

## Clinical phenotypes within nonconvulsive status epilepticus

Simona Lattanzi<sup>1</sup>  | Giada Giovannini<sup>2,3</sup>  | Francesco Brigo<sup>4,5</sup>  | Niccolò Orlandi<sup>2,6</sup>   
 Eugen Trinka<sup>7,8,9</sup>  | Stefano Meletti<sup>2,6</sup> 

<sup>1</sup>Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

<sup>2</sup>Neurology Unit, Baggiovara Civil Hospital, AOU Modena, Modena, Italy

<sup>3</sup>PhD Program in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy

<sup>4</sup>Department of Neuroscience, Biomedicine, and Movement Science, University of Verona, Verona, Italy

<sup>5</sup>Division of Neurology, Franz Tappeiner Hospital, Merano, Italy

<sup>6</sup>Department of Biomedical, Metabolic, and Neural Science, Center for Neuroscience and Neurotechnology, University of Modena and Reggio Emilia, Modena, Italy

<sup>7</sup>Department of Neurology, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria

<sup>8</sup>Center for Cognitive Neuroscience, Salzburg, Austria

<sup>9</sup>Public Health, Health Services Research and HTA, University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria

### Correspondence

Simona Lattanzi, Neurological Clinic,  
 Department of Experimental and Clinical  
 Medicine, Marche Polytechnic University,  
 Via Conca 71, 60020 Ancona, Italy.  
 Email: alfierelattanzisimona@gmail.com

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### Abstract

The study aimed to identify distinct phenotypes within nonconvulsive status epilepticus (NCSE). Consecutive episodes of NCSE in patients at least 14 years old were included. The level of consciousness was assessed through the Glasgow Coma Scale (GCS). Etiology of NCSE was defined as symptomatic (acute, remote, progressive) or unknown. Electroencephalographic (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, NCSE was classified as responsive, refractory, or superrefractory. Average linkage hierarchical cluster analysis was performed with Pearson correlation as similarity measure. Two hundred twenty-nine episodes of NCSE were included. Three clusters were identified. The first cluster linked GCS score 3–8, presence of spontaneous BS on EEG, acute symptomatic etiology, and treatment superrefractoriness. The second cluster gathered GCS score 9–12, presence of LPDs or GPDs on EEG, unknown etiology, and treatment refractoriness. The third cluster associated GCS score 13–15, absence of LPDs, GPDs, and spontaneous BS on EEG, and progressive and remote symptomatic etiology with treatment responsiveness. Phenotyping the heterogeneity of NCSE into electroclinical clusters can contribute to understanding correlations between pathologic and clinical domains, assessing the intrinsic severity of NCSE episodes, and estimating the likelihood of treatment responsiveness.

## KEY WORDS

hierarchical cluster analysis, phenotypes, status epilepticus

## 1 | INTRODUCTION

Status epilepticus (SE) is “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.”<sup>1</sup> According to clinical presentation, SE is classified on the basis of the presence of prominent motor symptoms and the degree of impaired consciousness.<sup>1</sup> Within the frame of the diagnostic classification system endorsed by the International League Against Epilepsy (ILAE), SE without prominent motor symptoms is termed nonconvulsive SE (NCSE). Far from being a single clinical entity, NCSE is characterized by marked heterogeneity in terms of electroclinical features, underlying etiologies, and prognosis.

The hierarchical cluster analysis (HCA) is a statistical methodology able to identify structures within a dataset. By classifying objects based on their (dis)similarities, it can reduce the multidimensionality of data and preserve homogenous groups. The algorithm sorts different variables into clusters; each cluster is distinct from the others, and the degree of association between variables is maximal if they belong to the same group and minimal otherwise.<sup>2</sup>

This study aimed to identify distinct phenotypes within a population of patients with NCSE using HCA.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

Consecutive episodes of NCSE occurring in patients at least 14 years old and prospectively registered at Baggiovara Civil Hospital (Modena, Italy) from September 1, 2013 to August 1, 2019 were reviewed. Before 2015, SE was considered to be a continuous seizure that lasts 5 min or longer or two or more discrete seizures between which there is not a complete recovery of consciousness.<sup>3</sup> After 2015, the operational definition proposed by the ILAE was adopted and prospectively applied<sup>1</sup>; the operational time indicating when a seizure is likely to be prolonged, leading to continuous seizure activity, which denotes SE, has been set at 5 min for tonic-clonic SE, 10 min for focal SE with impaired consciousness, and 10–15 min for absence SE.<sup>1</sup> The cases of SE that occurred before 2015 have been reviewed by two of the authors (S.M. and G.G.), and all met the ILAE diagnostic criteria. For all included cases, the diagnosis of NCSE was confirmed by the

application of the Salzburg electroencephalographic (EEG) criteria.<sup>4,5</sup>

