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An observational electro-clinical study of status epilepticus: From management to outcome

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ABSTRACT

Status epilepticus (SE) is a neurological emergency associated with a high morbidity and mortality. A prospective 3-year study was conducted in our hospital on 56 consecutive inpatients with SE. Demographic and clinical data were collected. EEG and clinical SE features were considered for the SE classification, both separately and together. The etiology of SE was determined. Patients were treated according to international standardized protocols of guidelines for the management of epilepsy. Response to treatment was evaluated clinically and electrophysiologically. Outcome at 30 days was considered as good, poor or death. Convulsive SE (CSE) was observed in 35 patients and non-convulsive SE (NCSE) in 21. Patients with CSE, in particular focal-CSE, were older than those with NCSE. As regards etiology, patients with SE secondary to cerebral lesions were the oldest, followed by patients with anoxic SE and those with toxic dysmetabolic SE. A first-line treatment was usually sufficient to control seizure activity in lesional and epileptic SE, while more aggressive treatment was necessary in all anoxic SE patients. Outcome was good in 35 patients, poor in 12, while 9 died. A prompt neurophysiological EEG evaluation, combined with the clinical evaluation, helps to make a rapid prognosis and take therapeutic management decisions. First-line treatments may be sufficient to control electro-clinical status in lesional and epileptic SE, while intensive care unit management, a more aggressive therapeutic approach and continuous EEG monitoring are recommended for refractory SE.

1. Introduction

Status epilepticus (SE) is a neurological emergency associated with a high morbidity and mortality.[1] In industrialized countries with Caucasian populations, the incidence of SE ranges from 9.9 to 41/100,000/year,[2–6] with a higher incidence in patients older than 60 years (54–86/100,000/year); this high variability is partially related to the different criteria used to diagnose SE.[7–9] According to Shorvon,[10] one of the most complete definitions of SE, based on both clinical and neurophysiological findings, is: "a condition in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms and with a highly variable pathophysiological, anatomical and aetiological basis". Hospitalization, accompanied by both clinical and neurophysiological investigations, of patients suspected of having SE is thus warranted to promptly diagnose this condition and provide optimal management.[9]

According to the electro-clinical features, SE is commonly classified as convulsive (CSE), non-convulsive (NCSE), generalized (SE-G) or focal (SE-F).[11] Moreover, the term NCSE is used in the literature to refer to both generalized SE and complex partial SE. The neurophysiological EEG evaluation, which demonstrates ongoing ictal activity, is fundamental to identify cases of unknown origin.[12] The exact diagnosis of each SE type is not only needed to guide treatment choices,[13] but also to evaluate the response to therapy and to correlate SE outcome with the prognostic factors.

The SE mortality rate is approximately 20%, with most patients dying as a result of the underlying condition (such as stroke), rather than of the status epilepticus itself.[14] Indeed, while 52% of SE cases in children are secondary to infections with fever, in adults the main causes of acute SE are an insufficient dosage of antiepileptic drugs, cerebrovascular events, hypoxia, metabolic causes and alcohol intoxication. Prognostic indicators of poorer outcome include older age and acute symptomatic etiology.[15] Results are less consistent for other variables, such as time-to-treatment or to seizure control and gender.[16] Rossetti et al.[17]

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proposed a prognostic score (Status Epilepticus Severity Score – STESS) based on four outcome predictors determined before administration of treatment: age with a 65-year cut-off, previous history of seizures, seizure type and extent of consciousness impairment. A scrupulous evaluation of SE outcome predictors might help to select the most appropriate treatment strategies for each patient. SE treatment protocols recommend a wide range of drug intensities, including small doses of benzodiazepines, combinations of intravenously administered antiepileptic drugs and coma-induction with appropriate anesthetic agents.[18] In 2006, a SE subcommission of the Guidelines Commission of the Italian League against Epilepsy drew up the guidelines for the management of SE in adults.[9] Although all the guidelines refer to convulsive, tonic–clonic generalized SE management, they may be extended to the treatment of every type of SE in clinical practice.

The aim of this study is to provide a report of a 3-year study on the diagnosis and management of SE, conducted in our university hospital, based on an analysis of the patients' demographic data, SE type, response to AED treatment and outcome.

