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ORIGINAL ARTICLE

Status epilepticus with prominent motor symptoms clusters into distinct electroclinical phenotypes

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Abstract

Background and purpose: Status epilepticus (SE) is a heterogeneous condition and considerable variability exists in its etiology, semiology, electroencephalographic correlates, and response to treatment. The aim of the present study was to explore whether distinct phenotypes may be identified within SE with prominent motor symptoms.

Methods: Consecutive episodes of SE with prominent motor symptoms in patients aged ≥14 years were included. Etiology of SE was defined as symptomatic (acute, remote, progressive) or unknown. Electroencephalogram (EEG) recordings were searched for lateralized periodic discharges (LPDs), generalized sharply and/or triphasic periodic potentials (GPDs), and spontaneous burst suppression (BS). According to treatment response, SE was classified into responsive, refractory and super-refractory. Average linkage hierarchical cluster analysis was performed with Pearson's correlation as a similarity measure.

Results: A total of 240 episodes of SE were identified. Three major clusters were found. The first cluster linked focal motor SE evolving into non-convulsive SE (NCSE), presence of LPDs/GPDs on EEG, unknown etiology and treatment refractoriness. The second cluster linked convulsive and myoclonic SE evolving into NCSE, presence of spontaneous BS on EEG, progressive symptomatic etiology and super-refractoriness. The third cluster linked convulsive and myoclonic SE not evolving into other semiologies, absence of LPDs/GPDs/spontaneous BS on EEG, acute symptomatic etiology and treatment responsiveness.

Conclusions: Distinct electroclinical phenotypes characterized by different response to pharmacological intervention can be identified within the heterogeneity of SE with prominent motor phenomena.

KEYWORDS
status epilepticus, hierarchical cluster analysis, phenotypes

INTRODUCTION

Status epilepticus (SE) represents a neurological emergency, characterized by high mortality and morbidity [1]. Conceptually, SE is defined as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures" [2]. The diagnostic classification system endorsed by the International League Against Epilepsy (ILAE) distinguishes SE with prominent motor symptoms from nonconvulsive SE (NCSE) and proposes a framework for clinical diagnosis, investigation, and therapeutic approach [2]. Remarkably, SE represents a heterogeneous condition rather than a single disease entity, and considerable variability exists with regard to etiology, semiology, electroencephalographic correlates and response to treatment.

Hierarchical cluster analysis (HCA) is an exploratory data analysis methodology used to identify structures within a dataset. The goal of the algorithm is reducing the multidimensionality of data while still preserving homogenous clusters. The HCA aims to sort different variables (or attributes) into subgroups such that the degree of association between variables is maximal if they belong to the same group and minimal otherwise [3]. This technique has been shown to improve the characterization of disease phenotype and is employed to describe groupings within different conditions, including chronic obstructive pulmonary disease, asthma, transient global amnesia and psychiatric disorders [4–8].

In the present study, we applied HCA to explore whether distinct phenotypes may be identified within a population of patients with SE with prominent motor symptoms.

METHODS

Participants

All consecutive SE episodes occurring in patients aged ≥14 years and prospectively registered at the Ospedale Civile Baggiovara (Modena, Italy) from September 1, 2013 to August 1, 2019 were reviewed. Before 2015, SE was considered as a continuous seizure that lasts ≥5 min or two or more discrete seizures, between which there is no complete recovery of consciousness [9]. After 2015, the operational definition proposed by the ILAE was adopted and prospectively applied [2]. In order to reduce possible selection bias in the years 2013 to 2015, before prospective adoption of the new ILAE definition of SE, all the SE episodes were reviewed by S.M. and G.G. In each case, the SE episode met the 2015 ILAE diagnostic criteria. Notably, for SE with a prominent motor component (convulsive), which is the subject of the present study, the definition adopted before 2015 meets the operational time criterion *t1* proposed by the new (2015) classification.

A specific "Status Epilepticus Form" was used to collect demographic and clinical information for each case, including age, gender, place of residence, site and date of SE onset, semiology of SE, etiology, type, duration, and dosage of anti-seizure medications (ASMs), anesthetic drugs and other therapies used, as previously reported [10–12]. The form was filled in by the first doctor who took care of the patient (in all cases, a neurologist or a neurointensivist) or by the staff of the neurophysiology unit who performed the first electroencephalogram (EEG) examination of a suspected SE case. It is worth noting that a neurology ward serves the hospital 24 h per day for 7 days per week, and the same neurophysiology staff record all the EEGs.

