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Clinical outcomes in patients with generalized periodic discharges

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ABSTRACT

Purpose: Generalized periodic discharges (GPDs) are frequently identified in the EEGs of hospitalized patients but their prognostic significance remains unclear. We retrospectively reviewed clinical data in patients with GPDs to elucidate factors associated with in-hospital mortality.
Method: We reviewed data from inpatients at three different hospitals affiliated with our institution in whom GPDs were reported on routine EEGs by fellowship-trained electroencephalographers during the years 2010–2012. Cox regression was used to determine statistical association between in-hospital death and demographics, medical comorbidities, neurological and neuroimaging abnormalities and antiepileptic drug use.
Results: We identified 113 patients with GPDs. The mean age was 70.4 years and 70 (61.9%) were women. There were 60 inpatient deaths (53.1%). The variables significantly associated with in-hospital mortality were dementia, poor mental status at the time of the EEG, chronic focal abnormalities on neuroimaging, cardiac arrest and chronic obstructive pulmonary disease (COPD).
Conclusion: Dementia, poor mental status during EEG, chronic focal abnormalities on neuroimaging, cardiac arrest and COPD are independently associated with increased in-hospital mortality in patients with GPDs ($P < 0.05$).

1. Introduction

Generalized periodic discharges (GPDs) are a distinct type of periodic pattern observed in the electroencephalogram (EEG) of patients with a variety of different conditions such as hypoxic-ischemic brain injury, intracranial hemorrhage, sepsis, metabolic dysfunction, certain infections such as Creutzfeldt–Jacob disease and subacute sclerosing pan-encephalitis and toxicity from medications such as cefepime, lithium, ifosfamide and baclofen [1–7]. They are believed to be caused by the disruption of thalamocortical pathways and may have a subcortical origin [3]. GPDs were first described in the 1950s [8]. At present, they are more frequently encountered due to the increasing use of continuous EEG monitoring [9]. GPDs are defined as any synchronous and relatively symmetric repetitive discharges with relatively uniform morphology and duration, with a definable and quantifiable interdischarge interval and recurrence of the wave form at nearly regular intervals [10]. We believe in the near future their recognition will only increase because of modern trends such as the increasing use of continuous EEG monitoring, increasing severity of underlying illnesses being managed in modern ICUs, and an aging population. GPDs are traditionally believed to be indicative of poor prognosis, but only a limited number of small outcome studies are available [2,3,9]. While prior studies found GPDs to be associated with poor outcomes [11–13], a recent matched case-control study of 200 patients with GPDs using multivariate regression did not find a direct independent association between GPDs and increased mortality when compared to matched controls. However, this study did find that GPDs were strongly associated with non-convulsive status epilepticus (NCSE), which itself was independently associated with increased mortality [9]. To our knowledge, no prospective or dedicated survival analyses describing both the outcome (mortality) and the follow-up period have been published. Thus, in spite of their increasing recognition, the true prognostic significance of GPDs remains unclear [9].

In a previous case-control study with 200 patients with GPDs matched to 200 controls [9], multivariate analysis found that underlying medical illness such as sepsis, cardiac arrest and coma

Abbreviations: GPDs, generalized periodic discharges; EEG, electroencephalogram; COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRI, magnetic resonance imaging; EMR, electronic medical record; LFT, liver function test; AED, antiepileptic drugs; PEG, percutaneous endoscopic gastrostomy; NCSE, non-convulsive status epilepticus; ICU, intensive care unit.

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were independently associated with increased in-hospital mortality in GPDs patients along with NCSE. That study demonstrates the role of etiology and severity of the primary disease process in determining in-hospital outcomes in patients with GPDs. GPD patients with a history of multiple medical problems had poor outcomes [9]. In our study we performed a survival analysis on 113 patients with GPDs, to assess the hypothesis that certain medical, neurological and neuroimaging abnormalities are associated with increased in-hospital mortality in patients with GPDs.

2. Methods

We reviewed data from adult inpatients (>18 years old) at three different hospital sites affiliated with our institution (the Moses, Weiler and Wakefield divisions of Montefiore Medical Center, University Hospitals of Albert Einstein College of Medicine, Bronx, New York) in whom GPDs were interpreted by fellowship trained electroencephalographers during a three year period from 2010 to 2012. The EEG reports were reviewed without reexamining the tracings. The study was approved by the Montefiore/Einstein Institutional Review Board. To be included in the study a patient had to have at least one routine EEG with GPDs during that hospital admission.

