Predictive factors of Status Epilepticus and its recurrence in patients with adult–onset seizures: A multicenter, long follow–up cohort study

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ABSTRACT

Purpose: Status epilepticus (SE) is associated with high morbidity and mortality. This multicenter retrospective cohort study aims to identify the factors associated with the occurrence of SE and the predictors of its recurrence in patients with adult–onset seizures.
Methods: We retrospectively analyzed data of 1115 patients with seizure onset>18 years, observed from 1983 to 2020 in 7 Italian Centers (median follow–up 2.1 years). Data were collected from the databases of the Centers. Patients with SE were consecutively recruited, and patients without SE history were randomly selected in a 2:1 ratio. To assess determinants of SE, different clinical–demographic variables were evaluated and included in univariate and multivariate logistic regression model.
Results: Three hundred forty–seven patients had a SE history, whereas the remaining 768 patients had either isolated seizures or epilepsy without SE history. The occurrence of SE was independently associated with increasing age at onset of disease (OR 1.02, 95% CI 1.01—1.03, $p<0.001$), female sex (OR 1.39, 95% CI 1.05—1.83, $p=0.02$) and known etiology (OR 3.58, 95% CI 2.61—4.93, $p<0.001$). SE recurred in 21% of patients with adult–onset SE and recurrence was associated with increasing number of anti–seizure medications taken at last follow–up (OR 1.88, 95% CI 1.31—2.71, $p<0.001$).

Conclusions: In patients with adult–onset seizures, SE occurrence is associated with known etiologies, advanced age and female sex. Patients with recurrent SE are likely to have a refractory epilepsy, deserving careful treatment to prevent potentially fatal events.

Introduction

Status epilepticus (SE) has been defined in 2015 by the International League Against Epilepsy (ILAE) task force [1] as a disorder caused by the failure of the pathophysiological mechanisms responsible for the self–limitation of an epileptic seizure or by the onset of mechanisms determining its self–maintenance. The incidence of SE is quite variable among studies, probably due to different inclusion criteria and SE definitions. In a population–based study conducted in the city of Salzburg, Austria,[2] the reported incidence of SE based on ILAE definition was 36.1 cases /100000 adults/ year. Previously, a systematic review [3] analyzing 7 population–based studies found a large incidence range in the adult population (4–27 cases /100000 inhabitants/year, rising to 15—86 cases/100000 inhabitants/year in the population over 65 years). With regard to SE–associated mortality, available data are not consistent: mortality is reported between 2 and 40% within 30 days from onset[3,4]. SE occurred within the context of epilepsy in less than half of patients, as 42—50% of adults had a previous history of epilepsy according to different studies [3,5–7]. The most widely recognized predictors of SE were increasing age, especially after 60 years [2,3,8–10] and the presence of a structural etiology for SE [10]. Conflicting data about different prevalence in males and females have been reported [10].

SE recurrence in patients with or without epilepsy is scarcely investigated. Studies evaluating the recurrence rate after a first SE evidenced a wide variability with percentages ranging from 10 to 56% [2–4]. In particular, some single center studies [2,3] reported a recurrence rate of about 20%. A systematic review [4] including 15 studies on children and 21 studies on adult patients with SE reported a recurrence risk between 10 and 56%, with a higher risk in pediatric patients and in studies with a longer follow-up [11–14]. Currently, only three studies[12–14] dealt specifically with predictors of SE recurrence, but only two of them included adult patients [12,13]. These two studies concluded that the absence of an acute symptomatic cause in occasion of the first SE and female sex may be predictors of recurrence. However, the first study [12] dealt with a mixed population, thus data about adults and elderly are difficult to extrapolate. A study done using a prospective registry in Lausanne, Switzerland [13] considered a population with adult–onset SE, but the relationship with previous diagnosis of epilepsy and the age at onset of previous seizures are unclear.

The present multicenter, retrospective study aimed to identify factors associated with the occurrence of SE in a population of patients with adult–onset epileptic seizures and factors associated with the recurrence of SE.

