Which EEG Patterns Warrant Treatment in the Critically Ill? Reviewing the Evidence for Treatment of Periodic Epileptiform Discharges and Related Patterns

Derek J. Chong and Lawrence J. Hirsch

Abstract: Continuous electroencephalographic monitoring in critically ill patients has improved detection of nonconvulsive seizures and periodic discharges, but when and how aggressively to treat these electrographic patterns is unclear. A review of the literature was conducted to understand the nature of periodic discharges and the strength of the data on which management recommendations have been based. Periodic discharges are seen from a wide variety of etiologies, and the discharges themselves are electrographically heterogeneous. This spectrum suggests a need to consider these phenomena along a continuum between interictal and ictal, but more important clinically is the need to consider the likelihood of neuronal injury from each type of discharge in a given clinical setting. Recommendations for treatment are given, and a modification to current criteria for the diagnosis of nonconvulsive seizures is suggested.

Key Words: PLEDs, PEDs, GPEDs, SIRPIDs, Critically ill, EEG, Nonconvulsive seizures, Nonconvulsive status epilepticus, Periodic discharges, Intensive care unit.

(*J Clin Neurophysiol* 2005;22: 79–91)

Recent studies have highlighted the improvement in nonconvulsive seizure detection using continuous electroencephalographic monitoring (cEEG) in critically ill patients (Claassen et al., 2004; Pandian et al., 2004). However, the pace of technological advances that now allows long-term recording of video-EEG has not been matched by that of increased understanding of the pathophysiology that creates the myriad of ambiguous but potentially ictal patterns, their clinical implications, or how aggressively to treat them.

Perhaps most problematic to clinician and electroencephalographer alike are periodic discharges. Although periodic and quasi-periodic discharges were reported a decade earlier, the term periodic lateralized epileptiform discharges (PLEDs) was first used by Chatrian et al. (1964). Since then there has been little progress, and more controversies have been raised than settled. The largest controversy is whether PLEDs are ictal, interictal, or simply postictal phenomena (Brenner, 2002; Brenner and Schaul, 1990; Pohlmann-Eden et al., 1996; Snodgrass et al., 1989). Many other patterns have since been described, with their clinical significance uncertain as well. The literature includes descriptions of PLEDs-proper and PLEDs-plus (Reiher et al., 1991) (Figs. 1 and 2), bilateral independent PLEDs (BIPLEDs) (Fig. 3), generalized periodic epileptiform discharges (GPEDs) (Fig. 4) with subclassification into periodic short-interval diffuse discharges (PSIDDs) and periodic long-interval diffuse discharges (PLIDDs) (Brenner and Schaul, 1990), and most recently stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) (Hirsch et al., 2004). Except for SIRPIDs, terminology has been based primarily on routine 20- to 30-minute EEG recordings.

Periodicity was initially thought to have been caused by disconnection of the cortex from subcortical structures, usually secondary to a large white matter lesion (Cobb and Hill, 1950). However, Chatrian et al. (1964), utilizing pathologic specimens, showed that a lesion anywhere can be associated with PLEDs. This was confirmed in a recent study in which MRI and computed tomography were performed after the appearance of PLEDs in 71 patients. The images showed that 11.3% had lesions solely in cortical gray matter, 4.2% had only subcortical white matter lesions, 1.4% had a sole subcortical gray matter lesion, and 5.6% had evidence of injury to all three areas (Gurer et al., 2004). The majority of the patients (64.7%) had lesions of cortical gray and subcortical white matter. In other studies, 27% to 29% of patients with PLEDs had no focal lesion at all (Garcia-Morales et al., 2002; Snodgrass et al., 1989).

The fact that periodicity has been found in a variety of situations and pathologies could reflect a limited ability of the brain to express itself through EEG, with divergent pathophysiologic processes expressed similarly (Garcia-Morales et al., 2002). PLEDs after acute infarct, for instance, arise from

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Columbia University Medical Center, New York, New York, U.S.A.

Address correspondence and reprint requests to Dr. Lawrence J. Hirsch, Comprehensive Epilepsy Center, Columbia University, Neurological Institute, Box NI-135, 710 West 168th Street, New York, NY 10032 U.S.A.; e-mail: Ljh3@columbia.edu.

FIGURE 1. An example of PLEDs-proper in a 74-year-old woman 11 days after cardiorespiratory arrest. The periodicity is relatively stable and there are no associated rhythmic discharges.

the ischemic penumbra experimentally (Hartings et al., 2003), but whether the cells here are apoptotic or regenerating is unknown. PLEDs may therefore be present both as a result of irreversible disintegrating circuitry, or they could be signs of a process of recovery (Brenner and Schaul, 1990). Thus, it is not surprising that it is difficult to make generalizations regarding management or prognostication with periodic discharges. Within each electrographic category, however, there are a few essential details to consider (Table 1; adapted from Brenner and Schaul, 1990; Fisch, 1999.) Clinicians need to note periodic discharges to help diagnose a few important or potentially treatable diseases and to recognize the high risk of seizures. For the electroencephalographer, there are several distinguishing EEG features that have value in terms of prognosis and their relationship to seizures.

PLEDS/BIPLEDS

The most common periodic discharges studied have been PLEDs, probably because they are the most common (Brenner and Schaul, 1990; Kuroiwa and Celesia, 1980). The most consistent finding, across all etiologies, seems to be that

PLEDs are highly associated with seizures. Clinical seizures or status epilepticus were seen during the course of illness in 126 (90%) patients in the series by Snodgrass et al. (1989), with 50% having partial motor status epilepticus, 22% partial motor seizures, 6% epilepsia partialis continua (EPC), 6% isolated generalized seizures, and 8% generalized status epilepticus. The study included both adult and pediatric populations aged 2 to 90 years with a mean age of 58 years. A review of this and 17 other studies determined a range of the incidence of seizures in the acute setting of PLEDs to be 58% to 100% (Pohlmann-Eden et al., 1996). Garcia-Morales et al. (2002) found a lower incidence of seizures (50%). This wide range of findings likely reflects the heterogeneity of patient inclusion, the wide variability of PLEDs, and the varied methods of ascertaining and defining seizure activity.

