ORIGINAL CONTRIBUTION

Prognostic Implications of Periodic Epileptiform Discharges

Daniel San juan Orta, MD; Keith H. Chiappa, MD; Alejandro Z. Quiroz, PhD; Daniel J. Costello, MD, MRCPI; Andrew J. Cole, MD, FRCPC

Background: Periodic epileptiform discharges (PEDs) are an abnormal finding on electroencephalograms (EEGs), the significance of which is uncertain.

Objective: To investigate long-term outcome in patients with PEDs.

Design: We retrospectively analyzed the outcomes of patients who had PEDs diagnosed during a 7-year period. We abstracted and tabulated clinical parameters from the time of EEG, imaging findings, EEG measurements, and subsequent clinical outcome from medical records. We used descriptive, inferential, and logistic regression analysis to determine the factors associated with clinical outcomes in patients with PEDs. We divided PEDs into the following subgroups: periodic lateralized epileptiform discharges (PLEDs), generalized PEDs, and bilateral PEDs and analyzed these subgroups individually.

Setting: University-affiliated teaching hospital.

Subjects: One hundred sixty-two patients with PEDs.

Results: We obtained complete clinical, neuroimaging, neurophysiologic, and long-term outcome data in 118 patients. In the subgroup of patients with PLEDs, absence of seizures at onset (odds ratio, 0.21 per point; 95% confidence interval, 0.04-0.97) and an acute etiology for the PLEDs (odds ratio, 0.14 per point; 95% confidence interval, 0.03-0.72) were associated with death. A nonneoplastic cause for PLEDs was associated with independent functionality (odds ratio, 0.45 per point; 95% confidence interval, 0.3-0.67).

Conclusion: In patients with PLEDs, the absence of clinical seizures at the time of detection and presumed acute etiology are associated with death, whereas a nonneoplastic etiology was associated with a good clinical outcome.

Arch Neurol. 2009;66(8):985-991

Author Affiliations: Epilepsy Service, Massachusetts General Hospital (Drs San juan Orta, Chiappa, Costello, and Cole); and Department of Biostatistics, Harvard School of Public Health (Dr Quiroz), Boston, Massachusetts.

While periodic epileptiform discharges (PEDs) are always an abnormal finding on electroencephalograms (EEGs), their significance is often uncertain. Although periodic lateralized epileptiform discharges (PLEDs) were first strictly defined by Chatrian et al in 1964,[1] over time the term has been applied to a spectrum of EEG findings. A growing number of apparently related abnormalities have been described, including bilateral independent PLEDs (BIPLEDS), generalized PEDs (GPEDs), and pseudo-PLEDs.[2] These are all contained within the term *periodic epileptiform discharges*. Whereas PLEDs and related discharges are most commonly encountered in acutely ill patients, chronic PLEDs are now well recognized.[3] The most common cause of PLEDs is an acute or subacute structural injury of the cerebral cortex, either diffuse or focal; however, PLEDs may also be seen in patients with a chronic static cerebral lesion or chronic epilepsy.[1] There is substantial controversy over whether PLEDs and related discharges represent an epileptic phenomenon meriting aggressive treatment, or alternatively are simply a marker of severe brain injury of little or no specificity.[3] While many studies have indicated that PLEDs are associated with a poor prognosis,[4-6] little attention has focused on determining whether intrinsic characteristics of the PLED-like discharges may carry more specific etiological, therapeutic, or prognostic implications.[6]

Our study aimed to investigate long-term outcome in patients with PEDs. We were particularly interested in determining whether the intrinsic characteristics of the PEDs, the acute clinical situation, or contemporaneous neuroimaging findings correlated with long-term outcome.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

