Review

Periodic electroencephalographic patterns: a controversial and infrequent finding

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Abstract

Periodic electroencephalographic patterns are discharges usually epileptiform in appearance, which occur at regular intervals associated with acute brain injury such as cerebral vascular disease and encephalitis. They are commonly classified as periodic lateralized epileptiform discharges, periodic lateralized epileptiform discharges bilateral independent, generalized epileptiform discharges, triphasic waves and stimulus-induced rhythmic, periodic or ictal discharges. The aim of this study is to make a review of the periodic EEG patterns, emphasizing the importance of their recognition and clinical significance. The clinical significance of the periodic EEG patterns is uncertain, it is related to a variety of etiologies and suggest that these patterns are unequivocally epileptogenic in some cases and these patterns associated with poor prognosis. Their recognition and classification are important to establish an accurate correlation between clinical, neurological, laboratorial and neuroimaging data with the EEG results, which allow making adequate therapeutic benefit of critical patient behavior.

Keywords
Periodic electroencephalographic patterns, periodic epileptiform discharges, generalized epileptiform discharges, triphasic wave.
Resumen

Los patrones electroencefalográficos periódicos (PEP) son descargas con apariencia epileptiforme que aparecen a intervalos regulares asociadas a una lesión cerebral aguda como la enfermedad cerebro vascular y las encefalitis. Estas descargas se producen a intervalos regulares y se clasifican comúnmente como: descargas epileptiformes lateralizadas periódicas, descargas epileptiformes lateralizadas periódicas independentes bilaterales, descargas epileptiformes generalizadas, las ondas trifásicas y las descargas ictales o periódicas rítmicas inducidas por estímulos. El objetivo de este trabajo es hacer una revisión de los patrones electroencefalográficos periódicos, haciendo énfasis en la importancia de su reconocimiento y su relevancia clínica. La importancia clínica de los patrones periódicos en el electroencefalograma es incierta y está relacionada con diversas etiologías. Algunos autores sugieren que estos patrones son inequívocamente epileptogénicos y se asocian con pronósticos desfavorables. Su reconocimiento y clasificación es importante para establecer una correlación exacta entre los datos clínicos, neurológicos, de laboratorio y de neuroimagen con los resultados del electroencefalograma, lo cual permitiría establecer conductas terapéuticas adecuadas en beneficio del paciente crítico.

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Palabras clave
Patrones electroencefalográficos periódicos, descargas epileptiformes periódicas, descargas epileptiformes generalizadas, ondas trifásicas.
Introduction

Periodic electroencephalographic patterns (PEPs) are always an abnormal finding on the electroencephalogram (EEG). PEPs consist of discharges with diverse forms, which usually have an epileptiform appearance and occur with a regular frequency or at regular intervals intermittently.\(^1\)

These patterns are usually classified as periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs (BIPLEDs), generalized periodic epileptiform discharges (GPEDs), triphasic waves, and stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs).

The term PLEDs was introduced in 1964 by Chatrian et al.,\(^2\) although the phenomenon was described for the first time in 1952 by Echlin et al.\(^3\) PLEDs are a relatively infrequent electroencephalographic pattern characterized by the presence of spike-and-wave complexes, or lateralized sharp waves or focal periodic or quasi-periodic present in most or all of the records.

The purpose of this review is to emphasize the importance and clinical significance of PEPs, considered controversial and infrequent. These patterns may be present in critically ill patients who need therapeutic interventions based on decision-making resulting from their interpretations, which is why we consider the approach of this topic of great importance.

Search strategy and selection criteria

A PubMed/MEDLINE search was performed using the following terms and phrases (combining two with the Boolean operator “and”): periodic epileptiform discharges, electroencephalography, PLEDs, BIPLEDs, GPEDs, triphasic wave, clinical significance, etiologies.

The following limits were established: “only items with links to free full text, Humans, Meta-Analysis, Practice Guideline, Review, English, Spanish, published in the last 10 years.”

On some occasions, publications cited in the articles initially selected were included, regardless of the year of publication, provided they presented current and important information for the development of the review. Only those articles in which the full text could be reviewed were used as references. Those that were considered to have important methodological deficiencies, that were not adequate to the specific topic, or which presented information that had been covered sufficiently in other texts that were considered of higher quality or more recently updated, were discarded.