2. Materials and methods

We conducted a 3-year prospective study for which we enrolled consecutive adult inpatients at the Policlinico Umberto I Hospital (Sapienza University of Rome), between January 1st 2007 and December 31st 2009. All the patients, who had been admitted to the emergency room or were already hospitalized in other medical and surgical divisions, were diagnosed as having SE, according to the clinical presentation and EEG findings. Our laboratory is the only emergency EEG Service at the Policlinico Umberto I University Hospital that is open 6 days a week, 12 hours a day. The hospital, which is located in the centre of Rome, has a secondary level emergency department to which patients with suspected neurological emergency conditions are electively transferred from the surrounding areas. Exclusion criteria were: patients < 18 years old; patients admitted overnight or on Sundays and treated for SE without an EEG recording. Patients received the best clinical treatment for the underlying disease, while the instrumental diagnosis included cerebral neuroimaging with CT or MRI.

2.1. EEG execution

An EEG with electro-cardiography (ECG) and electromyography (EMG) was performed with a digital apparatus (Micromed, Italy) and sampled at rate of 256 Hz. The following conventional chloride disc electrodes were applied on the scalp, according to the International 10-20 System: Fp2, Fp1, T4, T3, C4, C3, O2 and O1. After SE was diagnosed, the EEG recording was continued throughout the pharmacological treatment and for at least 30 min after resolution of the SE. In patients in whom the SE did not resolve, the EEG was performed again daily or upon request for clinical reasons.

2.2. SE antiepileptic treatment

According to the Italian guidelines for SE management,[9] treatment was administered using 4 standardized protocols, applied successively according to temporal parameters and the patient's response to AED drugs; each subsequent protocol was only applied if the previous protocol proved unsuccessful. The temporal parameters were: initial SE (within 30 min), established SE (within 90 min) and refractory SE (after 90 min). Protocol 1 for initial SE was based on lorazepam (0.05–0.1 mg/kg i.v. – maximum infusion rate 2 mg/min) or diazepam (0.1 mg/kg/i.v. – in 60 s). Protocol 2 for established SE was based on phenytoin (15–18 mg/kg i.v. at a maximum infusion rate of 50 mg/min). Protocol 3 for refractory SE was based on thiopental (5–7 mg/kg i.v. in 20 s followed by boluses at intervals of 2–3 min) or propofol (2–5 mg/kg i.v. bolus followed by continuous infusion up to 5 mg/kg/h). Administration of thiopental or propofol required the assistance of an anesthesiologist. Protocol 4, which was reserved for alternative therapies when previous drugs were ineffective or contraindicated, was based on sodium valproate (15 mg/kg i.v. over 5 min followed by 1–2 mg/kg/h as a continuous infusion, depending on the clinical response), midazolam (0.1–0.3 mg/kg as i.v. bolus, at a maximum infusion rate of 4 mg/min) and phenobarbital (10–20 mg/kg i.v. infused over 10 min – 50–75 mg/min). From 2008 onwards, intravenously administered levetiracetam (20 mg/kg i.v. infused over 15 min) was also used.[19]

To assess the response to therapy, EEG monitoring was performed throughout AED treatment in order to follow cortical electrical activity modifications, as well as for at least one hour after seizure activity cessation. We considered the treatment effective when the complete resolution of epileptic discharges was observed and persisted for at least 30 min after the end of treatment. Since patients were hospitalized in the Intensive Care Unit or other emergency departments, subsequent neurophysiological testing was performed daily or upon request for clinical reasons.

