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Does semiology of status epilepticus have an impact on treatment response and outcome?

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ABSTRACT

Objective: This study investigated whether there is an association between semiology of status epilepticus (SE) and response to treatment and outcome.
Method: Two hundred ninety-eight consecutive adult patients (160 females, 138 males) with SE at the University of Munich Hospital were prospectively enrolled. Mean age was 63.2 ± 17.5 (18–97) years. Patient demographics, SE semiology and electroencephalography (EEG) findings, etiology, duration of SE, treatment, and outcome measures were investigated. Status epilepticus semiology was classified according to a semiological status classification. Patient's short-term outcome was determined by Glasgow Outcome Scale (GOS).
Results: The most frequent SE type was nonconvulsive SE (NCSE) (39.2%), mostly associated with cerebrovascular etiology (46.6%). A potentially fatal etiology was found in 34.8% of the patients. More than half (60.7%) of the patients had poor short-term outcome (GOS ≤ 3) with an overall mortality of 12.4%. SE was refractory to treatment in 21.5% of the patients. Older age, potentially fatal etiology, systemic infections, NCSE in coma, refractory SE, treatment with anesthetics, long SE duration (>24 h), low Glasgow Coma Scale (GCS) (≤8) at onset, and high Status Epilepticus Severity Score (STESS-3) (≥3) were associated with poor short-term outcome and death ($p < 0.05$). Potentially fatal etiology and low GCS were the strongest predictors of poor outcome (Exp [b]: 4.74 and 4.10 respectively, $p < 0.05$).
Conclusion: Status epilepticus semiology has no independent association with outcome, but potentially fatal etiology and low GCS were strong predictive factors for poor short-term outcome of SE.

1. Introduction

The term nonconvulsive status epilepticus (NCSE) is widely used but not satisfactorily from a scientific point of view. In classification of medical conditions, we aim to provide precise terms and usually avoid negative terms. We aim certainly prefer to name a condition avoid what it looks like than what it does not. This is particularly true since status epilepticus (SE) is a serious neurological condition with various semiological and electrophysiological expressions. Status epilepticus with tonic–clonic activity is easily identified clinically. However, NCSE is clinically almost impossible to distinguish from states of confusion or dementia. Electroencephalography (EEG) recordings are mandatory to identify NCSE. The diagnostic difficulty may be the cause why the term NCSE is so popular. There is limited data available on semiological differences of SE on prognosis and outcome [1–4]. Our goal was to investigate the significance of SE semiology with respect to etiology, response to treatment, and outcome to better define the negative term NCSE.

2. Methods

2.1. Patient population

Two hundred ninety-eight adult patients (160 females, 138 males) aged 63.2 ± 17.5 (18–97) years who were diagnosed and treated consecutively for SE at the Department of Neurology of the University of Munich Hospital over a period of 6 years (between January 2000 and December 2006) were enrolled in the study. Demographics of the patients, SE semiology and EEG findings, etiology, duration of SE, neuroimaging and laboratory data, treatment, and outcome measures were entered into the database prospectively by the same neurologists (BF). Semiological changes over time during SE were noted in the clinical registry. Most of the patients were recruited from hospital wards (n = 158, 53%) and intensive care units (n = 119, 40%); others entered the study

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via the emergency unit (n = 13, 4%) or ambulance services (n = 8, 3%). The study was approved by the local ethics committee.

2.2. Definitions and classification of SE

Status epilepticus was defined as the occurrence of prolonged seizures or repetitive seizures between which there is incomplete recovery from baseline clinical conditions for more than or equal to 10 min [5]. With 10 min duration, we made sure not to confuse postictal states with NCSE. Diagnosis of SE was established clinically by trained physicians if the semiology was uniquely present. In case of unspecific clinical signs, the diagnosis of SE was established through EEG.

The SE semiology was classified according to the semiological classification of SE (SCSE) [5]. Changes of the semiology during SE were noted in the clinical registry. All SE events were further dichotomized into two main categories according to the presence or absence of prominent motor symptoms: motor SE and NCSE [5]. Subtle movements (facial twitching, eye deviation) and automatisms could be present in NCSE.

2.3. Clinical factors

The etiology of SE was defined according to the International League Against Epilepsy (ILAE) classification [6]. Patients with SE and known genetic or cryptogenic epilepsy without evidence for acute seizure provocation were grouped as remote symptomatic. Etiology that could possibly lead to death was categorized as 'potentially fatal'. Potentially fatal etiologies included acute central nervous system (CNS) infection, severe systemic infection, malignant brain tumor, acute large ischemic stroke or intracerebral hemorrhage, acquired immunodeficiency syndrome (AIDS) with CNS complications, and others [1,7].

Neuroimaging (computed tomography (CT) and/or magnetic resonance imaging (MRI)) was applied in all cases. Continuous EEG was obtained for at least 30 min including photic, sensory, and verbal stimulation in awake and comatose subjects. Electroencephalographies were performed with 21 electrodes placed according to the international 10–20 system and additional anterior temporal electrodes (FT9 and FT10). All tracings were reviewed by a board-certified epileptologist (SN). Electrographic patterns were only considered ictal if they showed typical spatiotemporal evolution in frequency, location, or morphology [8]. Patients with encephalopathic patterns such as burst suppression or triphasic waves were not included. Nonconvulsive status epilepticus was diagnosed by clinical semiology and EEG.

