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Clinical correlation and prognostic implication of periodic EEG patterns: A cohort study

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ABSTRACT

Objective: Despite increasing amounts of research on periodic discharges (PDs), large clinical studies regarding their prognostic value are lacking. The aim of the current study was to evaluate the clinical implications and prognostic value of PDs.
Methods: In this single-center retrospective cohort study, we included patients who underwent electroencephalographic recording either during hospitalization or from our outpatient clinics. Demographic data, associated seizure events, use of antiepileptic drugs, and outcomes at discharge were analyzed. Multivariate logistic regression analysis was used to evaluate associations between clinical factors and functional outcomes.
Results: Four hundred and twenty patients were enrolled during a 17-year period, with a mean age of 66 years. The main etiologies included systemic infection (24%), anoxia (15%), and ischemic stroke (12%). Recent seizures were identified in 283 patients (67%), of whom 84 (30%) had status epilepticus. One hundred and fifty-four patients (37%) did not survive to hospital discharge. In multivariate analysis, old age (>65 years; OR = 2.55; 95% CI = 1.57–4.16; $P < 0.001$) was the strongest predictor of mortality, followed by systemic infection, anoxic encephalopathy, cefepime encephalopathy, and the occurrence of status epilepticus. Conversely, the use of antiepileptic drugs was negatively associated with mortality (OR = 0.50; 95% CI = 0.28–0.87; $P = 0.02$).
Conclusions: PDs were associated with high rates of comorbidities and recent seizures, while the use of antiepileptic drugs was associated with a lower rate of mortality.

1. Introduction

Periodic electroencephalographic (EEG) activity is common in critically ill neurological patients as highlighted in the revised version of the Standardized Critical Care EEG Terminology (SCCET) proposed by the American Clinical Neurophysiology Society (ACNS). Due to its equivocal nature, the use of 'epileptiform' is no longer recommended, and the term 'periodic discharges' (PDs) has been suggested to be more appropriate (Hirsch et al., 2013).

Despite increasing amounts of research on PDs, their prognostic value and clinical implication remain controversial, and large studies on these issues are lacking. One case-control study reported a decrease in Modified Rankin Scale score in 62% of patients with PDs, but a mortality rate of only 5% (Sainju et al., 2015). In contrast, a higher mortality rate of 34%–41% has been reported in

Abbreviations: PD, periodic discharge; EEG, electroencephalographic; AED, antiepileptic drug; LPD, lateralized periodic discharge; BIPD, bilateral independent periodic discharge; GPD, generalized periodic discharge; GTCS, generalized tonic-clonic seizure; SPS, simple partial seizure; CPS, complex partial seizure.

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long-term follow-up studies (Kate et al., 2012; Walsh and Brenner, 1987). Some authors have suggested that PDs are initial ictal patterns (Garzon et al., 2001) and that they are highly associated (50% to 92% of cases) with the occurrence of clinical seizures (Baykan et al., 2000; Fitzpatrick and Lowry, 2007; Garcia-Morales et al., 2002; Orta et al., 2009; Sainju et al., 2015; Walsh and Brenner, 1987). Other authors have suggested that PDs are simply markers of non-specific brain injury that are often accompanied by underlying comorbidities, and that clinicians should treat the underlying infection or inflammatory condition without the use of antiepileptic drugs (AEDs) (Maingueneau et al., 1999; Nakamura et al., 2002; Shimada et al., 1989). Therefore, whether PDs should be treated with AEDs remains unclear. The aim of the current retrospective cohort study was to evaluate the characteristics and prognostic factors regarding different PD patterns and the potential influence of AED treatment.

2. Methods

2.1. Study subjects and EEG data collection

We searched our EEG database for all 20-min routine EEG recordings performed during a 17-year period (January 1, 1999–December 31, 2015) using the following keywords: repetitive discharge, periodic discharge, periodic epileptiform discharge, lateralized periodic discharge, periodic lateralized epileptiform discharge, bilateral independent periodic discharge, bilateral independent periodic lateralized epileptiform discharge, generalized periodic discharge, generalized periodic epileptiform discharge and their abbreviations PD, PED, LPD, PLED, BIPD, BIPLED, GPD, and GPED. The EEG recordings were obtained using the 10–20 International System of electrode placement. For the purposes of this study, we further categorized the PDs as LPDs, BIPDs, or GPDs. LPDs were defined as unilateral and bilateral synchronous but asymmetric, focal or regional periodic patterns. BIPDs were defined as bilateral independent, asynchronous, and lateralized periodic patterns. GPDs were defined as bilateral, bisynchronous and symmetric periodic patterns. When a patient had more than one EEG recording available, we only analyzed the first that showed evidence of a PD. This study was approved by the Institutional Review Board of Chang Gung Medical Foundation (201600678B0).

