Periodic EEG patterns: importance of their recognition and clinical significance

Padrões eletrencefalográficos periódicos: importância do seu reconhecimento e significado clínico

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The term “periodic” was first used by Cobb et al.1, in 1950, to describe periodically occurring discharges in electroencephalograms (EEG) of 5 patients with subacute progressive encephalitis. Periodic EEG patterns consist of various forms discharges, usually epileptiform in appearance, and apply to waves or complexes occurring in sequence at an approximately regular rate or intermittently regular intervals2,3. They are commonly classified as periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs or BIPLEDs, generalized epileptiform discharges (GPEDs) and triphasic waves2-7. Although not always epileptiform in appearance, triphasic waves are periodic and generalized, and many authors suggest that these patterns are unequivocally epileptogenic in some cases. Their recognition and classification are important to establish an accurate correlation between clinical, neurological, laboratorial and neuroimaging data with the EEG results.

Key words: electroencephalography, PLEDs, BIPLEDs, GPEDs, triphasic waves, SIRPIDs.

ABSTRACT

Periodic electroencephalographic (EEG) patterns consist of discharges usually epileptiform in appearance, which occur at regular intervals, in critical patients. They are commonly classified as periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs or BIPLEDs, generalized epileptiform discharges (GPEDs) and triphasic waves. Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs) are peculiar EEG patterns, which may be present as periodic 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 many authors suggest that these patterns are unequivocally epileptogenic in some cases. The recognition and classification are important to establish an accurate correlation between clinical, neurological, laboratorial and neuroimaging data with the EEG results.

Key words: electroencephalography, PLEDs, BIPLEDs, GPEDs, triphasic waves, SIRPIDs.

RESUMO

Padrões eletrencefalográficos (EEG) periódicos consistem em descargas geralmente epileptiformes em aparência, que ocorrem a intervalos regulares, em pacientes críticos. Esses padrões são habitualmente classificados como descargas epileptiformes periódicas lateralizadas (PLEDs), PLEDs bilaterais e independentes ou BIPLEDs, descargas epileptiformes periódicas generalizadas (GPEDs) e ondas trifásicas. Descargas rítmicas, periódicas ou ictais induzidas por estímulos (SIRPIDs) são padrões eletrencefalográficos peculiares, que podem se apresentar como descargas periódicas. O objetivo deste estudo é fazer uma revisão dos padrões EEG periódicos, enfatizando a importância do seu reconhecimento e seu significado clínico. O significado clínico dos padrões EEG periódicos é incerto. Está relacionado a uma variedade de etiologias e muitos autores sugerem que tais padrões sejam inequivocamente de natureza epileptogênica em alguns casos. O seu reconhecimento e classificação são importantes para estabelecer uma correlação acurada entre dados clínicos, neurológicos, laboratoriais e de neuroimagem com os resultados de EEG.

Palavras-Chave: eletroencefalografia, PLEDs, BIPLEDs, GPEDs, ondas trifásicas, SIRPIDs.

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Periodic EEG activity is commonly observed in critical patients, especially in the intensive care unit (ICU) setting, but, except for SIRPIDs, this terminology has been based primarily on routine 20-30 minute EEG recordings. They are indicative of significant acute or subacute brain impairment and may be lateralized or generalized. Periodic discharges should direct the attention to the high potential for seizures and convulsive or nonconvulsive status epilepticus, and many authors recommend the use of conventional antiepileptic drugs (AEDs) to manage any occurrence of these discharges.

Sekiguchi et al. described a case of PLEDs in an infant with congenital protein C deficiency. In cerebral infarction, PLEDs are usually recorded on the area adjacent to infarction, which is partially affected by the disease process and is able to generate electrical activity (unlike the area directly affected by infarction), but whether these cells are apoptotic or regenerating is unknown. Neufeld et al. and Chu et al. emphasized the importance of the presence of an structural brain lesion associated with metabolic disturbances in the production of PLEDs.

SIRPIDs recorded in the EEG; thus, they could be considered a nonspecific result of acute partial and transient functional denervation in a localized area of the cortex.

Reihler et al. proposed a subclassification of PLEDs in two major groups: PLEDs-proper, in which the periodicity of the discharges is relatively stable, the discharges are simply configured and uniform, and there are no associated rhythmic discharges; and PLEDs-plus, in which the periodicity of the discharges is variable and there is associated low amplitude rhythmic activity with the discharges. It seems that PLEDs-plus pattern is more associated with seizures, but few studies suggested significant risk stratification for it.

