Prognostic Implications of Periodic Epileptiform Discharges

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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.

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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 (GPELDs), 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.^^^4^ 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.^^^5^ While many studies have indicated that PLEDs are associated with a poor prognosis,^^^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 PLEDs, the acute clinical situation, or contemporaneous neuroimaging findings correlated with long-term outcome.
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. 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 30 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, border-zone 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 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.

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 reference 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.

### RESULTS

Table 2 presents the distribution of different PED patterns, patient demographics, and acuity of the underlying disease. Stroke was the most common cause of PLEDs and Bi 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...
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 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...
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. Most PEDs are lateralized (PLEDs) and they occur in individuals with normal cognitive function, while PLEDs are more commonly associated with underlying structural abnormalities. PLEDs are characterized by their lateralized or generalized; periodic or near periodic; or spike, spike-wave, or sharp-wave complex presentation throughout most or all of the recording.

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

<table>
<thead>
<tr>
<th>EEG Variable</th>
<th>Patients With PLEDs (n=79)</th>
<th>Patients With PLEDs or GPEDs (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-PED interval, ms</td>
<td>847 (501)</td>
<td>824 (613)</td>
</tr>
<tr>
<td>Duration of complex, ms</td>
<td>396 (156)</td>
<td>433 (181)</td>
</tr>
<tr>
<td>Amplitude, µV</td>
<td>81 (49)</td>
<td>76 (47)</td>
</tr>
<tr>
<td>No. of phases</td>
<td>3.6 (0.8)</td>
<td>3.5 (0.7)</td>
</tr>
<tr>
<td>No. of sharp phases</td>
<td>1.2 (0.4)</td>
<td>1.3 (0.5)</td>
</tr>
</tbody>
</table>

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

**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, 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, 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 other 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.
Periodic lateralized epileptiform discharges often occur in conjunction with acute seizures (often evident on the same EEG recording), mostly partial motor seizures. 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. 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. In this study, we found that patients with PLEDs 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 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. The incidence of subsequent seizures in adults with seizures at presentation and an EEG that shows PLEDs ranges from 10% to 56%, though 1 in 6 patients had never experienced seizures. Given the high risk of subsequent seizures in this group, patients should be treated with anticonvulsant drugs.

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. 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. 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 findings in patients with new-onset PLEDs, though nonlesional scans are seen in a fraction of patients. Apparently normal studies could be secondary to lower spatial resolution of computed tomography compared with MRI. Neuroimaging abnormalities are seen in 90% to 100% of patients with PLEDs. 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. The high resolution of modern neuroimaging techniques allows detailed characterization of different cerebral areas, including delineation of the junction of gray and white matter. A similar distribution of MRI abnormalities was seen in patients with PLEDs and BIPLEDs in prior studies. One study reviewed 71 adults with PLEDs and found that the
most frequent imaging abnormality was an acute cortical lesion with involvement of subcortical matter.\textsuperscript{23} 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.\textsuperscript{27}

A previous study compared morphologic variables (duration of individual complexes, stereotopy 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%.\textsuperscript{1,3,15,29} One study retrospectively analyzed the clinical outcomes of 39 patients for up to 37 months after discharge.\textsuperscript{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.\textsuperscript{37} Another study retrospectively analyzed 25 patients with GPEDs, of whom 8 (32%) were in status epilepticus.\textsuperscript{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.\textsuperscript{30}

Another study analyzed 37 patients with GPEDs and reported a 48.7% mortality at 1 month.\textsuperscript{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.

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