Although the exact temporal relationship between PLEDs and seizures is unclear (either the seizure has occurred, or one may soon occur), the seizures are typically in the setting of the acute illness (Chatrian et al., 1964; Pohlmann-Eden et al., 1996), with seizures occurring on the first day of illness in nearly half of patients (Snodgrass et al.,

FIGURE 2. Left hemispheric PLEDs during EPC, with motor activity of the right neck and upper extremity; cognitive involvement was difficult to discern in this 84-year-old woman with multiple medical problems and an acute left occipital stroke. The periodicity is variable and there is associated low-amplitude rhythmic activity with the discharges, which may be indicative of higher epileptogenicity than PLEDs without these features (compare with Fig. 1). This pattern would qualify as PLEDs-plus. In this particular case, the clear clinical correlate renders the pattern definitively ictal.

1989). PLEDs have been associated with focal destructive lesions, most commonly acute infarction, but also infections, hematomas, and tumors (Pohlmann-Eden et al., 1996) and, perhaps less frequently, demyelinating diseases, anoxia, primary epilepsy, and migraine (Garcia-Morales et al., 2002). The importance of a combined structural lesion with a metabolic disturbance has been emphasized (Chu, 1980; Janati et al., 1986; Raroque et al., 1993a), although it is clear that PLEDs can occur without either, such as PLEDs seen after status epilepticus in patients with chronic epilepsy (Garcia-Morales et al., 2002).

When PLEDs are seen in both hemispheres asynchronously, they are termed BIPLEDs (Brenner and Schaul, 1990). BIPLEDs are far less common than PLEDs but are also highly associated with seizures during the acute illness (78% of 18 patients [de la Paz and Brenner,

1981]). BIPLEDs are typically related to acute structural lesions with or without metabolic disturbances. The most common causes are anoxia, infection, and chronic epilepsy (de la Paz and Brenner, 1981). The clinical state and prognosis with BIPLEDs may be worse than with PLEDs (Brenner and Schaul, 1990). However, these observations have originated primarily from only two studies, one comparing 18 patients (including 5 children) with BIPLEDs to 45 patients with PLEDs (de la Paz and Brenner, 1981), and the other describing 4 patients with BIPLEDs following EPC (Snodgrass et al., 1989). Other small series exist (Raroque et al., 1993b; Striano et al., 1986). Thus, although it appears that BIPLEDs are more associated with coma and poor outcome than are PLEDs, it should be kept in mind that this conclusion is based on small numbers. A case of benign BIPLEDs has also been reported (Fushimi et al., 2003).

FIGURE 3. An example of BIPLEDs that developed in a 3.5-year-old boy after severe hypoxia from status asthmaticus. The patient had presented with subtle generalized status epilepticus and did not survive.

The data regarding PLEDs and BIPLEDs in the pediatric population are limited. A study from Taiwan reported a high association with CNS infection, accounting for 63.6% of the 44 cases of PLEDs or BIPLEDs, with herpes encephalitis accounting for 12 cases (Chen et al., 2003). PLEDs were also seen with the following etiologies: head injury (4), idiopathic epilepsy (3), and Reye syndrome (3). There was only one stroke in this review and only one in a study of 18 pediatric patients (Raroque et al., 1993b), which is not surprising in children. In the study by Raroque et al., BIPLEDs were noted in 5 cases; 4 were below one year of age, and the other was 8 years old. Anoxia accounted for 3 cases, and the others were due to infection. One patient from each etiology survived, but with new neurologic deficits.

As noted earlier, there are countless etiologies and multiple individual factors that lead to PLEDs and BIPLEDs; they are electrophysiologically heterogeneous as well. Studies have included wide ranges of morphology (single sharp wave of 60 milliseconds to complex polyphasic complexes lasting 1,000 milliseconds), amplitude (50–300 μV), and periodicity (recurring at 0.3- to 4-second intervals) (Pohlmann-

Eden et al., 1996). An argument for subclassification of PLEDs was made by Reiher et al. (1991). Although 5 levels of PLEDs were classified, there were 2 major groups: PLEDs-proper was defined as simply configured, uniform discharges, whereas PLEDs-plus required an accompanying low amplitude rhythmic discharge. In patients with seizures, there was often a transition from PLEDs-proper to PLEDs-plus, then to seizure, then a cycle back to PLEDs proper. In fact, 74% of the 50 patients with PLEDs-plus had a seizure recorded on EEG during the acute illness, compared with only 6% of the 34 patients with solely PLEDs-proper. Despite this potentially useful subcategorization, few have followed up to confirm, refute, or improve upon these findings.