Chong et al. reported their experience with 24-hour continuous EEG recordings (coEEG) and observed that PLEDs-proper rarely occurs in isolation, while the EEG typically fluctuating between PLEDs-proper and PLEDs-plus, with high seizures risk in these patients.

PLEDs are indicative of an acute non-specific brain dysfunction or unilateral brain lesion, usually destructive, and they are most often present in cases of cerebral infarction. They have also been described in the presence of fast-growing brain tumors (as glioblastoma multiforme), brain abscesses, viral encephalitis (especially related to the Herpes simplex virus), Creutzfeldt-Jakob disease (CJD), hematomas and, less frequently, in demyelinating diseases, anoxia, primary epilepsy, migraine and fat embolism syndrome, among others. Sekiguchi et al. described a case of PLEDs in an infant with congenital protein C deficiency. In cerebral infarction, PLEDs are usually recorded on the area adjacent to infarction, which is partially affected by the disease process and is able to generate electrical activity (unlike the area directly affected by infarction), but whether these cells are apoptotic or regenerating is unknown. Neufeld et al. and Chu et al. emphasized the importance of the presence of a structural brain lesion associated with metabolic disturbances in the production of PLEDs.
specific periodic EEG pattern. Garzon et al. performed a prospective and clinical study in 55 patients, with a total of 62 status epilepticus and 254 ictal/postictal EEG recordings, and analyzed the relationship between PLEDs and status epilepticus. They demonstrated that, although PLEDs were not always associated with seizures and status epilepticus, they can be unequivocally an ictal pattern. Increased focal glucose metabolism has been demonstrated associated with PLEDs, reinforcing their probable epileptogenic nature. Although they indicate an ictal pattern in some cases, PLEDs are usually considered an interictal change or an unstable ictal-interictal continuum. PLEDs are usually associated with obtundation in 95% of patients, focal seizures and focal neurological signs may occur in 80%, and epilepsy partialis continua in 30% of the patients. Clinical seizures or status epilepticus were seen during the course of illness in 126 (90%) patients in a study performed by Snodgrass et al., with 50% presenting partial motor status epilepticus, 22% partial motor seizures, 6% epilepsy partialis continua, 6% isolated generalized seizures and 8% generalized status epilepticus. The prevalence of PLEDs in routine EEG laboratories ranges from 0.1% to 1%. Bilateral Periodic Lateralized Epileptiform Discharges – BIPLEDs BIPLEDs occur when PLEDs are seen in both hemispheres, in an independent and asynchronous manner. This pattern is less common than PLEDs and is highly associated with seizures in acutely ill patients. In contrast to PLEDs, BIPLEDs may present as asynchronous complexes, usually differing in morphology, amplitude, rate of repetition, and site of maximal involvement. BIPLEDs are typically associated with acute structural lesions, with or without metabolic disturbances. The most common causes of BIPLEDs are toxic-metabolic encephalopathy and central nervous system infection, with a high incidence of coma state. Few studies demonstrated that clinical state and prognosis may be worse than with PLEDs, but a case of benign BIPLEDs has also been reported. In a study with 21 patients with BIPLEDs, Fitzpatrick et al. demonstrated a mortality rate of 52%, and De la Paz et al. studying 21 patients too, demonstrated a mortality rate of 61%. The true prevalence and incidence of BIPLEDs are unknown, with studies reporting an incidence of 4% to 22% in patients in the ICU, and a prevalence of 0.1% in routine EEG laboratories. Generalized Periodic Epileptiform Discharges – GPEDs GPEDs are defined as periodic complexes occupying at least 50% of a standard 30-minute EEG, projected over the both hemispheres, in a symmetric, diffuse and synchronous manner (although they may be more prominent in a given region, frequently the anterior regions). The discharges vary in shape, but usually are characterized by spikes or sharp waves of high amplitude. They are usually classified as PSIDDs and PLIDDs. According to the interval between the discharges, the burst suppression pattern may be present as GPEDs. PSIDDs have a periodicity less than 4.0 seconds and are more common and less specific than PLIDDs. Generally, PSIDDs are associated to toxic-metabolic encephalopathies, anoxic brain injury, CJD and subclinical or nonconvulsive status epilepticus. Sometimes, it is difficult to distinguish the etiology of GPEDs, even with history and clinical findings suggesting or not an epileptic or toxic-metabolic etiology. Central nervous system infection, as neurophilis, has been described in association with GPEDs in patients with cognitive and behavioral disorders. In a study with 25 patients presenting GPEDs, Husain et al. reported that 7 (28%) of them had toxic-metabolic encephalopathy, 10 (40%) had anoxia and toxic-metabolic encephalopathy, 8 (32%) had a primarily neurological process, and 8 (32%) were in status epilepticus. In practice, a clinical trial with AEDs is almost always warranted to differentiate nonconvulsive status epilepticus from severe encephalopathies although most patients will not respond clinically or electrographically. Gloor et al. suggested that the periodicity of the discharges might be related to the recovery cycle of both cortical and subcortical structures, and that the subcortical discharges may be responsible for the surface discharges, but their repetition rate depends upon cortical recovery time. They proposed an abnormal functional state in the central nervous system, permitting rapid generalization of neuronal discharges. In the CJD, the classic EEG patterns usually are characterized by PSIDDs, with biphasic or triphasic sharp waves, with a duration of 100-300 milliseconds and recurring at 0.7-1.5 second interval between the discharges, with symmetric and synchronous widespread. Traub et al. suggested, through experimental evidence and computer modeling, that synchrony and periodicity in the CJD may be related to a virus-induced fusion of neuronal processes, particularly dendrites, leading to an abnormal electrotonic coupling between cells, providing the basis for powerful excitatory interaction whereby large neuronal aggregates burst in near synchrony. Cortical synchronous discharges would give rise to sharp waves in the EEG, whereas similar discharges in brainstem, spinal cord or elsewhere could lead to myoclonic jerks. It is worth remembering, however, that the bioelectric cerebral activity is a dynamic process, with temporal variations and transient patterns, which could difficult the correct interpretation and show the necessity of serial EEGs in some cases, to establish the correct clinical and EEG correlation. In the early course of the CJD, diffuse slowing is the most common EEG finding, with GPEDs becoming evident within months after clinical onset, sometimes evolving from PLEDs (Fig 2A-2B).
in the early stages of CJD may resemble nonconvulsive status epilepticus too. The clinical and EEG correlation, response to AEDs and monitoring with serial EEG recordings may be helpful considerations in the differential diagnosis.