The duration of SE was determined by clinical observation or by electrographic seizure pattern in EEG of the patients with NCSE. The onset of NCSE was determined by the time in which the first EEG confirmed the presence of SE. The end point was determined when the clinical state was normalized and/or the EEG status was subsided. Patients had one or more EEGs for at least 30 min per day. Duration of SE could be determined precisely only in a subgroup of patients who had a continuous video-EEG monitoring. We grouped the patients into two according to the SE duration: group with SE duration less than 24 h and group with SE duration more than 24 h.

A stepwise treatment protocol was administered to most patients according to the current guidelines [9]. Intravenous (i.v.) benzodiazepines were administered as first line antiepileptic drugs (AEDs), followed by second line i.v. AEDs with phenytoin, phenobarbital, valproate acid, levetiracetam, or combinations if SEs continued. Coma induction with i.v. anesthetics (propofol, midazolam, thiopental, barbiturates, or rarely ketamine) were introduced after the failure of first and second line AEDs. Refractory SE (RSE) was defined as SE refractory to adequate administration of first and second line AEDs [7,10]. Super RSE was defined as SE that continues or recurs 24 h or more after the onset of anesthetics, including those cases in which SE recurs on the reduction or withdrawal of anesthetics [11].

Glasgow Coma Scale (GCS) was used at admission to the hospital [12]. Clinical status at discharge was graded according to the Glasgow Outcome Scale (GOS) [13]. Patients were dichotomized into 2 groups (good recovery or moderate disability, GOS > 3 vs severe disability, persistent vegetative state or death in hospital, GOS ≤ 3). Status Epilepticus Severity Score (STESS) was applied retrospectively (STESS-3: cutoff level to predict poor outcome ≥ 3 points) to estimate mortality risk [1,14].

2.4. Statistical analysis

For categorical variables, statistical analysis was carried out using Fisher's exact test or chi-square test, as appropriate. Differences between the groups for continuous variables were analyzed using independent Student's *t*-test or Mann–Whitney *U* test after testing for the normal distribution of the data. The level of significance was set as $p < 0.05$. Variables that were significantly different between the groups were included in a binary logistic regression model to evaluate predictors of poor outcome and refractoriness. Data were analyzed using statistical software (Statistical Package for Social Sciences (SPSS) ver. 18.0, IBM Corp., NY, USA). In case of more than one episode of SE through the study period, only the first admission was analyzed to avoid dependency between variables.

3. Results

The demographic features and difference of patient groups according to outcome are summarized in Table 1.

3.1. Semiology

Nonconvulsive status epilepticus (39.3%) was the most common SE type, followed by motor SE (31.9%) (Table 1). In the remaining patient group, motor SE developed into NCSE in 74 (24.8%) patients and was preceded by NCSE in 12 (4%) patients. The most common semiology subgroups in all SE episodes were dyscognitive SE in 49.6% (dialeptic SE in 25.2%, delirious SE in 14.4%, and aphasic SE in 6.4% of the patients), tonic–clonic SE in 35.6%, clonic SE in 26.8%, automotor SE in 14.7%, and NCSE in coma in 10.7% of the patients (Table 1). The most common SE semiology subgroups at presentation were dyscognitive SE in 86 (28.9%) (dialeptic SE in 16.4%, delirious SE in 7.4%, aphasic SE in 5%), tonic–clonic SE in 86 (28.9%), clonic SE in 56 (18.8%), and automotor SE in 29 (9.7%) patients. There were no patients with hypermotor, gelastic, autonomic, or other types of SE.

3.1.1. NCSE

Of the 117 patients who had only NCSE, 99 (84.6 %) patients were treated with first and/or second line AEDs, and 16 (13.6 %) patients were treated with additional continuous anesthetics. At discharge, 61 (52.1%) patients with NCSE had significant morbidity (GOS = 2 and GOS = 3), and 17 (14.5%) patients died. All of the patients with NCSE who were treated with continuous anesthetics (n = 16, 100%) had poor outcome (GOS ≤ 3), whereas only 62 of 99 (62.6%) patients with NCSE who were treated with i.v. AEDs had poor outcome ($p = 0.001$). Female patients (59.8% vs 40.2%, $p = 0.02$) were predominant in patients with only NCSE, compared with patients with only motor SE. The poor outcome (66.7% vs 49.5%) and mortality (14.5% vs 7.4%) were more prevalent in patients with only NCSE compared with patients with only motor SE, without a significant difference. Long SE duration (>24 h) (51.4% vs 11.5%, $p = 0.0001$) was more commonly observed in patients with only NCSE compared with patients with only motor SE. We did not find any significant difference regarding age, etiology, epilepsy history, GCS, STESS, and GOS scores between patients with only NCSE and patients with only motor SE.

Comatose state was the initial semiology in 13 of 32 patients (40.6%) with NCSE in coma. Comatose state emerged following tonic–clonic SE in 7 (21.8%), dyscognitive SE in 5 (15.6%), clonic SE in 4 (12.5%), myoclonic SE in 2 (6.2%), and tonic SE in 1 (3.1%) patients. Half of the patients (n = 16, 50%) with NCSE in coma had potentially fatal etiology. Most common etiologies of NCSE in coma were cerebrovascular disease in 17