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How to evaluate and assess the epileptogenic/seizure potential of periodic discharges along the ictal-interictal continuum?

Ictal potential and clinical approaches

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Abstract

The ictal–interictal continuum (IIC) is a concept used for those particular EEG patterns that do not meet the strict criteria for status epilepticus but may be associated with neuronal injury. The aim of this article is to review equivocal periodic patterns and to discuss their clinical significance along the IIC. The risk of seizures increases when the frequency of periodic discharges exceeds 2 Hz and when the pattern has features of superimposed rhythmic, sharp, or fast activity (*plus* modifier). Lateralized periodic discharges (LPDs) are one of the best examples of the IIC. Criteria have been proposed for identifying patterns along the IIC that we called "peri-ictal" LPDs. There is ongoing debate about when to treat patients with these EEG patterns along this spectrum. The term IIC is only an EEG description, and does not in itself reflect a clinical diagnosis, hence management is based on EEG alone. The decision to intensify treatment is based on the combination of EEG, the underlying etiology, the level of consciousness, comorbidities, imaging, and other surrogates of "damage."

Keywords
Continuous EEG monitoring · Periodic patterns · Peri-ictal · Intensive care unit · Management

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Introduction

The concept of an ictal–interictal continuum (IIC) was initially proposed to explain the nature of lateralized periodic discharges (LPDs) as "unstable neurobiological processes, … the patient's pre-existing propensity to have seizures" [19]. Indeed, LPDs may be either interictal or ictal but usually are associated in the subsequent hours or days with clinical or subclinical epileptic seizures (concept of IIC). The term IIC has seen wide adoption and was formally accepted by the American Clinical Neurophysiology Society (ACNS) as "a pattern that does not qualify as definite seizure, but there is a reasonable chance that it may be contributing to impaired alertness, causing other clinical symptoms, and/or contributing to neuronal injury" [10]. The aim of this article is to review periodic discharges (PD) and to discuss their clinical significance along the IIC.

Definitions proposed by the American Clinical Neurophysiology Society (2021)

The American Clinical Neurophysiology Society (ACNS) Subcommittee on Research Terminology for Continuous EEG revised the EEG terminology and aimed to avoid terms with clinical connotations such as "epileptiform" and "triphasic waves" [11]. EEG patterns are described initially (main term 1) as *generalized, lateralized, bilat-*

eral independent, multifocal, and unilateral independent and must be combined with a main term 2 that describes the appearance of the pattern. Then, modifiers may be applied [10]. The "plus" modifier, according to the ACNS (2021), refers to additional features that render the pattern more "ictal-appearing" than the same pattern without "plus."

Patterns in the IIC include PDs or spike-wave (SW) patterns occurring > 1 Hz and ≤ 2.5 Hz or any PDs or SW patterns ≥ 0.5 Hz and ≤ 1 Hz and have a "plus" modifier or fluctuation in frequency or any lateralized rhythmic delta activity (LRDA) ≥ 1 Hz with a "plus" modifier or fluctuation in frequency. Patterns must be recorded for at least 10 s. The term IIC is synonymous with "possible electrographic seizures" or "possible electrographic status epilepticus (SE)."

Seizure risk

There is some objective evidence that the risk of seizures increases when the periodic discharge frequency exceeds 2 Hz. In a study of comatose patients with high-grade spontaneous subarachnoid hemorrhage undergoing invasive monitoring—including depth electrodes, measurement of the partial pressure of oxygen in interstitial brain tissue, and regional cerebral blood flow—an increasing frequency of PD from 0.5 to 3 Hz was associated with an increase in regional cerebral blood flow (CBF) and a decrease in the partial pressure of oxygen, although the tissue oxygen began to drop to hypoxic values when the PDs exceeded 2 Hz [29].

