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Cyclic seizures in critically ill patients: Clinical correlates, DC recordings and outcomes

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HIGHLIGHTS

- Cyclic seizures (CS) are common in critically ill patients with acute/progressive brain injury.
- CS are often accompanied by synchronous infraslow oscillations of the EEG baseline on DC recordings.
- Understanding of this pattern may provide insight into the pathophysiology of seizure termination.

ABSTRACT

Objective: To describe EEG and clinical correlates, DC recordings and prognostic significance of cyclic seizures (CS).
Methods: We reviewed our prospective continuous EEG database to identify patients with CS, controls with non-cyclic status epilepticus (SE) and controls without seizure matched for age and etiology. EEG was reviewed with DC settings.
Results: 39/260 (15%) patients with electrographic seizures presented with CS. These patients were older (62 vs. 54 years; $p = 0.04$) and more often had acute or progressive brain injury (77% vs. 52%; $p = 0.03$) than patients with non-cyclic SE and had a lower level of consciousness, were more severely ill, than matched controls. CS almost always had focal onset, often from posterior regions. Patients with CS trended towards worse prognosis. When available (12 patients), DC recordings showed an infraslow cyclic oscillation of EEG baseline synchronized to the seizures in all cases.
Conclusions: CS occur mostly in older patients with acute or progressive brain injury, are more likely to be associated with poor outcome than patients with other forms of nonconvulsive SE, and are accompanied by synchronous oscillations of the EEG baseline on DC recordings.
Significance: CS are a common form of non-convulsive status epilepticus in critically ill patients and provide further insights into the relationship between infraslow activity and seizures; further study on this relationship may shed light on the mechanisms of seizure initiation and termination.

1. Introduction

Seizures are detected in 10–45% of critically ill patients undergoing continuous electroencephalographic (cEEG) monitoring (Carrera et al., 2008; Claassen et al., 2004; Kurtz et al., 2014; Oddo et al., 2009). Approximately half of these meet the criteria for status epilepticus (SE) (Claassen et al., 2004). SE can present as continuous ictal activity or as recurrent seizures without recovery of neurological baseline. Cyclic seizures (CS) have recently been described in critically ill patients (Friedman et al., 2008). They are characterized by the frequent recurrence of seizures at nearly regular intervals. The pathophysiological differences between these two types of

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seizures (continuous and prolonged vs. cyclic) may be related to the mechanisms responsible for seizure termination (Caspers and Speckmann, 1972) but are not completely understood. Similarly, the determinants, clinical correlates, and prognostic significance of cyclic seizures are largely unknown.

The aims of this study were to identify the clinical characteristics, EEG features and the outcome of patients with CS, compared to those with non-cyclic electrographic status epilepticus (SE), and to determine their relationship with very low frequency oscillations.

2. Methods

2.1. Study population

We maintain a prospective database of all patients undergoing cEEG monitoring in Yale-New Haven Hospital. Using this database, we identified all patients with electrographic seizures between May 2011 and May 2014. We reviewed each patient's EEG to identify those with CS, defined as a recurrence of seizures at nearly regular intervals with a frequency of greater than >3/h for at least one hour. A first control group consisted of all consecutive patients, during the same time period, with continuous and prolonged electrographic seizure activity consistent with electrographic SE (seizure duration >30 min). Patients with other patterns that met SE criteria were not included (e.g., recurrent seizures not fulfilling CS definition). A second control group consisted of patients during the same study period without seizures, matched for age (±10 years) and etiology with a 1:1 ratio.

2.2. EEG recordings and review

EEGs were recorded using 21 silver chloride electrodes placed according to the International 10–20 System with clinical amplifiers (Compumedics, Charlotte, NC, USA; Natus Medical, Pleasanton, CA, USA). One of these clinical systems (Compumedics) uses a true DC amplifier. The other has a 0.016 Hz hardware highpass filter. For the purpose of reviewing low frequency activity, EEG recordings acquired on the DC-coupled amplifier were displayed in a referential montage to the average. Figures were constructed using the time–frequency transformation (Fourier transform, 1–30 Hz, 2-s window, 50% overlap) of the EEG signal from the derivation where the ictal pattern was the most visible, using commercial software. Filtered raw EEG signals (1–70 Hz and DC-70 Hz) from the same derivation were analyzed.

2.3. EEG variables

We recorded seizure frequency (defined by the number of seizures per hour in the most frequent hour), duration, location of seizure onset and associated EEG findings.

We recorded the polarity and measured the peak-to-trough amplitude of fluctuations (defined in the DC recordings, displaying 500 s at a time) of the EEG baseline associated with seizures, as well as the latency from the trough of the fluctuation (maximum positivity, defined in the DC recordings, displaying 500 s at a time) to the seizure onset (defined in the 1–70 Hz filtered recording, displaying 10 s at a time) using the ruler built in the EEG review software. We quantified the reproducibility of these amplitude and latency measures within each patient with the coefficient of variation.

2.4. Clinical variables

We reviewed medical charts to collect data on demographics, etiology, treatment and outcome at hospital discharge. Etiology was divided into three categories: (1) acute or progressive brain injury, which included patients with acute stroke, anoxia and acute traumatic brain injury, hemorrhage, posterior reversible encephalopathy syndrome (PRES), encephalitis, new-onset refractory status epilepticus (NORSE), primary malignant brain tumors or metastases; (2) remote brain injury and epilepsy consisting of patients with a history of epilepsy and/or previous stroke, traumatic brain injury, neurosurgery or sequelae of encephalitis; and (3) toxic and metabolic encephalopathy, comprising patients with seizures secondary to intoxication, substance abuse, kidney or liver failure, or electrolyte imbalance without any known acute brain injury and without prior epilepsy.

Our primary and secondary outcome measures were functional status at discharge measured by the Glasgow Outcome Scale (GOS) and mortality during the hospital stay, respectively. Severity of critical illness was assessed with the Sequential Organ Failure Assessment (SOFA) score. Clinical variables included the presence of clinical seizures prior to monitoring, the presence of a clinical correlate to seizures during monitoring, need for mechanical ventilation, number of antiepileptic drugs and anesthetics required to treat seizures.

2.5. Statistical analysis

Variables were analyzed using the Fisher's exact test or the Mann–Whitney test, as appropriate. Statistical analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics are presented in Table 1.

Of the 1910 patients monitored during the study interval, we identified 260 (14%) patients with electrographic seizures. Of those, 39 (15%) patients had CS and 29 (11%) had continuous electrographic SE (for at least 30 min). When compared to patients with continuous SE, those with CS were older (median age 62 vs. 54, $p = 0.04$) and had a trend to lower score on the Glasgow Coma Scale (median of 9 vs. 11, $p = 0.08$). There was no difference in gender, occurrence of clinical seizures before monitoring, presence of a clinical correlate to seizures (seen in <1/3 of both groups), need for mechanical ventilation, total number of antiepileptic drugs or anesthetics used for treatment or admission SOFA score between groups. When compared to patients without seizure, patients with CS had a lower level of consciousness, were more severely ill, received mechanical ventilation more often, and received more anti-epileptic drugs.

3.2. Etiology

Data regarding etiology is presented in Table 2.

Cyclic seizure patients were more likely to have an acute or progressive brain injury (77% vs. 52%, $p = 0.03$). Encephalitis, hemorrhage and brain metastasis were the main causes in CS group, whereas PRES and primary brain tumors were similar in both groups.

3.3. EEG characteristics

EEG findings are presented in Table 3. CS were more often of focal onset than non-cyclic SE (35/39 [90%] vs. 11/23 [48%], $p = 0.004$), with almost half of CS (49%) originating from posterior regions.