What remains controversial is whether PLEDs constitute an ictal pattern. There is significant evidence that PLEDs are sometimes ictal. In 7 elderly patients, PLEDs were associated with a reversible confusional state that Terzano et al. (1986) concluded represented a form of nonconvulsive status epilepticus (NCSE). Increased local cerebral glucose metabolism has been demonstrated on positron emission tomography during PLEDs; because this is also seen during seizures,
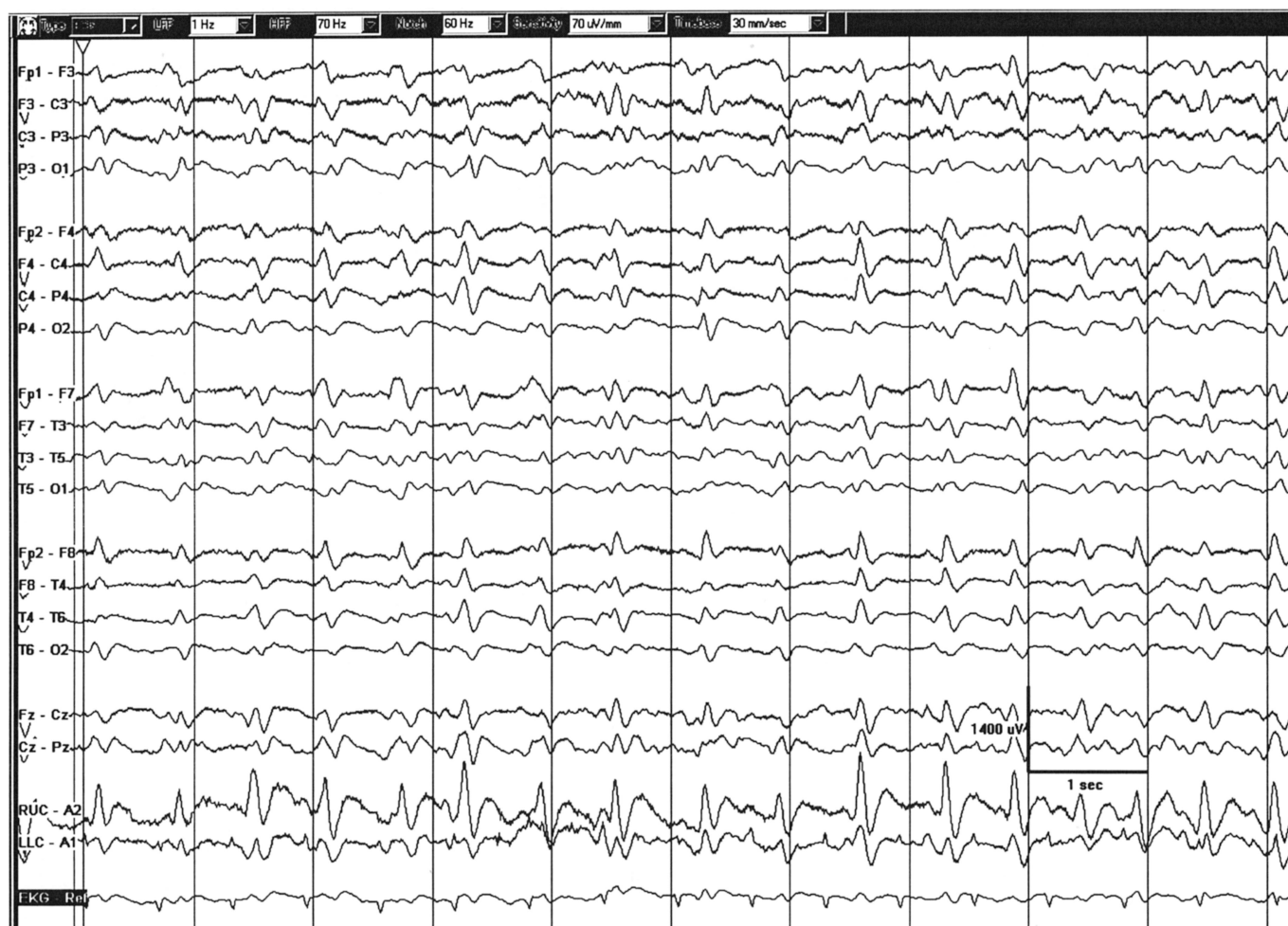
FIGURE 4. An example of GPEDs in a 62-year-old man with rapidly progressive dementia and probable Creutzfeldt-Jakob disease. The EEG was performed 3 months after symptom onset.

the authors concluded that this supported their ictal nature (Handforth et al., 1994). Studies with single photon emission computerized tomography have shown cases with increased regional blood flow in the area of the PLEDs that disappears with the resolution of the PLEDs, with seizure being the most likely explanation for this transient, focal hyperperfusion (Assal et al., 2001; Bozkurt et al., 2002). Perhaps most compelling, EPC (focal motor status epilepticus) can occur with PLEDs. This has been reported with a wide range of incidences, with EPC seen in 8 of 139, 7 of 45, and 13 of 26 patients with PLEDs in the series by Snodgrass et al. (1989), Baykan et al. (2000), and Kuroiwa and Celesia (1980), respectively. The fact that each epileptiform discharge can be time-locked to a focal movement cannot be refuted; thus, by definition, PLEDs are sometimes clearly ictal. In contrast, there are also reports of benign clinical courses with long-standing chronic PLEDs (Westmoreland et al., 1986) or BIPLEDs (Fushimi et al., 2003) that denote either a nonictal state or one that does not cause continued neuronal injury or additional neurologic dysfunction. With the heterogeneity of factors that cause PLEDs, and the actual heterogeneity of the PLEDs themselves in terms of focality, field, and spread, it is not surprising that data are divergent.

GENERALIZED PERIODIC EPILEPTIFORM DISCHARGES

Generalized periodic discharges have not been extensively studied, partly because of their rarity; for instance, GPEDs were noted in only 37 patients from almost 3,000 EEGs in 8 years at one center (Yemisci et al., 2003). Their relationship to seizures was documented in this same study, which reported that 89.5% of 37 patients had either a myoclonic seizure (35.2%), a GTC (21.6%), or were in status epilepticus (32.4%) within 48 hours of the detection of GPEDs. However, the authors did not comment on the relationship between the category of seizure and certain types

