Generalized periodic discharges in the critically ill

A case-control study of 200 patients

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ABSTRACT

Objective: Generalized periodic discharges are increasingly recognized on continuous EEG monitoring, but their relationship to seizures and prognosis remains unclear.

Methods: All adults with generalized periodic discharges from 1996 to 2006 were matched 1:1 to controls by age, etiology, and level of consciousness. Overall, 200 patients with generalized periodic discharges were matched to 200 controls.

Results: Mean age was 66 years (range 18–96); 56% were comatose. Presenting illnesses included acute brain injury (44%), acute systemic illness (38%), cardiac arrest (15%), and epilepsy (3%). A total of 46% of patients with generalized periodic discharges had a seizure during their hospital stay (almost half were focal), vs 34% of controls ($p = 0.014$). Convulsive seizures were seen in a third of both groups. A total of 27% of patients with generalized periodic discharges had nonconvulsive seizures, vs 8% of controls ($p < 0.001$); 22% of patients with generalized periodic discharges had nonconvulsive status epilepticus, vs 7% of controls ($p < 0.001$). In both groups, approximately half died or were in a vegetative state, one-third had severe disability, and one-fifth had moderate to no disability. Excluding cardiac arrest patients, generalized periodic discharges were associated with increased mortality on univariate analysis (36.8% vs 26.9%; $p = 0.049$). Multivariate predictors of worse outcome were cardiac arrest, coma, nonconvulsive status epilepticus, and sepsis, but not generalized periodic discharges.

Conclusion: Generalized periodic discharges were strongly associated with nonconvulsive seizures and nonconvulsive status epilepticus. While nonconvulsive status epilepticus was independently associated with worse outcome, generalized periodic discharges were not after matching for age, etiology, and level of consciousness. *Neurology*® 2012;79:1951–1960

GLOSSARY

AED = antiepileptic drug; **BIPLED** = bilateral independent periodic discharge; **CA** = cardiac arrest; **cEEG** = continuous digital EEG monitoring; **cIV** = continuous IV; **CJD** = Creutzfeldt-Jakob disease; **CSE** = convulsive status epilepticus; **CSz** = convulsive; **ED** = emergency department; **GOS** = Glasgow Outcome Scale; **GPD** = generalized periodic discharge; **ICU** = intensive care unit; **NCSE** = nonconvulsive status epilepticus; **NCSz** = nonconvulsive; **PLED** = periodic lateralized epileptiform discharge; **SE** = status epilepticus; **SIRPID** = stimulus-induced rhythmic, periodic, or ictal discharge; **SSPE** = subacute sclerosing panencephalitis; **TW** = triphasic-appearing wave.

Although periodic epileptiform discharges have been recognized for over half a century,[1,2] their underlying pathophysiology and clinical significance remain unclear. Reports have correlated periodic epileptiform discharges with seizures,[3] and poor outcome in patients with status epilepticus,[4] intracerebral hemorrhage,[5] and subarachnoid hemorrhage.[6] Lateralized periodic epileptiform discharges (also known as periodic lateralized epileptiform discharges [PLEDs]) have established associations with destructive focal lesions, usually acute, and seizures.[7] Generalized periodic discharges (GPDs) may result from thalamocortical pathway disruption associated with diffuse or multifocal cerebral dysfunction, or even systemic disease, but whether GPDs

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Supplemental data at www.neurology.org

Supplemental Data

From the Comprehensive Epilepsy Center (B.F.), Division of Critical Care Neurology (J.C.), Neurological Institute of New York, Columbia University, New York; Hotel-Dieu De France (K.A.K.), Universite Saint-Joseph, Lebanon; Department of Medicine (Division of Neurology) (J.J.), University of Alberta, Edmonton, Canada; Cognitive Neuroscience Division (D.M.A.), New York State Psychiatric Institute, New York; Neurological Associates, Inc. (J.W.), Henrico, VA; Intraoperative Neurophysiologic Monitoring (R.G.E.), Hospital for Special Surgery, New York, NY; and Division of Epilepsy/EEG (L.J.H.), Yale University School of Medicine, New Haven, CT.

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cause additional brain injury or if they are surrogate markers for the extent of brain injury remains unknown.

Prior investigations of GPDs consist of 2 small, unmatched case series[8,9] and subgroup populations in 2 additional case series.[10,11] In the last decade, increased awareness of nonconvulsive seizures and improved technology have led to increasing use of prolonged continuous digital EEG monitoring (cEEG) in the hospital setting, particularly in the intensive care unit (ICU). We performed a nested case-control study matching 200 inpatients undergoing cEEG with GPDs to controls. Our hypothesis was that GPDs would be associated with seizures, especially nonconvulsive ones, and worse outcome, independent of age, etiology, and level of consciousness.

METHODS

Patients. GPDs were defined as any pattern of synchronous (bihemispheric), repetitive discharges of similar morphology with quantifiable interdischarge interval recurring at nearly regular intervals.[10,12] Patients with isolated burst-suppression were excluded. Generalized periodic triphasic waves were included. Reports of cEEG recordings from inpatients >18 years old at the Columbia campus of the New York–Presbyterian Hospital from 1996 to 2006 were queried for "GPD," "GPED," "generalized periodic," or "triphasic."

