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Nonconvulsive status epilepticus after convulsive status epilepticus: Clinical features, outcomes, and prognostic factors☆

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ABSTRACT

Objectives: To investigate clinical characteristics and outcomes of nonconvulsive status epilepticus (NCSE) after convulsive status epilepticus (CSE) and determine risk factors for unfavorable outcomes.

Methods: We reviewed consecutive patients with NCSE after CSE over eight years in the neurological intensive care unit. Clinical presentations and the Salzburg EEG criteria for NCSE were used to identify patients with NCSE after CSE. Demographics, clinical features, and anti-epileptic treatment responses were collected and analyzed. Modified Rankin Scale (mRS) was used to evaluate three-month outcomes. A multivariate logistic regression model was used to determine independent prognostic factors.

Results: Among 145 consecutive patients with convulsive SE, 48 (33.1%) patents eventually evolved into NCSE. Two patients with cerebral anoxia were exclude. At three-month follow-up, 23 patients (50.0%) had mRS ≥ 3, and 16 (34.8%) died. Thirty-two patients (69.6%) were given continuous intravenous anesthetic drugs (CIVADs). Fourteen patients (30.4%) had CIVAD at the rate > 50% proposed maximal dose (PMD). There was a single predictor factor found significant after multivariate logistic regression analysis: the recurrence of EEG seizures within two hours of initiation of CIVAD at a dose of greater than half the proposed maximal dose (OR, 9.63; 95%CI, 1.08–86.18; p = 0.043). The use of CIVAD, even with a high dose (> 50% PMD), was not independently associated with unfavorable outcomes.

Conclusions: The recurrence of EEG seizures within two hours of initiation of CIVAD at a dose of greater than half the proposed maximal dose predicts unfavorable outcomes in NCSE after CSE. The refractoriness of the seizures might be a significantly greater risk for poor outcome in NCSE after CSE than treatment with CIVADs.

1. Introduction

Nonconvulsive status epilepticus (NCSE) persists in 14–34.3% of the patients with convulsive status epilepticus (CSE) (Delorenzo et al., 1998; Rudin et al., 2011), and it is the advanced condition of status epilepticus (SE) which indicates the end stage of refractory or inadequately treated convulsive SE. This particular situation was initially coined as subtle SE by Treiman et al. (1984) to describe the continuous and rhythmic phenomenon of more subtle motor twitches of the eyelid, jaw, face, trunk or extremities, which evolved from overt SE (Treiman et al., 1984). However, the term of subtle SE is ambiguous and was never used consistently in the literature. And the 2015 classification of SE from the International League Against Epilepsy (ILAE) mentioned "subtle SE" as a subset of "NCSE in coma", without specifying prior convulsive seizures or SE (Trinka et al., 2015). Some studies also used stuporous status, non-tonic–clonic status epilepticus or NCSE in coma synonymously for NCSE after CSE (Bauer and Trinka, 2010; Rossetti et al., 2007; Privitera et al., 1994).

Compared to the overt generalized convulsive SE (GCSE), NCSE after CSE has a much higher mortality rate (64.7% as one study reported in 1998) (Treiman et al., 1998), and usually is more refractory. However, few clinical investigations have specifically studied this advanced stage of CSE. We conducted a retrospective cohort study aiming to investigate the characteristics, clinical outcomes and prognostic factors for NCSE after CSE in order to provide clinical evidence for better medical intervention strategies.

Abbreviations: CIVADs, continuous intravenous anesthetic drugs; CSE, convulsive status epilepticus; GCSE, generalized convulsive status epilepticus; NCSE, nonconvulsive status epilepticus; NICU, neurological intensive care unit; PMD, proposed maximal dose; SE, status epilepticus

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2. Methods

This retrospective study was based the database of convulsive status epilepticus (CSE) patients in the neurological-intensive care unit (NICU) at Xijing hospital, China, a single tertiary academic hospital with more than 500 NICU admissions per year. Clinical trial was registered in ClinicalTrials.gov (NCT02269137). The ethics committee of the Xijing Hospital fully approved the study. All participants or their surrogate care providers gave informed consent prior to their inclusion. And the present study was conducted in accordance with Chinese laws and the Declaration of Helsinki.

2.1. Participants

From March 2008 to October 2016, consecutive patients with CSE and aged 12 years or older were reviewed. Among them, patients complicated with suspected NCSE were selected. The Salzburg EEG criteria for NCSE (Beniczky et al., 2013) were applied on them to identify the patients with definitive NCSE after CSE. Patients with cerebral anoxia were excluded due to its largely irreversible brain damage and poor outcome. Based on the operational definition of SE proposed by ILAE, CSE was defined as five minutes or more of continuous motor seizure activity or recurrent seizure activity without regaining full consciousness between episodes (Trinka et al., 2015). NCSE after CSE was defined as a type of SE, which evolved from generalized convulsive status epilepticus (GCSE) and happened in comatose patients, without motor movements or with manifestations of continuous and rhythmic phenomenon of more subtle motor twitches of the eyelid, jaw, face, trunk or extremities (Treiman et al., 1984; Meierkord and Holtkamp, 2007). Study neurologists reviewed clinical and EEG data for each patient and made the final decision about case eligibility.