Periodic Lateralized Epileptiform Discharges (PLEDs)

PLEDs are the most common PEP. These are spike-and-wave complexes followed by slow waves that repeat every 1 to 2 seconds. The periodic complexes are limited to a focal cerebral area (often a hemisphere).\(^2,6\) PLEDs have a frequency of 0.2-0.3 Hz, are often biphasic, triphasic, or polyphasic, and are associated with a localized attenuation of base activity between discharges.\(^4,3\) Periodicity is what characterizes this electroencephalographic pattern, generally varying less than 20% in the same subject but able to vary significantly between one patient and another.\(^6\) In 1950, Cobb\(^7\) attributed the periodicity of the discharges to a disconnection between the cortex and subcortical structures caused by a white matter lesion. However, through experimental studies, Chatrian\(^2\) showed that any injury could be associated with PLEDs. The prevalence of PLEDs in the routine EEG varies between 0.1% and 1%.\(^6,8\)

They are observed in the context of multifocal or diffuse brain lesions such as anoxia and they announce an unfavorable prognosis associated with a higher mortality. Approximately 80% to 90% of patients with PLEDs experience clinical seizure activity, mainly focal motor seizures. In 1991, Reiher et al.\(^9\) described the “PLED plus” entity characterized by PLED mixed with polyspikes of high frequency and low voltage. These have a stronger correlation with the presence of clinical crises and status epilepticus. PLEDs are generally not considered an ictal pattern, although this has
been reported and remains a subject of ongoing debate.10,11

**Bilateral independent periodic lateralized epileptiform discharges (BIPLEDs)**

Bilateral PLEDs which occur independently (BIPLEDs) were recognized by Chatrian in 1964,2 and characterized by de la Paz and Brenner in 1981.12

BIPLEDs occur when PLEDs are viewed in both hemispheres independently and asynchronously. This pattern is less common than PLEDs and is highly associated with the occurrence of seizures in patients with acute diseases.13 Unlike PLEDs, BIPLEDs can be presented as asynchronous complexes that usually differ in morphology, amplitude, frequency of repetition, and topography.14 Some studies report an incidence of BIPLEDs of 4 to 22% in the ICU and a prevalence of 0.1 in the routine EEG.2,6,15 A study by Fitzpatrick6 in 21 patients with BIPLEDs showed a mortality of 52% and a study conducted by de la Paz12 showed a mortality of 61%.

BIPLEDs are typically associated with acute structural injury with or without metabolic disorders.12,13,16 The most common cause of BIPLEDs is anoxic encephalopathy and central nervous system infections, with a high incidence of coma.12,16

**Generalized Periodic Epileptiform Discharges (GPEDs)**

Periodic discharges are defined by a “repetition of a waveform with a relatively uniform morphology and duration, with a quantifiable interdischarge interval between consecutive waveforms, and recurrence of the waveform at nearly regular intervals,” where waveforms are characterized by a duration of 0.5 s or less or limited to three phases.17

GPEDs occur in both hemispheres symmetrically, diffusely and synchronously.4 GPEDs are classified taking into account the interval between short and long discharges. Diffuse periodic discharges with short intervals (periodic short-interval diffuse discharges, PSIDDs) are those whose duration of the interval is between 0.5 and 4 sec. They occur in hypoxic or hepatic encephalopathies, drug toxicity, and neurodegenerative diseases such as Jakob Creutzfeldt disease.4 PSIDDs are associated with toxic-metabolic encephalopathies and anoxic brain damage and related to a fatal evolution and severe neurological sequelae, especially those associated with repetitive myoclonic jerks. Diffuse periodic discharges with long intervals (periodic long-interval diffuse discharges, PLIDDs) are those whose duration of the interval is between 4 and 30 sec.18

In a standard 20-minute EEG record, the incidence of GPEDs is approximately 1%,19,20 occurring in approximately 20% of patients in a coma due to a severe postanoxic encephalopathy after cardiac arrest,21-23 typically presenting in the first 12 to 48 hours after resuscitation.24,25 Other causes are diffuse metabolic encephalopathy,16,26 including encephalopathies associated with sepsis,19 acute brain damage, and cerebrovascular accident.23,27 An example of generalized periodic epileptiform discharges can be seen in Figure 1.

**Triphasic waves**

Generalized periodic discharges also include triphasic waves, a pattern initially described in 1950 by Foley.28 This term was coined in 1955 by Bickford29 in reference to their typical morphology characterized by three phases. They consist of periodic generalized acute waves or strongly contoured delta waves with a triphasic morphology (typically with a negative-positive-negative polarity, with a duration of each phase longer than the previous one), which are repeated between 1.0 and 3.0 Hz.