Episodes of SE with prominent motor symptoms were included in the present analysis. This choice was motivated by the exploratory nature of the study and the aim of additionally considering the response to treatment within the cluster analysis. Nowadays, for motor SE episodes the clinical diagnosis and time of onset are known, and treatment is almost always early. Conversely, in NCSE there is much greater variability in the timing of diagnosis and consequently also in the beginning of therapy. Therefore, for this first study, we preferred to conservatively consider only SE with prominent motor features in order to reduce possible bias.

With regard to SE semiology classification, patients with prominent motor symptoms included generalized convulsive, myoclonic, or focal motor SE [2], whereas SE without prominent motor symptoms (not convulsive) included patients in coma, and focal seizures with and without impaired consciousness. If one SE episode included bilateral tonic-clonic activity at any time, the event was classified as "convulsive" according to the ILAE 2015 classification, which takes into consideration the most overt semiology [2]. The evolution of semiology during any episode of SE was also considered; consequently, one SE episode could include more than one semiology type ("semiological sequence"). Salzburg diagnostic criteria were applied for nonconvulsive parts of the semiological sequences. [13,14]

Etiology of SE was defined as symptomatic (acute, remote, progressive) or unknown (i.e., cryptogenic) according to the classification proposed by the ILAE [2]; acute etiology referred to SE occurring within 7 days after the onset of the brain insult. Patients with hypoxic encephalopathy were excluded from the analysis.

Electroencephalogram recordings were searched for lateralized periodic discharges (LPDs), generalized sharply and/or triphasic periodic potentials (GPDs) and nonmedically induced (i.e., spontaneous) burst suppression (BS); for the definitions, the American Clinical Neurophysiology Society (ACNS) criteria were followed [15]. The EEGs were recorded using the international 10–20 system; each EEG recording was assessed by board-certified neurophysiologists. The examined test EEGs were standard EEG recordings of 20–40 min duration (mean duration 30 min).

According to response to treatment, SE was classified as responsive, refractory and super-refractory. Treatment responsiveness was defined as SE cessation after, at most, two treatment trials (first-line therapy with benzodiazepines followed by second-line treatment with one ASM administered intravenously). Refractory SE (RSE) was defined as a failure of first-line therapy with benzodiazepines and one second-line treatment with ASMs [16]. In super-refractory SE (SRSE), status continued or recurred despite the use of anesthetics for longer than 24 h [9]. Treatment followed an internal protocol (publicly available at http://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE_AOU.pdf), based on the recommendations of international guidelines [17,18]. The bolus and maintenance doses of drugs used are shown in Table S1.

Statistical analysis

Values are presented as mean ± SD or median (interquartile range [IQR]) for continuous variables and as number (%) of subjects for categorical variables. Agglomerative, within-group HCA was performed. Average-linkage was used as linkage criteria and Pearson's correlation as a measure of distance (similarity) between clusters. Semiology and dynamics of SE (convulsive only, focal motor only, myoclonic only, convulsive evolving into nonconvulsive, focal motor evolving into nonconvulsive, myoclonic evolving into nonconvulsive), EEG features (presence of LPDs/GPDs, presence of spontaneous BS, absence of LPDs/GPDs/spontaneous BS), etiology (acute symptomatic, progressive symptomatic, remote symptomatic, unknown), and response to treatment (responsiveness, refractoriness, super-refractoriness) were entered into the model. Results of HCA were graphically represented by the dendrogram, which records the sequences of merges and shows the hierarchical relationship between the clusters. The dendrogram is a tree-like diagram where the rescaled distance (or similarity) between two clusters is indicated on the horizontal axis: the shorter the distance, the closer the clusters. Distance between two clusters (or variables) is read between two vertical traits; the distance at which subclusters merge into a new cluster can be read out for any node in the dendrogram. Data analysis was performed using SPSS 19.0 statistical package for Windows.