In a large, multicenter study of 4772 consecutive critically ill adult patients undergoing continuous EEG monitoring, LPDs were associated with the highest risk of seizures, whereas generalized periodic discharges (GPDs) had a lesser risk with no association when frequencies were lower than 1.5 Hz [21]. Lateralized rhythmic delta activity was associated with seizures when the frequency was at 1.5 Hz or faster, while generalized rhythmic delta activity (GRDA) was not associated with seizures, regardless of the frequency of the pattern. For LPDs, LRDA, and GPDs, the faster the frequency of the pattern, the higher the association with seizures. The "plus" modifier was associated in all cases with additional risk.

The *2HELPS2B score* is a score calculated on a 1-h EEG that includes six variables allowing identification of those patients at risk of seizures [25]. This score recommends a particular duration of EEG monitoring to achieve a less than 5% risk of seizures. If the score is 0 (< 5% risk of seizures), 1-h EEG without seizure is adequate to conclude that seizures are unlikely to occur with a longer EEG. If the score is 1 (12% risk of seizures), at least 12 h of negative EEG is necessary, and if the score is ≥ 2 (> 25% risk of seizures), at least 24 h of negative EEG is required to reach 95% certainty of not detecting seizures.

- 2H: > 2 Hz pattern (any periodic or rhythmic pattern except GRDA); 1 point
- E: Epileptiform discharges, sporadic; 1 point
- L: Lateralized (LPDs, LRDA), or bilateral independent periodic discharges; 1 point
- P: "Plus" features (i.e., superimposed rhythmic, sharp, or fast activity); 1 point
- S: Seizure (history of seizure, remote or acute); 1 point
- 2B: Brief potentially ictal rhythmic discharges; 2 points

Individual types of periodic discharges

Lateralized periodic discharges

In 1964 Chatrian et al. proposed the acronym "PLEDs" (periodic lateralized epileptiform discharges) to describe (in 33 patients) those sharp-wave discharges occurring periodically or quasi-periodically at rates generally close to 1/s and separated by intervals of apparent inactivity [3]. In their series, most patients had seizures (88%). The acronym "PLEDs" was then endorsed [4], but with intense debate about the exact significance of the pattern. Since not all patients present with seizures, the word "epileptiform" was removed, and the acronym "LPDs" was proposed [11].

Lateralized periodic discharges represent one of the best examples of the IIC. Generally, LPDs may be considered an interictal EEG pattern reflecting nonspecific but "irritative" brain injury or, conversely, may be an ictal pattern reflecting, in these situations, a focal nonconvulsive status epilepticus (NCSE; [6]). Between this apparent dichotomous distinction there are "peri-ictal" LPDs [6]. Peri-ictal means that LPDs are temporally associated with focal seizures (clinical and/or subclinical), but the condition at the time of the recording does not meet the criteria for SE.

The classification of LPDs into LPDs-proper (LPDs without rhythmic discharges) and LPDs-plus (LPDs with rhythmic discharges) proposed by Reiher et al. in 1991 is still valid. Rhythmic discharges were defined as "any brief focal stereotyped rhythmic discharge closely associated in time and in spatial distribution to a higher amplitude interictal epileptiform discharge" [20]. When LPDs are associated with polyspikes, fast epileptic rhythms, the distinction between "plus" versus "proper" is quite easy, but this distinction is sometimes subjective, especially when the periodic pattern has only a spiky morphology. We propose adding to the definition of LPDs-plus the modifier "spiky" to the LPDs followed by associated slow afterwaves or periods of flattening, giving rise to a triphasic morphology [6]. The distinction of "proper" versus "plus" should be retained. LPDs-plus are more often associated with seizures than LPDs-proper. LPDs-plus commonly lie along the IIC. We defined a particular subtype of LPDs-plus that we called "LPDs-max" (periodic polyspike-wave activity and/or focal burst-suppression-like patterns; [6]). These LPDs-max do not lie along the IIC. They correspond to a focal NCSE favoring the temporo-parieto-occipital regions and are refractory to antiseizure drugs (ASD).

