Periodic Complexes: Classification and Examples

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Introduction

Continuous electroencephalography (cEEG) is an important diagnostic tool, frequently used to assess brain function and detect nonconvulsive seizures (NCS). The expansion of cEEG monitoring has led to the realization that rhythmic and periodic patterns are commonly seen in critically ill patients. Unfortunately, the significance and implications of many of these patterns remain poorly defined, making it difficult for the electroencephalographer to clearly communicate their meaning to the clinical team. For some of these patterns, there has been an association with increased risk of seizures and morbidity [1–4]. However, decision regarding if and how aggressively to treat these patterns remains controversial. Furthermore, the

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distinction between ictal and interictal can become blurred, making this decision even more challenging. Debate continues about whether these patterns intrinsically have potential for neuronal injury or whether they exist as an epiphenomenon of acute brain injury or encephalopathy [5]. A helpful conceptualization is to consider that each of these patterns lie on an ictal-interictal continuum (IIC), implying varying degrees of cortical irritability and need for treatment [6].

In the past 10 years, there has been a great deal of research dedicated to periodic and rhythmic patterns. The true incidence of these patterns remains unknown because some accounts of incidence are based on routine electroencephalography (EEG) that likely underestimate the incidence seen on cEEG monitoring. In addition, it is important to keep in mind that prior to the widespread use of cEEG, the patients undergoing cEEG monitoring were a selected population thought to be at greatest risk for seizures [7]. However, despite the limitations of this research, there is a developing understanding of the etiology of these patterns and their relationship to prognosis and outcome.

ACNS Terminology

The American Clinical Neurophysiology Society (ACNS) has created and revised a version of critical care EEG terminology with the goal of standardizing terminology to describe EEG patterns frequently encountered in critically ill patients [8, 9]. The aim of standardizing the terminology is to facilitate communication and allow multicenter research to attain a better understanding of the meaning of these patterns. This classification system was designed to avoid using terms that have become attached to certain clinical connotations (i.e., "triphasic waves"). In addition, the terminology does not include the terms "ictal," "interictal," and "epileptiform" in order to avoid the implication that these patterns definitively lie on one side of the IIC [8].

Excluding unequivocal electrographic seizures (i.e., generalized spike-and-wave discharges at 3 per second or faster and clearly evolving discharges that reach a frequency of more than 4 per second), the ACNS subcommittee divided the remaining EEG patterns into periodic discharges (PDs) or rhythmic delta activity (RDA). In addition, the most recent version of the guidelines introduced the category of spike-and-wave or sharp-and-wave (SW) [8]. To be characterized as a periodic or rhythmic pattern by ACNS terminology, the waveform must repeat for a minimal duration of six cycles (i.e., 1 per second for 6 s or 2 per second for 3 s) [9].

Two main terms are included in the description, term one which describes the location (ie, generalized (G), lateralized (L), bilateral independent (BI), or multifocal (Mf)) and term two which identifies the type of pattern (PDs, RDA, or SW) [8, 9]. Additionally, there are several modifiers as well as "minor" modifiers that further describe EEG patterns (see Table 1). One of the modifiers commonly used is the "plus" (+) descriptor. This descriptor implies an additional feature is present which suggests that the pattern is more ictal-appearing. The modifier "+F" can be used with PDs or RDA to describe superimposed fast activity only seen when the

Table 1 Main terms including some additional modifiers included in the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (2012 version)

Main term 1	Main term 2	Plus modifiers	
Generalized (*G*)	*Periodic discharges* (*PDs*)	+F	Superimposed fast activity (PDs and RDA only)
Lateralized (*L*)		+R	Superimposed rhythmic activity (PDs only)
Bilateral independent (*BI*)		+FR	Both superimposed fast and rhythmic (PDs only)
Multifocal (*Mf*)	*Rhythmic delta activity* (*RDA*)	+F	Superimposed fast activity (PDs and RDA only)
		+S	Superimposed sharp waves or spikes or sharply contoured (RDA only)
		+FS	Both superimposed fast and sharp waves or spikes or sharply contoured (RDA only)
	Spike-and-wave or sharp-and-wave (*SW*)	No plus modifiers	

Additional modifiers

Prevalence (% of record)	Rare <1 %		Occasional 1–9 %		Frequent 10–49 %		Abundant 50–89 %		Continuous ≥90 %
Duration (s)	Very brief <10 s		Brief 10–59 s		Intermediate 1–4.9 min		Long 5–59 min		Very long ≥1 h
Frequency (cycle/s)	<0.5	0.5	1	1.5	2	2.5	3	3.5	≥4
Sharpness (ms)	Blunt >200		Sharply contoured >200 with sharp morphology		Sharp 70–200		Spiky <70		
Stimulus-induced	Stimulus induced (SI-)		Spontaneous (Sp-)				Unknown		

Adapted from Gerard [10]

pattern is present. The modifier "+R" can only be used with PDs and connotes superimposed rhythmic or quasi-rhythmic delta activity. Finally, the modifier "+S" is used exclusively with RDA, when there are frequent intermixed sharp waves, spikes, or sharply contoured RDA.

The revised 2012 ACNS terminology included changes made based on solicited feedback and studies of inter-rater agreement on the use of the terminology. The first assessment found that inter- and intra-observer agreement for the presence/absence of rhythmic or periodic patterns and for localization of these patterns was moderate and agreement for the modifiers was slight to fair [11]. After initial changes were made to the criteria, an assessment was conducted using the interim version. Inter-rater agreement for the main terms was almost perfect, but agreement on modifiers was more variable [12]. In the most recent assessment, the inter-rater

agreement using the revised 2012 ACNS terminology was found to be almost perfect for the two main terms (i.e., pattern location (91 %) and pattern type (85 %)). Modifiers including sharpness, absolute amplitude, frequency and number of phases, and the + S modifier also had an "almost perfect" agreement (greater than 80 %), while the + F and + R modifiers had "substantial agreement." However, agreement for triphasic morphology and evolution were "moderate" (58 %) and "fair" (21 %), respectively [5]. While further work may need to be done to improve the understanding and reproducibility of some of the modifiers, main terms one and two seem to be easily recognized and reliable. As a result, they have now largely replaced older terminology in both clinical reports and cEEG literature.

An overview of each of the periodic patterns, alternative terminology, characteristics, prevalence, association with seizures, mortality rate, and common etiologies is listed in Table 2.