A specific Status Epilepticus Form was used to collect demographic and clinical information, including age, gender, Glasgow Coma Scale (GCS),<sup>6</sup> semiology, etiology, and dosage of antiseizure medications (ASMs), anesthetic drugs, and other therapies used. The form was filled in by the first physician (neurologist or neurointensivist) taking care of the patient. The GCS was evaluated at presentation in the Emergency Department for out-of-hospital SE episodes, and at the bedside for in-hospital-onset SE episodes.

Etiology of SE was defined as acute symptomatic, remote symptomatic, progressive symptomatic, or unknown (i.e., cryptogenic).<sup>1</sup> Acute etiology referred to SE occurring within 7 days after the onset of stroke or traumatic brain injury; in the presence of an active central nervous system infection; or during an active phase of multiple sclerosis or other autoimmune diseases. Etiology was also considered acute in the presence of severe metabolic derangements as documented within 24 h by specific biochemical or hematologic abnormalities, or drug or alcohol intoxication and withdrawal.<sup>7</sup> Patients with hypoxic encephalopathy were excluded from the analysis.

EEG recordings were reviewed for lateralized periodic discharges (LPDs), generalized sharply and/or triphasic periodic potentials (GPDs), and non-medically induced (i.e., spontaneous) burst suppression (BS); for definitions, the American Clinical Neurophysiology Society criteria were adopted.<sup>8</sup> 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 into responsive, refractory, and superrefractory. Treatment responsiveness was defined as SE cessation after 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.<sup>9</sup> In superrefractory SE, SE continued or recurred despite the use of anesthetics for longer than 24 h.<sup>3</sup> Treatment followed an internal protocol (publicly available at [http://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE\\_AOU.pdf](http://salute.regione.emilia-romagna.it/percorso-epilessia/PDTASE_AOU.pdf)) based on the recommendations of international guidelines.<sup>10,11</sup> The bolus and maintenance doses of drugs used are shown in Table S1.

## 2.2 | Statistical analysis

Values are presented as median (interquartile range) for continuous variables and number (percentage) of subjects for categorical variables. Agglomerative, within-group HCA was performed. Average linkage was used as linkage criteria and Pearson correlation as a measure of distance (similarity) between clusters. Etiology (acute symptomatic, progressive symptomatic, remote symptomatic, unknown), level of consciousness impairment according to GCS score (absent or minor, GCS score = 13–15; moderate, GCS score = 9–12; severe, GCS score = 3–8),<sup>6,12</sup> EEG features (presence of LPDs/GPDs, presence of spontaneous BS, absence of LPDs/GPDs/spontaneous BS), and response to treatment (responsiveness, refractoriness, superrefractoriness) 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.<sup>2</sup> The dendrogram is a treelike diagram where the rescaled distance (or similarity) between two clusters is indicated on the horizontal axis; the shorter is the distance, the closer are 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.

## 2.3 | Standard Protocol Approvals, Registrations, and Patient Consents

The local ethics committee approved the study (556/2018/OSS/AOUMO-RF-2016-02361365).

## 2.4 | Data Availability

Anonymized data will be shared upon request from any qualified investigator.

## 3 | RESULTS

Two hundred twenty-nine episodes of NCSE were identified. They occurred in 217 patients, of whom 75 (32.8%) had a prior history of epilepsy. The median age at SE onset was 77 (range = 67–84) years, and 75 (32.8%) episodes occurred in males. Two hundred twelve cases (92.6%) were first episodes of SE, and 17 (7.4%) were recurrences. Characteristics of SE episodes are summarized in Table 1.