After establishing the GPD cohort, all other patients monitored during the same period were screened. Based on 3 variables (age, category of presenting illness, and level of consciousness), a matched pair was identified for each GPD patient on a 1:1 basis.

Where possible, age was matched ±5 years (n = 312). Particularly for those monitored <2004, when study volume was much lower, age was matched ±20 years (n = 88). Level of consciousness upon cEEG initiation was categorized into 4 groups: awake; alert but abnormal; lethargic or stuporous; and comatose.[3] Categories of presenting illness were stratified as primary epilepsy, acute systemic illness, acute brain injury, and cardiac arrest (CA). Table 1 lists specific diagnoses. Patients were matched based on category of presenting illness.

Standard protocol approvals, registrations, and patient consents. This study was approved by the Columbia University institutional review board.

Data acquisition. Medical records were reviewed for gender; dates of hospitalization, ICU admission, transfer, and discharge; patient location at the time of cEEG; medical history; clinical seizures at admission, in the emergency department (ED), or during hospitalization prior to cEEG; treatment with continuous IV (cIV) or intermittent (PO or IV) antiepileptic drugs (AEDs); and the Glasgow Outcome Scale score (GOS)[13] upon discharge. cIV AEDs included midazolam, pentobarbital, and propofol.

cEEG was recorded using 21 electrodes placed according to the International 10–20 System by certified EEG technologists[3] and interpreted by board-certified electroencephalographers. Posterior dominant rhythm, reactivity, variability, stage N2 sleep transients, epileptiform discharges, periodic epileptiform discharges (PLEDs, GPDs, bilateral independent periodic discharges [BIPLEDs], and stimulus-induced rhythmic, periodic, or ictal discharges [SIRPIDs]), and rhythmic δ patterns were noted at any time and during each of the first 3 24-hour periods of the recording. Seizures were documented similarly, including time to first recorded seizure. Seizures were reported as convulsive (CSz) or nonconvulsive (NCSz). CSz were considered if any of the following were described: "tonic-clonic," "clonic," "twitching," "jerking," and other synonyms. NCSz were considered even if subtle movements (facial twitching, eye deviation) were observed on video, but not noted clinically. In general, electrographic patterns were only considered ictal if they showed clear evolution in frequency, location, or morphology. Status epilepticus (SE) was reported as convulsive (CSE) for CSz lasting longer than 5 minutes or if 2 or more occurred without a return to baseline in between, or nonconvulsive (NCSE) for continuous ictal-appearing patterns lasting >30 minutes or ictal patterns present more than 50% of 1 hour of EEG.

Data analysis. Data were analyzed using commercially available statistical software (SPSS 17.0, Chicago, IL). Univariate analysis was conducted using χ^2 or Fisher exact test for dichotomized and categorical variables, Mann-Whitney U test for nonnormally distributed continuous and ordinal variables, and Student t test for normally distributed continuous variables. All outcomes were dichotomized, either to death or to poor outcome, defined as GOS 4–5. Multivariate logistic regression models were used for associations with poor outcome. p Values < 0.05 were considered significant.

RESULTS

Overall, 200 patients were identified as having GPDs (figure 1). From 2003–2006, 138/3,064 (4.5%) patients undergoing cEEG had GPDs (table 1). Patients with GPDs were more often female (60.0% vs 46.0% of controls; $p = 0.005$). The most common etiologies were toxic-metabolic encephalopathy or sepsis, with stroke as the next most common. Among acute brain injuries, specific diagnoses were well matched except for ICH, which was less common in the GPD group (5.5% vs 11.0% in controls; $p = 0.046$).

GPDs were highly correlated with NCSz and NCSE (figure 2, A and B): 26.5% of patients with GPDs had NCSz vs 7.5% of controls ($p < 0.001$); 21.5% had NCSE vs 6.5% of controls ($p < 0.001$). GPDs were not associated with convulsive seizures or convulsive SE. In both groups, one-third of patients had CSz at some point, and <6% during cEEG. Overall, 46.0% of patients with GPDs had some type of seizure at some point, vs 34.0% in controls ($p = 0.14$).

GPD patients experienced focal seizures (46.4%) and generalized seizures (66.1%), whereas controls experienced primarily focal seizures (94.1%; $p = 0.002$). In the 92 patients with GPDs and seizures, a CSz was seen before detection of GPDs in 48.9% and a NCSz was documented before GPDs in 8.7%. A total of 39 patients had seizures after development of GPDs; 10 of these had no seizures before developing GPDs.

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Table 1 Patient demographics, n (%)