Standard protocol approvals, registrations, and patient consents

The scientific advisory boards of our institution approved the research protocol, and the local Ethics Committee approved the study (556/2018/OSS/AOUMO).

RESULTS

A total of 240 episodes of non-hypoxic SE with prominent motor symptoms were identified. They occurred in 217 patients, of which 81 (37.3%) had a history of epilepsy. The median (IQR) age at SE onset was 71 (59–82) years and 95 (39.6%) episodes occurred in males. Two-hundred and seven cases (86.3%) were first episodes of SE and 33 (13.7%) were recurrences. The characteristics of SE episodes are summarized in Table 1. Episodes of acute symptomatic SE were most commonly attributable to alcohol- or drug-related causes (31.7%), metabolic disturbances (20.1%) and cerebrovascular diseases (16.5%). Intracranial tumors (69.6%) represented the most frequent cause associated with progressive symptomatic SE. Remote

TABLE 1 Characteristics of status epilepticus episodes

	SE episodes (*n* = 240) *n* (%)
Etiology	
Acute symptomatic	139 (57.9)
Progressive symptomatic	56 (23.3)
Remote symptomatic	39 (16.3)
Unknown	6 (2.5)
Causes	
Cerebrovascular diseases	62 (25.8)
Alcohol-/drug-related	44 (18.3)
Intracranial tumors	39 (16.3)
Metabolic disturbances	28 (11.7)
Sepsis	22 (9.2)
Head trauma	12 (5.0)
CNS infections	7 (2.9)
Autoimmune disorders	7 (2.9)
Degenerative disorders	6 (2.5)
Others	7 (2.9)
Unknown	6 (2.5)
Semiological dynamics	
Convulsive only	42 (17.5)
Focal motor only	82 (34.2)
Myoclonic only	3 (1.3)
Convulsive evolving into NCSE	50 (20.8)
Focal motor evolving into NCSE	61 (25.4)
Myoclonic evolving into NCSE	2 (0.8)
Electroencephalographic pattern	
LPDs/GPDs	76 (31.7)
Spontaneous BS	2 (0.8)
No LPDs/GPDs/BS	162 (67.5)
Response to treatment	
Responsive	181 (75.4)
Refractory	35 (14.6)
Super-refractory	24 (10.0)

Abbreviations: BS, burst suppression; CNS, central nervous system; GPDs, generalized sharply and/or triphasic periodic discharges; LPDs, lateralized periodic discharges; NCSE, non-convulsive SE; SE, status epilepticus.

symptomatic SE was attributed to cerebrovascular diseases (89.7%) and head injury (10.3%). Out of 226 SE episodes with 30-day follow-up available, return to baseline conditions occurred in 111 (49.1%) and death in 48 (21.2%) cases.

The dendrogram in Figure 1 shows three major clusters. The first cluster linked focal motor SE evolving into NCSE, the presence of LPDs or GPDs on EEG, unknown etiology and treatment refractoriness. The second cluster linked convulsive and myoclonic SE evolving into NCSE, spontaneous BS on EEG, progressive symptomatic etiology and super-refractoriness. The third cluster linked convulsive and myoclonic SE not evolving into other semiologies, absence of LPDs, GPDs and spontaneous BS on EEG, acute symptomatic etiology and responsiveness to treatment. In addition, focal motor SE not evolving into other semiologies was associated with remote symptomatic etiology.

DISCUSSION

Three main clinical phenotypes linking distinct characteristics of semiology, EEG activity, etiology and responsiveness to treatment have been identified.

The semiological dynamics of SE contributed to marked differences across the phenotypes. Convulsive and myoclonic SE not evolving into other semiologies were linked to treatment responsiveness, whereas SE subtypes evolving into NCSE were grouped within the less benign clusters. Our observations suggest that refractoriness is not associated with prominent motor phenomena, but rather with the subsequent evolution into NCSE. These findings highlight how changes in semiology matter and build up the evidence that semiology that comes later can contribute to a greater extent to outcome. A recent population-based study evaluated the impact of changes of semiology during one episode of SE on outcome: SE with only prominent motor phenomena and without nonconvulsive semiology had significantly lower fatality rates than SE with nonconvulsive semiology at the end of the semiological sequence [19].