Periodic Discharges

PDs are discharges with both a uniform morphology and duration that repeat with a definable and quantifiable interval between consecutive waveforms [8]. These waveforms recur at nearly regular intervals [7]. The discharges can be generalized, lateralized, bilateral independent, or multifocal [8]. Common etiologies include infectious and toxic-metabolic etiologies.

Lateralized Periodic Discharges

Lateralized periodic discharges (LPDs) are discrete repetitive discharges that are lateralized to one hemisphere and have a consistent morphology that recur at periodic intervals, most frequently, between 0.5 and 3 Hz (Fig. 1). This pattern was first termed "periodic lateralized epileptiform discharges" (PLEDs) by Chatrian et al. in 1964 [18]. The term was then changed to LPDs as part of the new ACNS terminology [9]. Traditionally, the discharges are sharp waves or sharp wave complexes ranging from 50 to 300 μV. The new ACNS terminology proposes that the term applies to all PDs regardless of morphology. The discharges must be lateralized to one hemisphere but can be maximal in any focal area of the brain [18]. Most frequently, the field of discharges is broad, including the parasagittal chains and temporal chains of the ipsilateral hemisphere, though focal PDs are still considered LPDs. LPDs can involve the contralateral hemisphere; this is commonly seen if the discharges are maximal in the frontal or occipital regions; however, the discharges must have higher amplitude over one hemisphere [18]. It is important to exclude periodic artifacts that can mimic LPDs, most commonly electrocardiographic or pulse artifact.

LPDs are typically associated with ipsilateral cerebral dysfunction. As such, there is usually focal slowing or loss of the posterior dominant rhythm in that hemisphere. The contralateral hemisphere may show evidence of an encephalopathy, although it may also be unaffected.

Table 2 Overview of periodic discharges and rhythmic delta activity patterns

Consortium terminology	Other names	Characteristics	Prevalence	Association with seizures	Mortality rate	Common etiologies
LPDs Lateralized periodic discharges	PLEDs	Lateralized repetitive discharges recurring at 0.5–3 Hz; typically with broad field but may be focal	0.4–1 % (rEEG) 8 % (cEEG) [4, 13, 14]	49–100 % [4, 15–17]	24–53 % [13, 15]	Ischemic stroke [13, 15, 18] Neoplastic lesions [14] Viral encephalitis, ICH, SAH, and anoxic encephalopathy [18]
BIPDs Bilateral independent lateralized periodic discharges	BIPLEDs	Asynchronous periodic discharges occur independently but simultaneously over both hemispheres	0.1 % (rEEG) [15]	70 % [15]	Up to 61 % [15, 19, 20]	CNS infection, anoxia, chronic epilepsy, stroke, tumor, metabolic abnormalities, bilateral structural lesions[2,29]
GPDs Generalized periodic discharges	GPEDs	Synchronous discharges that are relatively symmetric in amplitude across homologous regions	0.01–1 % (rEEG) 4–8 % (cEEG) [3, 21, 22]	46 % [3]	36 % in one study [3]	Hypoxic ischemic injury (e.g., cardiac arrest), metabolic disorders, rarely SSPE or sCJD [15, 19], drug toxicities [2], late stages of status epilepticus [23]
GPDs-TW[a] Generalized periodic discharges Triphasic morphology	Triphasic Waves	Discharges consisting of three phases, each longer than the preceding one with a surface positive high-amplitude wave preceded and followed by negative waves with a smaller amplitude	20–57 % (rEEG) [1]	0–4 % [24, 25]	20–77 % [26, 27]	Metabolic encephalopathy, steroid responsive encephalopathy, toxic encephalopathy, postictal stupor [28]
LRDA Lateralized rhythmic delta activity		Rhythmic delta pattern as a repetitive waveform with relatively uniform morphology and duration; lateralized to one hemisphere	4.7 % (cEEG) [4]	63 % [4]	NR	CNS neoplasm, subarachnoid hemorrhage, subdural hemorrhage, intracerebral hemorrhage, ischemic stroke [1]
GRDA Generalized rhythmic delta activity		Rhythmic delta pattern with a generalized distribution	NR	NR	NR	Non-specific, including focal and diffuse processes, limbic encephalitis, toxic-metabolic encephalopathy

Abbreviations: *cEEG* continuous EEG, *CNS* central nervous system, *NR* not reported, *rEEG* routine EEG, *sCJD* sporadic Creutzfeldt-Jakob disease, *SSPE* subacute sclerosing panencephalitis, *PLEDs* Periodic lateralized epileptiform discharges, *BIPLEDs* Bilateral independent periodic lateralized epileptiform discharges, *GPEDs* Generalized periodic epileptifom discharges

[a]TW modifier can also be used with generalized spike-and-wave or sharp-and-wave term (GSW-TW)

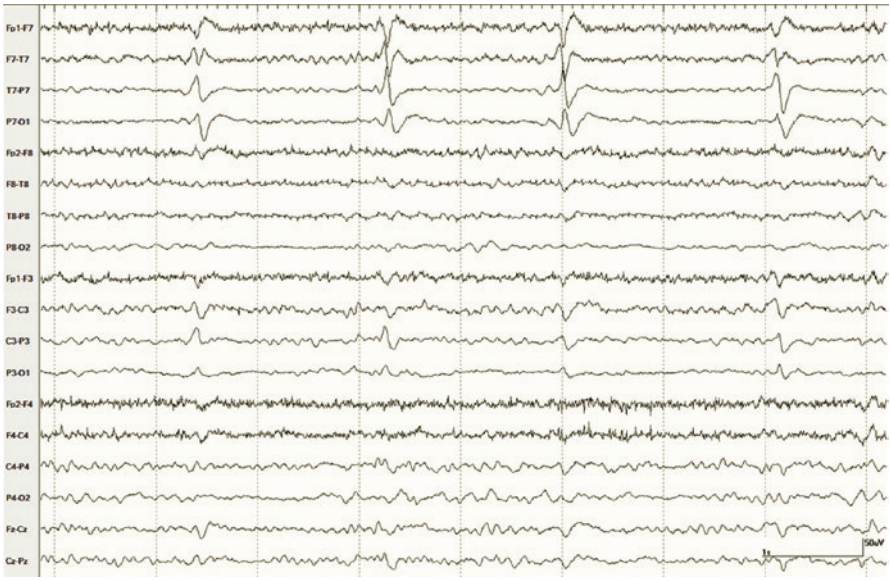

Fig. 1 Lateralized periodic discharges (LPDs) in a 61-year-old man with history of alcohol abuse initially presenting after a witnessed generalized tonic-clonic convulsion. In the emergency department, he was noted to have fever and right hemiparesis. CT of the brain demonstrated multifocal infarcts, including the left MCA territory and bilateral PCA infarcts, thought to be cardioembolic in etiology. LPDs seen here later evolved to discrete seizures

The overall incidence of LPDs was previously estimated to be 0.4–1 % based on routine EEG studies; however, a more recent study evaluating cEEG has reported an incidence as 8.6 % in patients with cEEG monitoring [4, 13, 14]. Classically, this pattern has been considered a transient phenomenon, usually seen within the first days of an acute brain insult and often resolving within days to weeks [13].