2.3. SE classification

The following data were analysed in all the patients: (1) demographic data (age, sex), with age being considered both by adopting a cut-off of 65 years, as generally reported in the literature, and as a continuous variable; (2) SE clinical type: convulsive (CSE) and non-convulsive (NCSE), according to the clinical neurological presentation (presence of focal neurological symptoms – i.e. positive or negative–, localized or diffuse movement disorders – i.e. clonic, tonic–clonic or myoclonia–, eyelid myoclonia, lack of response to simple commands, autonomic dysfunction and cognitive/consciousness alterations); (3) SE EEG features: focal (F-SE) or generalized (G-SE) epileptic discharges; (4) electro-clinical correlations, considering both points (2) and (3): non-convulsive focal and generalized SE (NCSE-F, NCSE-G), convulsive focal or generalized SE (CSE-F, CSE-G); (5) etiology of SE according to instrumental findings, neuroimaging study (cerebral CT and/or MRI scan) and/or blood examinations and classified as: (a) lesional SE, (b) primary epileptic SE, (c) toxic metabolic SE or (d) anoxic SE; (6) response to antiepileptic treatment protocols 1, 2, 3 or 4; (7) clinical outcome after 30 days as: (a) good (return to normal daily activities), (b) poor (persistence of neurological deficit) and (c) death.

2.4. Statistical analysis

Data are presented in raw numbers. Data were analysed using SPSS 16 for Macintosh. χ^2 and cross tabulation tables were used to compare differences in categorical variables. Student's t-test and ANOVA were used to determine differences between continuous variables in the categorical classes. Post-hoc analysis with Bonferroni's correction and Scheffè tests were used to determine multiple comparisons. Statistical significance was set at $p < 0.05$.

3. Results

Over a period of 3 years, we identified 56 patients with SE, 29 of whom were men and 27 women, with a mean age of 64.05 ± 20.4 years. The EEG was performed within 3.5 ± 2.8 h of the primary care physician's request. A full description of the population enrolled is provided in Table 1.

3.1. Clinical SE type (CSE/NCSE) and EEG SE type (F-SE/G-SE): age and sex

As regards the clinical SE type, convulsive status epilepticus was observed in 35/56 patients and non-convulsive status epilepticus

Table 1
Complete description of SE population.