METHODS

We searched the EEG database for all EEGs performed during a 7-year period (January 1, 2000-January 1, 2007) using the following key words: *repetitive discharge*, *periodic discharge*, *PEDs*, *PLEDs*, *BiPLEDs*, *GPEDs*, *periodic epileptiform*, *bilateral periodic epileptiform discharge*, and *generalized periodic epileptiform discharge*. We excluded EEGs with triphasic waves due to metabolic encephalopathy. We excluded repeated EEGs performed on the same patient and analyzed the first EEG that showed evidence of PEDs. We abstracted the clinical information written when the EEG was recorded. We recorded the following parameters: etiology, age, sex, acuity of illness, clinical examination findings, presence of recent clinical seizures, and history of epilepsy. We reviewed the neuroimaging findings and recorded the presence of cortical and subcortical injuries. We recorded the long-term outcome from the medical record. For the purpose of this study, we classified PEDs as PLEDs, BIPLEDs or GPEDs, using strictly adhered-to definitions. Periodic lateralized epileptiform discharges were characterized as lateralized or focal; periodic or near periodic; or spike, spike-wave, or sharp-wave complex presentations throughout most or all of the recording.[1] Generalized periodic epileptiform discharges were defined as the occurrence of periodic complexes occupying at least 50% of a standard 30-minute EEG over both hemispheres in a symmetric, diffuse, and synchronized manner,[2,7] and BIPLEDs were defined as bilateral independent periodic lateralized epileptiform discharges.[8] The periodicity (determined as a continuous variable based on measurement of interspike interval), duration of epileptiform complex (measured from first unequivocal deflection to unambiguous end, excluding any activity judged subsequently as slow wave), and amplitude of epileptiform complex (measured using a built-in EEG software tool using an ipsilateral ear referential montage) were calculated in 50 consecutive samples of EEG recordings obtained during a random 5-minute sample of recording. The voltage of the EEG background during the interspike interval was classified as low (<20 μV) or high (>20 μV). Morphologic variables of the epileptiform discharges were analyzed. Specifically, polarity, total number of phases, total number of sharp waves, and distribution were defined according to a previous study.[6] Neuroimaging study (computed tomography or magnetic resonance imaging [MRI] [1.5 or 3.0 T]) results were classified as normal or abnormal. When a patient had both studies available, we analyzed only the MRI findings. Abnormal studies were categorized by lesion localization as cortical and/or subcortical. Relevant cortical imaging abnormalities (on computed tomography and MRI) included increased signal intensity within the cortical ribbon, borderzone infarctions, and laminar necrosis. Notable subcortical imaging findings included increased signal intensity in the deep gray matter nuclei and white matter abnormalities. If a study showed both acute and chronic abnormalities, only the acute findings were analyzed.

All of the original EEGs and imaging studies were personally reviewed by Dr San juan Orta. The acuity of the patient's disease relative to the timing of the EEG recording was classified as acute (<4 weeks), subacute (4-8 weeks), chronic (>8 weeks), or acute-on-chronic (preexisting disease with acute worsening). The patient's functional outcome was assessed at discharge or on subsequent follow-up during the first year after the diagnostic EEG, when available. Level of functionality was divided into 3 categories: totally independent, partially dependent on family or nursing home, and death.

To facilitate a stratified logistic regression analysis, we divided the patients with PLEDs into 2 groups: PLEDs and combined BIPLEDs/GPEDs. A descriptive statistical analysis was implemented to obtain a representation of the clinical, neuroimaging, and neurophysiologic variables. Because the nature of the variable functional capacity is ordinal, logistical regression and adjacent categories logistical regression were applied to analyze the association between functional capacity and all relevant patient variables. The odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were calculated. To analyze the variability of the duration of the epileptiform complex, periodicity, and amplitude between the patient groups, a likelihood method approach was applied. In this case, a normal distribution was used and tested for the transformed standard deviations. To test the normality of the transformed standard deviations, Shapiro-Wilk and Anderson-Darling tests were performed. All statistics were performed using R software, version 2.6.0 (R Foundation, Vienna, Austria).

RESULTS

From 2000 to 2007, we recorded 25 486 EEGs in inpatients and outpatients. All of the EEG recordings were performed without sedative drugs for at least 30 minutes. All patients had digital EEG recordings with 24 scalp electrodes positioned according to the standard 10-20 system of placement, reformatted to both bipolar and off-head referential montages, with filter settings at 0.3 Hz and 70 Hz. We initially found 340 patients in the database using the initial keyword search. We excluded 110 duplicate studies and 68 EEGs that did not fulfill the definitions used for PLEDs, BIPLEDs, or GPEDs. Finally, we identified 162 patients in whom PLEDs or periodic lateralized epileptiform–like discharges were reported on at least 1 available EEG, which represents a prevalence of 0.6% among the inpatient and outpatient EEG recordings. Of these EEGs, 122 were available for morphologic analysis. Complete clinical information and neuroimaging findings were available in 121 of 162 patients, and 118 of 162 patients had follow-up information available. The 41 patients without available imaging studies often underwent imaging in another hospital prior to transfer to our institution and thus were not accessible. Similarly, patients with incomplete follow-up data were often transferred from outside hospitals and thus not observed in our institution after discharge.