Methods

In this retrospective analysis, we included patients with history of at least one SE, with or without a previous diagnosis of epilepsy, and patients with diagnosis of epilepsy or isolated epileptic seizures with no history of SE, followed up in 7 Italian Epilepsy Centers (Catanzaro, Chieti, Foggia, Novara, Pozzilli –IS, Reggio Calabria, Udine). Patients with SE were included according to the judgement of clinicians based on the definitions currently adopted in the different epochs from 1987 to 2020. Age ≤18 years at the onset of epileptic seizures or SE, post–anoxic SE and progressive symptomatic causes of seizures (i.e., tumor or other degenerative diseases, mainly including primary dementias or progressive encephalopathies) were considered exclusion criteria. All patients with history of SE, consecutively recruited from January 1983 to March 2020, were included in this analysis; conversely, patients with diagnosis of epilepsy without history of SE were randomly selected with the use of

a software–generated randomization list, with a 2:1 ratio, among all patients followed up during the same period. Recruited patients referred to the Centers through general practitioners, emergency departments or directly. Recruitment interval was not identical in all Centers, depending on the periods of activity and on the availability of reliable databases in the single Centers.

Statistical analysis

Variables were described as mean and standard deviation, median and interquartile range (continuous variables) or number and percentage (categorical variables). We searched for an association between the occurrence of SE and a number of clinical and demographic variables by means of univariate logistic regression analysis. The following variables were assessed: sex; age at onset of seizures (defined as age at the first epileptic seizure or age at the onset of *de novo* SE); family history of epilepsy (defined as presence of unprovoked epileptic seizures in first or second degree relatives); duration of illness in years; etiology of seizures (categorized as genetic, undetermined, vascular, genetic, inflammatory/ autoimmune, infectious, post–traumatic, malformative, other); number of anti–seizure medications (ASMs) taken at the last clinical observation, (categorized as 0,1,2,>2). In order to assess the independent determinants of SE, all variables significantly associated with the occurrence of SE were included in a logistic multivariate regression model. Similarly, determinants of SE recurrence were identified by performing univariate logistic regression analyses, considering the recurrence of SE as dependent variable and the following as independent variables: sex; age at epilepsy onset; family history of epilepsy; previous diagnosis of epilepsy; disease duration; etiology of seizures; SE semiology (motor vs. non motor); number of antiseizure medications (ASMs) taken at last clinical observation; clinical context of the first SE and of any subsequent SE (defined as acute symptomatic if occurring in close temporal relationship with a brain insult of metabolic, toxic, structural, infectious, or inflammatory origin; otherwise SE was defined as unprovoked [15]); refractoriness of the first SE to first–line parenteral benzodiazepine and to a second–line treatment with an appropriately dosed iv bolus of an ASM. All patients were treated according to the Guidelines or Recommendations of the Italian League Against Epilepsy, which have been updated during the considered time interval [16,17]. Before 2006, reference was made to the Epilepsy Foundation of America's Working Group on Status Epilepticus, published in 1993 [18]. A multivariate logistic regression testing all the variables that were significantly associated with the dependent variable at univariate logistic regression was also performed.

Variables such as drug resistance according to ILAE definition [19] and seizure freedom were also collected. However, due to the high number of missing values we preferred not to include them in the analyses.

All analyses were performed using the Statistical Package for Social Science (SPSS), version. 24. A p–value ≤ 0.05 was considered statistically significant.

Results

A total of 1115 patients were enrolled. Of these, 347 had at least one episode of SE and 768 did not. Data about the patients recruited in the single Centers are reported in the Supplementary Table. Median follow–up was 2.1 years, (IQR 0.1–6.9, mean 4.6 years). Demographic and clinical data of the whole sample are shown in Table 1.

Of note, about two thirds of patients presented with a de–novo SE.

Mortality due to SE (during seizures or in strict time correlation) was 48/347 (13%). Most patients who died during SE (44/48) deceased during the first episode, 2/48 during the second and one each during the third and fourth or subsequent episodes. Mortality was attributed to cardiovascular complications in most cases. The results of the logistic regression analyses are reported in Tables 3—4.