PLIDDs usually have a frequency of at least 4.0 seconds between the discharges. They are more specific with respect to the etiology and may be encountered in disorders like some toxic encephalopathies (for baclofen or ketamine, for example), anoxic brain injury and SSPE. In SSPE (suggested by the presence of PLIDDs in a child with dementia and myoclonic jerks), the stereotyped complexes, occurring at a regular interval and having a constant relationship to myoclonus, make this as one of the most characteristic and disease-specific of all EEG patterns. The early descriptions, by Cobb, in 1966, characterized the stage II of SSPE by bilaterally symmetrical and synchronous generalized, stereotyped high amplitude delta waves, called Radermacker or “R” complexes, recurring at regular intervals of 5 to 15 seconds, although less specific and atypical EEG changes have been described. With advancing disease, the interval between the discharges becomes progressively smaller. Silva et al. described an atypical clinical and EEG pattern in a 14-year-old boy with SSPE, who presented an initial EEG characterized by a left temporal focus which evolved to PLEDs. Typical GPEDs appeared during the 3rd and 4th weeks.

GPEDs are an uncommon EEG pattern with an overall incidence between 0.4% and 1% in EEG laboratory series. It seems that more than 50% of patients with GPEDs have definite seizures during the acute illness.

**Triphasic waves**

Generalized periodic discharges also include triphasic waves, a pattern initially described in 1950 by Foley et al., who named the waves as “blunted and spike waves”. Triphasic waves are periodic and generalized, typically frontally predominant and not always epileptiform in appearance (a reason for they are often not included in the GPEDs categorization). This pattern can occur in any toxic-metabolic or structural encephalopathy although the early descriptions associated its presence to hepatic encephalopathy. The three most common causes of triphasic waves are hepatic encephalopathy, renal failure (Fig 3) and anoxic injury. This term was coined by Bickford et al., in reference to the typical morphology, characterized by three phases. They consist of generalized periodic sharp waves or sharply contoured delta waves with a triphasic morphology (typically with a negative/positive/negativity polarity, with each phase lasting longer than the prior), recurring at 1.0 to 3.0Hz, with or without an anterior-posterior or posterior-anterior lag. When the term triphasic waves is used, it usually implies a pattern.
seen with a variety of encephalopathies, particularly hepatic or renal. It is worth to remember, however, that this term can be used to describe the morphology of waveform in that sharp and slow wave three phases complexes.