In historic literature based on routine EEGs, the most common etiology associated with LPDs is an acute or subacute structural lesion involving the cortex, typically caused by an ischemic stroke [13, 15, 18]. In the authors' series, neoplastic lesions were the most common cause of LPDs on cEEG, possibly reflecting a difference in monitoring practices [14]. Other etiologies include viral encephalitis (i.e., herpes encephalitis), intracranial hemorrhage, tumors, subarachnoid hemorrhage, and anoxic encephalopathy. LPDs have been described in posterior reversible encephalopathy syndrome, migraine, demyelinating diseases, Creutzfeldt-Jakob disease (CJD), and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) [29]. While stroke and hypoxic-ischemic encephalopathy are common etiologies for LPDs among neonates, an infectious etiology is more common in the rest of the pediatric population. One study found that 2/3 of pediatric patients with LPDs had central nervous system infections [30].

The majority of patients with LPDs do not have a prior history of epilepsy; however, seizures occur in the majority of patients with LPDs during their

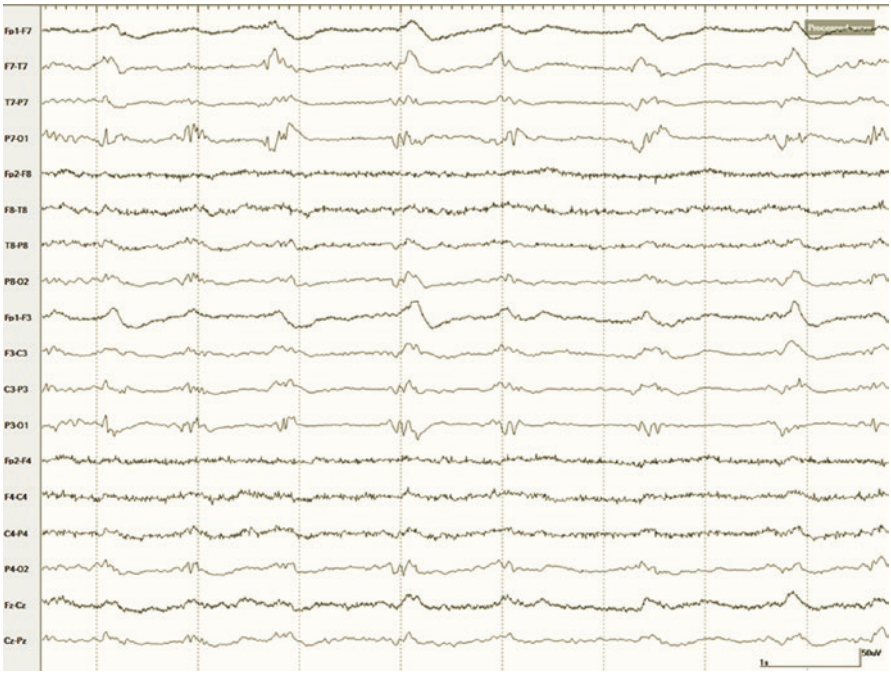

Fig. 2 Lateralized periodic discharges with fast activity (LPDs + F) in a 55-year-old woman with history of diabetes presenting with hyperglycemia and altered mental status. Continuous EEG demonstrated 1 Hz left hemispheric LPDs + F as well as frequent electrographic seizures arising from the left parieto-occipital region

hospitalization, seen in 49–100 % of patients with LPDs [4, 15–17]. The most common seizure type associated with LPDs is focal motor seizures [13, 16, 18]. Both clinical and nonconvulsive seizures are associated with LPDs. One study found that of all patients with seizures identified during continuous monitoring, 40 % had LPDs. The majority of the seizures identified were nonconvulsive. Furthermore, approximately 20 % of patients with LPDs had their first seizure after the first 24 h of continuous monitoring, compared to 8 % of patients without LPDs [31].

A subtype of LPDs, namely, LPDs + F (or previously PLEDs+), were first described as LPDs with superimposed rhythmic discharges, typically low-voltage fast activity. This pattern has been reported to be more frequently associated with clinical or electrographic seizures compared to LPDs alone (74 % vs. 6 %, respectively, in one study) [32] (Fig. 2).

LPDs are typically considered ictal if the PDs are time locked to electromyographic recordings demonstrating clonic activity. This pattern is frequently associated with LPDs arising from the hemisphere contralateral to the focal clonic seizures (Fig. 3).

In most studies, LPDs have been associated with a high mortality rate in adults, ranging from 24 to 53 % [13, 15]. LPDs have been found to be an independent