Among the variables associated to the occurrence of SE, the following ones maintained a significant association in multivariate analysis: female sex (odds ratio, OR 1.39, 95% confidence interval, CI 1.05—1.83, $p=0.02$), age at seizures onset (OR 1.02, 95% CI 1.01—1.03, $p<0.001$, with the odds of SE increasing of 2% for every year of increasing age), and presence of a structural/defined etiology (OR 3.58, 95% CI 2.61—4.93, $p<0.001$).

SE recurred in 73/347 of patients, representing 21% of this group. Of the 347 patients with SE included in this study, 209 (60%) were followed up for at least one year and 143 (41%) for at least two years. SE was refractory in 127/339 (37%) patients at first episode, in 16/73 (22%) at second episode, in 5/25 (20%) at third episode and in 4/14 (29%) at fourth episode. At last observation, significantly more patients with a first non–refractory SE were treated with a single ASM compared to those with a first refractory SE (65% vs. 33%, $p<0.001$). At the multivariate regression model, two variables were significantly associated with SE recurrence. The number of ASMs taken at last follow–up was associated with a higher recurrence risk (OR 1.88, 95% CI 1.32—2.67, $p<0.001$) and the first refractory SE was associated with reduced risk (OR 0.42, $p=0.01$, 95% CI 0.22—0.81).

We performed a sensitivity analysis excluding all patients who deceased during the first SE ($n=44$). At the analysis on the remaining 303 patients, only the number of ASMs taken at last follow–up remained significantly associated with the recurrence of SE (OR 1.71, 95% CI 1.17—2.52, $p=0.006$), while first refractory SE was no more associated (OR 0.50, 95% CI 0.25—1.00, $p=0.051$).

Discussion

The present study analyzed the factors associated with the occurrence and the recurrence of SE in a sample of patients with adult–onset seizures or SE referring to 7 Italian Centers. The main strengths of our study are represented by the very large sample and by the geographical representation of the included population, coming from Centers distributed across Italy. In our cohort, SE recurrence and mortality were in line with reported literature data [2–4].

In this study, we found that female sex was associated with an increased risk of SE occurrence. Data about a possible gender difference in the incidence of SE are conflicting. Some authors reported a higher incidence in males [20,21], while other studies found the opposite [22,23]. In a meta–analysis [10], there was no difference between females and males in terms of the crude annual incidence rate of SE. None of these studies searched for a possible independent role of sex in predicting the occurrence of SE. An increased susceptibility to the development of SE in females has been described in various animal models [24–27]. Indeed, in various murine experimental models of toxin–induced seizures and SE, female sex was associated with increased seizure severity [24] and shorter time to seizure and SE induction [25,26], with a possible link to estrogen cycle [26]. A study on spontaneous epilepsy in dogs [27] also showed that the incidence of cluster seizures was higher in females, especially in intact animals. Thus, a possible role of female sex and estrogens (particularly during reproductive age) might be at the basis of an increased susceptibility to SE. However, since mean age in our cohort was quite high, it is reasonable that most women were in post–menopausal age, thus the real contribution of hormonal differences may be low and other, unknown causes may play a role.

Table 2
Additional characteristics of the 347 patients with status epilepticus.

Features	N.	%
Recurrent status epilepticus	73	21
Semiology		
– *focal motor*	148	43
– *focal non convulsive with or without impairment of awareness*	22	6
– *generalized convulsive*	67	19
– *generalized non convulsive*	110	32
1st status epilepticus was provoked	119	34
1st status epilepticus was refractory	128	37
1st status epilepticus during epilepsy course (vs. *de novo*)	101	29
Deceased during status epilepticus	48	14

Table 1
Clinical and demographic characteristics of the study population ($n=1115$)