Characteristics	Patients with GPD (n = 200)	Control patients (n = 200)	Total	p[a]
Age, y (range)	66 (18–96)	66 (19–95)	66 (18–96)	
Female	120 (60)	92 (46)	212 (53)	0.005
Past medical history				
Major medical problems[b]	152 (76)	139 (69.5)	291 (72.8)	
Stroke	32 (16)	35 (17.5)	67 (16.8)	
Prior neurosurgery	14 (7)	10 (5)	24 (6)	
Single seizure	13 (6.5)	11 (5.5)	24 (6)	
Brain tumor	12 (6)	8 (4)	20 (5)	
Epilepsy	6 (3)	8 (4)	14 (3.5)	
Location				
Ward	21 (10.5)	29 (14.5)	50 (12.5)	
Neuro ICU	85 (42.5)	85 (42.5)	170 (42.5)	
Other ICU	93 (46.5)	86 (43)	179 (44.8)	
Category of presenting illness				
Acute brain injury	88 (44)	88 (44)	176 (44)	
Ischemic stroke	30 (15)	38 (19)	68 (17)	
Acute hydrocephalus or EVD	29 (14.5)	33 (16.5)	62 (15.5)	
IVH	22 (11)	35 (17.5)	57 (14.3)	
SAH	25 (12.5)	31 (15.5)	56 (14)	
CNS infection	27 (14)	16 (8)	43 (10.8)	
ICH	11 (5.5)	22 (11)	33 (8.3)	0.046
CNS tumor	11 (5.5)	8 (4)	19 (4.8)	
SDH	10 (5)	8 (4)	18 (4.5)	
TBI	6 (3)	7 (3.5)	13 (3.3)	
Acute systemic illness	76 (38)	76 (38)	152 (38)	
Toxic-metabolic[c]	111 (55.5)	118 (59)	229 (57.3)	
Sepsis	70 (35)	72 (36)	142 (35.5)	
Alcohol use	3 (1.5)	11 (5.5)	14 (3.5)	
Cardiac arrest	29 (14.5)	29 (14.5)	58 (14.5)	
Epilepsy	7 (3.5)	7 (3.5)	14 (3.5)	
Level of consciousness at time of cEEG				
Awake	1 (0.5)	1 (0.5)	2 (0.5)	
Abnormal but alert	16 (8)	18 (9)	34 (8.5)	
Lethargic or stuporous	71 (35.5)	73 (36.5)	144 (36)	
Coma	112 (56)	108 (54)	220 (55)	

Abbreviations: cEEG = continuous EEG monitoring; EVD = external ventricular drain; GPD = generalized periodic discharge; ICH = intracerebral hemorrhage; ICU = intensive care unit; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage; TBI = traumatic brain injury.

[a] A p value < 0.05 was considered significant. Only significant p values are included in this table. p Values refer to comparison between the GPD group and the control group.

[b] Major medical problems included 2 or more chronic medical conditions requiring medication or resulting in hospitalization, including but not limited to diabetes, congestive heart failure, peripheral vascular disease, kidney failure, or transplant.

[c] Patients were allowed to have a combination of presenting illnesses if each were contributing to the acute presentation. In many cases, patients with acute brain injury or cardiac arrest also had toxic-metabolic encephalopathy.

Seizures were recorded on cEEG in 73 patients. A total of 56 patients with GPDs had seizures on cEEG vs 17 controls ($p < 0.001$). PLEDs were recorded in 21.5% of GPD patients vs 10% of controls ($p < 0.001$); BIPLEDs occurred in 10.5% of GPD patients vs 1.5% of controls ($p < 0.001$). Excluding the 55 with co-occurring patterns and their controls, 30/145 (20.7%) patients with GPDs had seizures on cEEG vs 14/145 (9.7%) controls ($p = 0.009$). Excluding the 29 CA patients in each group, 47/171 (27.5%) GPD patients had seizures on cEEG vs 15/171 (8.8%) controls ($p < 0.001$). In CA patients, 9/29 (31.0%) with GPDs had seizures vs 2/29 (6.9%) controls (table e-1 on the *Neurology*® Web site at www.neurology.org; $p = 0.044$).

Of the 73 patients with seizures on cEEG, 4 had intermittent cEEG data before first seizure and were excluded from timing analysis. In the remaining 69, first seizure was recorded in <24 hours in 81.2%: 41/53 with GPDs vs 15/16 controls ($p < 0.001$; figure 2C). A total of 22.6% of those with GPDs and seizures had their first seizure recorded after 24 hours: between 24 and 48 hours for 2 with GPDs and 1 control, and after 48 hours for another 10, all with GPDs.

Overall, 196/400 patients had poor outcome (GOS 4–5; figure 3A). There was no significant difference in outcome between patients with GPDs and controls: 51.5% with GPDs had poor outcome vs 46.5% of controls (NS); 41.0% died vs 34.5% of controls (NS). Excluding 7/200 GPD patients with Creutzfeldt-Jakob disease (CJD), a chronic condition, there remained no significant difference in outcome between GPDs and controls. GPD patients experienced longer ICU stays (18 days vs 15 days, $p = 0.002$) and longer cEEG monitoring (7 days vs 3 days, $p < 0.001$). A total of 19.0% with GPDs and 18.5% of controls were independent at discharge.

Excluding CA patients, 36.8% with GPDs died vs 26.9% of controls ($p = 0.049$; see figure 3B). A total of 45.6% with GPDs had poor outcome vs 38.6% of controls (NS); an outcome difference of ≥10.7% would have been required for significance at 80% power. CA patients alone had a mortality of 65.5% with GPDs vs 79.3% without GPDs (NS; figure 3C). Good outcome (GOS 1–3) was noted in 4/29 with GPDs after CA and 2/29 without GPDs after CA (NS).

Independent predictors of worse outcome in all patients were coma, sepsis, CA, and NCSE (table e-2). CNS infection was associated with a lower chance of poor outcome. In GPD patients, a past medical history of multiple medical problems also predicted worse outcome.

