Generalized periodic discharges (GPDs) are EEG waveforms seen in the set of many different types of encephalopathies. They are generalized, morphologically similar waveforms that recur at a regular frequency. Some authors have tried to evaluate GPDs based on their morphologic characteristics, while others have focused on prognosis and survival statistics. Exploration of these questions has shed light to new theories and fostered much discussion. The evolution of the terminology used to describe GPDs reflects the attempt of neurologists to grasp a better understanding of these waveforms.

Our knowledge of GPDs is limited and evolving as new information comes to light. In this article, we will begin with a review of the history and nomenclature of GPDs, followed by information on the etiology and pathophysiology of GPDs. Then, the discussion will turn to the treatment and prognostic value of these waveforms.

DEFINITION AND NOMENCLATURE
Historically, GPDs were referred to as generalized periodic epileptiform discharges. Other periodic discharges were also referred to as “epileptiform.” An expert panel of the American Clinical Neurophysiology Society reviewed the literature and determined that the association of periodic discharges with epileptiform activity was not a consistent feature of these discharges. Thus, the word “epileptiform” was eliminated from the terminology as not to imply an etiology in the nomenclature. A new terminology was proposed for all types of periodic discharges, and that terminology is used in this article.

Generalized periodic discharges are repeated generalized waveforms with relatively uniform morphology and duration with a quantifiable interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals. These discharges are further described as being frontally predominant, occipitally predominant, midline predominant, or generalized, not otherwise specified. Additionally, modifiers should be used to describe the following features of the GPDs:

1. Prevalence—how much of the record per epoch contains the GPDs
2. Duration—how long does the GPD activity continues during the recording, in minutes or hours
3. Frequency—the number of GPDs occurring in 1 second
4. Number of phases—the number of baseline crossings in a typical GPD waveform
5. Sharpness—the time in milliseconds for the sharpest and the most prominent phase of the GPD
6. Amplitude—the highest amplitude of the GPD waveform in an anterior–posterior bipolar montage should be measured; amplitude of the GPD can also be measured relative to the background activity
7. Polarity—whether the highest amplitude of the GPD is negative, positive, or unclear
8. Stimulus induced—whether the GPDs occur spontaneously or are induced with a stimulus
9. Evolving or fluctuating—whether the GPDs change in frequency, morphology, or location (evolution) or whether the changes are present but not enough to be classified as evolving (fluctuating)
10. Plus—whether additional features make the GPD pattern appear more epileptiform.

Other minor modifiers can also be included when describing GPDs. These include the following terms:

1. Quasi—used to modify the rhythmic or periodic nature of the GPDs
2. Sudden or gradual onset—used to describe how GPDs appear, suddenly (previously called paroxysmal) or over several seconds
3. Triphasic morphology—used to describe the shape of the GPDs
4. Lag of waveforms—either an anterior to posterior or a posterior to anterior lag may be seen in various components of the GPD.

Not all modifiers need to be used when describing GPDs. However, whichever ones are most appropriate for the individual situation should be considered.

Generalized periodic discharges should be distinguished from other periodic discharges. They are differentiated from lateralized periodic discharges (LPDs) by the unilateral nature of LPDs. Bilateral but asymmetric patterns are often also classified as LPDs, with lateralization toward the side with the more prominent waveform. These LPDs are thought to be projected to the contralateral side. Both GPDs and LPDs that are projected to the contralateral side are synchronous discharges. Bilateral independent periodic discharges are bilateral discharges, but they are asynchronous, that is, they do not occur in both hemispheres simultaneously. Additionally, bilateral independent periodic discharges may be symmetric or asymmetric. Finally, multifocal periodic discharges have at least three independent, lateralized patterns. At least one of these lateralized discharges must be in each hemisphere.