Episodes of acute symptomatic SE were most commonly due to cerebrovascular diseases (28.2%), metabolic disturbances (21.5%), alcohol/drug-related causes (17.4%), and

**TABLE 1** Characteristics of status epilepticus episodes

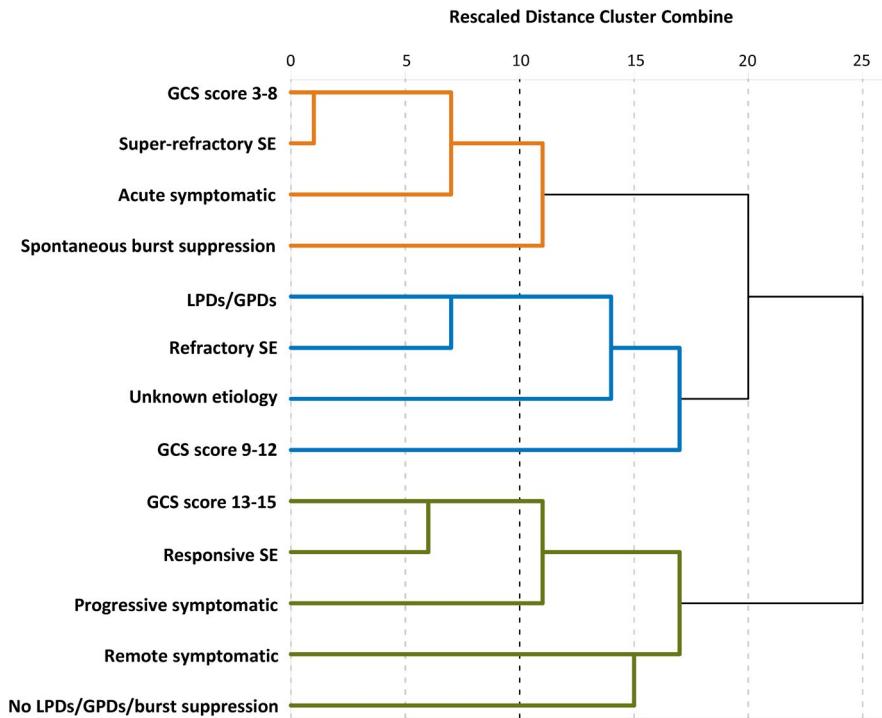
Characteristic	Status epilepticus episodes, n = 229
Etiology	
Acute symptomatic	149 (65.1)
Remote symptomatic	39 (17.0)
Progressive symptomatic	33 (14.4)
Unknown	8 (3.5)
Causes	
Cerebrovascular diseases	75 (32.8)
Metabolic disturbances	32 (14.0)
Intracranial tumors	26 (11.4)
Alcohol/drug-related	26 (11.4)
Sepsis	25 (10.9)
CNS infections	17 (7.4)
Head trauma	9 (3.9)
Unknown	8 (3.5)
Others	11 (4.8)
Level of consciousness impairment	
GCS score 3–8	61 (26.6)
GCS score 9–12	69 (30.1)
GCS score 13–15	99 (43.2)
Electroencephalographic pattern	
LPDs/GPDs	61 (26.6)
Spontaneous burst suppression	2 (.9)
No LPDs/GPDs/burst suppression	166 (72.5)
Response to treatment	
Responsive	182 (79.5)
Refractory	26 (11.3)
Superrefractory	21 (9.2)

Note:: Data are presented as n (%).

Abbreviations: CNS, central nervous system; GCS, Glasgow Coma Scale; GPD, generalized sharply and/or triphasic periodic potential; LPD, lateralized periodic discharge.

sepsis (16.8%). Remote symptomatic SE was mainly attributed to cerebrovascular diseases (84.6%), and intracranial tumors (72.7%) represented the most frequent causes associated with progressive symptomatic SE. Of 209 SE episodes with 30-day follow-up available, return to baseline condition occurred in 71 (34.0%) and death in 67 (32.1%) cases.