CLINICAL FINDINGS

Table 1 presents the distribution of different PED patterns, patient demographics, and acuity of the underlying disease. Stroke was the most common cause of PLEDs and Bf in 46.3% (n=38) and 30.4 (n=7) of patients, respectively. In the GPEDs group, the underlying cause was mainly stroke and metabolic disorders (**Table 2**). The acuity of the underlying disease was chronic in 41 patients (50%) with PLEDs. Bilateral independent PLEDs and GPEDs were more likely to be associated with either acute or subacute disease; combined acute and subacute disease accounted for 73.8% of BIPLEDs and 70.5% of GPEDs. The overall prevalence of clinical seizures in patients at the time of EEG recording or during the hospitalization was 59%. Seizures were detected in 70% of patients with PLEDs, 43% of patients with BIPLEDs, and 29.4% of patients with GPEDs. In patients with PLEDs and seizures or BIPLEDs and seizures, the most common etiology was

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

stroke, occurring in 30.5% and 13.0% of patients, respectively. Seizures in patients with GPEDs were more likely to have an underlying metabolic cause (Table 2). Patients' neurological findings, frequency of acute seizures, and history of epilepsy are summarized in **Table 3**. Two patients had normal neurological examination results—one patient (with PLEDs) had chronic medically intractable epilepsy and another patient (with GPEDs) had a diagnosis of Gaucher disease. The functional outcomes of each patient group (with a mean follow-up of 18 months) are summarized in **Table 4**. The main outcomes among all of the patients combined was independent (n=25 [39%]) and dependent (n=61 [54%]) functionality, and death (n=33 [28%]). Patients in the BIPLEDs group had a 39.1% chance of a fatal outcome and a 21.7% chance of an independent recovery. Patients in the PLEDs and GPEDs groups had a smaller chance of a fatal outcome (24%-29%), while approximately half were left with residual disability resulting in functional dependence.

NEUROIMAGING FINDINGS

Table 5 presents the neuroimaging findings of 121 patients with PLEDs, BIPLEDs, and GPEDs and the distribution of the abnormalities in cortical and subcortical areas, separate and combined. The only patient with PLEDs and a normal MRI result had intractable epilepsy. Six normal computed tomography results (4.9%) were found in 4 patients with PLEDs (4.8%) and 2 patients with BIPLEDs (9.0%). Most patients had coexistent cortical and subcortical imaging abnormalities (64.9% of patients with PLEDs, 55% of patients with BIPLEDs, and 35.2% of patients with GPEDs). A small proportion had isolated cortical abnormalities (23.3% of patients with PLEDs, 30% of patients with BIPLEDs, and 19.6% of patients with GPEDs) or isolated subcortical abnormalities (11.6% of patients with

Table 1. Characteristics of Patients With Periodic Epileptiform Discharges

	Patients, No. (%)		
Characteristic	PLEDs (n=82)	BIPLEDs (n=23)	GPEDs (n=17)
Age, median (range), y	64 (13-92)	67 (36-85)	64 (26-80)
Female sex	47 (57.3)	15 (65.2)	9 (52.9)
Disease stage			
Acute	29 (35.3)	16 (69.5)	11 (64.7)
Subacute	4 (4.8)	1 (4.3)	1 (5.8)
Chronic	41 (50)	5 (21.7)	5 (29.4)
Acute-on-chronic	8 (9.7)	1 (4.3)	0

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; GPEDs, generalized periodic epileptiform discharges; PLEDs, periodic lateralized epileptiform discharges.

Table 3. Neurological Examination, Seizures at Onset, and History of Epilepsy in Patients With Periodic Epileptiform Discharges

	Patients, No. (%)		
Clinical Finding	PLEDs (n=82)	BIPLEDs (n=23)	GPEDs (n=17)
Neurological examination			
Focal	60 (73.1)	10 (43.4)	3 (17.6)
Coma	14 (17.0)	11 (47.8)	12 (70.5)
Coma and focal	7 (8.6)	2 (8.6)	1 (5.8)
Normal	1 (1.2)	0	1 (5.8)
Seizures			
Acute seizure	57 (70.3)	10 (43.4)	5 (29.4)
History of epilepsy	13 (22.8)	3 (13)	2 (11.7)

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; GPEDs, generalized periodic epileptiform discharges; PLEDs, periodic lateralized epileptiform discharges.

Table 4. Functional Capacity of Patients With Periodic Epileptiform Discharges With Follow-up of at Least 1 Year

	No. (%)		
Functional Capacity	PLEDs (n=79)	BIPLEDs (n=23)	GPEDs (n=17)
Dependent	43 (54.4)	9 (39.1)	9 (52.9)
Death	19 (24.0)	9 (39.1)	5 (29.4)
Independent	17 (21.5)	5 (21.7)	3 (17.6)

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; GPEDs, generalized periodic epileptiform discharges; PLEDs, periodic lateralized epileptiform discharges.