A set of criteria with both EEG criteria and clinical/neuroimaging procedures was proposed by designating the pattern as ictal/peri-ictal or as an interictal/irritative brain injury (**Table 1**; **Fig. 1**). Besides LPDs-proper versus LPDs-plus, the periodicity of the pattern is an essential element that should be taken into account. The more the pattern appears "rhythmic," the higher the index of epileptogenicity. In the study that included 4772 consecutive critically ill adult patients (see previous section), LPDs with frequencies from 0.5 to 2.5 Hz were the

Table 1 Comparison between the different types of LPDs [♂]

Interictal/irritative brain injury	Peri-ictal/ictal
1. LPDs-proper	*1.* LPDs-plus
2. Periodicity ≤ 0.5 Hz[a]	*2.* Periodicity ≥ 1 Hz[a]
3. Monomorphic activity	*3.* Spatiotemporal evolution of the EEG pattern
–	*4.* Neurological signs and seizure disorders[b]
	5. Neuroimaging results

LPDs lateralized periodic discharges
[a]Between 0.5 and 1 Hz, the ***plus*** modifier and the spatiotemporal evolution of the pattern can make the difference
[b]Time-locked signs linked to the LPDs can be considered to be sufficient to classify the phenomenon as ictal, regardless of the other criteria

only patterns associated with seizures [21]. A significant association between LPD frequency and 18-fluorodeoxyglucose uptake on positron emission tomography (PET) was reported in nine patients. The LPDs at 1 Hz had a metabolic demand that was 100% higher than LPDs at 0.5 Hz, and when over 1 Hz, the demand was 309% higher [27]. We suggest that LPDs with a periodicity greater than or equal to 1 Hz are associated with ictal or peri-ictal patterns, i.e., along the IIC, whereas a periodicity of less than or equal to 0.5 Hz is associated with interictal/irritative brain injury. Between 0.5 and 1 Hz, the plus modifier and the spatiotemporal evolution of the pattern make the difference.

Neuroimaging procedures such as single-photon emission computed tomography (SPECT) or PET scan have been suggested in cases of suspected focal NCSE. Although revealing, these procedures are not well suited for emergency situations. With the development of stroke centers, brain magnetic resonance imaging (MRI) is available 24/7 in most public and private hospitals, and hence the use of arterial spin labeling (ASL), an MRI sequence that does not require a contrast injection, is a promising technique for evaluating focality in cerebral perfusion and therefore, in cases where focal SE is suspected [22].

Generalized periodic discharges

Generalized periodic discharges may be observed in many different situations. Triphasic waves (TWs) were included in this category with the modified term of "GPDs with triphasic morphology" [11], but the prognosis of TWs seen in toxic/metabolic encephalopathies is different from that of GPDs found in post-cardiac arrest anoxic brain damage. Furthermore, GPDs may be observed in NCSE. Possible SE is proposed when the discharge is less than 2.5 Hz with fluctuation without definite evolution [16]. This concept of fluctuation without evolution is also used in the recent definition of IIC for periodic patterns. Fluctuating patterns include "patterns fluctuating from 1 to 1.5 to 1 to 1.5 Hz; alternating between two morphologies repeatedly; or spreading in and out of a single additional electrode location repeatedly" [10].

Generalized periodic discharges related to anesthetic withdrawal can be seen after burst-suppression patterns induced by pentobarbital [12] and more rarely after propofol [12]. This pattern associating delta waves and more or less typical TWs was initially described in the recovery phase after self-poisoning with short-acting barbiturates, phenobarbital, and non-barbiturates hypnotic drugs [7]. This aspect should be recognized so as to avoid interpreting this pattern as being along the IIC and, therefore, possible a state of NCSE in a comatose patient. The GPDs related to anesthetic withdrawal seem to correspond to a transient and resolving encephalopathy [12].