The dendrogram shows three clusters (Figure 1). The first cluster linked the severe impairment of consciousness (GCS score = 3–8), the presence of spontaneous BS on EEG, acute symptomatic etiology, and treatment superrefractoriness. The second cluster gathered GCS score = 9–12, the presence of LPDs or GPDs on EEG, unknown etiology, and treatment refractoriness. The third cluster associated absent or minor consciousness impairment at presentation (GCS score = 13–15), the absence of LPDs, GPDs, and spontaneous BS on



**FIGURE 1** Dendrogram based on the hierarchical cluster analysis of clinical data from 229 episodes of nonconvulsive status epilepticus (SE). The horizontal axis denotes the linkage distance. Distance is calculated and rescaled from 0 to 25 according to the measure of similarity (Pearson correlation) and the cluster algorithm (average linkage). The dendrogram shows three clusters: (1) Glasgow Coma Scale (GCS) score 3–8, presence of spontaneous burst suppression (BS) on electroencephalogram (EEG), acute symptomatic etiology, treatment superrefractoriness; (2) GCS score 9–12, presence of lateralized periodic discharges (LPDs)/generalized sharply and/or triphasic periodic potentials (GPDs) on EEG, unknown etiology, treatment refractoriness; and (3) GCS score 13–15, no LPDs/GPDs/spontaneous BS on EEG, progressive and remote symptomatic etiology, treatment responsiveness

EEG, and progressive and remote symptomatic etiology with treatment responsiveness.

#### 4 | DISCUSSION

Three distinct phenotypes have been recognized within the NCSE, and differences in the level of consciousness, EEG activity, etiology, and responsiveness to treatment distinguish the clusters. The findings suggest that the degree of consciousness impairment can be accompanied by distinctive EEG patterns and underlie different etiologies, which carry a differential responsiveness to treatment.

The degree of impaired consciousness contributed to mark differences across the phenotypes.

Consciousness impairment is a continuous variable, which can be assessed either qualitatively or quantitatively.<sup>1</sup> A system of classification that is relatively observer-independent can overcome the limits of subjective assessments of quantitative consciousness (e.g., somnolent, stuporous, comatose, deeply comatose), which define each level of consciousness by evaluating observations and responses that are subject to wide variations in interpretation. The GCS provides a structured method for assessment of the level of consciousness.

Introduced in 1974 at the University of Glasgow by Teasdale and Jennett to classify traumatic brain injury,<sup>6</sup> the GCS became one of the most widely used and validated assessment tools to objectively describe the extent of impaired consciousness in acute medical and trauma patients.

The Axis I (semiology) of the current classification system of SE considers the degree of impaired consciousness as one main criterion and makes a clear-cut dichotomous distinction between NCSE with coma and NCSE without coma.<sup>1</sup> Exploratory studies have, however, shown that different degrees of consciousness impairment can be related to a different prognosis.<sup>13</sup> In a cohort of adult patients with SE, case fatality was lower among patients presenting fully awake and aware with reduced cognition than in somnolent, stuporous, or comatose patients.<sup>14</sup> In a prospective study aimed at characterizing a critically ill cohort with SE by the illness severity scoring systems, the GCS was the only component to remain significantly different between patients with and without return to baseline.<sup>15</sup> So far, no data exist correlating the responsiveness to treatment with the level of consciousness, however assessed.

The given EEG pattern mirrored the depth of unresponsiveness. Spontaneous, non-medically induced BS, which indicates severe brain dysfunction, was linked with the lowest GCS scores, and the “benign” EEG pattern lacking BS,

LPDs, and GPDs correlated with normal or mildly impaired consciousness. The presence of LPDs or GPDs, which belong to the so-called “ictal–interictal continuum,” where ictal activity merges with an interictal or “irritative” state,<sup>16</sup> clustered with a moderate degree of consciousness impairment. The prognostic implications of the EEG patterns are likely to be related to the underlying etiology. The association of acute symptomatic etiology with the worst-case cluster is in line with evidence that most cases of comatose NCSE are acute symptomatic with a severe underlying acute brain disorder and a very poor response to treatment.<sup>13</sup> Conversely, remote and progressive symptomatic causes appeared to be less prone to evolve into RSE. Interestingly, the link between treatment refractoriness and unknown etiology resembled “cryptogenic” new onset RSE, which is a condition with new onset of RSE without a clear acute or active structural, toxic, or metabolic cause in a patient without active epilepsy.<sup>17</sup>

So far, most of the research in the field of SE has focused on the prediction of functional outcome, and the available clinical scoring systems have been developed to prognosticate survival versus death and functional postdischarge outcome. All these scores have poor accuracy in the prediction of treatment refractoriness,<sup>18</sup> and none integrates data on either consciousness level, EEG activity, or etiology.