Table 2. Etiology and Seizure Occurrences in Patients With Periodic Epileptiform Discharges

	No. (%)					
	PLEDs		BIPLEDs		GPEDs	
Etiology	Patients (n=82)	Seizures	Patients (n=23)	Seizures	Patients (n=17)	Seizures
Stroke	38 (46.3)	25 (30.5)	7 (30.4)	3 (13.0)	6 (35.2)	1 (5.8)
Tumors	25 (30.4)	21 (25.6)	2 (8.6)	1 (4.3)	1 (5.8)	1 (5.8)
Infection	9 (10.9)	5 (6.0)	3 (13.0)	2 (8.6)	0	0
Metabolic	4 (4.8)	2 (2.4)	5 (21.7)	2 (8.6)	6 (35.2)	3 (17.8)
Other	4 (4.8)	3 (3.6)	6 (26.0)	2 (8.6)	4 (23.5)	0
Trauma	2 (2.4)	1 (1.2)	0	0	0	0
Total		57 (**70**)		10 (**43**)		5 (**29.4**)

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; GPEDs, generalized periodic epileptiform discharges; PLEDs, periodic lateralized epileptiform discharges.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

Table 5. Neuroimaging Findings in Patients With Periodic Epileptiform Discharges

	No. (%) of Patients by Periodic Epileptiform Discharge Type										
	PLEDs				BIPLEDs				GPEDs		
		Abnormal				Abnormal				Abnormal	
Imaging	Normal	Cortical	Subcortical	Both	Normal	Cortical	Subcortical	Both	Cortical	Subcortical	Both
MRI	1 (1.2)	13 (16.8)	8 (10.38)	40 (51.9)	0	5 (25)	3 (15)	10 (50)	3 (17.6)	4 (23.5)	4 (23.5)
CT	4 (4.8)	5 (6.4)	1 (1.2)	10 (12.9)	2 (9.0)	1 (5)	0	1 (5)	3 (17.6)	1 (5.8)	2 (11.7)
Total	5 (**6**)	18 (**23.3**)	9 (**11.6**)	50 (**64.9**)	2 (**9.0**)	6 (**30**)	3 (**15**)	11 (**55**)	6 (**19.6**)	5 (**29.3**)	6 (**35.2**)

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; CT, computed tomography; GPEDs, generalized periodic epileptiform discharges; MRI, magnetic resonance imaging; PLEDs, periodic lateralized epileptiform discharges.

Table 6. EEG Variables in Patients With Follow-up of at Least 1 Year

	Mean (SD)	
EEG Variable	Patients With PLEDs (n=79)	Patients With BIPLEDs or GPEDs (n=63)
Inter-PED interval, ms	847 (501)	824 (613)
Duration of complex, ms	396 (136)	433 (181)
Amplitude, μV	81 (49)	76 (47)
No. of phases	3.6 (0.8)	3.5 (0.7)
No. of sharp phases	1.2 (0.4)	1.3 (0.5)

Abbreviations: BIPLEDs, bilateral periodic epileptiform discharges; EEG, electroencephalography; GPEDs, generalized periodic epileptiform discharges; PED, periodic epileptiform discharge; PLEDs, periodic lateralized epileptiform discharges.

PLEDs, 15% of patients with BIPLEDs, and 29.3% of patients with GPEDs). However, the number of patients in each cohort was unequal.

EEG FINDINGS

Table 6 summarizes the comparison of EEG findings between the PLEDs cohort (n=79) and the combined BIPLEDs/GPEDs cohort (n=63). In the BIPLEDs cohort, we analyzed each hemisphere independently. Statistically significant differences were not evident in the parameters analyzed. Low amplitude intervals were evident in 43 patients with PLEDs (58%) and 20 patients in the combined BIPLEDs/GPEDs group (31%). Acute seizures were evident on the analyzed EEG recordings in 69% of the PLEDs group and 35% of the BIPLEDs/GPEDs group. In both the PLEDs and BIPLEDs/GPEDs groups, the maximum amplitude was seen in the frontocentral regions, followed by the frontotemporal regions. Negative polarity of the waves was recorded in 67% of the PEDs.

