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The relevance of timing in nonconvulsive status epilepticus: A series of 38 cases☆

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ABSTRACT

Background: Timing in the management of nonconvulsive status epilepticus (NCSE) seems to be one of the most important modifiable prognostic factors. We aimed to determine the precise relationship between timing in NCSE management and its outcome.
Methods: We performed a cross-sectional study in which clinical data were prospectively obtained from all consecutive adults with NCSE admitted to our hospital from 2014 to 2016. Univariate and multivariable regression analyses were performed to identify clinical and timing variables associated with NCSE prognosis.
Results: Among 38 NCSE cases, 59.9% were women, and 39.5% had prior epilepsy history. The median time to treatment (TTT) initiation and the median time to assessment by a neurologist (TTN) were 5 h, and the median time to first electroencephalography assessment was 18.5 h; in the cases with out-of-hospital onset ($n = 24$), the median time to hospital (TTH) arrival was 2.8 h. The median time to NCSE control (TTC) was 16.5 h, and it positively correlated with both the TTH (Spearman's rho: 0.439) and the TTT (Spearman's rho: 0.683). In the multivariable regression analyses, the TTC was extended 1.7 h for each hour of hospital arrival delay ($p = 0.01$) and 2.7 h for each hour of treatment delay ($p < 0.001$). Recognition delay was more common in the episodes with in-hospital onset, which also had longer TTN and TTC, and increased morbidity.
Conclusions: There were pervasive delays in all phases of NCSE management. Delays in hospital arrival or treatment initiation may result in prolonged TTC. Recognition of in-hospital episodes may be more delayed, which may lead to poorer prognosis in these cases.

1. Introduction

Nonconvulsive status epilepticus (NCSE) is a time-dependent neurological emergency with high morbimortality [1]. The likelihood of irreversible neuronal injury associated with prolonged seizures depends on a wide range of factors [2,3]. Seizure duration is one of the few modifiable and most important predictors [4], and there is some evidence that a therapeutic delay can lead to refractoriness [5], longer-lasting status epilepticus (SE), and increased risk of permanent brain damage [6].

In recent times, the International League Against Epilepsy (ILAE) Task Force on Classification of Status Epilepticus has emphasized the relevance of timing when assessing a seizure. The ILAE has proposed two operational dimensions regarding the length of the seizure [7]: the time beyond it should be considered as an abnormally prolonged seizure, t1, and the time after which epileptic activity could lead to irreversible brain damage with long-term consequences, t2. For convulsive tonic–clonic SE, both time points have been estimated as 5 min and 30 min, respectively, based on animal and clinical research. Data are not fully available for NCSE, since most studies have focused on convulsive forms, but the ILAE has proposed both time points to be 10 min (t1) and >60 min (t2) for focal SE with impaired consciousness. Moreover, nonconvulsive clinical features are usually subtle and nonspecific [8],

Abbreviations: ASD, antiseizure drug; BZD, benzodiazepine; EEG, electroencephalography; HCSC, Hospital Clínico San Carlos; ICU, intensive care unit; ILAE, International League Against Epilepsy; IQR, interquartile range; LEV, levetiracetam; mRS, modified Rankin Scale; NCSE, nonconvulsive status epilepticus; SE, status epilepticus; STESS, status epilepticus severity score; TTC, time to control; TTE, time to electroencephalography; TTH, time to hospital; TTI, time to ICU; TTN, time to neurologist; TTT, time to treatment; VEEG, video-EEG; VPA, valproic acid.

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so the occurrence of NCSE may be unnoticed leading to a substantial delay in its diagnosis and therapy initiation [9]. When suspected, electroencephalography (EEG) constitutes the essential diagnostic and monitoring tool [10].

Our principal aim was to analyze the relationship between NCSE duration and its outcome. We also explored the influence of other clinical variables, as well as the differences between those NCSE starting in patients already admitted to hospital and those episodes of community onset.

2. Methods

2.1. Patients

We performed a cross-sectional study of a cohort of patients diagnosed with NCSE in Hospital Clínico San Carlos (HCSC) from 1 January 2014 to 31 May 2016. Our medical institution is an academic tertiary hospital and serves a population of 364,345 inhabitants living in an urban area of Madrid (Spain). The study protocol was approved by the HCSC Comité Ético de Investigación Clínica.

Data from all consecutive NCSE in patients aged ≥16 years admitted to any department of HCSC were prospectively recorded, excluding those NCSE associated with acute postanoxic encephalopathy. Informed consent was obtained from all patients and/or next-of-kin. Nonconvulsive status epilepticus was defined following the last ILAE description and classification of SE [7] as the occurrence of continuous seizures without prominent motor symptoms lasting more than 10 min, or the succession of nonconvulsive seizures without full recovery. Nonconvulsive status epilepticus diagnosis was usually confirmed by ictal EEG recordings. In the cases in which EEG performance was not available during the episode, we reached the diagnosis through three possible scenarios: 1) when the patient had prior history of nonconvulsive seizures with equal semiology that had been previously EEG-registered, 2) when the postictal EEG revealed focal epileptiform activity corresponding to the semiology of the SE, or 3) when the administration of intravenous antiseizure drugs (ASDs) provided an immediate and complete recovery and the postictal EEG showed focal slowing that progressively resolved during the monitoring, suggesting a postictal state [11]. All episodes were assessed by neurologists, and EEG recordings were obtained in all cases.