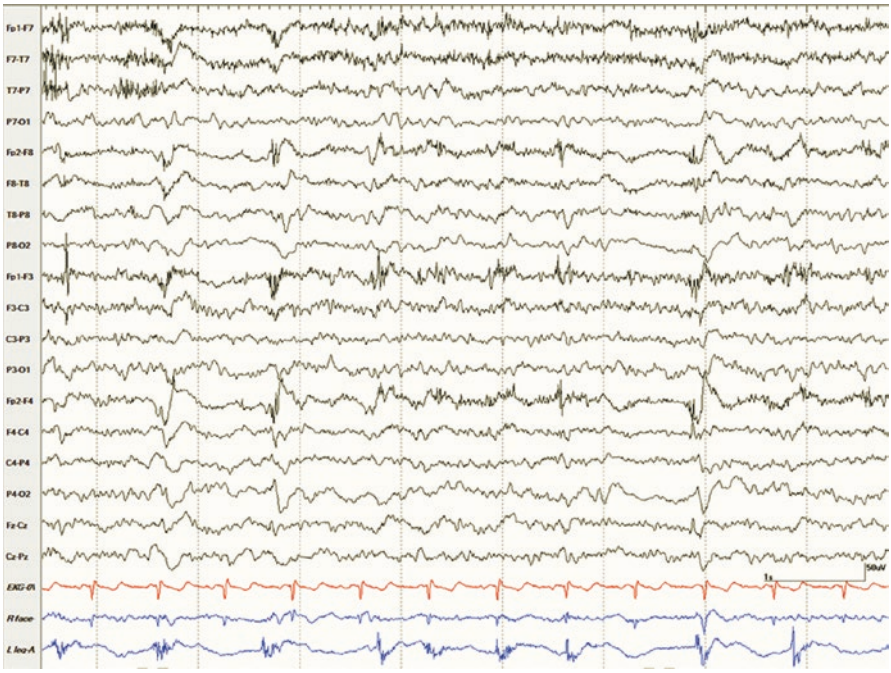

Fig. 3 Ictal lateralized periodic discharges (LPDs) in an 87-year-old woman who presented with altered mental status and rhythmic clonic movements of her left face, arm, and leg after probable convulsion at home. EEG demonstrates lateralized periodic discharges, maximal over the right frontocentral region, time locked with focal movements of the left lower extremity (i.e., EMG lead, "L leg"). MRI of the brain was negative for a focal lesion. Etiology cryptogenic, suspected to be infectious vs. inflammatory

predictor of poor outcome (moderate to severe disability or death) in patients with subarachnoid hemorrhage, intracerebral hemorrhage, and patients in the medical intensive care unit [33–35]. Interestingly, in one study of adult patients, the occurrence of seizures in patients with LPDs was associated with a lower likelihood of death as a clinical outcome compared to LPDs that occurred without seizures [15]. In one study of 44 pediatric patients with LPDs, the mortality rate was 23 % and morbidity rate was 50 % [30]. Of the patients with LPDs, a better prognosis is seen among patients with a prior history of epilepsy or children with acute infections.

On account of the strong association with seizures, most experts agree that if LPDs are seen on EEG, the patient should be treated with at least one antiepileptic drug (AED) to prevent further seizures. Whether or not to "treat" LPDs to resolution of the pattern remains highly controversial. A common practice has been to "treat" LPDs when the pattern has a clear clinical correlate. However, the most commonly recognized clinical correlate is clonic motor jerking, which has been shown to be principally a manifestation of the location of LPDs or underlying lesion in or near the motor cortex [36]. LPDs in other locations may have subtle clinical correlates such as aphasia, eye deviation, or cognitive changes, which are subtle and

particularly hard to recognize when a patient is in coma [29]. For example, evaluating whether frontopolar or occipital LPDs have a clinical correlate in a patient in iatrogenic coma is not feasible. This does not necessarily mean that all LPDs should be treated aggressively. LPDs can often be seen following clinical seizures or resolution of status epilepticus (SE). They may also be very resistant to escalating medications and can take days to weeks to resolve; thus, it is unclear if aggressive treatment with sedating medications or anesthesia is always warranted [13, 37]. Ultimately, the decision to treat must account for the underlying etiology and overall clinical context including the progression of the patient's EEG patterns. While there is no agreed-upon prescription for treating LPDs, a common approach in a patient who has had nonconvulsive status that converted to complex LPDs is to watch the LPDs for at least 1–2 days and continue the observation without intervention as long as there is progressive improvement in the complexity and frequency of the LPDs (Fig. 4).

LPDs can also be associated with corresponding regional increases in cerebral perfusion or glucose metabolism on single-photon emission computed tomography (SPECT) or positron emission tomography (PET) [38, 39]. Whether these functional imaging studies should have a role in determining the appropriate degree of intervention has not been established.

Bilateral Independent Lateralized Periodic Discharges

Bilateral independent lateralized periodic discharges (BILPDs) are asynchronous PDs that occur independently but simultaneously over both hemispheres. Discharges are typically sharp waves, spikes, or polyspikes, though epileptiform morphology is not required under ACNS criteria [2, 9]. The independent left and right complexes seen in BILPDs usually differ in morphology, amplitude, repetition rate, and site of maximal involvement (Fig. 5) [19].

BILPDs are much less common than other rhythmic and periodic patterns. They have been reported in 0.1 % of routine EEGs [15]. The etiologies associated with this pattern include CNS infection, anoxia, chronic epilepsy, stroke, tumor, metabolic abnormalities, and bilateral structural lesions [2, 19]. The bilateral involvement of the discharges likely reflects more diffuse disease, and as such, these patients have a higher likelihood of associated coma compared to unilateral discharges [15, 19].

BILPDs are seen much less frequently than unilateral LPDs, and therefore, the data regarding the significance of this pattern is limited. While both LPDs and BILPDs are associated with a high frequency of seizures, generalized seizures are more common with BILPDs compared to focal seizures seen in LPDs [19]. More recent studies have found that patients with BILPDs were less likely to have seizures compared to LPDs (43 % vs. 70 %, respectively) [15]. However, interestingly, in one series of patients with CNS infections, 100 % of patients with BILPDs (4/4) had electrographic seizures compared to 57 % (8/14) of patients with LPDs with seizures.