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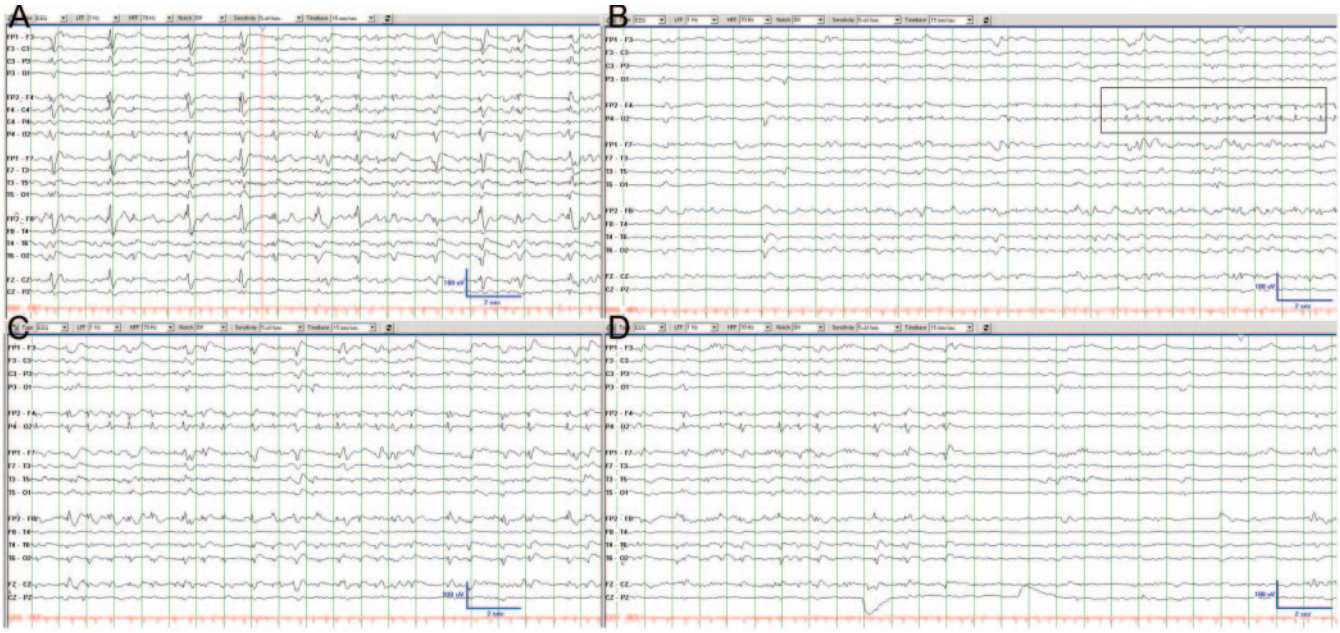
Figure 1 Generalized periodic discharges with a focal seizure



A woman in her 40s, 3 days after liver transplantation complicated by sepsis and renal failure. She was comatose. (A) Her initial continuous EEG monitoring demonstrated frequent generalized periodic discharges, occasionally with triphasic morphology. (B–D) Three consecutive pages of EEG about 2 hours later, when she developed focal status epilepticus with right hemisphere onset, maximal in the right frontal parasagittal region (box in B) that evolved before ending abruptly (halfway through panel D). There was no clinical correlate on video.

DISCUSSION In this study, we matched 200 consecutive cEEG patients with GPDs to controls based on age, category of presenting illness, and level of consciousness. GPDs had a significant association with NCSz (26.5% with GPDs vs 7.5% of controls) and NCSE (21.5% vs 6.5%), but not CSz. In both groups, one-third of patients had CSz at some point, and <6% had CSz during cEEG. Just over half of patients with GPDs had no seizures at any time. Seizures in those with GPDs were more likely to be delayed, with the first seizure occurring >24 hours after the start of cEEG in about one-quarter of patients (vs 6% of controls). Contrary to our hypothesis, GPDs were not independently associated with worse outcome. While 41.0% with GPDs died during hospitalization and an additional 40.0% were severely impaired at discharge, there was no difference in outcome compared to matched controls without GPDs. When CA patients were excluded, GPDs were associated with increased mortality on univariate analysis. Multivariate predictors of poor outcome overall were coma, sepsis, CA, and NCSE, but not GPDs.

Table 2 details prior studies of GPDs.[8–11] Of note, there were significantly more women in our GPD group compared with controls (60% vs 46%). In 2 prior studies,[9,11] women also comprised more than half (57.1%), but these were not controlled cohorts. There are several possible explanations for this observation—hormonal, genetic, epidemiologic—but these remain speculative.

GPDs remain relatively uncommon, but were seen in approximately 4.5% of more than 3,000 consecutive inpatients undergoing cEEG, compared with 0.06%–0.24% undergoing routine EEG.[8,10,11] As cEEG use becomes more widespread, GPDs are likely to be detected with increasing frequency, similar to experience with NCSz.[3,14]

In our study, 46.0% with GPDs had seizures overall and 23.5% had SE; during cEEG, most seizures were NCSz and would have gone unrecognized without cEEG, consistent with other investigations.[3,14,15] In a prior GPD series,[9] 32.0% had SE. However, in their cohort, 40.0% had a history of prior seizures (vs 6.5% in our study). In a second study,[8] 89.2% had seizures within 48 hours of EEG: 32.4% had SE during the EEG, 21.5% had CSz after EEG, and 35.2% had myoclonic jerks ("myoclonic status"[16]). Their cohort was quite different from ours: chronic conditions associated with myoclonic seizures were included, such as subacute sclerosing panencephalitis (SSPE; 29.7%, their largest subgroup) and CJD (10.8%), which in our study were absent (SSPE) or rare (CJD; 3.5%). Neither study included control groups. We found that when controlling for age, category of presenting illness, and level of consciousness, only NCSz and NCSE, not CSz, were associated with GPDs.

