for patients lost to follow up or dying during the study period, a survival analysis was performed, which identified a recurrence rate of 32 %. This is strikingly similar to the population-based study specifically designed for this question, based on a Rochester (MN) cohort, which retrospectively found a recurrence of 32% over 10 years (with 82% of recurrences presenting within 2 years)[10]. It appears however clearly higher than 10% over 7 years reported in a retrospective hospital-based cohort in Boston (MA)[6], and than 13% over two years in the Richmond and German population-based studies[2, 11]. These important differences probably relate to

different methodologies, such as prospective versus retrospective assessments, hospital versus population-based cohorts, and possible under-ascertainment in some retrospective studies.

Women with focal SE, a lower STESS score, and without potentially fatal etiologies were significantly more frequently found among patients experiencing recurrent SE. The survival analysis allows assessing if these variables represent predictors of recurrence, or are rather biased by mortality in incident SE episodes or loss to follow-up; this approach showed that an etiology other than acute symptomatic at incident SE independently forecasts SE recurrence: as much as 50% of patients without an acute etiology will indeed recur within 4 years. This observation is reminiscent of the situation following incident seizures[8], but differs somewhat from the findings of the afore-mentioned US study on SE relapse, which showed that the risk of recurrence was influenced by progressive symptomatic, but not acute symptomatic conditions[10]. While in that study response to the first antiepileptic agent was inversely correlated with the risk of recurrence[10], in our analysis SE refractoriness (i.e., response to the first two treatments) was not. These discrepancies may reflect, at least in part, the markedly different period between the two studies (1965-1984 versus 2006-2014), which probably influenced not only diagnosis, but also treatment protocols. Of note, in our registry the vast majority of patients received a second agent; this represents a common practice in an emergency clinical setting[20].

The tendency to a female predominance in subjects with recurrent SE (borderline significant in our survival analysis) has been previously outlined[10], and might reflect the fact that men tend to be more prevalent than women among incident SE patients[11,]

[20], with a trend towards a higher mortality[4, 21], even if several studies do not consider gender as an independent risk factor for death[5-7]. This aspect might be at least in part explained by different comorbidities depending on the gender; for example, males suffer more frequently from cardiovascular diseases than women[4, 22], and SE associated with stroke portends a higher mortality at the incident episode[23]. However, while in our analysis we did not consider medical comorbidities (these were shown to have only a limited impact on SE prognosis[24]), there was no significant difference in terms of specific etiologies among men and women experiencing a SE relapse.

Mortality and morbidity, significantly less frequent in recurrent SE, were related to the severity of each SE episode, rather than the recurrence itself. An underlying severe SE etiology was the most important predictor of poor outcome in our cohort, in line with several prior studies on SE prognosis[4-7, 24, 25]; however, those studies did not specifically take into account recurrence status. Furthermore, the STESS, reflecting episode severity, also represents an independent marker of poor prognosis, as already found in former studies in our[12, 24] and other cohorts[15, 16]. In the present analysis, GCSE and NCSEC were associated with incident SE without recurrence, a finding that has been previously mentioned[6]. An explanation could be that these seizures types may represent more severe SE episodes, with lower likelihood of survival[6, 15], or that consequent anticonvulsant treatment initiated at the first episode prevents relapsing episodes. It has already been showed that the degree of neuronal damage after a SE depends on its duration; it is therefore possible to postulate that a longer SE causes greater neuronal injury that can act as a chronic trigger for recurrent SE [26].

To best of our knowledge, this represent the first hospital-based study comparing incident and recurrent SE in adults, analyzing survival free of SE recurrence and its relationship with clinical variables; furthermore, we assessed a contemporary cohort of patients over a clearly defined time span. The previous retrospective population-based study[10] included a pediatric population, with peculiar clinical aspects that are often different from adult SE (e.g., different rates of infections, genetic abnormalities, and cerebral malformations), the studied population was considerably smaller, and the time span (extending between 1965 and 1984) may have significantly influenced SE diagnosis and management, as stated previously. Furthermore, the population-based study conducted in Germany in 2001 and in Richmond in 1996 also mentioned SE recurrence rate, but did not attempt identifying risk factors for recurrence, nor its specific prognostic role[2, 11].