Whole cohort ($n=1115$)			Patients with SE ($n=347$)		Patients without SE ($n=768$)	
	N°	%	N°	%	N°	%
Patients with SE	347	31	–	–	–	–
Sex (female/male)	534/581	48/52	184/163	53/47	350/418	46/54
Family history of epilepsy	116	10	19	5	97	13
Age at epilepsy onset in years: median (IQR)	52 (21—70)	–	66 (49—77)		46 (29—65)	
Disease duration in years: median (IQR)	5 (1—14)	–	2.1 (0.7—10.5)	–	6.3 (1.4—15.2)	–
Follow–up duration in years: median (IQR)	2.0 (0.1—6.9)	–	1.5 (0.06—6.5)	–	2.6 (0.2—7.2)	–
Referral modality (diagnosis at the participating Centre)	733	66	270	78	462	60
Deceased during follow–up	97	9	33	10	64	8
Etiology						
– *Presumed genetic cause (previously "idiopathic")*	63	6	7	2	56	7
– *Undetermined*	394	35	54	16	340	44
– *Vascular*	347	31	155	45	192	25
– *Genetic*	15	1	7	2	8	1
– *Inflammatory/autoimmune*	63	6	43	12	20	3
–*Infectious*	38	3.5	25	7	13	2
– *Post–traumatic*	50	4.5	11	3	39	5
– *Malformative*	61	5.5	9	3	52	7
– *Other*	84	7.5	36	10	48	6
No. of ASMs taken at last observation						
– *None*	97	9	44	13	53	7
– *One*	682	61	148	43	535	70
– *Two*	189	17	61	18	128	17
– *More than two*	78	7	31	9	47	6
– *Unknown*	61	6	57	17	4	0.5

ASM: antiseizure medications; IQR: interquartile range; SE: status epilepticus.
The additional variables for patients with SE are shown in Table 2.

Table 3

Univariate and multivariate logistic regression for predictors of occurrence of status epilepticus.

Logistic regression (occurrence of status epilepticus in 1115 patients)	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age at epilepsy onset	1.04	1.03—1.04	**<0.001**	1.02	1.01—1.03	**<0.001**
Disease duration	0.96	0.95—0.98	**<0.001**	0.99	0.97—1.00	0.10
Family history of epilepsy/febrile seizures	0.40	0.24—0.67	**<0.001**	0.71	0.41—1.24	0.19
Etiology (definite *vs* idiopathic/undetermined)	4.62	3.41—6.26	**<0.001**	3.58	2.61—4.93	**<0.001**
No. of antiseizure medications taken at last observation	1.12	0.93—1.34	0.25			
Sex (female vs. male)	1.35	1.05—1.74	**0.02**	1.39	1.05—1.83	**0.02**

OR: odds ratio; CI: confidence interval.

Table 4

Univariate and multivariate logistic regression for predictors of recurrence of status epilepticus.

Logistic regression (recurrence of status epilepticus in 347 patients)	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age at epilepsy onset	0.98	0.97—0.99	**0.01**	0.99	0.9—1.01	0.40
Disease duration	1.03	1.01—1.06	**0.02**	1.02	0.99—1.05	0.29
Family history of epilepsy/ febrile seizures	2.99	1.16—7.73	**0.02**	1.60	0.54—4.73	0.40
Etiology (definite *vs* idiopathic/ undetermined)	1.36	0.67—2.76	0.39			
No. of antiseizure medications taken at last observation	1.85	1.34—2.56	**< 0.001**	1.88	1.31—2.71	**0.001**
Previous diagnosis of epilepsy	1.89	1.10—3.26	**0.02**	0.98	0.48—2.02	0.97
1st status epilepticus was not provoked	2.11	1.15—3.88	**0.02**	1.67	0.87—3.19	0.12
1st status epilepticus was refractory	0.42	0.23—0.76	**0.01**	0.43	0.23—0.82	**0.01**
Semiology (Non convulsive vs other semiology)	0.82	0.48—1.39	0.46			
Sex (female vs. male)	1.05	0.63—1.77	0.85			

OR: odds ratio; CI: confidence interval.