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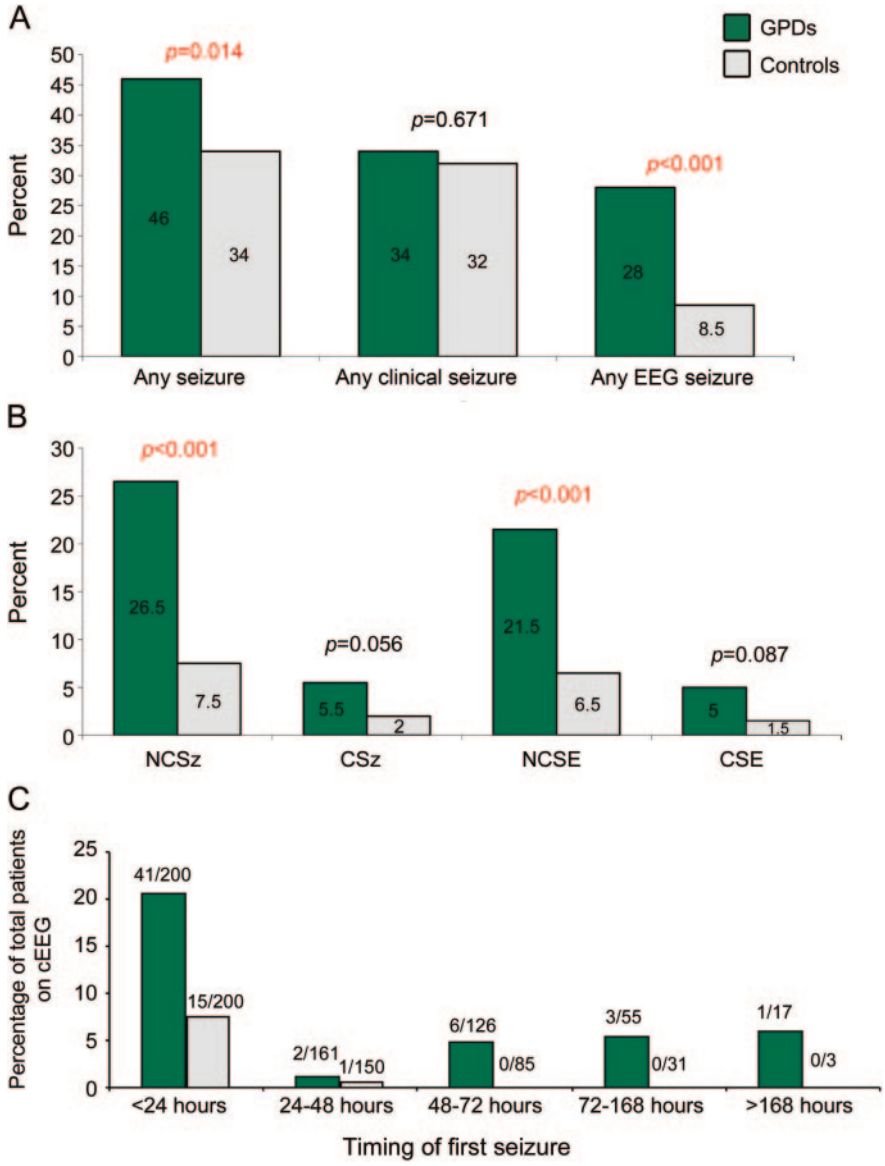
Figure 2 Generalized periodic discharges (GPDs) and seizures



(A) Comparison of seizure occurrence at any time in patients with GPDs vs controls (%). (B) Comparison of seizures during continuous EEG monitoring (cEEG) in patients with GPDs vs controls (%). (C) Timing of first recorded seizure in patients with GPDs vs controls (patients with first seizure/total patients consecutively monitored on cEEG). CSE = convulsive status epilepticus; CSz = convulsive seizure; NCSE = nonconvulsive status epilepticus; NCSz = nonconvulsive seizure; Sz = seizure.

Overall in-hospital mortality for GPD patients was 41.0% (65.5% with CA and 36.8% without CA). A prior study[9] documented 64.0% mortality, but anoxia comprised 40.0% of the patients (vs 14.5% in our study). Excluding those, 46.7% of their patients died, similar to our results. A second study[8] documented a mortality of 48.7%, but while their cohort included a similar proportion of CA patients as ours (18.9%), it included 7 with burst-suppression patterns, which we excluded. Burst-suppression is associated with poor outcome, especially after CA, and all 7 patients died. Excluding burst-suppression, mortality in their cohort was 36.7%. One GPD subgroup[11] had 29.7% mortality after up to 1 year follow-up, lower than ours perhaps because 5/17 of these patients had so-called chronic (>8 weeks) GPDs. Again, these prior studies had no control groups. Despite the relatively poor outcomes, when we matched patients for age, category of presenting illness, and level of consciousness, there was no definite independent association between GPDs and outcome, although a small association remains possible.