2.2. Clinical and outcome assessment

For each episode, we registered patient demographic data (age, sex), previous seizure history, etiology, and semiology of NCSE according to the ILAE classification [7], and the place of onset (out-of-hospital vs. in-hospital). Comorbidities were assessed using the Charlson Comorbidities Index [12], and the Status Epilepticus Severity Score (STESS) [13] was also recorded.

Time information was collected in hours and treated as a continuous variable, in a similar framework to the stroke code. The onset of symptoms (if not witnessed, the last known baseline status of the patient) was taken as time reference. Thereby, we obtained the time to hospital (TTH), the time to assessment by a neurologist (TTN), the time to treatment (TTT) initiation, the time to the first EEG (TTE), the time to intensive care unit (ICU) (TTI) admission, and the time to SE control (TTC), defined as the return of the patient to baseline functional status or the absence of EEG seizure activity. Recognition delay, defined as the absence of clinical suspicion of NCSE after at least one evaluation of the medical or paramedical team, was also registered.

The sequence of ASDs administered was enumerated, including anesthetics. Those patients who required ICU management and coma induction were also registered.

Electroencephalography exams were either prolonged video-EEG (VEEG) monitoring or routine 20-minute EEG. All cases and EEG recordings were reviewed by at least two neurologists specialized in epilepsy.

Outcome variables included TTC, mortality, and morbidity. For the latter, we calculated the difference between the baseline modified Rankin Scale (mRS) [14] and the mRS at hospital discharge and assessed the appearance of any new neurological disability at hospital discharge (cognitive or motor sequelae).

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23. Statistical significance was set at a p value < 0.05.

First, we performed an exploratory univariate analysis. Qualitative variables were summarized by their frequency distribution and compared using the Pearson χ^2 or the Fisher's exact tests. The continuous variables showed non-normal distribution. They were summarized as median and interquartile range (IQR) and compared using the Mann–Whitney U test or the Kruskal–Wallis H test. The nonparametric Spearman's rho coefficient was calculated to assess the correlation between quantitative continuous variables. Finally, multivariate regression analyses were carried out in order to identify clinical variables independently associated with the outcome variables. We performed linear regression analyses for quantitative variables (TTC) and logistic regression analyses in case of qualitative variables (mortality and morbidity). All possible confounders obtained from the univariable analysis and defined as presenting a p value < 0.1, as well as other variables known to have significant confounding effects from other studies were included in these analyses.

3. Results

3.1. Demographic and clinical variables

Between January 2014 and May 2016, 38 episodes of NCSE affecting 37 patients were included (one patient had two episodes more than one year apart). Nonconvulsive status epilepticus diagnosis was confirmed by ictal EEG in 26 episodes (68.4%). In eight cases (21.1%), it was based on the history of prior nonconvulsive seizures with equal semiology. Among the remaining four patients (10.5%), two presented focal postictal epileptiform activity harmonious with the semiology of the episode; in the other two patients, the symptoms recovered completely after the administration of intravenous ASDs, and the postictal EEG revealed focal slowing that progressively resolved during the monitoring.

The descriptive results of the global series, as well as the univariable comparisons between in-hospital and out-of-hospital episodes are presented in Table 1. Median age was 78 years (IQR: 61–83), 59.9% were women, and the median baseline mRS was 2 (IQR: 1–3). The proportion of patients with prior history of epilepsy was 39.5%.

The most frequent NCSE semiology was focal with impairment of consciousness (n = 26, 68.4%). The most common etiology group was known acute (n = 11, 28.9%), which comprised the following specific causes: cerebrovascular disease (n = 4), metabolic disturbances (n = 3), low levels of ASDs (n = 2), low levels of ASDs plus metabolic disturbances (n = 1), and cerebrovascular disease plus low levels of ASDs (n = 1). The known remote etiology group (n = 9, 23.7%) included cerebrovascular disease (n = 8) and frontotemporal dementia (n = 1). In the group of defined electroclinical syndrome (typical absence status epilepticus, n = 6, 15.8%), the specific causes were sleep deprivation (n = 3), low levels of ASDs (n = 2), and low levels of ASDs plus metabolic disturbances (n = 1). There was only one case with known progressive etiology, which was due to an underlying glioblastoma multiforme. In 11 cases (28.9%), the etiology could not be identified.

In the out-of-hospital group, median TTH was 2.8 h (IQR: 1.6–4.6). In the global series, median TTN was 5 h (IQR: 2.5–12.0), median TTT was 5 h (2.4–12.9), and median TTE was 18.5 h (5.1–27.0).