Triphasic waves are periodic and generalized, usually have a frontal predominance and do not always have an epileptiform appearance (a reason why they are often not included in the GPEDs category).4,13 This pattern can occur in any toxic metabolic or structural encephalopathy, although the first descriptions were associated with hepatic
encephalopathy.\textsuperscript{26,30,31} Recent studies by Foreman\textsuperscript{32} conclude that the triphasic wave is a clinically ambiguous electroencephalographic descriptor that is not reliable in the prediction of seizures or in the presence of toxic-metabolic encephalopathy. An example of triphasic waves can be seen in Figure 2.

Rhythmic ictal or periodic discharges induced by stimuli.

These EEG patterns were first described by Hirsch in 2004,\textsuperscript{33} observing that by stimulating patients in a coma or stupor, EEG patterns of ictal appearance were obtained. These were referred to as stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs). The SIRPIDs are considered periodic when it comes to recurrent epileptiform discharges at regular or almost regular intervals, with an identifiable inter-discharge interval. Some patients with clinical seizures have SIRPIDs, especially focal motor seizures, but this pattern is usually purely an electroencephalographic change that is not accompanied by obvious clinical manifestations. The pathophysiology, clinical, therapeutic, and prognosis of the SIRPIDs is not yet well defined.\textsuperscript{33,35,36}

Etiology

The PLEDs suggest an acute brain dysfunction of diverse etiology or a unilateral brain injury, usually of a destructive nature. This pattern has been described in patients with cerebrovascular accidents, rapidly growing brain tumors such as glioblastoma multiforme, brain abscesses, viral encephalitis, Jakob Creutzfeldt disease, bruising, and less frequently in patients with demyelinating diseases, anoxia, primary epilepsy, and migraines, among others.\textsuperscript{13,35-39}

In cases of cerebral infarction, PLEDs are obtained in the area adjacent to the infarction. This area is partially affected by the disease but is still capable of generating electrical activity. Some authors emphasize the importance of the presence of structural brain injury associated with metabolic disorders in the production of PLEDs.\textsuperscript{13,40,41}

BIPLEDs and GPEDs are associated with diffuse or multifocal brain damage as occurs in anoxia and announce an unfavorable prognosis with high mortality.\textsuperscript{4,6,12,42}

A study conducted by Orta\textsuperscript{16} reported that approximately 45% of patients with periodic

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Generalized epileptiform discharges in a male 8-year-old patient with herpetic viral encephalitis.}
\end{figure}
Epileptiform discharges presented evidence of an associated acute etiology, particularly patients with BIPLEDs and GPEDs. On the other hand, there was a statistical association between acute etiology and a higher probability of death only in those patients who had PLEDs. However, patients with BIPLED and GPED had a higher mortality (29%-39% vs 24%) than the PLED group.

Some authors have studied the association of GPEDs with structural damage. Structural changes have been observed in approximately 78% of patients with GPEDs, most have found a predominance of subcortical lesions typically in subcortical gray matter either alone or in combination with cortical lesions. The absence of structural lesions in magnetic resonance imaging has been reported in 20-25% of patients with GPEDs.

**Evolution**

PLEDs are usually associated with acute-subacute presentation of the underlying disease process. In patients with chronic brain diseases, PLEDs are usually observed during an acute process. The PLEDs are transient and resolve spontaneously between two to three weeks, the discharges tend to decrease in amplitude and distance until they disappear.

Chronic PLEDs have been reported in patients with chronic epilepsy, during alcohol withdrawal or in chronic toxic metabolic syndrome. Many authors consider PLEDs the reflection of acute brain damage associated or not with seizures depending on many factors, such as individual propensity, the existence of underlying processes and the coexistence of metabolic disorders. The evolution is more related to the age of the patient and the etiology than to the specific periodic pattern.

Gurer reported that 7% of the 71 adults studied exhibited chronic PLEDs and that chronic lesions were found in 35% of these patients. Fitzpatrick showed a similar incidence of 10% attributable to the presence of a cortical dysplasia or a severe distant brain injury, all had partial seizures. Fushimi described a patient who presented bilateral PLEDs for more than six months and stated that there were no notable symptoms except for a slight deterioration of memory. Da Silva and Bartolucci reported that the PLEDs disappeared before four days in most of their patients and that this pattern was replaced by the...
appearance of a slow base activity, delta rhythms, voltage suppression periods, and focal paroxysmal activity.

**Ictal vs. interictal pattern**

Garzón performed a prospective study in 55 patients, with a total of 62 epileptic status and 254 ictal/postictal EEG records and analyzed the relationship between PLEDs and status epilepticus.