The role of underlying illness and its severity in determining outcome in this cohort of mostly critically ill patients is underscored by multivariate analy-

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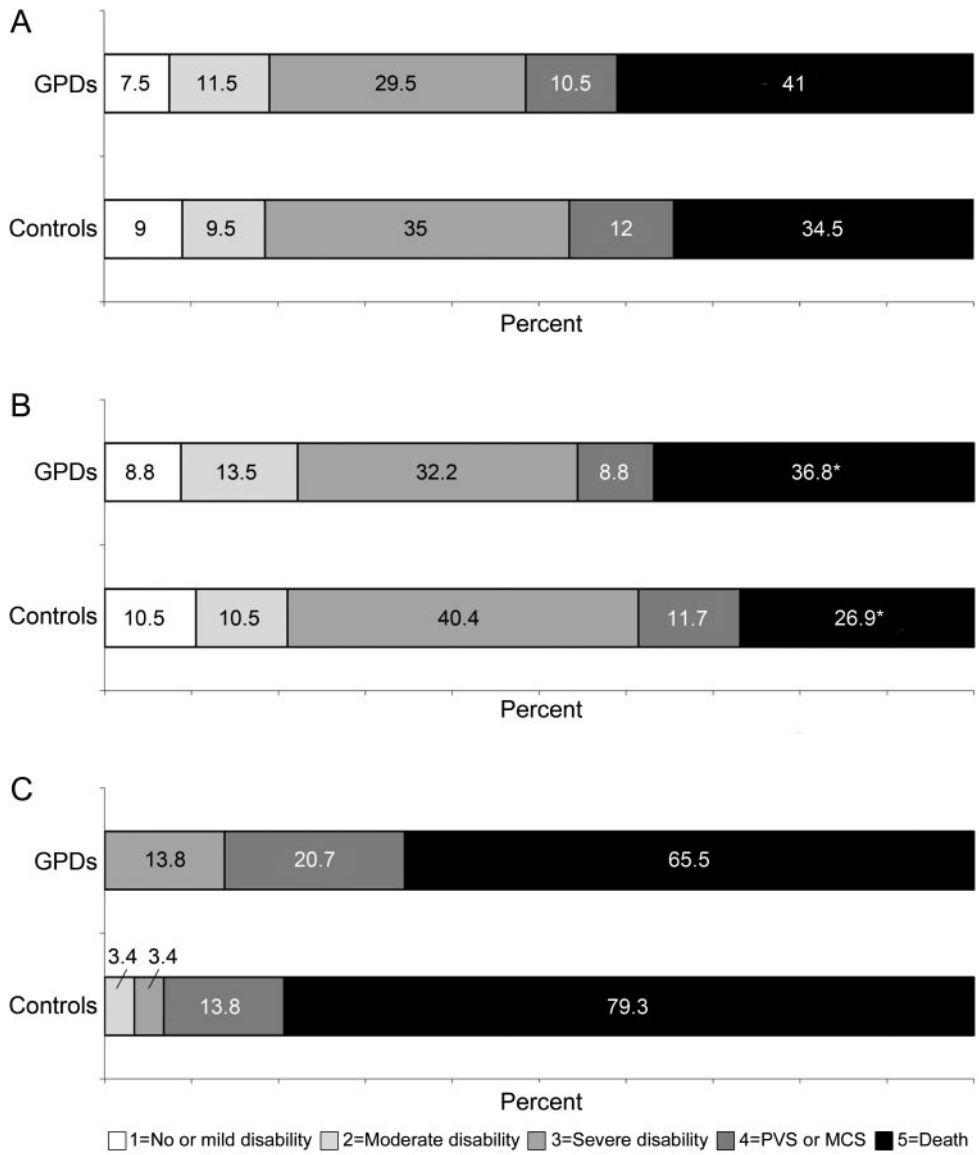
Figure 3 Functional outcome at hospital discharge (%)



(A) All patients (n = 200 in each group). (B) Excluding cardiac arrest (n = 171 in each group). (C) Cardiac arrest only (n = 29 in each group). *$p = 0.049$. GPD = generalized periodic discharge; MCS = minimally conscious state; PVS = persistent vegetative state.

sis in which coma, sepsis, and CA were significant predictors of poor outcome. In addition, we found that NCSE confers independent risk of poor outcome once age, category of presenting illness, and level of consciousness are controlled. This is consistent with a prior report of NCSE after control of CSE.[17] Both delays to diagnosis of NCSE and duration of NCSE have been reported to be associated independently with mortality in patients with acute neurologic injury.[18] Periodic epileptiform discharges or electrographic seizures have also been shown to be independent risk factors for poor outcome in medical ICU patients without acute neurologic injury undergoing cEEG.[19] Our center has reported that periodic epileptiform discharges independently associate with poor outcomes in poor-grade SAH and ICH, but when stratified, only lateralized discharges maintain this association, not generalized discharges. While overall outcome was not associated with GPDs in our current study, GPDs were strongly associated with NCSz and NCSE.