Patient	Sex	Age	SE type				SE pathophysiology		Therapy	Outcome
			Clinical SE	EEG SE	Electro-clinical SE	SE description	Etiology	Neuroimaging findings		
1	F	65	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Neoplasia	Protocol-1	Good
2	M	77	NCSE	F-SE	NCSE-F	CPSE	Lesional	Ischemia	Protocol-1	Good
3	M	73	CSE	F-SE	CSE-F	SPSE-disphasic	Lesional	Hemorrhage	Protocol-1	Poor
4	M	72	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-2	Good
5	M	84	CSE	F-SE	CSE-F	SGCSE	Lesional	Subdural hemorrhage	Protocol-4	Death
6	F	65	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Good
7	M	36	NCSE	G-SE	NCSE-G	ASE	Epileptic (IGE)	Normal	Protocol-1	Good
8	F	46	NCSE	F-SE	NCSE-F	CPSE	Lesional	Herpetic encephalitis	Protocol-1	Good
9	M	56	CSE	F-SE	CSE-F	PGCSE	Epileptic (IGE)	Normal	Protocol-1	Good
10	M	43	CSE	G-SE	CSE-G	GMSE	Epileptic (CGE)	Normal	Protocol-1	Good
11	M	18	NCSE	G-SE	NCSE-G	ASE-ME	Epileptic (IGE)	Normal	Protocol-1	Good
12	M	48	NCSE	F-SE	NCSE-F	CPSE	Lesional	Subdural hemorrhage	Protocol-1	Good
13	F	20	NCSE	G-SE	NCSE-G	AASE	Epileptic (LGS)	Normal	Protocol-1	Good
14	F	81	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Subdural hemorrhage	Protocol-1	Poor
15	M	61	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Good
16	F	91	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Death
17	M	19	CSE	F-SE	CSE-F	PGCSE	Epileptic (IGE)	Normal	Protocol-1	Good
18	F	67	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-3	Death
19	M	83	NCSE	F-SE	NCSE-F	CPSE	Lesional	Venous thrombosis	Protocol-1	Good
20	F	76	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-3	Death
21	M	56	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Neoplasia	Protocol-1	Good
22	F	85	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-2	Poor
23	M	52	CSE	F-SE	CSE-F	SPSE-disphasic	Metabolic (NKH)	Normal	Protocol-1	Good
24	F	59	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Subdural hemorrhage	Protocol-1	Good
25	F	86	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Subdural hemorrhage	Protocol-1	Good
26	M	71	NCSE	F-SE	NCSE-F	CPSE	Lesional	Ischemia	Protocol-2	Good
27	M	62	CSE	F-SE	CSE-F	SGCSE	Lesional	Ischemia	Protocol-3	Poor
28	M	54	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Good
29	M	89	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Poor
30	F	61	NCSE	F-SE	NCSE-F	CPSE	Lesional	Cerebral vasculitis	Protocol-2	Good
31	M	39	NCSE	G-SE	NCSE-G	ASE	Epileptic (CGE)	Normal	Protocol-1	Good
32	F	89	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-1	Good
33	M	88	NCSE	F-SE	NCSE-F	CPSE	Lesional	Ischemia	Protocol-2	Poor
34	F	86	CSE	F-SE	CSE-F	SGCSE	Lesional	Subdural hemorrhage	Protocol-1	Poor
35	M	67	CSE	F-SE	CSE-F	SGCSE	Lesional	Ischemia	Protocol-3	Good
36	M	82	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Subarachnoid hemorrhage	Protocol-2	Good
37	F	91	NCSE	F-SE	NCSE-F	CPSE	Lesional	Subdural hemorrhage	Protocol-1	Good
38	F	94	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Subdural hemorrhage	Protocol-2	Death
39	F	76	NCSE	F-SE	NCSE-F	CPSE	Lesional	Capsular hemorrhage	Protocol-1	Good
40	M	56	NCSE	F-SE	NCSE-F	CPSE	Lesional	Hemorrhage	Protocol-4	Good
41	M	66	NCSE	G-SE	NCSE-G	ASE	Epileptic (CGE)	Normal	Protocol-1	Good
42	M	80	CSE	F-SE	CSE-F	SGCSE	Lesional	Subarachnoid hemorrhage	Protocol-4	Good
43	F	22	NCSE	F-SE	NCSE-F	CPSE	Lesional	Hemorrhage	Protocol-4	Poor
44	F	50	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-3	Death
45	F	85	CSE	F-SE	CSE-F	SGCSE	Lesional	Ischemia	Protocol-4	Poor
46	F	45	NCSE	G-SE	NCSE-G	GNSE	Metabolic	Normal	Protocol-4	Good
47	F	70	NCSE	F-SE	NCSE-F	CPSE	Lesional	PRES	Protocol-2	Good
48	F	83	NCSE	G-SE	NCSE-G	ASE	Epileptic (IGE)	Normal	Protocol-1	Good
49	F	74	NCSE	G-SE	NCSE-G	GNSE	Metabolic (SH)	Normal	Protocol-3	Good
50	M	67	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-4	Death
51	F	62	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-4	Death
52	M	59	CSE	G-SE	CSE-G	GMSE	Anoxic	Normal	Protocol-4	Death
53	M	40	CSE	G-SE	CSE-G	GMSE	Lesional	CADASIL	Protocol-4	Poor
54	F	21	NCSE	F-SE	NCSE-F	CPSE	Lesional	Glioblastoma	Protocol-4	Poor
55	M	57	CSE	G-SE	CSE-G	GMSE	Epileptic (IGE)	Normal	Protocol-1	Good
56	F	82	CSE	F-SE	CSE-F	SPSE-motor	Lesional	Ischemia	Protocol-2	Poor

Legend: M: male; F: female; CSE: convulsive status epilepticus; NCSE: non-convulsive status epilepticus; F-SE: focal status epilepticus; G-SE: generalized status epilepticus; SPSE: simple partial status epilepticus; CPSE: complex partial status epilepticus; SGCSE: secondary generalized status epilepticus; PGCSE: primary generalized status epilepticus; GMSE: generalized myoclonic status epilepticus; ASE: absence status epilepticus; ASE-ME: absence status epilepticus with myoclonic eyelid; AASE: atypical absence status epilepticus; GNSE: generalized non-convulsive status epilepticus; IGE: idiopathic generalized epilepsy; CGE: cryptogenic generalized epilepsy; NKH: non-ketotic hyperglycemia; PRES: posterior reversible encephalopathy syndrome; LGS: Lennox–Gastaut syndrome; CADASIL: cerebral autosomal dominant arteriopathy; SH: severe hypothyroidism.

in the remaining 21/56 patients. As regards the SE type, no difference was observed for age when the cut-off was 65 years or gender. When age was considered as a continuous variable, patients with CSE were found to be significantly older than patients with NCSE (ANOVA: $F = 4.616$, $p = 0.036$).