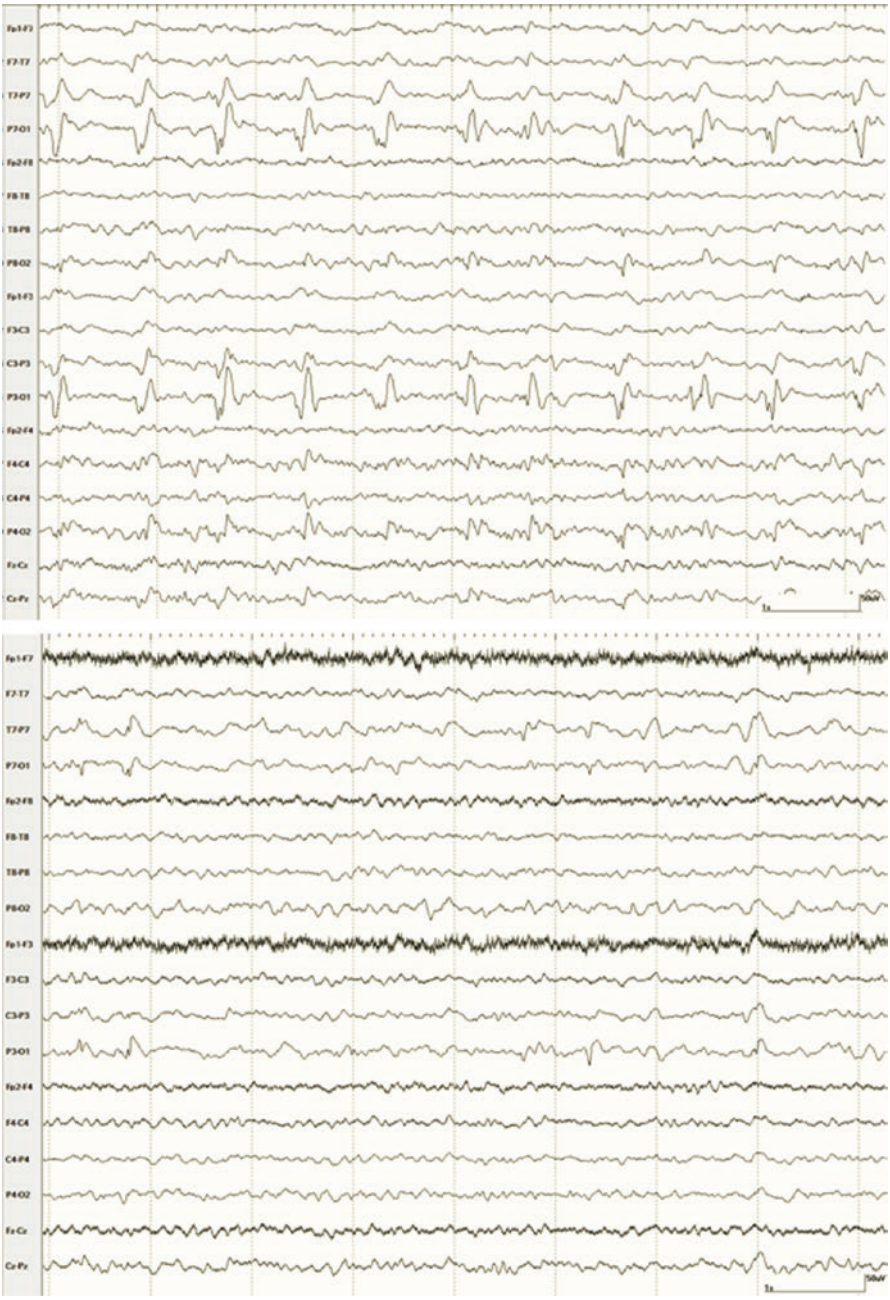

Fig. 4 Evolution of lateralized periodic discharges with fast activity (LPDs + F) in a 65-year-old woman over the course of 1 month. The patient has a history of monoclonal gammopathy of unknown significance (MGUS), HTN, and lupus who initially presented with confusion and gait instability. MRI revealed posterior reversible encephalopathy syndrome (PRES) involving the left occipital region. Frequent focal left occipital seizures and persistent LPDs were present on initial 24 h continuous EEG record. Seizures responded to multiple antiepileptic medications (valproic acid, levetiracetam, lacosamide, and clonazepam) but LPDs + F persisted. Periodic discharges improved in frequency, complexity, and morphology over the course of a month, while the patient continued the same antiepileptic medication regimen

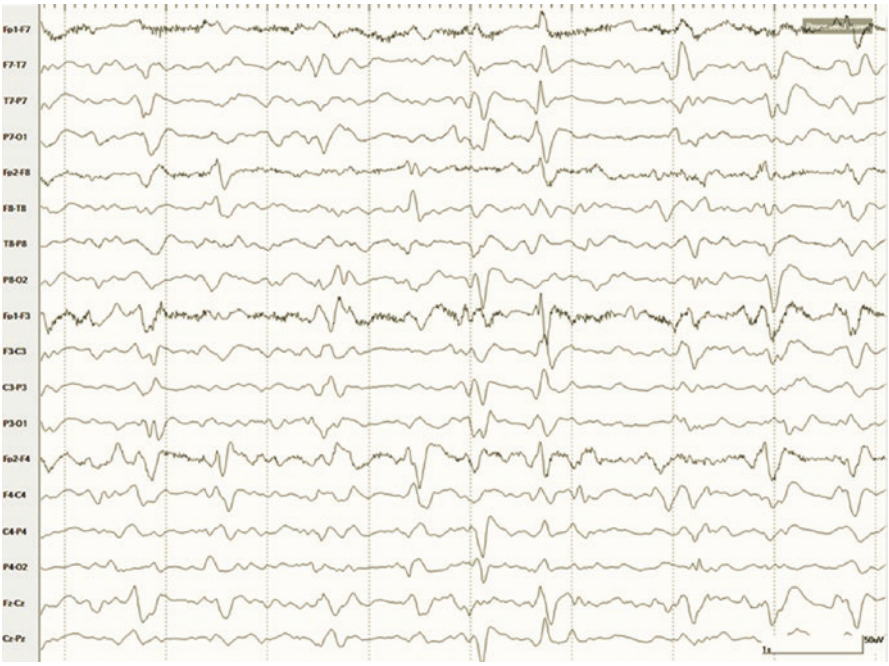

Fig. 5 Bilateral independent lateralized periodic discharges (BILPDs) in a 94-year-old woman who presented with Non-ST segment elevation myocardial infarction (NSTEMI) followed by pulseless electrical activity (PEA) arrest. Hypothermia protocol was performed. Patient remained comatose, and EEG was obtained to evaluate for subclinical seizures. Continuous EEG demonstrated LPDs, arising independently from the bifrontal regions (BILPDs)

Compared to LPDs, the mortality rate for patients with BILPDs is higher, up to 61%; however it does not appear that functional outcomes among survivor are significantly different [15, 19, 20]. It does not appear that functional outcomes among survivors are significantly different [15].

As with LPDs, vigilance with cEEG monitoring is recommended for patients with BILPDs given the increased risk of seizures, and at least one prophylactic AED is often started though this practice is less well-described and likely less uniform than that for LPDs. Again, it is unclear if there is value in attempting to "treat" BILPDs to resolution. If possible, correcting the underlying etiology is an important part of treatment. In some cases, BILPDs may represent nonconvulsive status epilepticus (NCSE), and attempts should be made to treat the pattern, especially if there is no alternative explanation for the patient's mental status.