The earliest observations of GPDs encompassed the original descriptions of SSPE,[1,2] as well as their almost pathognomonic presence in the setting of rapidly progressive dementia and myoclonus in sporadic CJD.[20,21] Other specific etiologies have included phencyclidine or ketamine toxicity, anesthetic use, and barbiturate overdose.[21] GPDs may occur in hepatic and renal disease, CNS infection (herpes simplex encephalitis), hypoxic-ischemic encephalopathy,

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Table 2 Major findings and comparison of studies on generalized periodic discharges

	Design	No.	Mean age, y (range)	Definition of GPDs	Prevalence	Included (%)	Excluded	Etiology (%)	Neurologic examination (%)	Sz types (%)	Outcome (%)	Reference
GPD studies	Retrospective case series	25	60.9 (NA)	50% of standard 20-min EEG	NA	Sharp waves (52); slow waves (12); triphasic-like waves (36)	Suppression-burst; continuous triphasic waves; intermittent runs of slow waves (i.e., FIRDA)	Anoxic + toxic-metabolic (40); primary neuro (32); toxic-metabolic (28)	Anoxic + toxic-metabolic (5.2)[a]; primary neuro (3.4)[a]; toxic-metabolic (4.6)[a]	SE (32)	Discharge mortality: anoxic + toxic-metabolic (90); primary neuro (38); toxic-metabolic (57); overall (64)	9
	Retrospective case series	37	45 (17–82)	50% of standard 20-min EEG	0.15%–0.18%	PSIDDs (40.5); PLIDDs (40.5); suppression-burst (18.9)	Iatrogenic GPDs (i.e., thiopental)	SSPE (29.7); metabolic (21.6); hypoxic (18.9); sepsis (16.2); CJD (10.8); HSE (2.7)	Lethargy/stupor (59.5); coma (40.5)	Myoclonic (35.2); SE during EEG (32.4); GTC (21.6); total (89.2)	30-day mortality: PSIDDs (53.3); PLIDDs (20); suppression-burst (100); overall (48.7)	8
	Retrospective matched controlled cohort	200	66 (18–96)	As per ACNS criteria[b]	4.5%	Any generalized periodic discharge (including triphasic or triphasic-like waves)	Suppression-burst	Acute brain injury (44); acute systemic illness (38); arrest (14.5); epilepsy (3.5)	Awake (0.5); abnormal but alert (8.5);, lethargy/ stupor (35.5); coma (56)	CSz (34); NCSz (26.5); SE (23.5); CSE (5); NCSE (21.5); any Sz overall (46)	Discharge GOS: GOS 1–3 (48.5); PVS or MCS (10.5); death (41)	NA
Subgroup analyses	Retrospective case series	36	NA (6–86)	≥10 min of continuous periodicity or consistent state-dependent periodicity (i.e., anesthesia-induced suppression-burst)	0.24%	Slow-wave complexes (44.4); sharp transients (2.8); triphasic waves (22.2); suppression-bursts (30.6)	NA	Drug-related (38.9); anoxia (16.7); Metabolic (16.7); hypoxia (13.9); SSPE (11.1); epileptic encephalopathy (2.8)	NA	NA	Discharge (or resolution of acute insult) examination: normal (36.1); abnormal (19.4); death (44.4)	10
	Retrospective case series	17	64 (26–80)	50% of standard 30-min EEG	0.06%	Any generalized periodic discharge plus acute (< 4 wk; 64.7); subacute (4–8 wk; 5.8); chronic (>8 wk; 29.4)	Triphasic waves due to metabolic encephalopathy	Stroke (35.2); metabolic (35.2); other (23.5); tumor (5.8)	Normal (5.8); focal (17.6); coma (47.8); coma/focal (5.8)	CSz (29.4)	Discharge (or up to 1 year) functional outcome: independent (17.6); dependent (52.9); death (29.4)	11

Abbreviations: CJD = Creutzfeldt-Jacob disease; CSE = convulsive status epilepticus; CSz = convulsive seizure; FIRDA = frontal intermittent rhythmic δ activity; GOS = Glasgow Outcome Scale score; GPD = generalized periodic discharge; GTC = generalized tonic-clonic seizure; HSE = herpes simplex encephalitis; MCS = minimally conscious state; NA = not applicable; NCSE = nonconvulsive status epilepticus; NCSz = nonconvulsive seizure; PLIDD = periodic long-interval (4–30 s) diffuse discharge; PSIDD = periodic short-interval (0.5–4 s) diffuse discharge; PVS = persistent vegetative state; SE = status epilepticus; SSPE = subacute sclerosing panencephalitis; Sz = seizure.

[a] Mental status in Husain et al.[9] was coded on a scale from 0–6, where 0 = awake and fully oriented and 6 = unresponsive to maximum painful stimulation.

[b] American Clinical Neurophysiology Society (ACNS) criteria (Hirsch et al.[33]) for generalized periodic discharges includes frontally predominant or occipitally dominant synchronous, relatively symmetric discharges along with repetition of the discharges with relatively uniform morphology and duration between consecutive waveforms.