Our study has some limitations. First, it is limited to a single-center, hospital-based cohort; therefore, some SE episodes may have been treated in other hospitals. However, it seems unlikely that a significant proportion of recurrences were missed, as we showed that SE episodes treated exclusively in regional hospitals of our region represented only 11% of the SE episodes treated in our center[27]. Furthermore, the present design allowed a uniform, prospective collection of comprehensive clinical data, likely conferring a strengthened internal validity. Second, despite an 8-year period study, the median follow up was only 0.3 years (up to 4 years) for each patient; this was, however, calculated rather conservatively. If we had assumed that lack of further clinical notes in our computerized database implied recurrence-free survival, we would have underestimated the recurrence following overestimation of the denominator: it seems indeed likely that several patients do not die in the third-level

hospital, but rather at home or in peripheral facilities. We acknowledge that further efforts to trace survivors lost to follow-up were not undertaken, since this study was approved by the Ethics Committee as a purely observational, without any contact to patients. Third, there is a lack of information about chronic antiepileptic treatment during follow up, apart from drug withdrawal as a SE etiology. While it was recently outlined that adherence to treatment guidelines is not related to SE prognosis[28], we acknowledge that it is impossible to formally exclude that this aspect might have somewhat influenced the recurrence rate. Fourth, additional recurrent seizures lasting less than five minutes during following up were not taken into account in the analysis. Therefore, it was not possible to assess if SE recurrences were part of epilepsy following an incident SE episode, but this study aimed to analyze specifically SE, the most severe expression of epileptic seizures. Etiology categorization as potentially fatal is somewhat arbitrary, but has been showed to better account to the outcome than the ILAE etiological definition.[17,18]

Conversely, we undertook great caution in excluding patients having presented an incident SE episode before the study period (5% of the whole cohort, broadly comparable to the non adjusted overall 13% recurrence rate of SE), while some previous studies[6, 11] did not mention this information in their exclusion criteria. We included patients with SE lasting less and more than 30 minutes, but we did not find any significant difference in their prevalence among incident a recurrent SE. Moreover, given the prospective assessment of the vast majority of clinical parameters and the large studied cohort, which is larger than the aforementioned population-based (183 in [10]; 166 in [2]; 150 in [11]) and hospital-based analyses (107 in [6]) taken together, we believe that this study adds important information regarding

current knowledge of the profile of SE patients at risk of recurrence. Early identification of such subjects may influence the management of their clinical follow-up; furthermore, the awareness that a better prognosis in patients with SE relapse as compared to incident SE is not due to recurrence itself but rather to well-known SE outcome predictors related to the underlying SE severity and etiology, underscores the need of a clinical management tailored to the specific patient profile[29].

The work described is consistent with the Journal's guidelines for ethical publication.

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Drs Tsetsou and Novy do not report any disclosure.

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Authors contribution:

Dr Tsetsou: Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting/revising the manuscript for content, including medical writing for content.

Dr Novy: Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting/revising the manuscript for content, including medical writing for content. Statistical analysis.

Dr Rossetti: Study concept and design. Acquisition of data. Analysis and interpretation of data. Drafting/revising the manuscript for content, including medical writing for content. Statistical analysis. Study supervision and coordination.

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Figures legends

Figure 1A. Cumulative survival ratio without recurrence for the whole study cohort (Kaplan-Mayer). **Figure 1B.** Cumulative survival rate without recurrence; the light grey line represents patients with acute symptomatic etiology for the incident SE episode, the black line patients with non-acute symptomatic etiology.

Figure 2: Mortality rates in incident / recurrent SE episode

Table 1: Demographic and clinical characteristics associated with recurrent as compared to incident SE episodes.

|	Incident only SE n=509 (episodes)	Recurrent SE n=100 (episodes)	P	Test
Age (years)	Mean= 61.03 SD: 18.463	Mean= 62.33 SD: 18.893	P=0.524	t
Women	242 (48%)	68 (68%)	P<0.001	X^2
STESS	Median= 3 (range=0-6)	Median= 2 (range=0-5)	P<0.001	U
Previous seizures	197 (39%)	100 (100%)	P<0.001	X^2
Potentially fatal etiology	271 (53%)	30 (30%)	P<0.001	X^2
Acute symptomatic etiology	303 (60%)	56 (56%)	p=0.510	X^2
GCSE / NCSEC	233 (46%)	29 (29%)	P=0.002	X^2
Time to treatment<1h	185 (36%)	38 (38%)	P=0.976	X^2
Refractory SE (>2 AED needed)	173 (34%)	42 (42%)	P=0.125	X^2
Intubation for treatment	55 (11%)	6 (6%)	P=0.143	X^2
Duration >30 minutes	470 (93%)	92 (92%)	P=0.9	X^2

SD= standard deviation, SE= status epilepticus, STESS= status epilepticus severity score, GCSE=
generalized convulsive status epilepticus, NCSEC= non convulsive status epilepticus in coma, AED=
antiepileptic drugs.

Table 2: Variables (assessed during the incident SE episode) associated with SE

recurrence (Cox regression analyses).