This researcher showed that although PLEDs were not always associated with seizures and status epilepticus, it could be unequivocally an ictal pattern. An increase in focal glucose metabolism has been shown to be associated with PLEDs, reinforcing their probable epileptogenic nature.

Other investigators consider the PLEDs an interictal change or an unstable ictal-interictal continuum; although their pathophysiology is unknown, they could indicate an ictal pattern in some cases.

Studies have reported that PLEDs are generally associated with the state of clouding in 95% of patients, focal seizures and neurological signs in 80%, and a continuous partial epilepsy in 30% of patients. A study conducted by Snodgrass reports clinical seizures or status epilepticus in the course of the disease in 90% of patients: 50% presented a partial motor status epilepticus, 22% partial motor seizures, 6% continuous partial epilepsy, 6% isolated generalized seizures, and 8% generalized epileptic state.

Seizures that occur in patients with PLEDs may be partial, generalized sensorimotor seizures, complex partial epileptic status, and continuous partial epilepsy.

PLEDs plus and BIPLEDs plus have stronger correlations with clinical crises and status epilepticus. Foreman demonstrated a strong association between non-convulsive status epilepticus and GPEDs while the presence of triphasic waves has a low association with the development of epileptic seizures.

Baykan reported that the extension of PLEDs is also important with respect to the association with seizures. Their results showed that PLEDs that appeared prominent on one side but with a slight contralateral spread had a stronger relationship with status epilepticus or with frequent recent seizures than when PLEDs presented a very strict location.

The pathophysiological processes underlying the PLDEs are still controversial. Some studies have reported hypermetabolism and hyperfunction in the PLED centers studied through PET and SPECT respectively. Hypermetabolism is a condition usually associated with ictal patterns, PLEDs, in this case, represent a partial epileptic state. Other authors through studies conducted with SPECT and IMR concluded that this pattern was probably ictal. The increase in cerebral focal blood flow and metabolism found during PLEDs is in contrast to the hypometabolism usually seen during interictal discharges. Finally, Singh concluded that the pattern was ictal and that it should be considered as an epileptic state due to the presence of a continuous pattern, it would also be a continuous partial epilepsy. Many authors consider it a non-convulsive status epilepticus, a subtle status, or a partial status epilepticus.

Nei reported that PLEDs are the only characteristic of the EEG related to a poor prognosis in epileptic status regardless of the etiology. Snodgrass found that most EEGs with PLEDs were obtained within the first four days with convulsive activity or epileptic status and postulated that the phenomenon of PLEDs in the EEG could be considered as the final stage of epileptic status.

PLEDs can be considered as an electroencephalographic activity closely associated with recent seizures, which is a manifestation of an increase in neuronal excitability caused by various etiologies. A study by Orta reports that the absence of seizures at the beginning (acute etiology) was associated with death.
PLEDs should be verified in patients in intensive care units who do not recover their usual alert level. If there is severe brain disease in the terminal phase, then medication with antiepileptic drugs should not be considered.

Some authors have reported that antiepileptic medication has been effective. Terzano$^6_1$ reported that carbamazepine (CBZ) was effective, concluding that acute PLEDs can represent a non-convulsive status epilepticus. In this same study, the authors observed that patients did not respond adequately to mental tests when the frequency of discharge of PLEDs was 2/sec, 25% responded correctly when the frequency was 0.5/sec, and significantly 80% responded correctly when there were no PLEDs. Corda$^6_2$ also used CBZ to normalize the “electroclinical state.” Medication with barbiturates and phenytoin has not been very helpful, however, good responses to treatment with sodium valproate and felbamate have been reported, resulting in the abolition of PLEDs.$^6_3,6_4$

In certain medical conditions, specific medications not considered antiepileptic drugs can be effective. For example, in a patient with herpes simplex encephalitis, acyclovir was administered and the PLEDs disappeared.$^6_5$ In a case of meningoencephalitis, corticosteroid therapy was dramatically effective.$^6_6$ In the case of PLEDs associated with multiple sclerosis, intravenous steroids are needed for complete recovery, although standard antiepileptic drugs are partially effective.$^6_7$
Conclusions

The clinical importance of PEPs remains uncertain and controversial. PEPs are seen in a wide range of etiologies and they are electrographically heterogeneous. Therefore, patients should be carefully investigated for infectious, toxic-metabolic, and/or intracranial lesions, and a non-convulsive status epilepticus should be considered. Its recognition is important to try to establish an exact correlation between the clinical, neurological, laboratory, and neuroimaging data with the results of the EEG and to guide the therapeutic decisions.

Conflicts of interest
The authors declare that there are no potential conflicts of interest to report regarding this scientific report.

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