Independent periodic discharges

De la Paz and Brenner in 1981 suggested that an activity may be bilateral and independent [4]. They proposed the acronym "BIPLEDs" (bilateral independent periodic lateralized epileptiform discharges), now simplified to "bilateral independent periodic discharges" (BIPDs; [11]). The authors reported seizures in 78% of 18 patients with BIPDs and 82% of 45 patients with LDPs [4]. Typically, BIPDs are observed in comatose patients with acute lesions. The prognosis is poor. A large, multicenter study of critically ill adult patients undergoing continuous EEG monitoring found a trend toward an association with seizures in patients with BIPDs, especially with a "plus" modifier, but the small sample size did not allow the authors to draw definite conclusions [21]. A retrospective, multicenter study including 25 comatose patients found clinical or electrographic seizures in 72% of the cases [5]. The commonest conditions of BIPDs were cardiac arrest, central nervous system infections, and acute/chronic ischemic/hemorrhagic stroke. In this series, there was a trend toward an association between a lower frequency of discharges and seizures, and a trend toward an association with seizures if the frequencies of periodic discharges were symmetric between the two hemispheres.

In about three quarters of cases, BIPDs indicate a severe neurologic dysfunction associated with seizures. Two or more independent periodic discharges should probably place this IIC pattern toward that of an ictal pattern. Moreover, NCSE may be considered when BIPDs have superimposed rhythmic discharges (BIPDs-plus) as well as when there is a spatiotemporal evolution of the pattern [16].

Stimulus-induced rhythmic, periodic, or ictal discharges

The acronym "SIRPIDs" (stimulus-induced rhythmic, periodic, or ictal discharges) was used to describe discharges elicited by stimulation [9]. These SIRPIDs have been described in a broad range of conditions [13]. Hirsch et al. [9] found an association with electrographic seizures in 50% of patients, and Braksick et al. in about 25% [2]. However, other studies did not report an association [13]. Case reports did not show an increase in focal CBF on SPECT [24, 30]. Kaplan and Duckworth reported on one patient with a left frontal intracerebral hemorrhage and focal SIRPIDs (stimulus-induced LPDs) over the left frontal region with arousals but without progression to seizures. After 1 mg of lorazepam, the