Generalized Periodic Discharges

Prior to the new ACNS terminology, generalized periodic discharges (GPDs) were referred to as generalized periodic epileptiform discharges (GPEDs) [8, 9]. GPDs are synchronous discharges that are relatively symmetric in amplitude across homologous regions of the brain [7]. Discharges may be frontally or occipitally predominant. According to the ACNS criteria, discharges are most frequently

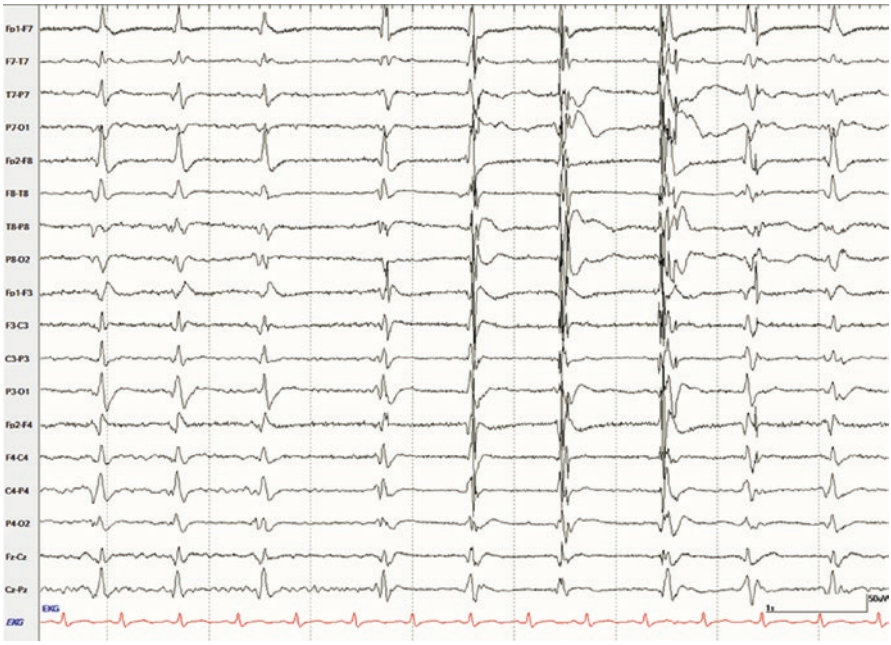

Fig. 6 Generalized periodic discharges (GPDs) seen in a 63-year-old man with a history of hypertension with asystole in the setting of profound hypoglycemia. The patient underwent hypothermic protocol. EEG demonstrates generalized periodic discharges intermittently time locked with whole-body myoclonus

spikes, polyspikes, or sharp waves and have a negative polarity, although blunt PDs can also be considered GPDs [2, 15]. Between runs of PDs, typical patterns include diffuse delta slowing or attenuation (Fig. 6) [7].

GPDs have been reported in 4–8 % of patients undergoing cEEG and 0.01–1 % of routine EEGs [3, 6, 23]. This pattern can be seen in up to 20 % of patients in coma with severe postanoxic encephalopathy after cardiac arrest [40].

It has been hypothesized that GPDs may result from disruption of the thalamocortical pathway with diffuse or multifocal cerebral dysfunction or systemic disease [3]. Common etiologies include hypoxic ischemic injury (i.e., cardiac arrest), metabolic disorders, sporadic CJD, and subacute sclerosing panencephalitis [15, 41]. Drug toxicities associated with GPDs include cefepime, baclofen, lithium, phencyclidine, ketamine, barbiturates, and anesthetics [2, 21, 41]. GPDs may also be seen in the late stages of generalized convulsive SE and after the SE has resolved [22]. The pattern can also represent NCSE, even without preceding convulsions. In particular, GPDs occurring at a frequency greater than 2.5 Hz should raise suspicion for NCSE, although this is not the only criteria [42].

The presence of GPDs in an EEG record has been associated with seizures [23]. The most comprehensive study to date included 200 patients with GPDs with matched controls and found that almost one half of patients with GPDs had a

seizure at some point during their hospital stay (although this was not statistically different than matched controls). Of note, there was no difference in outcome or mortality between the patients with GPDs and the matched controls. However, NCSE was found to be associated with worse outcome for patients both with and without GPDs [3].

Given the common association between NCS and GPDs, it is important to continue careful monitoring in patients with GPDs in order to detect and treat NCSE. Treatment of the underlying etiology is of the utmost importance in patients with GPDs. The use of AEDs in patients with GPDs is even less understood and more controversial than it is in the setting of other patterns. In general, many experts do not start AEDs for GPDs where a correctable toxic or metabolic etiology is suspected, though some feel it may hasten recovery and prevent seizures in the brain's transient period of increased irritability. On the other hand, if there is no explanation for the patient's mental status and/or the pattern meets criteria for NCSE, treatment should be considered [3, 6, 23]. A "trial" of a benzodiazepine or another antiepileptic drug can be considered in uncertain cases. In order for such a trial to be considered positive, both the electrographic pattern and the patient's mental status must improve [43].

The treatment of GPDs in the setting of anoxia, particularly if associated with myoclonus, is especially controversial. Some consider the threshold to treat GPDs associated with myoclonia lower than GPDs with nonconvulsive symptoms; however, in postanoxic encephalopathy, it is thought that the treatment may be futile given a higher incidence of neuronal necrosis and a greater risk of poor outcome [44]. Some authors have suggested that the background between individual discharges may be useful in prognosis and the utility of antiepileptic drug treatment [1, 44].

Generalized Periodic Discharges: Triphasic Morphology

The triphasic wave (TW) pattern was first described in the context of hepatic coma in 1955 [45]. Over time, this term has become pathognomonic of a metabolic encephalopathy. In fact, electroencephalographers have been found to choose to report triphasic waves rather than GPDs based on the clinical history when classifying an EEG pattern [46]. In order to extract clinical implications from EEG terminology, the revised ACNS proposed standard terminology considers triphasic waves to be a type of PDs (GPDs-TW) or occasionally a sharp-and-wave subtype (GSW-TW) [9].

The TW modifier is used to define repetitive electrographic discharges consisting of three phases, each longer than the preceding one; a surface positive high-amplitude (typically greater than 70 μV) wave preceded and was followed by negative waves with smaller amplitude [9, 47]. GPD-TWs are typically diffuse, although may have an anteroposterior or a posteroanterior time lag seen in bipolar montages and may show a frontocentral or frontoparietal predominance. Typically, individual complexes exceed 0.3 s (Fig. 7).