FUNCTIONAL CAPACITY AND LONG-TERM FOLLOW-UP

There was no statistical association between the histories of seizures, neuroimaging studies (normal or abnormal [cortical or subcortical abnormalities or both]), neurological findings, or functional outcome. The lack of a statistical association was evident when all types of PEDs were analyzed collectively and when particular types of PEDs (PLEDs, BIPLEDs, or GPEDs) were analyzed independently. However, 4 major clinically relevant findings were evident in the statistical analysis of this cohort of patients. First, in patients with PLEDs, logistic regression analysis showed that the occurrence of seizures was statistically less likely to be associated with death as a clinical outcome. Calculation of the likelihood of death as an outcome in patients with PLEDs and seizures compared with patients with PLEDs without seizures gave an OR of 0.21 (95% CI, 0.04-0.97). Second, calculation of the likelihood of death as an outcome in patients with a chronic etiology for PLEDs compared with patients with an acute etiology for PLEDs showed an OR of 0.14 (95% CI, 0.03-0.72). When the adjacent categories logistic regression model was applied in the analysis, a similar association was found when we compared the odds of death and of dependent functional capacity. Third, the OR of death and seizures vs death and no seizures favors the latter, with ORs of 0.281 (95% CI, 0.9-0.89) and 0.14 (95% CI, 0.03-0.62) for the comparison between the groups' chronic etiology and acute etiology, respectively. Fourth, the OR for patients with a dependent functional outcome to have a neoplastic etiology for PLEDs rather than a vascular etiology was 0.45 (95% CI, 0.3-0.67). In the inferential analysis, using a likelihood approach between the EEG parameters of amplitude, inter-PED interval, duration of complexes, and the functional outcome, we found an overlap of the likelihood CIs at a level of 0.1465 of the relative likelihood functions of the standard deviations of the measurements of these variables in each group of the functional outcome, which is equivalent to the 95% CI. Hence, no statistical associations were detected between these EEG parameters and the functional outcome.

COMMENT

Periodic epileptiform discharges are an uncommon EEG pattern characterized by lateralized or generalized; periodic or near periodic; or spike, spike-wave, or sharp-wave complex presentations throughout most or all of the recording.[1] Most PEDs are lateralized (PLEDs) and they are usually seen diffusely over 1 cerebral hemisphere but may be localized to a single region. Periodic lateralized epileptiform discharges have a frequency of 0.2 to 3.0 Hz; are

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

often biphasic, triphasic, or polyphasic in form; and are associated with a localized attenuation in the background activity present between discharges.[1,2,5-7,9-11] Periodicity, the hallmark of PLEDs, generally varies less than 20% within an individual EEG but may vary significantly from patient to patient.[5,12] Generalized periodic epileptiform discharges are defined as periodic complexes occupying at least 50% of a standard 30-minute EEG over both hemispheres in a symmetric, diffuse, and synchronized manner.[2,7] The prevalence of PLEDs ranges from 0.1% to 1% in routine EEGs.[1,5,7,11,13-16] The true incidence is likely higher, as many patients with PLEDs may not undergo EEG, particularly those without a recent seizure or altered mental status.[5] Similarly, the true prevalence and incidence of BIPLEDs and GPEDs are unknown, with studies reporting an incidence of 4% to 22% of BIPLEDs in patients in the intensive care unit[1,5,17,18] and a prevalence of 0.1% in routine EEG.[5] Our study showed prevalences of 0.09% for BIPLEDs and 0.06% for GPEDs.

The generally older mean age (56-64 years) reported in the literature and the extremely rare occurrence of PLEDs in children suggest that PLEDs are predominantly an age-related phenomenon.[11,13-15] The patients in this study had an age and sex distribution consistent with previous articles. Patients whose EEGs show PLEDs usually have an acute (or subacute) hemispheric disease process as well as a decreased level of consciousness, focal neurological signs, seizures, and acute illness.[9,10,15] They can be seen less commonly with a remote cerebral lesion, though chronic PLEDs are now well recognized.[3] Bilateral independent PLEDs and GPEDs are seen in multifocal or diffuse cerebral injuries, such as anoxia, and herald a less favorable prognosis with higher mortality.[2,5,8,12] Overall, 45% of our patients with PEDs had evidence of an associated acute etiology, particularly patients with BIPLEDs and GPEDs. However, an acute etiology was statistically associated with an increased probability of death only in patients with PLEDs. This restricted association may be due to the small number of patients in the BIPLED and GPED groups. Nonetheless, the patients with BIPLEDs and GPEDs had a higher mortality (29%-39% vs 24%) than the PLEDs group. We did not determine the prevalence of chronic PLEDs in this study.

Consistent with previously reported clinical series,[15,19] the most common cause of the PLEDs in our series was cerebrovascular disease. In terms of prognosis, our study showed that in patients with PLEDs, a nonneoplastic etiology was associated with a better long-term prognosis. This association could be explained by the natural history of brain tumors leading to dependence and death in many patients.[20] Another possible explanation is that the underlying cause of PLEDs is more acute and immediately life-threatening than neoplasia in many patients with PLEDs (despite the poor prognosis of many brain tumors). Presently, it is unclear whether the neurophysiologic nature of PLEDs, irrespective of underlying cause, affects clinical outcome. For example, it is not established that PLEDs associated with an underlying brain tumor are intrinsically more life-threatening than PLEDs associated with a subdural hematoma; rather, the underlying disease process predicts clinical outcome.