	Unadjusted			Adjusted		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Gender (female)	1.49	0.91-2.43	0.09	1.59	0.97-2.65	0.060
Age (older)	1	0.99-1.02	0.18			
Previous seizures	1.31	0.81-2.10	0.27			
Acute symptomatic etiology	0.52	0.32-0.84	<0.01	0.5	0.31-0.82	0.005
Potential fatal etiology	0.84	0.51-1.36	0.47			
GCSE/NCSEC	0.79	0.49-1.28	0.34			
Duration <30 minutes	1.11	0.51-2.44	0.79			
STESS score (greater)	1.05	0.88-1.24	0.60			
Refractory SE (>2 AED needed)	1.16	0.68-1.97	0.59			
Intubation for treatment	1.69	0.84-3.40	0.15			

SE= status epilepticus, STESS= status epilepticus severity score, GCSE= generalized convulsive status

epilepticus, NCSEC= non convulsive status epilepticus in coma, AED= antiepileptic drugs.
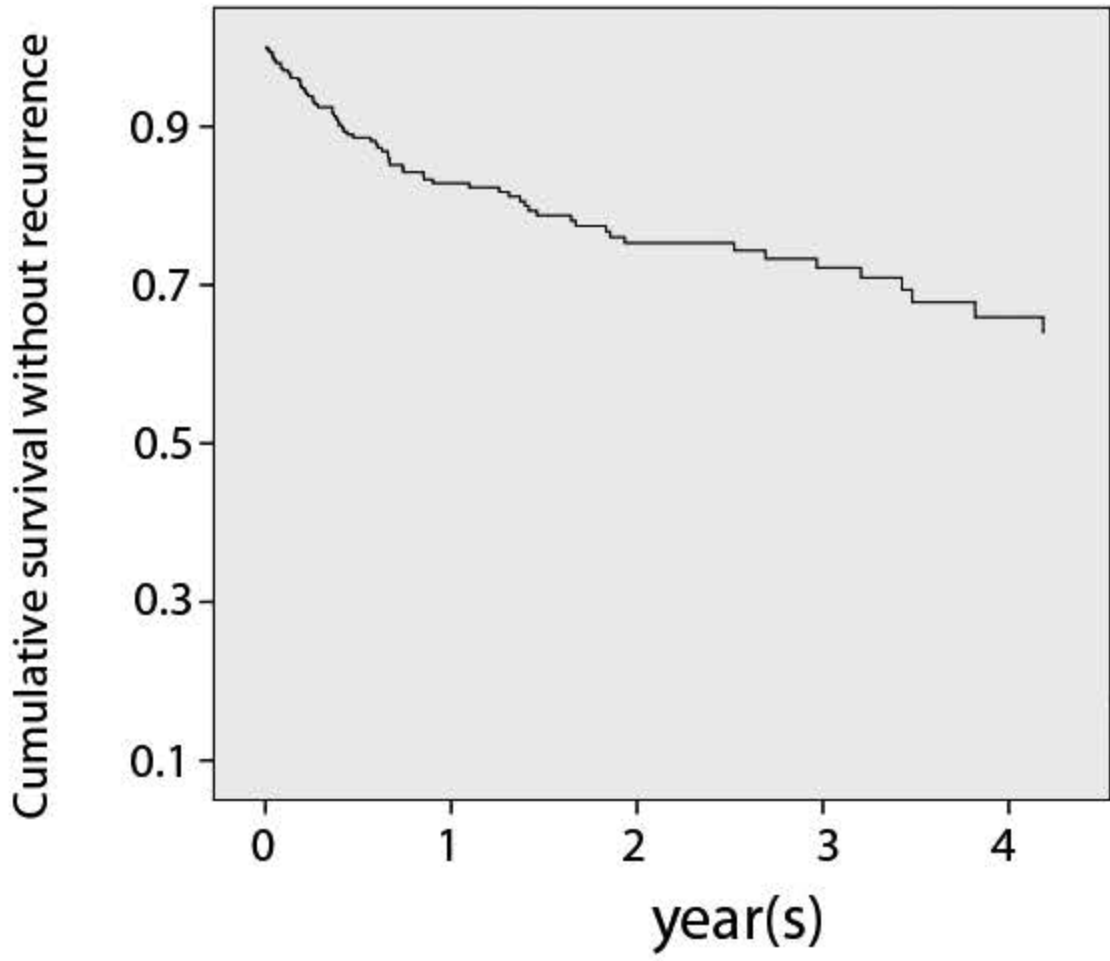
Year of follow-up	0	1	2	3	4
Total number of patients	509	168	99	65	33
Number of recurrence	48	12	3	4	1
Cumulative recurrence proportion	0.13	0.21	0.24	0.3	0.32

p=0.012
(Fisher's test)