As regards the EEG SE type, generalized SE was observed in 17/56 and partial SE in the remaining 39/56 patients. No difference was observed for gender. Patients with focal SE were older, both when a cut-off of 65 years was used ($\chi^2 = 4.75$, $p = 0.03$) and when age was considered as a continuous variable (ANOVA: $F = 7.954$, $p = 0.007$).

As regards the clinical and EEG SE type taken together, no differences were observed for sex or age when a cut-off of 65 years was adopted. When age was instead considered as a continuous

Table 2
Type of SE (clinical, EEG and both) correlation with age and sex.

	Sex (M/F)	Age < 65 years	Age ≥ 65 years	Age ($\mu \pm$ SD)
Clinical SE				
CSE	19/16	13	22	68.46 ± 16.8
NCSE	10/11	11	10	56.7 ± 23.9 *
EEG SE				
F-SE	20/19	13	26	68.85 ± 19.4
G-SE	9/8	26	6 *	53.06 ± 18.8 **
Clinical + EEG SE				
CSE-F	14/12	7	19	72.12 ± 16.9
CSE-G	5/4	6	3	57.89 ± 11.8
NCSE-F	6/7	6	7	62.31 ± 22.9
NCSE-G	4/4	5	3 **	47.62 ± 24.3

Legend: CSE: convulsive status epilepticus; NCSE: non-convulsive status epilepticus; F-SE: focal status epilepticus; G-SE: generalized status epilepticus; CSE-F: convulsive focal status epilepticus; CSE-G: convulsive generalized status epilepticus; NCSE-F: non-convulsive focal status epilepticus; NCSE-G: non-convulsive generalized status epilepticus.
* $p < 0.05$.
** $p < 0.005$.

variable, ANOVA revealed a significant difference for age between the four groups (ANOVA: $F = 3.911$, $p = 0.014$), with patients with focal SE (CSE or NCSE) being older.

The data are summarized in Table 2.

3.2. SE etiology

Lesional SE was observed in 37/56 patients, epileptic SE in 10/56 patients, toxic-dysmetabolic SE in 3/56 patients and anoxic SE in 6/56 patients. No differences were observed in gender as regards the SE etiology. A significant difference was observed for age and SE etiology, both when a cut-off of 65 years was adopted ($\chi^2 = 9.056$, $p = 0.029$) and when age was considered as a continuous variable (ANOVA: $F = 5.715$, $p = 0.002$): the oldest patients were those with lesional SE, followed by patients with anoxic SE and those with toxic dysmetabolic SE. Patients with epileptic SE were the youngest. Post-hoc analysis with Bonferroni's correction showed that the difference within groups was significant only in lesional vs epileptic patients ($p = 0.001$). The clinical and EEG data divided according to etiology are shown in Table 3.

3.3. SE treatment

Thirty out of 56 patients displayed complete SE regression after being treated with protocol 1, 9/56 after protocols 1 + 2, 9/56 after protocols 1 + 2 + 3 while 8/56 needed protocol 4 to control epileptic activity. If we consider the type of SE according to the clinical classification (CSE vs NCSE), no difference emerged in the number of protocols needed to eliminate epileptic activity. If we consider the SE according to the EEG findings (F-SE and G-SE), a difference in response to treatment emerged, with protocol 1 most frequently proving to be sufficient to successfully treat F-SE ($\chi^2 = 1.170$, $p < 0.009$). As regards SE etiology, a difference in the response to treatment was observed ($\chi^2 = 3.873$, $p < 0.000$), with protocol 1 most frequently proving to be sufficient to successfully treat patients with lesional and epileptic SE, while protocols 3 or 4 were needed in all anoxic patients. The data are presented in Table 4.