TABLE 1. EEG and Clinical Characteristics of the Periodic Discharges

	PLEDs	BIPLEDs	GPEDs	
			PSIDDs	PLIDDs
Inter-discharge interval	Typical: 0.5 to 4 s, up to 8 s	Typical: 0.5 to 4 s, up to 8 s	0.5–4 s	4–30 s
Topography	Lateralized (contralateral spread common)	Independently lateralized	Diffuse	Diffuse
Rate of focal or tonic-clonic seizures	High, approximately 80%	Typically lower than in PLEDs but still high	Variable/unclear but not rare	Rare
Associated myoclonus	Rare	Rare	Common with CJD but often not time-locked	Common with SSPE, time-locked
Mental status	Altered	Altered	Altered	Variable
Outcome*	Variable*	Variable*	Variable*	Variable*
Morphology/other characteristics	Morphology variable. Associated with EPC	Morphology variable	Sharp waves, spikes, polyspikes, or sharply-contoured delta waves	Variable; often complex, stereotyped, polyphasic bursts, lasting 0.5–3 s
Etiology	Acute structural lesion: Infarct, ICH, tumor, infection; occasionally no lesion. After SE. Increased risk with metabolic disturbance. **HSE**	Anoxia, bilateral acute lesions. Occasionally unilateral or no lesion apparent. **HSE**	Metabolic encephalopathy, anoxia. NCSE. After SE. Lithium, baclofen, **CJD**	Toxins (PCP, ketamine barbiturates, anesthetics), anoxia **SSPE**

Abbreviations: BIPLEDs bilateral independent periodic lateralized epileptiform discharges; CJD Creutzfeldt-Jakob disease; EPC epilepsia partialis continua; GPEDs generalized periodic epileptiform discharges; HSE herpes simplex encephalitis; ICH intracerebral parenchymal hemorrhage; NCSE, nonconvulsive status epilepticus; PCP phencyclidine; PLEDs periodic lateralized epileptiform discharges; PLIDDs periodic long interval diffuse discharges; PSIDDs periodic short interval diffuse discharges; SE status epilepticus; SSPE subacute sclerosing panencephalitis. The most important diagnoses to consider are in bold.

*Outcome appears more highly correlated with etiology than with appearance of the periodic discharges.

Adapted from (Brenner and Schaul 1990 and Fisch 1999)

of GPEDs or to prognosis. It was reported that burst-suppression (included as "GPEDs" in this series), whether caused by hypoxia (3 patients) or sepsis and/or metabolic disease (4 patients), had 100% 1-month mortality.

An earlier study investigated the EEG components of GPEDs and found few relationships to etiology, propensity to seize, or prognosis (Husain et al., 1999). The amplitude of the background activity between the periodic discharges (the inter-GPED amplitude) was higher in those diagnosed with status epilepticus (34 versus 17 μV) but was also higher in those who were alive at discharge (33 versus 18 μV). The amplitude of the actual epileptiform discharge (110 versus 80 μV) and its duration (0.5 versus 0.3 s) were also greater in those who met criteria for status epilepticus, but because of extensive variability and overlap, this was not thought to be clinically useful for an individual patient. In this study, 25 adults over a 22-month time period met the criteria for GPEDs. The authors concluded that patients whose clinical history and EEG are consistent with status epilepticus should be managed aggressively with antiepileptic drugs (AEDs),

but that treatment is likely futile for those with GPEDs and very low inter-GPED amplitude after anoxia. The specific application of this recommendation only to the postanoxic setting is a crucial point, because even in their small population, one patient with a toxic-metabolic encephalopathy had among the lowest of inter-GPED amplitudes and was eventually discharged home. It is the existence of GPEDs after anoxia, in particular, that seems to impart a devastating prognosis, with a separate study finding 100% mortality within 1 month regardless of the type of GPED: burst-suppression (n = 7), generalized repetitive sharp transient (n = 1), or generalized triphasic waves (n = 2) (Kuroiwa and Celesia, 1980). However, clinical examination and somatosensory and brainstem-evoked potentials may have greater ability to prognosticate in the postanoxic setting (Robinson et al., 2003; Young et al., 2004)

There are two diseases classically associated with subtypes of GPEDs. Subacute sclerosing pan-encephalitis (SSPE) should always come to mind with GPEDs that have long intervals between complex, polyphasic discharges.

These fall into the category of PLIDDs, with the category inclusive of an interval of 4 to 30 seconds (Brenner and Schaul, 1990); in SSPE, they are typically 5 to 7 seconds apart in the early stages of the disease while patients are still ambulatory (Markand and Panszi, 1975). With time or progression of the disease, the background becomes more abnormal and the interval tends to shorten; Wulff (1982) reported a dramatic change in interburst interval duration, decreasing from 80 seconds to 2 seconds in less than a year. Discharges usually become associated with myoclonic jerks, with PLIDDs eventually disappearing at the end stage (Brenner and Schaul, 1990). Initially, the discharges in SSPE can be unilateral and be superimposed on an otherwise normal background (Markand and Panszi, 1975; Shivji et al., 2003). The electrographic hallmarks of SSPE are specific, can be found relatively early in the disease process, and there is evidence that immunotherapies may alter the course and length of survival (Gascon, 2003; Tomoda et al., 2003), making recognition crucial despite its rarity (Dunand and Jallon, 2003). The PLIDDs of SSPE can be mimicked after phencyclidine or ketamine intoxication. PLIDDs are also seen on rare occasions following anoxia, anesthetic use, and barbiturate overdose (Brenner and Schaul, 1990).

The other disease often associated with GPEDs is sporadic Creutzfeldt-Jakob disease, where diagnosis is important clinically and epidemiologically. The electrographic hallmarks of Creutzfeldt-Jakob disease are periodic sharp wave complexes that are usually diffuse, with intervals between the GPEDs usually approximately 1 second, falling into the category of PSIDDs (0.5–4.0-second intervals). Early in the course of the disease, diffuse slowing is the most typical EEG finding, with the GPEDs (PSIDDs) becoming evident within months after clinical onset, sometimes evolving from PLEDs (Brenner and Schaul, 1990; Yemisci et al., 2003). Interestingly, GPEDs are not seen in new-variant Creutzfeldt-Jakob disease; in fact, the EEG can be surprisingly normal despite severe cognitive impairment (Zeidler et al., 1997).

Despite the poor prognoses for the disease processes mentioned earlier, GPEDs in other clinical situations could have more positive outcomes, such as when they occur in the setting of potentially reversible metabolic derangements like hyponatremia, uremia, and hepatic failure in addition to herpes simplex encephalitis, disseminated intravascular coagulation, and sepsis (Brenner and Schaul, 1990).