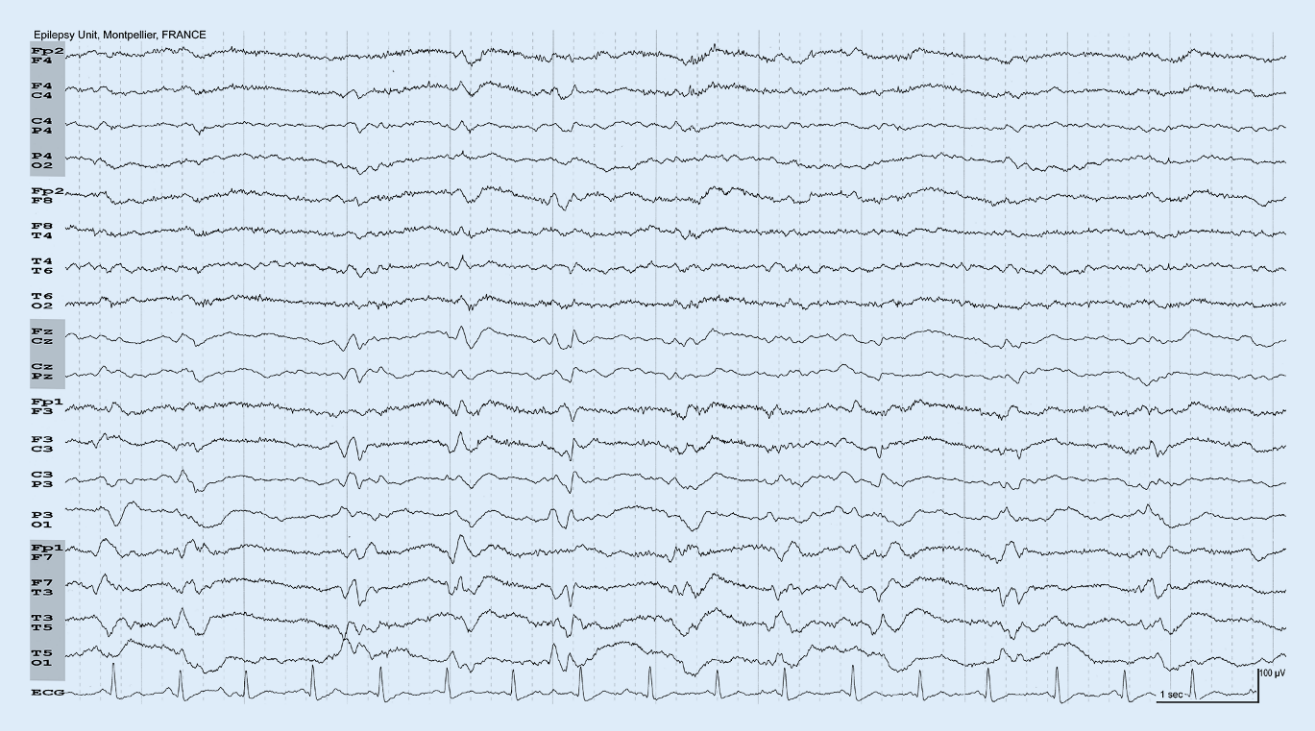

Fig. 1 ▲ Peri-ictal lateralized periodic discharges (LPDs). EEG of a 70-year-old woman with one cerebral metastasis. Predominance of the LPDs over the left temporal lobe. The intervals between the paroxysms are not constant, around 1 s. The morphology of the LPDs also varies. This fluctuation in pattern indicates a need for prolonged or continuous EEG to detect seizures. One subclinical seizure over the left temporal lobe was recorded 10 min later

patient opened her eyes, and her responsiveness and language improved [15].

In patients with brain injury, SIRPIDs are relatively common, and the effect of sensory stimulation in comatose patients was described more than 50 years ago [7]. Where SIRPIDs lie along the IIC is uncertain. In metabolic/toxic encephalopathies with TWs, and in Creutzfeldt–Jakob disease, SIRPIDs may be seen as a pattern of transition from sleep to wakefulness [7]. In these situations, these patterns may be incorrectly characterized as being ictal or lying along the IIC. In order to avoid confusion, we proposed changing the meaning of the SIRPIDs acronym to "stimulus-induced rhythmic or periodic intermittent discharges" [7].

Burst suppression

Spontaneous burst-suppression patterns are seen in early severe neonatal and infantile epilepsies [18]. Burst-suppression patterns or GPDs may be observed in the late stage of insufficiently treated or untreated generalized tonic–clonic SE [28]. Apart from these possibilities, spontaneous burst-suppression patterns are only observed in comatose patients and represent a pattern of severe metabolic, toxic, and postanoxic encephalopathies. Spontaneous burst-suppression patterns must not be considered as an ictal pattern or to lie along the IIC. However, as the patient is in a coma with a striking EEG (e.g., after baclofen intoxication), the diagnosis of NCSE in a comatose patient is sometimes made. One must be wary of drawing overly simplistic conclusions regarding EEG and coma [8]. The EEG alone cannot explain the origin of a coma, as it may just represent an epiphenomenon [23].

Managing the ictal–interictal continuum

There is no consensus regarding the optimal treatment of patients with EEG patterns that lie along the IIC, and an individualized approach is required. The approach should include the EEG pattern and, above all, the clinical context (etiology, level of consciousness, comorbidities) as well as associated studies, including neuroimaging procedures (MRI, SPECT, PET, etc.). In comatose patients with spontaneous subarachnoid hemorrhage, PD frequencies above 2 Hz were considered to be potentially harmful to brain tissue [29]. After analyzing 5427 continuous EEG monitoring, Struck et al. determined that any periodic patterns of more than 2 Hz were associated with a risk of having seizures [26]. To provide an optimal strategy involves proposing a treatment for a specific periodic pattern related to a specific etiology and in a particular clinical context. The prognosis of patients with BIPDs is different from that of patients with LPDs, in whom the prognosis depends on the etiology, the localization, the extent of the lesion, and its chronic or acute nature.