Periodic lateralized epileptiform discharges often occur in conjunction with acute seizures (often evident on the same EEG recording), mostly partial motor seizures.[5,8-12,19] Some specific PLED patterns called *PLEDs plus* or *BIPLEDs plus*, characterized by PLEDs combined with high-frequency, low-voltage polyspike rhythms, have a stronger correlation with clinical seizures and status epilepticus.[5,21] In our series, the incidence of clinical seizures ranged from 29% to 70% (GPEDs, n=5 [29%]; BIPLEDs, n=10 [43%]; and PLEDs, n=57 [70%]) and were mainly generalized tonic-clonic seizures. The higher frequency of seizures in the PLEDs group could be due to the increased clinical recognition of convulsive seizures compared with focal clinical seizures or nonconvulsive seizures.

In previous studies, the localization of the PLEDs or seizures at onset has not been shown to relate to functional outcome.[11,15] In this study, we found that patients with PEDs who did not have clinical seizures at onset were more likely to die. Patients with PLEDs were more likely to have associated clinical seizures (57 of 82 patients [70%]), whereas patients with BIPLEDs or GPEDs were less likely to have associated seizures (10 of 23 patients [43%] and 5 of 17 patients [29%], respectively). This observation is probably likely explained by a more severe and diffuse cerebral injury in patients with PEDs who do not have seizures. Another possibility is that PLEDs associated with recent seizures are transient manifestations of increased neuronal excitability, irrespective of the underlying etiology.[22] The incidence of subsequent seizures in adults with seizures at presentation and an EEG that shows PLEDs ranges from 10% to 56%,[11,15,16] though 1 in 6 patients had never experienced seizures.[22] Given the high risk of subsequent seizures in this group, patients should be treated with anticonvulsant drugs.[16]

Whether PEDs are an interictal or ictal activity remains unclear, despite reports of regional increases in cerebral blood flow, oxygen use, or hypermetabolism associated with PLEDs.[23,24] In agreement with the literature, our patients with PLEDs showed mainly focal neurological deficits reflecting focal disease, while our patients with BIPLED or GPED patterns showed a higher incidence of coma, reflecting a more diffuse disease.[8,11] Neuroimaging studies indicate that PEDs may arise from a variety of structural substrates, including chronic and subcortical lesions. Acute cortical lesions with involvement of subcortical white matter are the most common imaging finding in patients with new-onset PLEDs, though nonlesional scans are seen in a fraction of patients.[6,8,25] Apparently normal studies could be secondary to lower spatial resolution of computed tomography compared with MRI.[26] Neuroimaging abnormalities are seen in 90% to 100% of patients with PLEDs.[6,25] In our series, imaging studies were abnormal in 95% of patients, most commonly with both cortical and subcortical injury. This imaging pattern could be a consequence of using strict criteria for delineating abnormalities in gray matter and white matter as well as the increased number of patients who underwent MRI during their hospitalization than in prior studies.[6,25] The high resolution of modern neuroimaging techniques allows detailed characterization of different cerebral areas, including delineation of the junction of gray and whiter matter. A similar distribution of MRI abnormalities was seen in patients with PLEDs and BIPLEDs in prior studies.[25,26] One study reviewed 71 adults with PLEDs and found that the

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

most frequent imaging abnormality was an acute cortical lesion with involvement of subcortical matter.[25] Postmortem studies further delineate the pathologic lesions associated with PLEDs. Our findings correlate with those of a postmortem study in which 9 patients with periodic EEG patterns were found to have cortical, subcortical, or combined lesions: 5 had cortical and subcortical gray matter and white matter lesions, 3 had cortical and subcortical gray matter lesions, and 1 had a cortical gray matter lesion; none had isolated white matter lesions.[27]

A previous study compared morphologic variables (duration of individual complexes, stereotypy of morphology, degree of intervening slow rhythms, and frequency) in PLEDs associated with a cortical lesion and those associated with a subcortical lesion and reported that these 2 groups represented different populations of neurons.[6] The duration of PLEDs associated with cortical abnormalities on imaging was found to be significantly longer than that of PLEDs associated with a subcortical imaging abnormality. Periodic lateralized epileptiform discharges of cortical origin were found to have more morphologic variability than PLEDs of subcortical origin.[6] However, in that study, the EEG variables were scored on only one 30-second epoch of recording, and the morphology variability was scored subjectively.

To our knowledge, no other study has investigated the relationship between the localization of imaging abnormalities in patients with PLEDs and long-term outcomes. Our study showed that the location of imaging abnormalities was not related to the functional outcome or mortality. The long-term outcome in adults whose EEGs showed PLEDs had received little attention since they were first reported.[15,28,29] Our results are in agreement with those previously reported in the literature, which also reported high mortality, ranging from 25% to 41%.[1,5,15,29] One study retrospectively analyzed the clinical outcomes of 39 patients for up to 37 months after discharge.[15] They found that the patients with an acute stroke had poor prognoses compared with patients with potentially reversible etiologies. In our study, we did not find any statistical relationship between the neurological findings or the history of seizure and the functional outcome.