Though rarely encountered in the past, GPEDs may now be recognized more often because of the increasing use of cEEG in the intensive care unit. At our center, 7.5% of 570 consecutive patients undergoing cEEG and not seizing clinically had GPEDs (Claassen et al., 2004), although our criteria did not require GPEDs to be present for the majority of the recording as some others have required during routine EEGs. In three prior studies, GPEDs were "generalized,

synchronous, periodic or near periodic complexes that occupied at least 50% of a standard 20-minute EEG" (Husain et al., 1999; Kuroiwa and Celesia, 1980; Yemisci et al., 2003). How to define GPEDs in the age of continuous monitoring has yet to be determined, and new studies using cEEG need to address the occurrence, the natural history in specific clinical situations, and whether treatment has any effect on outcome. Standardized terminology is currently being proposed (Hirsch et al., 2005), but until additional studies are performed, it will remain unclear whether GPEDs provide any independent prognostic information or require treatment.

The category of generalized periodic discharges also includes triphasic waves. Triphasic waves are periodic and generalized, typically frontally predominant (Brenner, 2002); because they have generally not been considered epileptiform, they are often not included in the GPED categorization. They are characteristically seen in metabolic encephalopathies, most classically hepatic, but of many etiologies. The mental status change combined with fluctuating generalized periodic discharges at more than 1 per second can make triphasic waves indistinguishable from NCSE both clinically and electrographically (Sheridan and Sato, 1986). A frontal-occipital lag has been described, but our experience has shown that this phenomenon can be present in association with definite status epilepticus as well. Differentiation was once made with the intravenous administration of benzodiazepines. It is now clear that both triphasic waves and NCSE can clear electrographically after such treatment, and concomitant clinical improvement is necessary before the diagnosis of NCSE can be proclaimed (Fountain and Waldman, 2001).

Electroencephalographers should avoid being dogmatic when trying to distinguish metabolic periodic discharges from seizure-related periodic discharges because this distinction is often not possible with EEG alone, even when considering the response to benzodiazepines.

CLINICAL ISSUES

Acute Management

There is no formal standard of care for PLEDs. However, based on the current literature, we think that a reasonable approach includes an investigation into the cause, initiation of conventional AED prophylaxis for seizures, and continued EEG monitoring for potential nonconvulsive seizures or status epilepticus. Investigation for the cause of PLEDs can include broadening the history to specifically screen for common and important causes (see Table 1). The history may warrant urgent imaging for a focal lesion (MRI, if possible), and cerebrospinal fluid analysis for evidence of herpes simplex encephalitis or other encephalitides. Reasonable conventional AED choices include those that can be titrated to therapeutic levels rapidly. Levetiracetam is a pop-

ular choice at our center for two reasons: it can be started at therapeutic doses on the first day and has no significant pharmacologic interactions, both important in the acute setting. However, it cannot be given intravenously as of yet. It requires dose modification with renal impairment, serum levels are not rapidly available, and formal data on effectiveness in this setting are sparse. Furthermore, its behavioral side effects are well described (Kossoff et al., 2001; Youroukos et al., 2003), which adds another potential cause of agitation in already easily agitated patients.

Oxcarbazepine and carbamazepine dosages can also be rapidly elevated if sedation, dizziness, and ataxia are not concerns. Phenytoin (or fosphenytoin) and valproate are often used; advantages include intravenous formulations, familiarity from years of use, the ease of monitoring drug levels, and lack of marked sedation or respiratory depression. Serum levels of the free fraction should be followed, especially with phenytoin in polytherapy and in those with low albumin levels (both valproate and phenytoin are highly protein-bound, as are benzodiazepines). Phenytoin can have unpredictable effects on liver induction when initially used, often playing havoc with warfarin dosing, antimicrobials levels, and chemotherapy. Valproate can cause lowered platelet counts (Banerjea et al., 2002; Gidal et al., 1994) and rare impairment of coagulation even with adequate platelet counts (Kis et al., 1999), potentially related to liver production of factor XIII (Pohlmann-Eden et al., 2003; Teich et al., 2004). Both intravenous phenytoin and phenobarbital commonly cause hemodynamic instability if given quickly (Treiman 1998) and can cause hypersensitivity reactions that can be severe; phenytoin (and fosphenytoin) can cause cardiac conduction abnormalities and arrhythmias as well (Kaplan 2000). Intramuscular fosphenytoin avoids the hemodynamic issues and is a reasonable way to obtain rapid, therapeutic phenytoin levels outside of the setting of status epilepticus (when intravenously should be used) (Hirsch and Claassen, 2002).

Gabapentin, perhaps the most benign of all the AEDs, has shown promise in an animal model of acute symptomatic nonconvulsive seizures (Williams et al., 2004) and can be started at high doses quite safely. Other newer AEDs can also be used, including topiramate and zonisamide, but there has not been extensive experience rapidly titrating them to therapeutic levels. Both are carbonic anhydrase inhibitors and can exacerbate acidosis.

There are limited data regarding GPEDs, but they do support the use of AEDs owing to the high association with seizures during the acute illness (Yemisci et al., 2003). Of course, GPEDs should lead one to consider the diagnosis and treatment of the reversible causes of GPEDs and altered mental state discussed earlier.

In the case of prolonged unreactive burst suppression, treatment is likely to be futile aside from reversible causes such as drug overdose (Husain et al., 1999; Kuroiwa and Celesia, 1980; Yemisci et al., 2003; Young, 2000; Young et al., 1999); more data are required before definitive recommendations can be made.

Understanding periodic patterns has become even more complex with documentation of stimulation-induced or state-dependent periodic patterns. In the past, the state-dependence was considered evidence that an electrographic pattern was less likely to be ictal (Brenner, 2002; Reiher et al., 1991). However, Hirsch et al. (2004) reported not only periodic patterns, but also patterns clearly meeting criteria for electrographic seizures (both focal and generalized) but consistently elicited by stimulation; these ictal patterns were seen in 18 of 33 patients with SIRPIDs. In one case, the stimulation-induced pattern had a clinical correlate of twitching as well. Identification of SIRPIDs has raised more questions than answers at this point, but until more is known about them and their potential to cause harm, it would seem prudent to at least treat with conventional AEDs. It is not clear at this time if the relationship to stimulation should make one more or less likely to treat a particular pattern.