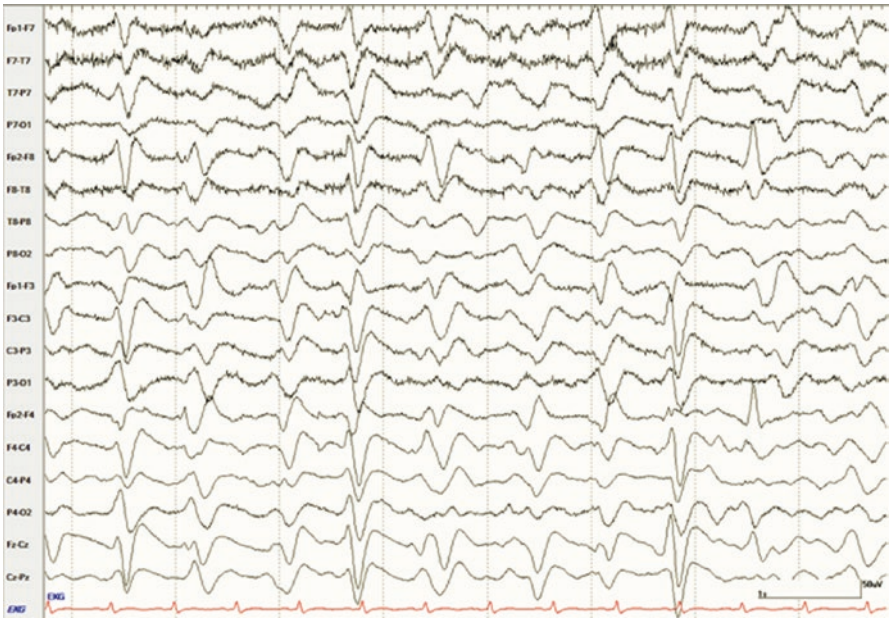

Fig. 7 Generalized periodic discharges with a triphasic morphology (GPDs-TW) seen in a 47-year-old woman with history of epilepsy, depression, anxiety, and polysubstance abuse who presented with fulminant hepatic failure after an acetaminophen overdose

Traditionally, GPD-TWs have been associated with metabolic encephalopathy. They are highly characteristic of hepatic encephalopathy but not pathognomonic [48]. Other possible etiologies include renal failure, toxic encephalopathies, steroid-responsive encephalopathy, sepsis-associated encephalopathy, and postictal stupor [28]. Studies have shown that the majority of patients with GPD-TWs have a combination of at least two pathologic conditions and/or neuroradiologic abnormalities, and over one quarter of patients have been found to have elements of all three abnormalities [28]. It has been general consensus that GPD-TWs represent the overall derangement of thalamocortical circuits that result from metabolic, toxic, infectious, and structural cerebral abnormalities, rather than being considered intrinsically epileptogenic [28, 49]. Rarely have they been found to be associated with seizures, estimated at 0–4 % [24, 25].

GPD-TWs may be seen as an ictal pattern which can be difficult to differentiate from NCSE [28]. It has been suggested that GPD-TWs typically disappear with sleep, and this is one method to distinguish between them and an ictal pattern [50]. It was previously thought that only epileptiform discharges would respond to benzodiazepines; however, GPD-TWs of metabolic origin also respond temporarily to benzodiazepines, making it difficult to distinguish between the two entities [51]. For this reason, as discussed above, a positive benzodiazepine trial requires both improvement in the EEG pattern and the patient's mental state [43].

The presence of GPD-TWs has been associated with high mortality, in the range of 20–77 % [26, 28]. However, a recent study evaluated encephalopathic patients GPD-TWs, and matched controls (encephalopathic patients without GPD-TWs) found that when the EEG background activity and GCS were matched, GPD-TWs were not specifically associated with death [27]. Therefore, this pattern likely does not intrinsically impact mortality, rather the comorbid conditions associated with it affect outcome.

It is still not clear whether GPD-TWs represent a distinct entity from GPDs or GSWs. Treatment of GPD-TWs (or GSW-TWs) should be similar to the approach to GPDs. Again, a focus on addressing the underlying pathologic conditions that may predispose the patient to this pattern is especially important. However, it is important to keep in mind that the triphasic morphology does not in and of itself predict a metabolic cause, and the possibility that this represents a potentially ictal pattern should be considered.

Rhythmic Delta Activity

Intermittent rhythmic delta activity (IRDA) was first described by WA Cobb in 1945 [52]. The ACNS terminology defines RDA as a repetitive waveform with relatively uniform morphology and duration. In contrast to PDs, RDA occurs without an interval between consecutive waveforms. In order for the pattern to be considered rhythmic, the duration of one cycle should vary by less than 50 % from the duration of the subsequent cycle for the majority of the cycle pairs. In addition, the rhythmic activity must be less than or equal to 4 Hz [9]. There are two basic patterns of RDA, namely, lateralized and generalized.

Lateralized Rhythmic Delta Activity

Lateralized rhythmic delta activity (LRDA) is a rhythmic delta pattern lateralized to one hemisphere (Fig. 8). A recent study described the largest cohort of patients with LRDA to date [4]. Using the same definition of LRDA as described above, they found 27 subjects with LRDA out of 558 individuals older than 1 month of age who had cEEG or an urgent EEG over the course of 1 year (i.e., 4.7 %). Typically, the duration of LRDA was brief or very brief (less than 1 min and less than 10 s, respectively), made up of runs of monomorphic, 50–200 μV sinusoidal or sharply contoured delta activity. Most often, the frequency was 1–2 Hz or 2–3 Hz. Most commonly, the foci of LRDA are anterior (typically frontal or temporal). When the morphology of LRDA was compared to LPDs, LPDs were typically slower (less than or equal to 1 Hz) and occurred in longer runs (greater than 1 min, often between 5 min and 1 h).

In terms of associated pathology, similar to LPDs, LRDA is most commonly associated with an acute or remote cerebral injury, frequently involving the cortex, juxtacortical white matter, and/or deep gray structures. If a patient has a single focal lesion, LRDA is typically localized in the same region as the lesion [4, 52]. In the