2.2. Clinical data collection

Historical clinical data were obtained by medical record review and included age, gender, etiology, occurrence and type of recent clinical seizures, and the administration of AEDs. Recent clinical seizures were defined as at least one clinical seizure that occurred within 1 week after the appearance of PDs.

A retrospective chart review of neuroimaging findings and other investigations was conducted for each patient to determine the primary underlying etiology. The etiologies of the patients' diseases related to the time of the EEG recording included stroke (ischemic or hemorrhagic), anoxic encephalopathy, central nervous system (CNS) infection, systemic infection requiring treatment with antibiotics, Creutzfeldt-Jakob disease, metabolic derangements (any of the following: liver enzymes >twice the normal upper limit, elevated ammonia level, creatinine level >1.5 mg/dL, hemoglobin <8.0 mg/dL, sodium level <125 or >150 mEq/L), brain tumor, trauma, and carbapenem-related causes. Cefepime encephalopathy was considered to be a separate entity from drug-related causes due to its distinct pathophysiology in critically ill patients.

The patients' functional outcomes were assessed at discharge or at an outpatient follow-up visit within 1 month after the diagnostic EEG. The level of functional outcome was classified as being independent (the patients could carry out their normal activities of daily living), dependent (the patients could not carry on without assistance), and death.

2.3. Statistical analysis

All statistical analyses were performed using SPSS v.22.0 (SPSS Inc., Chicago, IL, USA). Descriptive summaries were reported as mean ± standard deviation for numerical variables, and as number (percentage) for categorical variables. The χ^2 test was used for statistical analysis of variables. Conditional univariate and multivariate logistic regression models were used to analyze associations between functional outcomes and predictive factors. The independent variables used in the univariate logistic regression model were chosen based on the characteristic data, and included the three patterns of PDs, gender, age, the use of AEDs, presence of clinical seizure, the five most common etiologies, and chronic epilepsy. Variables with a P value ≤ 0.1 in the univariate analysis were considered to be candidate variables for the multivariate regression models. The magnitude of association was reported as odds ratio (OR) and corresponding 95% confidence interval (CI). The predictive ability of the final model was quantified using area under the receiver operating characteristic curve analysis. A P value <0.05 was defined as being statistically significant.

3. Results

3.1. Demographic data

From 1999 to 2015, we performed 15942 EEG recordings in inpatients and outpatients. We initially identified 519 recordings in the database using the keyword search, representing a prevalence rate of 3.2% among all inpatient and outpatient EEG recordings. Of these, 99 duplicate studies were excluded. Thus, 420 patients in whom PDs were reported on at least one available EEG were enrolled in this study. The mean age of the patients was 66 ± 18.4 years (range; 6–99 years), and 205 (48.8%) were male.

Detailed etiologies, clinical seizure patterns, and functional outcomes of the patients are shown in Fig. 1. Systemic infection was the leading etiology of PDs (24%), followed by anoxic encephalopathy (15%) and ischemic stroke (12%). Other etiologies included metabolic disorders (8%), cefepime encephalopathy (8%), CNS infection (7%), Creutzfeldt-Jakob disease (5%), brain tumors (5%), hemorrhagic stroke (5%), trauma (4%), and carbapenem-induced encephalopathy (0.2%). We were unable to identify any acute etiology in 30 patients (7%). Of these patients, 22 (5%) had chronic epilepsy and the etiology was undetermined due to inadequate retrospective data in the other eight.

A total of 283 patients (67%) had at least one clinical seizure within 1 week after the appearance of PDs. The most common seizure pattern was generalized tonic-clonic seizures (GTCS; 35%), followed by simple partial seizures (SPS; 26%) and complex partial seizures (CPS; 9%). Of note, 84 patients (30%) had status epilepticus during the course of their illness.

The overall mortality rate during hospital admission was 37%, and the mean duration from EEG onset of PDs to mortality in these patients was 30 days (median: 17 days; range, 1–180 days). Of the remaining patients, 192 (46%) were classified as being dependent with regards to their activities of daily living, compared to only 74 (17%) who were classified as being independent.

3.2. Distribution of different PD patterns and clinical correlations

The distribution of different PD patterns and associated clinical characteristics are shown in Table 1. Approximately half of the patients had LPDs (191, 45%), compared to 100 (24%) with