In the vast spectrum of what constitute PLEDs, BI-PLEDs, and GPEDs, it is likely that an electrographic pattern could fit both the definition of one of these periodic patterns, and the criteria proposed by Young et al. (1996) for nonconvulsive seizures. It may very well be that some PLEDs are ictal while others are interictal. Unfortunately, there is currently little guidance available to make the differentiation. This lack of knowledge is paralleled by the uncertainty in the management of even unambiguous cases of nonconvulsive status epilepticus. Thus, if we were to treat all PLEDs as if they represented NCSE, there would still be no consensus as to the aggressiveness of care (Brenner, 2002), or what the electrographic goal of treatment is. Incidentally, the same holds true for EPC.

For patients in whom a strong clinical suspicion of nonconvulsive seizures or NCSE exists, a bolus of intravenous benzodiazepine can be used as a test; patients who definitively improve clinically (e.g., become more alert or their aphasia resolves) should at least be considered to have been in a seizure or NCSE, regardless of the EEG pattern. Resolution of periodic discharges with benzodiazepines occurs reliably in metabolic causes of periodic discharges (such as triphasic waves) as well and does *not* necessarily imply NCSE (Fountain and Waldman, 2001). Thus, clinical improvement should be a defining criterion, but resolution or improvement in epileptiform discharges without a clinical change or without normalization of the background EEG is not helpful in determining whether the EEG pattern was ictal. Unfortunately, this equivocal result is quite common in critically ill patients with periodic discharges, leaving the issue unresolved in many patients.

Even in a specific case where an EEG pattern is determined to represent NCSE, there is no clear answer how

aggressively to treat. In a retrospective study, Litt et al. (1998) found a higher risk of death in the elderly after treatment of NCSE with intravenously benzodiazepines. This study, in addition to others, led to a review article by Kaplan (2000) arguing against routinely treating NCSE aggressively, which then also tempers aggressive management of PLEDs. Aggressive management typically refers to continuous intravenous infusions of benzodiazepines, barbiturates, or propofol, and usually requires intubation.

Long-Term Management

The final clinical questions are reserved for if, and when, the patient makes it out of the intensive care unit: Do I continue an AED, and for how long? Of 9 patients with PLEDs and new-onset seizures during the acute illness, 6 (67%) reported seizures after hospitalization (Schraeder and Singh, 1980). Only one of these patients was living independently after discharge. Another study found that 4 of 9 patients with new-onset seizures and PLEDs continued to have seizures after the acute setting (Walsh and Brenner, 1987). The authors concluded that most patients with PLEDS and concomitant seizures continue having seizures after hospitalization and that this warrants long-term antiepileptic medication. A more recent study found late seizures in 14 of approximately 50 patients (28%) who had PLEDs and acute seizures and survived; however, there may have been incomplete ascertainment of late seizures (Garcia-Morales et al., 2002).

It would seem reasonable to forego long-term treatment for a patient who had acute PLEDs that resolved without any definite seizures, perhaps tapering AEDs over a month or so after the acute illness. Combining the limited data regarding long-term treatment for acute symptomatic seizures with PLEDs with data from the poststroke seizure literature (Silverman et al., 2002), another reasonable suggestion would be continued AED treatment for 3 to 12 months for those with PLEDs and seizure(s) in the acute setting. Clinicians should individualize long-term treatment decisions, however, and possibly consider the presence or absence of epileptiform discharges on a routine EEG before considering AED withdrawal. Unfortunately, there are currently no data to support or refute this. Should long-term therapy be considered necessary, issues regarding enzyme-inducing drugs and anticoagulation or chemotherapy, for instance, may prompt a switch to another medication. There are indications that phenytoin, phenobarbital, and benzodiazepines adversely affect motor recovery after stroke, and avoidance of these agents has been advocated (Camilo and Goldstein, 2004).

CONTINUED RESEARCH

There is potential for cEEG to have greater impact on clinical care, but more research is needed. Recent work in animal studies looks promising. Hartings et al. (2003) developed a rat model integrating focal ischemia, the most common cause of PLEDs, and 72-hour continuous intracranial EEG monitoring. They characterized seizures, PLEDs, and intermittent rhythmic discharges after middle cerebral artery occlusion. The potential of this model lies in the ability to control the infarct size, reperfusion, and the ability to electrographically record from time zero. Remarkably, nonconvulsive seizures occurred within 1 hour of artery occlusion in 13 of 16 animals. The animals had an average of 10 seizures, typically ending within a few hours. PLEDs were correlated with the ischemic penumbra, whereas the core of the infarct had no PLEDs. Early onset of PLEDs correlated with more prolonged seizure activity. PLEDs occurred in 10 of 16 rats; they were seen before seizures in 6 rats. Although there was no difference in core infarct volume between animals with and without PLEDs, there were few animals in the analysis.

Their follow-up study involved assessing the efficacy of 7 AEDs infused intravenously 20 minutes after permanent middle cerebral artery occlusion (Williams et al., 2004). The incidence and total duration of nonconvulsive seizures, size of infarct, neurologic score, and mortality were analyzed. Surprisingly, ethosuximide and gabapentin showed the best profiles. Both of these medications have relatively few side effects, making this finding potentially extraordinary if replicated and then confirmed in humans. Valproate and fosphenytoin were considered the next-best choices. Dextromethorphan, phenobarbital, and midazolam produced no overall benefit and could have contributed to recurrent EEG abnormalities and worse outcomes. These findings add urgency to our need for randomized treatment trials in humans. The effect of treatment on infarct size was significant using four of the drugs, but the correlation between nonconvulsive seizures and infarct size was only weakly significant. Thus, it cannot be determined whether the drugs themselves had a neuroprotective effect, or whether treatment of seizures reduced infarct size.