Electroencephalographic patterns and etiologies also contributed to define the different phenotypes of SE with prominent motor symptoms. Spontaneous, non-medically induced BS, which, as expected, had an overall low occurrence, was associated with SRSE, periodic discharges linked with RSE, and the absence of any of these EEG features clustered with responsive SE. These findings emphasize the utility of EEG in the assessment of SE and expand the correlations described between periodic discharge

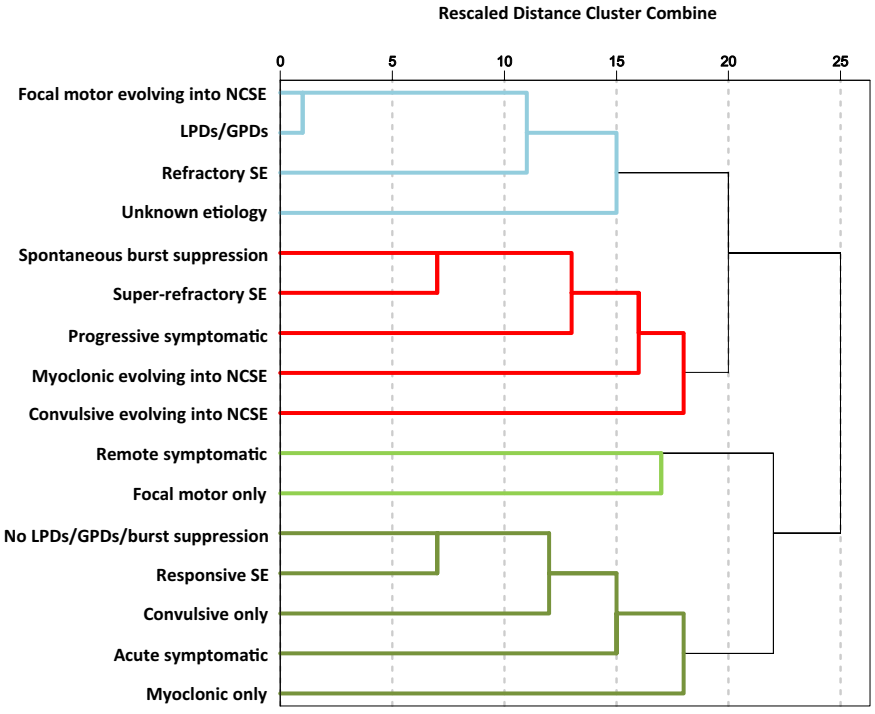

FIGURE 1 Dendrogram of clinical features in status epilepticus (SE). Dendrogram based on the hierarchical cluster analysis of clinical data from 240 episodes of SE with prominent motor symptoms. The horizontal axis denotes the linkage distance. Distance is calculated and rescaled from 0 to 25 according to the measure of similarity (Pearson's correlation) and the cluster algorithm (average linkage). The dendrogram shows three major clusters: (i) focal motor SE evolving into non-convulsive SE (NCSE), presence of lateralized periodic discharges (LPDs)/generalized sharply and/or triphasic periodic discharges (GPDs) on electroencephalogram (EEG), unknown etiology, treatment refractoriness; (ii) myoclonic/convulsive SE evolving into NCSE, presence of spontaneous burst suppression (BS) on EEG, progressive symptomatic etiology, treatment super-refractoriness; (iii) convulsive only/myoclonic only SE, no LPDs/GPDs/spontaneous BS on EEG, acute symptomatic etiology, treatment responsiveness. Remote symptomatic etiology resulted associated with focal motor SE not evolving into any other semiology.

and BS with in-hospital mortality and poor functional outcome at discharge [20,21]. These EEG correlates have also been included in the Epidemiology-based Mortality score in Status Epilepticus (EMSE) and, when present, contribute to the total score by adding mortality risk points [21]. The impact of etiology on mortality and functional recovery has been extensively documented [22]. Conversely, few and inconsistent data exist on the relationship between etiology and responsiveness to ASMs. Acute symptomatic etiologies as a whole have been associated with RSE in some studies, but not in others, and such discrepancy may be explained by the wide spectrum of causes encompassed in this category [23,24]. The exclusion of patients with hypoxic encephalopathy may have contributed to the association between acute symptomatic etiology and responsive SE in the present study. Remote symptomatic etiology did not result in a distinct cluster, but was more closely linked with the favorable one (phenotype), reinforcing the evidence that remote symptomatic causes are less prone to evolve into RSE [25]. Conversely, progressive symptomatic etiology clustered with poor response to pharmacological treatment, suggesting that a progressive brain injury is more likely to trigger and sustain the process of refractoriness.