Few studies have studied the relationship between the intrinsic characteristics of periodic discharges and long-term outcomes. One retrospective study of 55 EEGs that showed PLEDs analyzed the periodicity of the PLEDs and reported that in patients with PLEDs due to acute viral encephalitis, the discharges were more regular than in those with PLEDs associated with other causes. In that study, patient age, clinical state, and timing of seizures were not associated with the periodicity of PLEDs.[17] Another study retrospectively analyzed 25 patients with GPEDs, of whom 8 (32%) were in status epilepticus.[30] The study compared both GPEDs in patients in or not in status epilepticus. In the status epilepticus group, the GPEDs were higher in amplitude (110 vs 80 μV, $P<.05$) and of longer duration (0.5 vs 0.3 seconds, $P<.05$), and the inter-GPED amplitude was higher (34 vs 17 μV, $P<.05$). The 9 patients (36%) alive at discharge were more likely to be younger (51 vs 68 years, $P<.05$), have a better mental status at the time of their EEG, and have a higher inter-GPED amplitude (33 vs 18 μV, $P<.05$) compared with those who had died.[30] Another study analyzed 37 patients with GPEDs and reported a 48.7% mortality at 1 month.[31] The mortality was 100% in patients with an intrinsic burst-suppression GPED pattern. The mortality was 53.3% in patients whose GPEDs had a shorter inter-GPED interval (0.5-4.0 seconds) compared with a lower mortality rate of 20% in those who had GPEDs with a longer (4-30 seconds) interval. However, these studies analyzed a small number of patients, did not clearly define how the EEG sample was chosen, and reported marked variability of morphologic parameters within and between individuals. In contrast to these studies, ours did not find any statistically significant association between the amplitude, inter-PLED interval, duration of complexes, or the functional outcome.

Accepted for Publication: March 28, 2009.
Correspondence: Daniel San juan Orta, MD, Epilepsy Service, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (investigacionclinica@innn.edu.mx).
Author Contributions: *Study concept and design:* San juan Orta, Chiappa, and Cole. *Acquisition of data:* San juan Orta and Chiappa. *Analysis and interpretation of data:* San juan Orta, Chiappa, Quiroz, Costello, and Cole. *Drafting of the manuscript:* San juan Orta, Chiappa, and Quiroz. *Critical revision of the manuscript for important intellectual content:* San juan Orta, Chiappa, Costello, and Cole. *Statistical analysis:* Quiroz. *Obtained funding:* Cole. *Administrative, technical, and material support:* San juan Orta, Chiappa, Costello, and Cole. *Study supervision:* San juan Orta, Chiappa, and Cole.
Financial Disclosure: None reported.
Funding/Support: The study was funded by a grant from Mexico in Harvard. Dr San juan Orta is supported by an Epilepsy and Clinical Neurophysiology Fellowship.

REFERENCES

1. Chatrian GE, Shaw CM, Leffman H. The significance of periodic lateralized epileptiform discharges in EEG: an electrographic, clinical and pathological study. *Electroencephalogr Clin Neurophysiol.* 1964;17:177-193.
2. Brenner RP, Schaul N. Periodic EEG patterns: classification, clinical correlation, and pathophysiology. *J Clin Neurophysiol.* 1990;7(2):249-267.
3. Téllez-Zenteno JF, Pillai SN, Hill MD, Pillay N. Chronic PLEDs with transitional rhythmic discharges (PLEDs-plus) in remote stroke. *Epileptic Disord.* 2007;9(2):164-169.
4. Treiman DM. Controversies in clinical neurophysiology: which EEG patterns of status epilepticus warrant emergent treatment? *J Clin Neurophysiol.* 1997;14(2):159.
5. Fitzpatrick W, Lowry N. PLEDs: clinical correlates. *Can J Neurol Sci.* 2007;34(4):443-450.
6. Kalamangalam GP, Diehl B, Burgess RC. Neuroimaging and neurophysiology of periodic lateralized epileptiform discharges: observations and hypotheses. *Epilepsia.* 2007;48(7):1396-1405.
7. Kuroiwa Y, Celesia GG. Clinical significance of periodic EEG patterns. *Arch Neurol.* 1980;37(1):15-20.
8. de la Paz D, Brenner RP. Bilateral independent periodic lateralized epileptiform discharges: clinical significance. *Arch Neurol.* 1981;38(11):713-715.
9. Markand ON, Daly DD. Pseudoperiodic lateralized paroxysmal discharges in electroencephalogram. *Neurology.* 1971;21(10):975-981.
10. Schwartz MS, Prior PF, Scott DF. The occurrence and evolution in the EEG of a lateralized periodic phenomenon. *Brain.* 1973;96(3):613-622.
11. García-Morales I, García MT, Galán-Dávila L, et al. Periodic lateralized epileptiform discharges: etiology, clinical aspects, seizures, and evolution in 130 patients. *J Clin Neurophysiol.* 2002;19(2):172-177.
12. Snodgrass SM, Tsuburaya K, Ajmone-Marsan C. Clinical significance of periodic lateralized epileptiform discharges: relationship with status epilepticus. *J Clin Neurophysiol.* 1989;6(2):159-172.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013