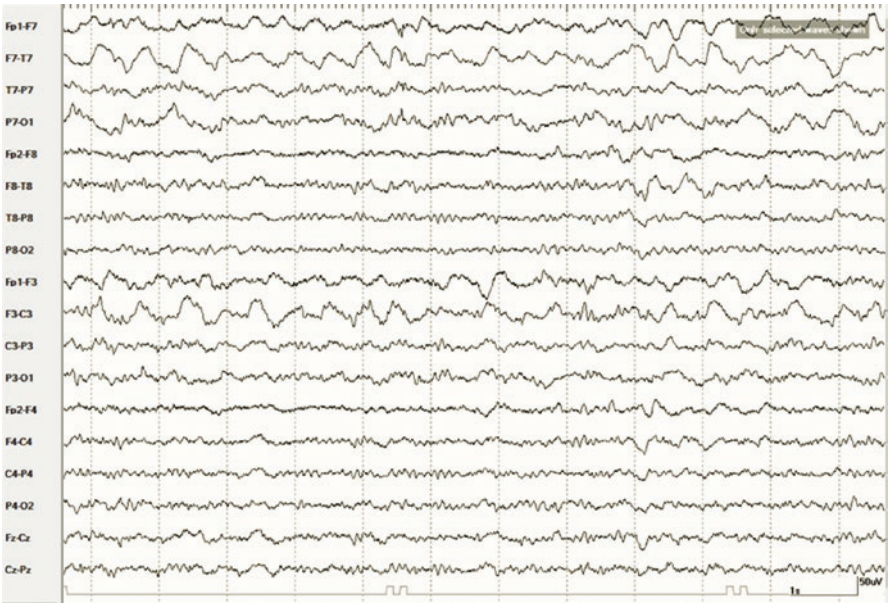

Fig. 8 Lateralized rhythmic delta activity (LRDA), maximal in the left frontal region, in a 61-year-old man with history of focal epilepsy and a left frontotemporal glioblastoma multiforme s/p resection who presented with intermittent aphasia

aforementioned study, almost one quarter of patients had a history of epilepsy [4]. The authors found that approximately 60 % of the patients with LRDA were found to be stuporous or comatose; otherwise, LRDA was not associated with obvious clinical manifestations.

Over half of patients (63 %) with LRDA were found to have acute seizures during their hospital stay. This is similar to patients with LPDs, although is significantly higher than in patients with focal nonrhythmic slowing and controls. Of note, if patients have both LRDA and LPDs, the incidence of seizures has been found to be 84 % [4].

Given the shared implications of LPDs and LRDA, it is reasonable to approach LRDA in a fashion similar to LPDs. As discussed, there is a high incidence of seizures seen in association with LRDA; starting an AED to prevent further seizures is reasonable. In the case of frequent or continuous LRDA, more aggressive treatment may be merited in specific clinical situations where the pattern may represent an ictal pattern even in the absence of clear evolution.

Generalized Rhythmic Delta Activity

RDA seen diffusely is classified as generalized rhythmic delta activity (GRDA). GRDA is a relatively new term, and as such, there is limited data in the literature.

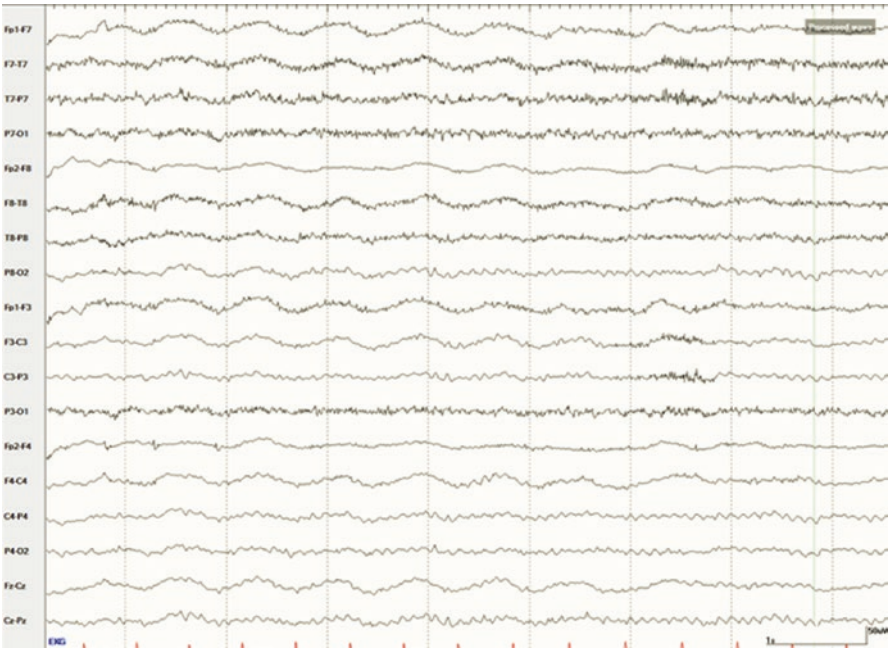

Fig. 9 Generalized rhythmic delta pattern (GRDA) seen in a 26-year-old woman with NMDA receptor antibody limbic encephalitis

Intermittent GRDA is associated with a broad range of neurologic abnormalities, both diffuse and focal processes, including inflammatory, vascular, neoplastic, degenerative, or traumatic disorders [53–56]. As such, its significance is typically considered relatively non-specific. This pattern is more frequently seen in older patients and inpatients, and it has a higher rate of comorbidity compared to controls [56]. Interestingly, in one series evaluating EEG features seen in anti-N-methyl-D-aspartate (NMDA) encephalitis, almost one half of patients (47.8 %) had GRDA (Fig. 9) [57].

The majority of the literature addressing rhythmic delta patterns focuses on frontal intermittent rhythmic delta activity (FIRDA). FIRDA was first described by Cobb in 1945 and, over time, has been thought to be a possible indicator of deep midline lesions and increased intracranial pressure [55]. This pattern can be considered bilateral independent lateralized rhythmic delta activity (BILRDA) or GRDA, depending on the maximal location and field involved in the rhythmic activity.

FIRDA can be seen as a normal response to hyperventilation, although should be limited to hyperventilation alone. In other contexts, this pattern is rarely seen on EEG; FIRDA has been reported in less than 1 % up to 6 % of EEG recordings [56, 58]. There is a reportedly low incidence of seizures in patients with FIRDA (i.e., 9 % of all patients with this pattern in one study) [4].

When GRDA is seen on EEG, treatment should usually be guided by the underlying etiology and comorbid conditions.

Spike-and-Wave and Sharp-and-Wave

This pattern was a new addition to the 2012 version of the ACNS nomenclature. It is defined as a polyspike, spike, or sharp wave with an after-going slow wave that occurs in a regular alternating pattern with no interval between the discharges. Given the recent addition of this terminology, there is limited research on this pattern. Therefore, incidence and treatment implications have not yet been established.

Conclusions

While there remains much to be understood about rhythmic and periodic patterns on cEEG, understanding the common means of characterizing them allows for better communication of difficult to describe findings. In doing so, it is important to acknowledge both what is and is not known about the meaning and treatment implications of these patterns. Future prospective studies will hopefully help clinicians gain an understanding of the pathophysiology underlying these patterns, the impact on neuronal injury, and their effect on functional outcome and, ultimately, use them as a tool to guide treatment decisions to improve prognosis and outcome.

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