Studies in humans have also attempted to show an association between seizures and worse outcome. Seizures after intracranial hemorrhage were associated with an increase in midline shift on serial computed tomography scans and a trend toward poorer outcomes (Vespa et al., 2003). Inclusion was heterogeneous, including both convulsive and nonconvulsive seizures in addition to prehospital and in-hospital seizures. The major difficulty in these, and all other clinical studies, is in finding a significant-sized population with homogeneous characteristics, including demographics, etiology, severity, degree and type of epileptiform activity, and the duration of periodic discharges or seizures.

Well-designed studies are clearly needed. The primary question to be answered is one of brain injury and patient outcome, not whether a periodic pattern constitutes a seizure.

Determination of cellular injury can be assessed in a number of ways. One method utilizes biomarkers that appear

specific to neuronal damage, such as neuron-specific enolase, a glycolytic enzyme found only within neurons and neuroendocrine cells (Kleine et al., 2003). In the animal literature, neuron-specific enolase correlates with the amount of histologic injury after lithium/pilocarpine-induced status epilepticus in the rat model (Sankar et al., 1997). Elevated levels of serum neuron-specific enolase have been documented in patients after generalized convulsive seizures, nonconvulsive seizures, and NCSE (Buttner et al., 1999; DeGiorgio et al., 1995, 1996, 1999; Palmio et al., 2001; Rabinowicz et al., 1995, 1996; Tumani et al., 1999). Interestingly, elevations were found in patients with seizures (including nonconvulsive ones) even when there was no known acute brain injury. Particularly significant elevations were seen in critically ill patients with "subtle" or nonconvulsive status epilepticus (DeGiorgio et al., 1999)—exactly the patients in whom treatment controversies arise. However, results should be considered preliminary because the conclusions were based on small numbers and were either not statistically significant or did not use appropriate controls, such as critically ill patients in whom biomarkers can rise (Kleine et al., 2003) even without seizures. These findings are at least suggestive that nonconvulsive seizures themselves can sometimes lead to additional neuronal injury. Further work is required to identify those most at risk of seizure-related neuronal injury.

CONCLUSIONS

Over 40 years have passed since the first formal definition of periodic discharges was published, and yet we are still in the infancy of understanding them. The causes of periodic discharges are heterogeneous and multifactorial. The complexity makes generalizations difficult, and so far studies have been unable to adequately address many basic questions. There are currently few clinically relevant differentiations between the subclasses of periodic discharges, and attempts for further subclassification may provide more accurate predictions of seizures and outcome by using a combination of EEG and clinical history. In the setting of PLEDs, regardless of etiology, there is a high overall risk for seizures, with associations ranging from 50% to 100%, with an even wider range of reported status epilepticus, from 0% to 64%. Differentiating between PLEDs proper and PLEDs plus appeared to provide significant risk stratification in the only study that has looked at this (Reiher et al., 1991), with PLEDs plus being more associated with seizures. Theoretically, a recording with only PLEDs proper would be considered low risk for seizures. However, in our experience with 24-hour cEEG recordings, PLEDs proper rarely occurs in isolation, with the EEG typically fluctuating between PLEDs proper and PLEDs-plus; seizure risk is quite high in these patients. We have also noted that recordings with BIPLEDs tend to have periods with PLEDs and GPEDs intermingled. Thus,

categorization and correlation with clinical factors for most of these EEG patterns may turn out to be challenging.

It is clear that PLEDs are *sometimes* ictal. However, we and others (Pohlmann-Eden et al., 1996) view PLEDs as on an unstable ictal-interictal continuum; we consider PLEDs proper to be on the interictal end of this (Fig. 5). In our opinion, the criteria for electrographic seizure by Young et al. (1996) are currently the best available, with two important caveats. (1) The criteria were meant to be specific for seizures but not necessarily sensitive. Thus, a pattern that does not fulfill these criteria could still be ictal but it cannot be proven based on the EEG pattern alone. (2) "Improvement in EEG" with an AED was considered evidence of seizure (their secondary criterion 4). This requires clarification to avoid classifying nonictal patterns as ictal. As discussed previously, nonictal periodic patterns such as triphasic waves associated with a metabolic encephalopathy are often eradicated with a bolus of benzodiazepines (Fountain and Waldman, 2001; Hirsch et al., 2004), thus potentially qualifying for a seizure by the original criteria. We suggest a more stringent requirement that normal EEG patterns that were previously absent must appear for the EEG response by itself to suggest seizure. Our modified criteria for defining an electrographic seizure are listed in Table 2. Our criteria also include an arbitrary minimum duration of 10 seconds to be considered a seizure.

Periodic discharges are typically slower than 3 per second, falling under primary criteria 2 or 3, with secondary criteria to differentiate ictal from nonictal. The cut-off of 3 per second seen within the primary criteria was at least partly in recognition of the epileptic encephalopathies, such as the Lennox Gastaux syndrome, where nearly continuous repetitive spike-wave discharges occur, but those below 3 per second ("slow spike and wave") are typically considered interictal rather than ictal (Young GB, personal communication 2005). Periodic discharges with significant evolution in periodicity and amplitude would fall under primary criterion 3.

Diagnostically, it is clear that the EEG cannot pinpoint an exact etiology, but GPEDs with long interdischarge intervals should raise suspicion of SSPE, whereas short-interval GPEDs should raise suspicion of Creutzfeldt-Jakob disease, though metabolic encephalopathy will be encountered much more frequently. The diagnosis of herpes simplex encephalitis is better made through imaging and cerebrospinal fluid studies; however, in the correct clinical setting, PLEDs may warrant specific consideration of this treatable condition.