Sometimes, when patients present confused and obtunded and rhythmic sharp waves resembling triphasic waves appear in the EEG, it is difficult to distinguish nonconvulsive status epilepticus from toxic-metabolic encephalopathy. In these situations, some authors recommend the use of benzodiazepines administration to verify the resolution of EEG changes in the cases of nonconvulsive status epilepticus even though triphasic waves may be abolished by benzodiazepines administration, as demonstrated by Foutain et al.

Boulanger et al. compared the 87 EEGs of 71 patients with triphasic waves and 27 EEGs of 13 patients with nonconvulsive status epilepticus, and showed that, when compared to triphasic waves, epileptiform discharges associated with nonconvulsive status epilepticus had a higher frequency.

Fig 2. Periodic lateralized epileptiform discharges (PLEDs) in the right hemisphere, predominantly over the frontotemporal regions (A), with some widespread, evolving to generalized periodic epileptiform discharges (GPEDs) (B) in an EEG of a 50-year-old woman with rapidly progressive cognitive impairment, altered mental status and muscle spasms. The clinical picture, the neuroimaging studies, the absence of toxic-metabolic disorders and no improvement with antiepileptic drug allied to the EEG periodic patterns supported the presumptive diagnosis of Creutzfeldt-Jakob disease.

Fig 3. Pseudoperiodic runs of triphasic sharp waves in a background generalized slowing EEG. This record corresponds to a metabolic (renal failure) encephalopathy in a 69-year-old man, presented with an altered mental status.
shorter duration of phase one, extra-spikes components and less generalized background slowing. Noxious or auditory stimulation frequently increased the triphasic waves and had no effect on the epileptiform pattern. The authors concluded that certain EEG criteria and the response to stimulation are very helpful in distinguishing triphasic waves from generalized nonconvulsive status epilepticus.

**Stimulus-induced Rhythmic, Periodic or Ictal Discharges – SIRPIDs**

SIRPIDs were first described in 2004 by Hirsch et al., who recorded coEEG and digital video in critically ill patients in the ICU setting. They have noted striking EEG patterns when stuporous or comatose patients were stimulated and noted that many of these patterns appear ictal, but were consistently elicited by stimulation. They named these EEG patterns as SIRPIDs and defined them as periodic, rhythmic or ictal appearing discharges that were consistently induced by alerting stimuli, such as auditory, sternum rub, examination, suctioning, turning and other patient-care activity. They consider SIRPIDs as periodic when the pattern consist of epileptiform discharges recurring at regular or nearly regular intervals, with an identifiable interdischarge interval. The specific periodic patterns were classified as periodic epileptiform discharges (PEDs) and subdivided in PLEDs, BIPLEDs, GPEDs and triphasic waves. Some patients present clinical seizures with SIRPIDs, especially focal motor seizures, but this pattern is usually a purely electrographic change, with no obvious clinical manifestations. The pathophysiology, exact clinical, therapeutic and prognostic significance of SIRPIDs is still undefined.

**Final remarks**

The clinical significance of the periodic EEG patterns remains uncertain. Many authors suggest that they are unequivocally epileptogenic in some cases, and that aggressive treatment with AEDs is still unclear. A clinical trial with AEDs to treat a possible nonconvulsive status epilepticus is indicated on the majority of the cases although most patients will not respond clinically or electroencephalographically.

Periodic patterns are seen from a wide variety of etiologies, and the discharges themselves are electrophysiologically heterogeneous. So, the patients should be carefully investigated for toxic-metabolic, infectious diseases and/or intracranial lesions, and nonconvulsive status epilepticus should be considered. Their recognition is important to try to establish an accurate correlation between clinical, neurological, laboratory and neuroimaging data with the EEG results and to guide the decisions making.

**References**