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hypoglycemia, hyperosmolarity, Alzheimer disease, steroid-responsive encephalopathy and autoimmune thyroiditis (or Hashimoto), or with medication toxicity: lithium, ifosfamide, and baclofen.[16]

Diffuse cerebral gray matter involvement may link these various associated etiologies. The classic pathologic study by Gloor et al.[22] demonstrated that diffuse cortical and subcortical gray matter disease was required for the development of bilateral periodic epileptiform discharges; white matter involvement was incidental. Gloor et al. concluded that the electrophysiology reflects an abnormal system in which networks of damaged neurons (either cortical or subcortical) discharge and become aberrantly synchronized, thereby appearing generalized, with relatively fixed discharge intervals related to a prolonged refractory period.

Subsequent to the work of Gloor et al., animal experiments have suggested periodic epileptiform discharges may represent the EEG correlate of dying neurons.[23] Alternatively, a hypothetical progression of CSE culminating in a final stage of coma and periodic epileptiform discharges representing ongoing ictal activity has been termed "subtle status epilepticus."[24] As the term has been used in many clinical situations and for many forms of SE without major convulsive movements, we have instead suggested the more specific "status epileptics terminans" for this final smoldering stage of SE.[25] These seemingly disparate interpretations of GPDs are not necessarily mutually exclusive. A parsimonious explanation is that periodic epileptiform discharges represent "a dynamic…state in which unstable neurobiological processes create an ictal-interictal continuum" linking neuronal injury to metabolic dysfunction in their pathophysiology.[7] In the case of generalized periodic epileptiform discharges, it is possible that a subset may be unrelated to seizures (i.e., not on this ictal-interictal continuum at all), but simply represent the electrophysiologic correlate of metabolic encephalopathy.

GPDs vary in appearance from patient to patient and distinctions have been made based on the presence of slow-wave, spike-wave, or triphasic-appearing waves (TWs) in prior studies.[9,10] In one, the amplitude and duration of GPDs were larger and the interdischarge amplitude preserved in patients who subsequently developed SE.[9] However, waveform characteristics overlapped extensively, and the differences were not large enough to help at the individual patient level. Particularly in comatose patients, making morphologic distinctions between seizure-related GPDs (which lie along the ictal-interictal continuum) and metabolic encephalopathy-related GPDs (typically called "triphasic waves") is difficult, if not impossible, in a given patient.[9,26] Although some have attempted to use IV benzodiazepine response to help differentiate between the two, metabolic encephalopathy-related GPDs (without evidence of seizures) commonly resolve with benzodiazepines.[27] Partly for these reasons, we did not exclude TWs from this study of GPDs. In fact, in our experience, the use of the term "TWs" rather than "GPDs" is related more to clinical history than the waveforms: several of our patients' cEEG reports used both terms at different times, sometimes for similar patterns, in the same 24-hour study. It is possible that some in our cohort had pure metabolic encephalopathy, which provides some limitation to this study. Only carefully designed prospective, blinded studies can address whether EEG alone can help distinguish "TWs" from other forms of GPDs, assuming that there is a fundamental difference. For now, it appears that regardless of morphology, GPDs reflect a common manifestation of a variety of pathologies and are highly associated with NCSz and NCSE.

There are a number of additional limitations to the current study. First, it is retrospective and based on chart review. Second, EEG characteristics, while described by a small group of board-certified electroencephalographers, are prone to low interobserver reliability; standardization of EEG terminology should ultimately remedy this.[12] Third, we did not account for specific anesthetic cIV medications, newer AED medications, or clinical response to AEDs. Finally, care of the patients was heterogeneous depending on the setting and nature of the illness, which may have led to different outcomes. Particularly in critically ill patients, withdrawal of care may be a significant determinant of outcome, but was not specifically addressed.

Further questions remain to be answered. Is there a role for AEDs in patients with GPDs before development of unequivocal seizures? Is there any role for attempting to suppress GPDs? Are there subgroups in which GPDs provide independent prognostic information such as after CA[9,28,29]? Specific morphologic characteristics of the waveforms need to be studied prospectively and, specifically with regard to cEEG, should be re-evaluated to refine terminology. The American Clinical Neurophysiology Society (ACNS) Subcommittee on Research Terminology for Continuous EEG Monitoring[12] provides a framework for the study of periodic epileptiform discharges in the future.

GPDs were highly associated with NCSz and NCSE, but had no definite independent prognostic value. Treatment of the underlying etiology and careful monitoring for and treatment of NCSE are the most important considerations in the care of

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patients with GPDs. Patients with GPDs should undergo cEEG to identify NCSE, which is independently associated with worse outcome in patients with and without GPDs. We believe aggressive treatment of GPDs should be reserved for cases in which there is definite NCSE based on evolving EEG patterns or clinical features, or if there is evidence of ongoing neuronal injury.[30–32]

AUTHOR CONTRIBUTIONS

Dr. Foreman was involved in data collection, data analysis, data interpretation, literature review, writing, and manuscript revisions. Dr. Claassen was involved in data analysis, data interpretation, manuscript review and revisions, supervision, and study design. Dr. Abou Khaled was involved in data collection, initial data interpretation and analysis, writing and preparation of abstract/poster of initial data, literature review, and manuscript review. Dr. Jirsch was involved in data collection, initial data analysis, initial study design, and manuscript review. Dr. Alschuler was involved in data collection and manuscript review. Dr. Wittman was involved in data collection and manuscript review. Dr. Emerson was involved in data collection, data interpretation, and manuscript review. Dr. Hirsch was involved with data analysis, data interpretation, manuscript review and revisions, supervision, and study design.

DISCLOSURE

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