13. Raroque HG Jr, Wagner W, Gonzales PC, et al. Reassessment of the clinical significance of periodic lateralized epileptiform discharges in pediatric patients. *Epilepsia*. 1993;34(2):275-278.
14. Terzano MG, Parrino L, Mazzucchi A, Moretti G. Confusional states with periodic lateralized epileptiform discharges (PLEDs): a peculiar epileptic syndrome in the elderly. *Epilepsia*. 1986;27(4):446-457.
15. Walsh JM, Brenner RP. Periodic lateralized epileptiform discharges: long-term outcome in adults. *Epilepsia*. 1987;28(5):533-536.
16. Schraeder PL, Singh N. Seizure disorders following periodic lateralized epileptiform discharges. *Epilepsia*. 1980;21(6):647-653.
17. Gross DW, Wiebe S, Blume WT. The periodicity of lateralized epileptiform discharges. *Clin Neurophysiol*. 1999;110(9):1516-1520.
18. Chen KS, Kuo MF, Wang HS, Huang SC. Periodic lateralized epileptiform discharges of pediatric patients in Taiwan. *Pediatr Neurol*. 2003;28(2):100-103.
19. Pohlmann-Eden B, Hoch DB, Cochius JI, Chiappa KH. Periodic lateralized epileptiform discharges: a critical review. *J Clin Neurophysiol*. 1996;13(6):519-530.
20. Nieder C, Astner ST, Mehta MP, Grosu AL, Molls M. Improvement, clinical course, and quality of life after palliative radiotherapy for recurrent glioblastoma. *Am J Clin Oncol*. 2008;31(3):300-305.
21. Reiher J, Rivest J, Grand'Maison F, Leduc CP. Periodic lateralized epileptiform discharges with transitional rhythmic discharges: association with seizures. *Electroencephalogr Clin Neurophysiol*. 1991;78(1):12-17.
22. Baykan B, Kinay D, Gökyigit A, Gürses C. Periodic lateralized epileptiform discharges: association with seizures. *Seizure*. 2000;9(6):402-406.
23. Handforth A, Cheng JT, Mandelkern MA, Treiman DM. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: further evidence that PLEDs are a manifestation of partial status epilepticus. *Epilepsia*. 1994;35(4):876-881.
24. Ergün EL, Salanci BV, Erbaş B, Saygi S. SPECT in periodic lateralized epileptiform discharges (PLEDs): a case report on PLEDs. *Ann Nucl Med*. 2006;20(3):227-231.
25. Gurer G, Yemisci M, Saygi S, Ciger A. Structural lesions in periodic lateralized epileptiform discharges (PLEDs). *Clin EEG Neurosci*. 2004;35(2):88-93.
26. Raroque HG Jr, Purdy P. Lesion localization in periodic lateralized epileptiform discharges: gray or white matter. *Epilepsia*. 1995;36(1):58-62.
27. Gloor P, Kalabay O, Giard N. The electroencephalogram in diffuse encephalopathies: EEG correlates of gray and white matter lesions. *Brain*. 1968;91:779-802.
28. Westmoreland BF, Klass DW, Sharbrough FW. Chronic periodic lateralized epileptiform discharges. *Arch Neurol*. 1986;43(5):494-496.
29. PeBenito R, Cracco JB. Periodic lateralized epileptiform discharges in infants and children. *Ann Neurol*. 1979;6(1):47-50.
30. Husain AM, Mebust KA, Radtke RA. Generalized periodic epileptiform discharges: etiologies, relationship to status epilepticus, and prognosis. *J Clin Neurophysiol*. 1999;16(1):51-58.
31. Yemisci M, Gurer G, Saygi S, Ciger A. Generalized periodic epileptiform discharges: clinical features, neuroradiological evaluation and prognosis in 37 adult patients. *Seizure*. 2003;12(7):465-472.

©2009 American Medical Association. All rights reserved.
Downloaded From: http://jamanetwork.com/ on 05/25/2013