Some shortcomings of the present analysis need to be considered. The study involved one single tertiary care center, a limited set of variables collected in a real-world setting were considered, and residual confounding due to unmeasured or incompletely characterized covariates could have resulted in biases. Further, we investigated episodes of SE instead of patients with first SE, which might have also biased the results. It is also worth emphasizing that HCA is an exploratory statistical approach, largely aimed at finding out associations rather than proving causality. Appropriately targeted studies in larger populations at different sites and including additional clinical, laboratory and imaging variables are required to externally validate the clusters, identify potential clinical correlation in terms of survival or neurological status on recovery, and explore whether clinical phenotypes may also be identified within the NCSE population.

The present analysis provides novel insights into the correlations between pathologic and clinical domains of SE with prominent motor symptoms. The study provides real-world data for anchoring the current systematization of SE and possibly represents a prolegomenon for a topologic, multidimensionally integrated classification system. So far, most of the research in the field of SE has been directed to quantify severity and predict functional outcome rather than explore mutual relationships between semiology, EEG activity, etiology and clinical course and identify distinct phenotypes. Currently, there are four published scales evaluating SE prognosis: the Status Epilepticus Severity Score (STESS) [26,27], the EMSE [21], the modified STESS [28], and the Encephalitis Nonconvulsive Status Epilepticus Diazepam Resistance Imaging Tracheal Intubation (END-IT) score [29]. These clinical scoring systems aim to predict survival versus death in the hospital setting [21,28] and functional post-discharge outcome [29]. Although these prognostic scores can assess individual risk and stratify patients in interventional studies, they have poor accuracy in the prediction of refractoriness to medications [11]. To date, no reliable tools are available to inform clinicians on the clinical course of SE.

In conclusion, phenotyping the vast heterogeneity of SE with prominent motor symptoms into distinctive clusters may offer useful guidance, both in research and clinical practice, to predict treatment response by means of electroclinical variables, and pave the way for the development of novel approaches to estimating the likelihood of favorable and unfavorable response to pharmacological intervention. The continuous exploration and advancements in characterization of SE may improve outcome prediction and guide intervention strategies.

CONFLICTS OF INTEREST

Simona Lattanzi has received speaker's or consultancy fees from Eisai, GW Pharmaceuticals and UCB Pharma, and has served on advisory boards for Arvelle Therapeutics, BIAL and GW Pharmaceuticals. Francesco Brigo has acted as a consultant for Eisai. Eugen Trinka has received speaker's honoraria from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals Inc., LivaNova and Novartis, consultancy funds from UCB, Biogen, Gerot-Lannach, Bial, Eisai, Takeda, Newbridge, GW Pharmaceuticals, Sunovion Pharmaceuticals Inc. and Novartis, and directorship funds from Neuroconsult GmbH. E. Trinka's institution received grants from Biogen, Red Bull, Merck, UCB, the European Union, the FWF *Österreichischer Fond zur Wissenschaftsförderung* and the *Bundesministerium für Wissenschaft und Forschung*. Stefano Meletti received research grant support from the Ministry of Health, from the nonprofit organization "*Fondazione Cassa di Risparmio di Modena - FCRM*", and has received personal compensation as a scientific advisory board member for UCB and EISAI. The remaining authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Giada Giovannini: Data curation (equal); Methodology (equal); Writing – review and editing (equal). **Francesco Brigo:** Methodology (equal); Writing – review and editing (equal). **Niccolò Orlandi:** Data curation (equal); Methodology (equal); Writing – review and editing (equal). **Eugen Trinka:** Methodology (equal); Writing – review and editing (equal). **Stefano Meletti:** Data curation (equal); Methodology (equal); Supervision (equal); Writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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