Routine EEGs were recorded using 21 electrodes placed according to the International 10–20 system [14]. All patients included in this study had received neuroimaging in the form of a computed tomography (CT) scan during the hospitalization in which GPDs were recorded. The patient's electronic medical record was reviewed for age, gender, body weight (kg), the presence of hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cancer (of any type), liver dysfunction (abnormal LFTs), renal dysfunction (creatinine >1.3), hemodialysis, dementia, COPD, sepsis, any seizures (clinical or electrographic), cardiac arrest (which includes cardiorespiratory arrest), the patient's mental status at the time of the EEG recording, neuroimaging abnormalities, antiepileptic drug (AED) use and the length of hospitalization (days). Mental status at the time of the EEG was classified into three stages of severity (MS-1, MS-2 and MS-3). The description of the patient's mental status as recorded by the primary teams in their progress notes on the day of the EEG study was used to determine the stage. MS-1 included patients who were described as being awake, alert, attentive, oriented or following requests. MS-2 included patients who were described as being confused, disoriented, inattentive, delirious, or stuporous. MS-3 included patients who were described as comatose or unresponsive. Since this classification was retrospective, only three distinct sub-groups were chosen to minimize selection bias. AEDs included continuous or intermittent leviracetam, phenytoin, valproic acid, lacosamide, benzodiazepines, barbiturates, and propofol. The classification of "any seizure" was used for any clinical event suspected to be a seizure by the primary teams or electrographic seizures recorded during the EEG. No separate category was made for status epilepticus. The only EEG features included in the analysis were the presence of GPDs and whether seizures were present.

Any patients with acute ischemic infarction, acute intracranial hemorrhage or acute hypoxic-ischemic injury on neuroimaging were classified as "acute neuroimaging abnormalities" regardless of the presence of coexisting chronic findings. Patients with only findings of old infarcts or mass lesions were classified as "chronic focal neuroimaging abnormalities". Patients without such acute or chronic focal neuroimaging abnormalities but a radiological report of small vessel disease or "white matter changes" were characterized as having leukoaraiosis. We did not quantify the white matter disease or other neuroimaging abnormalities based on severity.

For data analysis commercially available statistical software (SPSS 24.0, Chicago, IL) was used. Cox-regression (multivariate survival analysis) was used to determine statistical associations between in-hospital mortality (outcome) and the clinical predictors as listed above. Length of follow-up was the duration of hospitalization. P values <0.05 were considered as statistically significant. Discharge records were reviewed for a description of the patient's mental status at the time of discharge (similarly classified as MS-1, MS-2, or MS-3), post-discharge site of care, and the presence of either a tracheostomy or a percutaneous endoscopic gastrostomy (PEG). This study did not include post-discharge follow-up.

3. Results

A total of 113 patients were identified as having GPDs on a routine EEG during their inpatient hospitalization. Their mean age was 70.4 years and 70 (61.9%) were women. Overall there were 60 in-hospital deaths (53.1%) and 53 patients were discharged. The average length of hospitalization was slightly higher in those discharged compared to those who died (mean 40.7 days vs. 36.4 days).

A comparative descriptive analysis of patients who were discharged and those who suffered in-hospital deaths is presented in Table 1. Both groups were comparable with respect to age, gender, body weight, medical comorbidities such as diabetes, hypertension, cancer, liver dysfunction and neurological comorbidities such as dementia and seizures, exhibiting only minor differences as shown in Table 1. Certain medical conditions such as coronary artery disease, congestive heart failure, renal dysfunction and sepsis were more prevalent in those who suffered in-hospital deaths. The overall number of patients in the sample with cardiac arrest was 29 (25.6%) of whom 21 (72.4%) died in the hospital. The mental status during the EEG of a majority of those who died in-hospital was classified as MS-3 (comatose or unresponsive). About 45.0% of patients had either an acute or a chronic focal abnormality on neuroimaging, excluding those with only leukoaraiosis. Acute abnormalities such as acute infarctions, hemorrhage or hypoxic-ischemic injury were the most common neuroimaging abnormalities, found in 37 patients (32.7%). Chronic focal abnormalities such as an old stroke or mass lesion were present in 14 patients (12.3%). Leukoaraiosis was reported in 21 patients (18.5%). The neuroimaging studies were interpreted as normal in 41 (36.2%) of the patients. Further details of the neuroimaging findings are shown in Table 2.

The results of survival analysis using Cox regression modeling are shown in Table 1. We found that a poor mental status (MS-2 and MS-3), dementia, chronic focal abnormalities on neuroimaging, cardiac arrest and COPD were independently associated with increased in-hospital mortality ($P < 0.05$). Among the 29 patients with cardiac arrest there were 22 deaths (75.8% mortality) and among the 84 without cardiac arrest there were 38 deaths (45.2% mortality). The presence of COPD was not independently associated with cardiac arrest (binary logistic regression model, $P < 0.962$).

Factors such as seizures, acute neuroimaging abnormalities, age, gender, body weight and medical comorbidities (hypertension, diabetes, coronary artery disease, congestive heart failure, cancer, sepsis, liver or renal dysfunction and hemodialysis use) were not significantly associated with increased in-hospital mortality in our sample of patients with GPDs. Of the 86 patients with GPDs who were on anti-epileptic medications, 48 (55.0%) died. Of the 27 patients not on anti-epileptic medications, 12 died (44.0%). There was no significant association between AED use and in-hospital mortality ($P = 0.801$).