3.4. SE outcome

Outcome was good in 35/56 patients, poor in 12/56 patients, while 9/56 patients died. No difference was observed for sex and age either when a cut-off of 65 years was adopted or when age was considered as a continuous variable, though a trend toward a worse outcome and death did emerge in older patients. A significant difference was observed in outcome as regards the

Table 3
Etiology of SE, sex, age, and SE type.

Etiology	M/F	Age < 65 years	Age ≥ 65 years	Age ($\mu \pm$ SD)	Clinical SE type		EEG SE type		Clinical + EEG SE type			
					CSE	NCSE	F-SE	G-SE	CSE-F	CSE-G	NCSE-F	NCSE-G
Lesional	18/19	11	26	70.2 ± 18.3	24	13	36	1	23	1	13	0
Epileptic	8/2	8	2	43.7 ± 21.8	4	6	2	8	2	2	0	6
Toxic-dysmetabolic	1/2	2	1	57 ± 15.1	1	2	1	2	1	0	0	2
Anoxic	2/4	3	3 *	63.5 ± 8.7 **	6	0	0	6	0	6	0	0
Total	29/27	24	32									

Legend: CSE: convulsive status epilepticus; NCSE: non-convulsive status epilepticus; F-SE: focal status epilepticus; G-SE: generalized status epilepticus; CSE-F: convulsive focal status epilepticus; CSE-G: convulsive generalized status epilepticus; NCSE-F: non-convulsive focal status epilepticus; NCSE-G: non-convulsive generalized status epilepticus.
* $p < 0.05$.
** $p < 0.005$.

Table 4
Response to treatment, SE type and etiology.

Treatment protocol	Clinical SE type		EEG SE type		SE etiology			
	CSE	NCSE	F-SE	G-SE	Lesional	Epileptic	Toxic	Anoxic
Protocol-1	18	12	22	8	19	10	1	0
Protocol-2	5	4	9	0	9	0	0	0
Protocol-3	5	4	6	3	7	0	1	1
Protocol-4	7	1	2	6 **	2	0	1 **	5

Legend: CSE: convulsive status epilepticus; NCSE: non-convulsive status epilepticus; F-SE: focal status epilepticus; G-SE: generalized status epilepticus; BDZ: benzodiazepines; PHT: phenytoin.
** $p < 0.005$.

Table 5
SE outcome, demographic CSE type and etiology.

Outcome	M/F	Age < 65 years	Age ≥ 65 years	Age ($\mu \pm SD$)	Clinical SE type		EEG SE type		Clinical + EEG SE type			
					CSE	NCSE	F-SE	G-SE	CSE-F	CSE-G	NCSE-F	NCSE-G
Good	21/14	17	18	60.6 ± 19.3	17	18	25	10	15	2	10	8
Poor	5/7	4	8	67.8 ± 25.7	9	3	11	1	8	1	3	0
Dead	3/6	3	6	72.2 ± 15	9	0 *	3	6 *	3	6	0 **	0

Legend: CSE: convulsive status epilepticus; NCSE: non-convulsive status epilepticus; F-SE: focal status epilepticus; G-SE: generalized status epilepticus; CSE-F: convulsive focal status epilepticus; CSE-G: convulsive generalized status epilepticus; NCSE-F: non-convulsive focal status epilepticus; NCSE-G: non-convulsive generalized status epilepticus.
* $p < 0.05$.
** $p < 0.005$.

clinical SE type ($\chi^2 = 9.09$, $p = 0.011$), the EEG SE type ($\chi^2 = 8.418$, $p < 0.015$) and both ($\chi^2 = 2.594$, $p < 0.000$), with a better outcome emerging in CSE, F-SE and CSE-F. The data are shown in Table 5.

A significant difference was observed in outcome when patients were divided according to etiology ($\chi^2 = 4.274$, $p = 0.000$), with a better outcome being observed in epileptic SE and toxic SE patients, and a worse outcome in anoxic SE patients. As expected, a significant difference was observed between the different treatment protocols ($\chi^2 = 2.332$, $p = 0.001$), with those responding to protocol 1 having a better outcome than those requiring protocols 3 and 4.