The age at seizure onset was directly related to an increased occurrence of SE. Although late onset epilepsy generally carries a good prognosis in terms of response to ASM monotherapy, even at low dosages [28], the onset of SE is more frequent after the age of 60 [8,10,29]. A meta–analysis [10] conducted on 43 studies found that advanced age (>60 years) was associated with an increased incidence rate of SE as compared to younger subjects. A possible explanation is that some acute causes of SE, such as stroke, brain anoxia, neurodegenerative disorders or neoplasm are more frequent in the elderly than in younger people [30]. Transcranial Magnetic Stimulation studies showed an age–related reduction of the intracortical inhibition in healthy elderly [31–33], probably reflecting an age–related failure in intracortical inhibitory mechanism able to interrupt epileptic seizures, which may explain an increased tendency to develop SE in the elderly.

We also showed a direct link between the occurrence of SE and the presence of a structural alteration of the cerebral parenchyma, in line with literature data. A meta–analysis [10] showed that the occurrence of SE was more frequent in the presence of specific etiologies, including cerebrovascular diseases and central nervous system infections. A

further study, not included in the meta–analysis, considered patients over 70 years with SE and reported the presence of defined causes in the majority of them, especially cerebrovascular diseases and neoplasms[8]. This may confirm that advanced age and etiology cooperate in the pathophysiology of the SE in the elderly.

Our study also showed that SE was less likely to recur if the first episode was classified as refractory. However, the sensitivity analysis performed excluding the patients who died during the first SE did not confirm the result. This is in line with the knowledge that refractory SE is associated with increased mortality [3,4].

Lastly, our study found an association between the number of ASMs taken at the last clinical observation and the recurrence of SE. The larger number of administered ASMs may be considered as an indirect marker of drug resistance [34], a variable that we unfortunately were not able to evaluate. Literature data about the relationship between SE and drug resistance in epilepsy are not homogeneous as a relationship between drug resistance and history of SE is described by some authors [11,35], but denied by others [36]. A study that specifically evaluated the link between SE and drug resistance in adult patients [37] found that a history of epilepsy and the presence of cortical structural abnormalities at neuro-imaging are, along with the duration of the SE, predictors of drug resistance after a first episode of SE. Of note, these features are notoriously predictors of drug resistance independently from SE [38]. The relationship between SE and drug resistance, therefore, remains unclear.

This work has some limitations. It is a retrospective study, with all the methodological defects of this type of work. In particular, some patients with SE, especially if acute symptomatic, may not have been referred to epilepsy centers but exclusively to emergency units. Moreover, non–convulsive SE may be difficult to diagnose and thus may be under–recognized. This limit can be partly overcome by the inclusion of consecutive cases and by a strict cooperation between emergency units and epilepsy centers, which is usual in many of the included centers. As it was entirely conducted in Italy, the results may not be generalizable to different geographic areas of the world (particularly, low–income countries). Moreover, many patients were lost at follow–up (about 40% of patients with SE and about half of patients without SE had a follow–up shorter than 1 year), preventing us to analyze data on drug resistance and long–term seizure freedom. Of note, both works analyzing predictors of SE recurrence [12,13] show a high proportion of patients lost at follow–up; for instance, in the Lausanne study [13] only 168/509 (33%) of patients are still in observation after one year. In both studies [12,13], the majority of SE recurrences occur within the first year and the likelihood of recurrence becomes negligible after 2 years. Moreover, most of the patients with SE included in the present study were followed for at least one year and almost half reached a 2–year observation period. In addition, disease duration did not attain statistical significance in the multivariate analysis model. Taken together, these data indicate that it is unlikely that a longer observation could have led to an increased incidence of SE recurrence. Third, SE duration was not reliably recorded and thus could not be evaluated as a possible predictor of recurrence. Finally, ictal or interictal EEG data were not included in the analysis, nor were those on duration and on the response to acute symptomatic treatment. The latter two features can reliably be analyzed in prospective studies.

In conclusion, the present work has reaffirmed in a large and representative sample that the occurrence of SE is associated with definite etiologies, advanced age and may be more likely in females. The recurrence of SE is not a very frequent event in adults. Since we hypothesize that treatment with a greater number of ASMs is a marker of drug resistance, we can conclude that patients with recurrent SE are more likely to have a refractory epilepsy, thus deserving particular attention from the treating physicians to prevent potentially fatal events.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2021.07.009.

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