Periodic discharges should clue the clinician into the high potential for seizures and status epilepticus, including nonconvulsive status epilepticus. We currently recommend conventional AED coverage to manage any occurrence of periodic discharges. If nonconvulsive seizures and NCSE are clinically questioned, possibly due to waxing-and-waning mental status changes correlated with EEG findings, attempts to break the ongoing seizure can be made through use of an
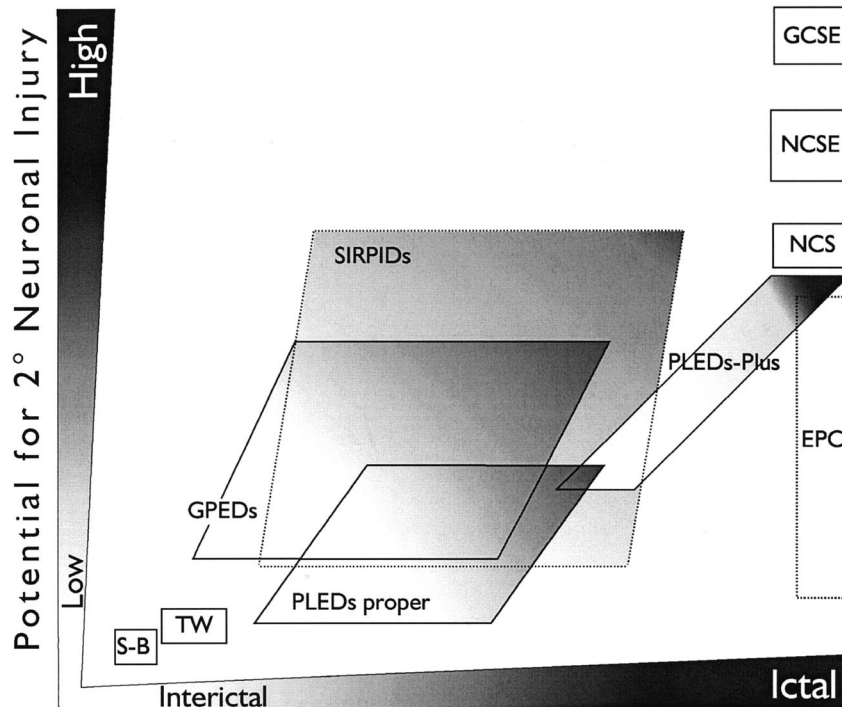
The Ictal-Interictal-Injury Continuum

FIGURE 5. This plot demonstrates various clinicoelectrographic diagnoses depicted on the ictal-interictal continuum. The potential for secondary (2°) neuronal injury, shown on the y-axis, should be a more important indicator of whether treatment should be aggressive. This figure represents our current understanding of electroclinical entities along two distinct dimensions. The placement of each entity on the graph is approximate and conceptual, with further study required to improve precision and accuracy. Note that if clinical correlate is present with any of the patterns, it would be considered ictal by definition, though this does not necessarily suggest an appreciable increase in the likelihood of neuronal injury. EPC, epilepsia partialis continua; GCSE, generalized convulsive status epilepticus: GPEDs, generalized periodic epileptiform discharges; NCS, nonconvulsive seizures; NCSE, nonconvulsive status epilepticus; PLEDs, periodic lateralized epileptiform discharges; S-B, suppression-burst; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges; TW, triphasic waves.

TABLE 2. Criteria for Non-Convulsive Seizure

Any pattern lasting at least 10 seconds satisfying any one of the following 3 primary criteria:

Primary Criteria:

1. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave or sharp-and-slow wave complexes at ≥3/sec.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/sec and the secondary criterion.
3. Sequential rhythmic, periodic, or quasi-periodic waves at ≥1/sec and unequivocal <u>evolution</u> in frequency (gradually increasing or decreasing by at least 1/sec, e.g. from 2 to 3/sec), morphology, or location (gradual spread into or out of a region involving at least 2 electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not adequate to satisfy evolution in morphology.

Secondary criterion:

Significant improvement in clinical state or appearance of previously-absent normal EEG patterns (such as a posterior dominant rhythm) temporally coupled to acute administration of a rapidly-acting AED. Resolution of the "epileptiform" discharges leaving diffuse slowing without clinical improvement and without appearance of previously-absent normal EEG patterns would not satisfy the secondary criterion.

AED = antiepileptic drug;
  Modified from (Young et al. 1996).

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intravenous bolus of benzodiazepine and multiple conventional AEDs that do not lead to coma, respiratory depression, or the need for pressors. The literature does not support aggressive treatment requiring intubation outside of the setting of generalized convulsive status epilepticus, though this has certainly not been adequately studied.

It is unclear how long to continue AEDs in survivors of the acute illness who have had PLEDs or GPEDs. Our fairly arbitrary recommendations include tapering of AEDs if the periodic discharges were not associated with a seizure, but continuing treatment for 3 months to 1 year before considering AED withdrawal if acute symptomatic seizures were associated with the periodic discharges.

The EEG can give some indication of prognosis. Patients with GPEDs or burst-suppression after cardiac arrest have a poor outcome, and treatment for seizures has not been helpful to date. Among those with GPEDs, patients with higher interdischarge amplitude tend to have better outcomes, as do those with GPEDs in settings other than after anoxia and in younger patients. Although we recommend maintaining a therapeutic dose of at least one conventional AED in patients with GPEDs, no further specific recommendations are possible, allowing significant room for clinical judgment on an individualized basis.

New animal models show great promise in their theoretical ability to answer many questions about periodic discharges and nonconvulsive seizures after brain insult, possibly directing therapy in new directions. In humans, 24-hour continuous monitoring has increased seizure and periodic discharge detection. This affords a great opportunity to improve our ability to predict and prevent seizures, to prognosticate, and to potentially prevent seizure-associated neuronal injury. For research to be helpful with cEEG, there must be standardization of the nomenclature used to describe periodic and rhythmic patterns and carefully designed research directed at determining which EEG patterns are associated with ongoing neuronal injury.

ACKNOWLEDGMENTS

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