As the above discussion implies, triphasic waves are now also considered a type of GPD. Previously, they were not included in the classic generalized periodic epileptiform discharge literature. However, because of their morphologic similarity and generalized, synchronous, and symmetric nature, they are now considered GPDs. This is particularly appropriate as the term GPD does not imply an epileptic etiology. Traditionally, triphasic waves have been associated with metabolic encephalopathies. The overlap in the waveform spectrum of triphasic waves and GPDs is reflected in the new terminology. If triphasic waves comprise most of the EEG recording, they are described as “persistent, continuous, two per second GPDs (with triphasic morphology).”

Generalized periodic discharges were previously divided into three types:

1. Periodic, short-interval, diffuse discharges that were seen most often in Creutzfeldt–Jakob disease (CJD)
2. Periodic, long-interval, diffuse discharges that were seen with subacute sclerosis panencephalitis and drug toxicity
3. Burst suppression that can be iatrogenically induced or result from many causes, such as hypoxic–ischemic encephalopathy, coma, or drug use (such as anesthesia administration or barbiturate overdose).

These classifications are not widely used in the literature any more. Rather the various types of GPDs are now described using the various modifiers noted above.

**ETIOLOGY**

The occurrence of GPDs alludes to a global encephalopathy. Many different types of encephalopathies can result in GPDs. Common etiologies include anoxia, toxic/metabolic derangements, infections, acute neurologic injury, nonconvulsive status epilepticus (NCSE), and hypothermia. While GPDs are nonspecific for etiology, various features can help differentiate between various types of encephalopathies.

**Anoxic Encephalopathy**

Generalized periodic discharges have been reported frequently in patients with anoxic encephalopathy (Fig. 1). The morphology of the GPDs does not appear to be remarkably different in patients with anoxic encephalopathy compared with other types of encephalopathy. They can be seen within 12 to 24 hours after the onset of the anoxic injury. Many other EEG patterns, such as rhythmic discharges, LPDs, burst suppression, and background suppression, can also be seen with anoxic encephalopathy, but GPDs suggest a more severe brain injury.

Generalized periodic discharges can also occur with other patterns, such as rhythmic discharges in the alpha and theta frequency.

**Toxic/Metabolic Encephalopathy**

Historically, the EEG hallmark of toxic/metabolic encephalopathies was thought to be triphasic waves. These waveforms are now called GPDs with triphasic morphology in an attempt to dissociate etiology from the description. As their name suggests, these waveforms have three distinct phases. They were classically associated with hepatic encephalopathy, but later they were noted to occur in other types of metabolic disorder. However, GPDs with triphasic morphology should not automatically lead to a diagnosis of a toxic/metabolic encephalopathy. In many cases, these waveforms occur in patients with brain lesions with a superimposed metabolic disorder. Up to 31% of patients with GPDs with triphasic morphology have a metabolic, infectious, and structural etiology, while only 7% have only a metabolic etiology.

Generalized periodic discharges with triphasic morphology at times look very similar to spike and wave discharges seen in NCSE, making the distinction between toxic/metabolic and NCSE challenging. The anterior–posterior lag typically seen in GPDs with triphasic morphology or their response to a trial of benzodiazepines do not differentiate nonepileptiform from epileptiform GPD patterns. However, various other features of GPDs with triphasic morphology can suggest a toxic/metabolic encephalopathy versus NCSE (Table 1). The duration of the first phase and the entire complex is shorter in NCSE. The angles subtended between the various phases of the complex are bigger (more blunted), and the amplitude of the second phase is greater in toxic/metabolic encephalopathy. The discharge is seen more frequently in the frontocentral areas in toxic/metabolic encephalopathy, while it is more often frontopolar in NCSE. Additionally, patients with NCSE have a discharge frequency greater than 2.5 cycles per second, extra spike components, and less background slowing. A typical GPD with triphasic morphology pattern is presented in Figure 2A. Figures 2B–2D show source modeling images for the GPDs seen in Figure 2A. Note their frontocentral prominence.
Infections

Generalized periodic discharges have been described as a classic finding in various types of infections. Generalized periodic discharges with short intervals between discharges, typically 0.5 to 4 seconds (previously called periodic short-interval diffuse discharges), are classically associated with CJD, although there is low specificity for this association (Figs. 3A and 3B). In the patient, the GPDs are often accompanied by jerking artifact from the accompanying myoclonus. Of note, a new variant CJD does not show these findings. Subacute sclerosis panencephalitis is associated with a characteristic GPD pattern of high-voltage, polyphasic complexes intervened by long intervals of 4 to 30 seconds (periodic long-interval diffuse discharges). In children, GPDs are common with encephalitis of various types. Systemic infections and sepsis can also cause a GPD pattern, and these are often similar to those seen in toxic/metabolic encephalopathies.