2.2. Treatment protocol

All the patients received consults from the same team of neurologists regarding evaluation and diagnosis, and followed the same treatment algorithm. The management of CSE and subsequent NCSE was based on the Chinese expert consensus (Neurocritical Care Group from Chinese Medical Association's Neurology Chapter, 2014): benzodiazepines were used initially as the first-line agents; for the patients lacking of response to the first-line treatment, intravenous sodium valproate or phenobarbital sodium was adopted as the second-line therapy; if both first-line and second-line agents failed, a third-line treatment with continuous infusion of anesthetics (either midazolam or propofol) is needed. An additional second-line agent was given before the use of CIVADs. Simultaneous polytherapy of third-line agents (continuous infusion of anesthetics) is administered once continuous infusion of a single anesthetic fails to control SE (Meierkord and Holtkamp, 2007; Kälviäinen, 2007; Glauser et al., 2016; Sutter et al., 2016). The initial loading dose for midazolam is 0.2 mg/kg, for propofol is 2 mg/kg. Proposed maximal dose (PMD) of continuous infusion rate for Midazolam is 0.4 mg/kg/h, for Propofol is 10 mg/kg/h (Neurocritical Care Group from Chinese Medical Association's Neurology Chapter, 2014; Meierkord et al., 2010). Bedside video-EEG (Solar 2000 N, Solar Electronic Technologies Co., Ltd, Beijing, China) was set for every SE patient to guide the AED treatment and detect the occurrence of NCSE. An array of 20 scalp electrodes were arranged to continuously record for at least 48 h. All the EEG findings when SE was happening were recorded, and were interpreted by two board-certified epileptologists who were blind to all clinical data.

2.3. Definition of variables

The following potential predictor variables, which might have possible associations with functional outcomes of NCSE after CSE, were chosen for statistical analysis. Three of the chosen variables regarding demographics and medical history: age, gender and history of epilepsy. Two variables regarding the severity of medical illness: Status Epilepticus Severity Score (STESS) and APACHE II score. Responsible etiologies for SE were recorded and classified according to the proposal of the International League Against Epilepsy (ILAE) in 2015 (Trinka et al., 2015). The durations of CSE and subsequent NCSE were also recorded. Three variables regarding the medical intervention were chosen: use of CIVADs, use of CIVAD > 50% PMD, and use of tracheal intubation. Five variables regarding the refractoriness of NCSE after CSE were chosen: EEG seizures within two hours after the first CIVAD, EEG seizures within two hours after the dose of CIVAD raised up > 50% PMD, breakthrough seizures, withdrawal seizures, and CIVADs changed. Three variables concerned complications and hospital course: hypotension requiring pressors, pulmonary infection, and NICU length of stay. Breakthrough seizures were defined as any clinical or EEG seizures occurring under the initial CIVAD treatment after the first 6 h; withdrawal seizures were defined as any seizures occurring within 48 h after initially discontinuing or tapering the CIVAD; and CIVAD was changed when the patient was switched from the initial to a second CIVAD (monotherapy) due to poor seizure control (Claassen et al., 2002). EEG seizures were defined as any spikes, sharp waves, or sharp-and-slow wave complexes lasting for ≥ ten s at either a frequency of at least three per second or a frequency of at least one per second with clear evolution in frequency, morphology, or location (Claassen et al., 2014).

2.4. Outcome assessment

The clinical outcome was assessed three months after NICU discharge by a trained study assistant, who was blind to the clinical data, via telephone interviews. In the cases when the patient was incapable to complete the interview, the first choice for a proxy was the spouse/live-in companion. Modified Rankin Scale (mRS) was used to evaluate the outcome of NCSE after CSE: favorable outcome was defined as a mRS score < 3, while unfavorable outcome was defined as a mRS score ≧ 3.

2.5. Statistical analysis

Categorical variables were analyzed using $\chi 2$ test analysis, and continuity correction when appropriate. For continuous variables, the Shapiro-Wilk test was used to distinguish between normal and non-normal distributions. Normally distributed variables were analyzed by using the Student *t*-test and non-normally distributed variables by using the Mann-Whitney *U* test. Univariate and multivariate logistic regression were used to examine the associations between potential risk factors and short-term outcome by estimating odds ratios (ORs) and associated confidence intervals (CIs). Age, gender, use of CIVADs, use of CIVAD > 50% PMD, and variables with a significance level < 0.2 in the univariate analysis were included in the multivariable logistic regression model using a backward elimination procedure. The Two-sided p values ≦ 0.05 were considered significant. Statistical analysis was performed with SPSS version 22 software (SPSS Inc., Chicago, IL).

3. Results

Between March 2008 and October 2016, 145consecutive patients with CSE and aged 12 years or older were reviewed. Forty-eight of them (33.1%) eventually evolved into NCSE. Two patients with cerebral anoxia were excluded. At three-month follow-up, 23 (50.0%) patients attained favorable outcomes (mRS < 3), and 23 patients (50.0%) had unfavorable outcomes (mRS ≥ 3). There were sixteen patients (34.8%) died in total, and one patient died during hospitalization.

The median age of enrolled patients was 23 years old. The gender distribution was balanced (Table 1). 19.6% of all the patients had pre-existing epilepsy. Thirty-two patients (69.6%) had NCSE after CSE due to acute symptomatic etiologies (Fig. 1). Acute CNS infection was the