When diagnostic uncertainty exists regarding the ictal or non-ictal nature of a particular EEG pattern, typically when epileptiform discharges are below 2.5 c/s, an ASD diagnostic trial can be tried, with a definite diagnosis of NCSE made when improvements in both the EEG and the clin-

ical state occur [14]. Intravenous benzodiazepine injections (BZP) are traditionally used. A scenario often seen in clinical practice is that clinical improvement is not evident because the patient is now sleeping after the injection. The Salzburg consensus criteria considered these situations "possible" NCSE [17], leaving the clinician uncertain. The TWs disappear when patients fall asleep and reappear upon awakening [7]. The diagnosis of an encephalopathy with TWs is made when improvement in both the EEG and induction of sleep occur, only to see the subsequent reappearance of GPDs with TW morphology after external stimuli are applied [8]. To diminish the potential sedative effects of BZPs, the sequential administration of low doses of short-acting BZP or non-sedating ASDs is proposed [1].

Conclusion

Ictal–interictal continuum (IIC) explains the spectrum of EEG discharges falling short of a strict definition of SE, but where there still may be a damaging effect on the patient. The number of cycles per second and "plus" modifiers appear to be essential elements. The EEG operator may move the IIC cursor toward the appropriate end of this spectrum (interictal or ictal), but one should keep in mind that the term IIC is only an EEG description and does not in itself reflect a clinical diagnosis. The clinical context and other studies (e.g., MRI, SPECT, PET) should be used to optimize management.

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Zusammenfassung

Wie lässt sich das epileptogene/anfallserregende Potenzial periodischer Entladungen entlang des iktal-interiktalen Kontinuums bewerten und beurteilen? Iktales Potenzial und klinische Ansätze

Das iktal-interiktale Kontinuum (IIK) ist ein Konzept, das für jene besonderen Elektroenzephalogramm(EEG)-Muster verwendet wird, welche die strengen Kriterien für einen Status epilepticus nicht erfüllen, aber mit einer neuronalen Schädigung in Verbindung gebracht werden können. Ziel des vorliegenden Artikels ist es, die Untersuchung mehrdeutiger periodischer Muster vorzustellen und ihre klinische Bedeutung entlang des IIK zu erörtern. Das Risiko epileptischer Anfälle steigt, wenn die Frequenz der periodischen Entladungen 2 Hz übersteigt und das Muster Merkmale einer überlagerten rhythmischen, spitzen oder schnellen Aktivität (Plus-Modifikatoren) aufweist. Periodische lateralisierte Entladungen (LPE) sind eines der besten Beispiele für das IIK. Es wurden Kriterien zur Identifizierung von Mustern entlang des IIK vorgeschlagen, die hier als „periiktale" LPE bezeichnet wurden. Es gibt eine Kontroverse darüber, wann Patienten mit EEG-Mustern entlang dieses Spektrums behandelt werden sollten. Der Begriff IIK ist lediglich eine EEG-Beschreibung und spiegelt keine klinische Diagnose wider, sodass die Behandlung allein auf der Grundlage des EEG erfolgt. Die Entscheidung, die antiepileptische Behandlung zu intensivieren, basiert auf der Kombination aus EEG, der postulierten zugrunde liegenden Ätiologie, dem Bewusstseinszustand, den Begleiterkrankungen, den Befunden der Bildgebung und anderen Surrogaten für eine neuronale Schädigung.

Schlüsselwörter
Kontinuierliche EEG-Überwachung · Periodische Muster · Peri-iktal · Intensivstation · Behandlung

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