Acute Neurologic Injury

Patients presenting with acute neurologic injuries often have GPDs. Common etiologies for neurologic injury resulting in GPDs include stroke, intracerebral hemorrhage, and head injury. Unique morphologic features of GPD in patients with acute neurologic injury have not been described.

Nonconvulsive Status Epilepticus

An important differential diagnosis for any patient with GPDs is NCSE. The Salzburg EEG criteria for definite NCSE requires the frequency of the GPDs (or LPDs) to be

![Figure 1](image-url) Generalized periodic discharges from a 50-year-old woman with asthma and cocaine abuse who presented after cardiac arrest. The generalized periodic discharges occur at a frequency of 1 to 2 cycles per second on a suppressed background.

### Table 1. Differentiating GPDs With Triphasic Morphology

<table>
<thead>
<tr>
<th>Feature</th>
<th>Toxic/Metabolic Encephalopathy</th>
<th>NCSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of phase I of waveform</td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td>Duration of entire waveform</td>
<td>Longer (mean 0.32 second)</td>
<td>Shorter (mean 0.12 second)</td>
</tr>
<tr>
<td>Angles between phases</td>
<td>Larger (blunted)</td>
<td>Smaller (sharp)</td>
</tr>
<tr>
<td>Amplitude of phase II</td>
<td>Higher (mean 110 μV)</td>
<td>Lower (mean 87 μV)</td>
</tr>
<tr>
<td>Location</td>
<td>Frontocentral</td>
<td>Frontopolar</td>
</tr>
<tr>
<td>Discharge frequency</td>
<td>≤2.5 cycles/second</td>
<td>&gt;2.5 cycles/second</td>
</tr>
<tr>
<td>Extra spike components</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Background slowing</td>
<td>More</td>
<td>Less</td>
</tr>
</tbody>
</table>

Adapted from Boulanger et al. and Kaplan and Sutter.

GPD, generalized periodic discharges; NCSE, nonconvulsive status epilepticus.
FIG. 2. A, Generalized periodic discharges with triphasic morphology from a 72-year-old woman with myelodysplastic syndrome, renal failure, and altered mental status. Notice the triphasic nature and the anterior to posterior lag of the waveforms. B, Dipole source modeling shown on a three-dimensional brain model for the generalized periodic discharges shown in (A). Notice the frontocentral nature of the dipole. C and D, Source localization using Swarm optimization for the generalized periodic discharges shown in (A) shown on a standard MRI (C) and a three-dimensional brain model (D). Most prominent localization is in the frontocentral region.
greater than 2.5 cycles per second, or if less than 2.5 cycles per second, the discharge must be associated with subtle clinical activity or have spatiotemporal evolution of the graphoelements (Fig. 4). Possible NCSE may still be present even if these criteria are not met; this occurs with GPDs less than 2.5 cycles per second with fluctuation of the graphoelements or if the EEG pattern improves and background activity returns with the use of intravenous antiseizure drugs (ASDs) (Table 2).21

Attempts have been made to analyze the characteristics of the GPDs that are slower than 2.5 cycles per second to see which features are suggestive of NCSE. Features of GPDs with triphasic morphology that are more consistent with NCSE than toxic/

**FIG. 3.** A, Generalized periodic discharges from a 70-year-old woman with confusion, speech alteration, confusion, and generalized myoclonus. Cerebrospinal fluid evaluation for 14-3-3 protein was positive. A presumptive diagnosis of CJD was made. Notice the broad generalized periodic discharges that are frequently interrupted by very sharp myoclonic artifact. The EEG also appears to be suppressed on the right side. B, Diffuse-weighted MRI scan from the patient shown in (A). Notice the abnormal areas of cortically based diffusion restriction bilaterally, worse on the right. Such findings can be noted in CJD. CJD, Creutzfeldt–Jakob disease.