Although preliminary, the findings of this analysis build up the actual classification system of SE. They pave the way for thinking of SE within the framework of a multidimensional systematization that subsumes and integrates at once clinical, EEG, and etiological axes, and suggest that a more nuanced categorization of the degree of consciousness impairment in patients with NCSE can contribute to providing prognostic insights and be informative of the likelihood of treatment responsiveness. Of note, the advantages of the GCS include its simplicity, short administration time, reliability, validity, stability, cost-free availability, and ease of access.<sup>19</sup> Different limits of the study also need to be acknowledged, including the recruitment at a single tertiary care center and the collection of a limited set of variables in a real-world setting, which may have resulted in potential sources of biases. Of note, the lack of data about the prehospital administration of benzodiazepines did not allow evaluating the potential confounding effect on the level of consciousness as measured by the GCS at presentation. Although misdiagnosis can occur and cases may have been inappropriately categorized as acute symptomatic, this risk is minimized by the adoption of a definition of acute etiology that distinguishes the time interval between the insult and SE occurrence according to the underlying clinical conditions. The average age of the included population was quite old, and most episodes of NCSE occurred in females. Although these demographic characteristics substantially confirmed the overall distribution of SE incidence, with the highest estimates after 60 years of age and the prevalence of female sex in cases of NCSE,<sup>14,20</sup> the recruitment at a single tertiary center may limit

the representativeness and generalizability of the study results to the general NCSE population and different settings.

Finally, considering HCA, this is a technique primarily aimed at exploring associations rather than proving causality; it involves arbitrary decisions, and results can be influenced by chosen distance functions. In this regard, although “model-based” clustering algorithms can offer the advantage of identifying subgroups based on a probabilistic model and a posteriori membership rather than dissimilarity measures, it is worth emphasizing that HCA is easy to understand and implement and does not require specific conditional independence modeling assumptions to be met.<sup>21,22</sup> Furthermore, the algorithm of HCA produces a clear graphical depiction of the clusters, displaying the order by which segments are grouped together. Importantly, the hierarchical tree or dendrogram allows appreciation of the relative distance, degree of similarity, and mutual relationships between the variables and thus provides useful cues and insights to interpret and understand the pathophysiological mechanisms and clinical reasons that may underlie and explain the clustering.<sup>3,23,24</sup> Moreover, we considered widely shared electroclinical variables that are easily reproducible and testable in subsequent validation studies.

Phenotyping the heterogeneity of NCSE into distinctive electroclinical clusters can contribute to identifying and understanding correlations between pathologic and clinical domains, assessing the intrinsic severity of SE episodes, and estimating the likelihood of response to pharmacological intervention. The continuous exploration and advancements in the characterization of NCSE may offer useful advice to inform clinical practice.

Prospective studies are warranted to externally validate the reliability and predictive accuracy of the identified clusters and provide useful complement with data on additional variables.

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## CONFLICT OF INTEREST

S.L. has received speaker's or consultancy fees from Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, and GW Pharmaceuticals. F.B. has acted as a consultant for Eisai. E.T. has received speaker's honoraria from UCB, Biogen, Gerot-Lannach, BIAL, Eisai, Takeda, Newbridge, Sunovion Pharmaceuticals, LivaNova, and Novartis; consultancy funds from UCB, Biogen, Gerot-Lannach, BIAL, Eisai, Takeda,

Newbridge, GW Pharmaceuticals, Sunovion Pharmaceuticals, and Novartis; and directorship funds from Neuroconsult. E.T.'s institution has received grants from Biogen, Red Bull, Merck, UCB, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, and Bundesministerium für Wissenschaft und Forschung. S.M. has received research grant support from the Ministry of Health and from the nonprofit organization Fondazione Cassa di Risparmio di Modena and has received personal compensation as a scientific advisory board member for UCB and EISAI. Neither of the other authors has any conflict of interest to disclose. 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.

## ORCID

- Simona Lattanzi  <https://orcid.org/0000-0001-8748-0083>  
 Giada Giovannini  <https://orcid.org/0000-0002-3585-5872>  
 Francesco Brigo  <https://orcid.org/0000-0003-0928-1577>  
 Niccolò Orlandi  <https://orcid.org/0000-0002-5717-7363>  
 Eugen Trinka  <https://orcid.org/0000-0002-5950-2692>  
 Stefano Meletti  <https://orcid.org/0000-0003-0334-539X>

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## SUPPORTING INFORMATION

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

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