4. Discussion

There is no universally accepted definition of SE in clinical studies. Traditionally, a diagnosis of SE, when convulsive, is based upon clinical evidence of repeated, clustering seizures, and may be easier to make than in the absence of clinical signs.[11] Indeed, when SE is non-convulsive, EEG-based evidence of epileptic activity is required to confirm a diagnosis that may only be suspected on the basis of clinical findings.[10] Therefore, when EEG is not available, NCSE may be suspected, though not confirmed, which highlights the importance of the role played by EEG in the diagnosis and management of SE.

The diagnosis-related problems (i.e. clinical vs electro-clinical) may hamper the interpretation and comparison of results from different studies, since diagnostic criteria are not homogeneous. In our study, we characterized SE according to both its clinical presentation (convulsive or non-convulsive) and to the EEG findings (focal or generalized). Our data based on a clinical and electro-clinical evaluation confirm the widespread observation that clinically convulsive SE and patients with focal EEG alterations are older than those with non-convulsive SE and generalized EEG abnormalities. This observation is probably related to the etiology: brain damage (stroke or brain tumors) that induces "lesional" SE is typical of older patients. By contrast, patients with anoxic SE, generally secondary to cardiac arrest, and toxic dysmetabolic SE are generally younger than patients with brain lesions. As expected, epileptic subjects presenting a SE represented the youngest group of patients.

SE is usually characterized by a significant short-term morbidity and mortality. Moreover, since SE is a neurological emergency, patient institutionalization and prompt medical treatment is recommended.[2,18] Although there is a large consensus for an aggressive treatment of generalized convulsive SE, agreement is lacking as to what the proper management of NCSE should consist of.[20,21] International guidelines for convulsive SE management suggest that benzodiazepines and phenytoin should be used as first- and second-line treatments, though the authors of some studies[22] have pointed out that as many as 35–45% of patients with SE may be unresponsive to these approaches. However, it should be borne in mind that SE in those studies was considered in general terms, there being no distinction between the convulsive and non-convulsive types or the different etiologies. In our patients, we observed a difference in the response to treatment only when SE was considered according to the EEG findings and etiology: protocol 1 (i.v. benzodiazepines) proved to more effectively control focal SE, which is more often observed in patients with a lesional or epileptic etiology. On the other hand, a more aggressive approach, requiring combined treatments or sedation in intensive care units, was required in anoxic patients, which probably reflects the more complex cardiovascular instability of such patients.

As regards outcome, it should be borne in mind that the underlying condition inducing the SE, rather than SE itself, may be the main reason for the high mortality rate, which is approximately 20%.[14] Previous studies have shown that older age and acute symptomatic etiology are related to the worst outcomes.[15] In this regard, a prognostic score (Status Epilepticus Severity Score – STESS) that takes into account age > 65 years, previous history of seizures, seizure type and extent of consciousness impairment has recently been proposed as an outcome measure in clinical practice.[17]

Our study confirms the role of age in SE prognosis; interestingly, only a trend toward a significantly poorer prognosis emerged when age was considered as a continuous variable. This finding may be ascribed to the fact that the prognosis of SE is more closely related to its etiology than to the SE itself. To sum up, the prognosis was best in patients with CSE, particularly those with focal SE, in whom the etiology was epileptic or toxic and who only received first-line treatment, regardless of their age and gender. Previous studies have shown that myoclonic SE in anoxic encephalopathy is associated with a poor outcome and that treatment of SE does not generally influence the prognosis.[16] In our patients, more intensive treatment was associated with a poor outcome owing to the severity of the clinical conditions: the outcome in patients who responded to protocol 1 was better than that in patients who received protocols 3 and 4. This is, however, to be expected given that the clinical conditions of patients who require multiple aggressive approaches are evidently more complex.

5. Conclusions

The accurate characterization of SE is fundamental. A prompt neurophysiological EEG evaluation with continuous EEG monitoring, when available, combined with a clinical evaluation helps to make an accurate prognosis and select the most appropriate therapy. In lesional and epileptic SE, first-line treatments and subsequent periodical standard EEG may be sufficient to control the electro-clinical status, while intensive care unit management with a more aggressive therapeutic approach and continuous EEG monitoring are recommended for refractory SE.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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