**FIG. 4.** Generalized periodic discharges from 57-year-old man who was status post aortic aneurysm surgery and was noted to have altered mental status and twitching. The generalized periodic discharges occur at a frequency of 2.5 to 3 cycles per second. This generalized periodic discharge pattern is consistent with nonconvulsive status epilepticus.
metabolic encephalopathy have already been presented above and in Table 1. The GPD characteristics (morphology, amplitude, GPD duration, inter-GPD interval, and inter-GPD amplitude) may suggest which ones are associated with NCSE. Generalized periodic discharges with a high amplitude (mean = 110 μV), longer duration (mean = 0.5 seconds), and preserved inter-generalized periodic epileptiform discharge amplitude (mean = 34 μV) were more likely to be associated with NCSE in one study. Other investigators have noted similar findings. Generalized periodic discharges without tricpheric waves (i.e., those with spike, polyspikes and others), focal findings on EEG, interburst suppression of less than 10 μV, history of epilepsy, or a structural abnormality on neuroimaging were more likely to be associated with NCSE. Less risk of seizures was associated when the EEG was reactive to stimulation, a posterior dominant rhythm was present, and sleep/wake cycles could be seen. Based on these data, the authors proposed a GPD score based on which treatment decisions can be made. They proposed that GPDs without tricpheric waves = 3 points, focality on EEG = 2 points, and history of epilepsy = 1. If the score is 6, treatment with ASD should be considered, while if the score is 1, treatment should be withheld. For in between scores, treatment decisions are less clear.

**Hypothermia**

Induced hypothermia for surgical procedures, such as aortic surgery, can result in GPDs (Fig. 5). When temperature falls below 30°C, periodic discharges often appear. Although GPDs are common, LPDs, bilateral independent periodic discharges, and multifocal periodic discharges can also occur. As the temperature drops further, burst suppression and finally electrocerebral inactivity occur. As the temperature falls, the inter-GPD interval increases, and the amplitude of the background activity decreases. Toward the end of the surgery, GPD and other periodic discharges reappear when the temperature is between 20°C and 30°C. With the return of normothermia, the GPDs disappear and are replaced by mixed frequency EEG activity. Generalized periodic discharges seen in this setting are not suggestive of epileptic activity and do not need to be treated with ASDs.

The temperature needs to approach 30°C for GPDs and other periodic discharges to be seen. Thus, with therapeutic hypothermia (temperature reduction to 33°C–36°C) used in the treatment of anoxic encephalopathy, these EEG patterns are usually not seen.

### PATHOPHYSIOLOGY

The pathophysiology of GPDs is not well understood. One report theorizes that selective synaptic failure, either by disturbed excitation of inhibitory interneurons or by intrinsic failure of the interneurons, causes disinhibition of excitatory pyramidal cells, thus causing GPDs. The concern for synaptic neurotransmission dysregulation may arise in a variety of manners.

Ischemia, postanoxic encephalopathy, toxic/metabolic derangements, and infections interrupt or change cerebral synaptic neurotransmissions in several ways: blood–brain barrier breakdown, inflammation, neurotransmitter imbalances, and apoptosis. One proposed mechanism is that the excitatory pyramidal cells to inhibitory interneurons are sensitive to hypoxia because they are high energy consumers, with fast-spiking interneurons being severely affected. The inhibitory interneurons would usually feed forward to inhibit the pyramidal cells (referred to as a feedforward inhibitory network) in a properly functioning system. In an interrupted system, this disinhibition of the excitatory pyramidal cells in the setting of hypoxia or ischemia propagates GPDs.

### NEUROIMAGING

The impact of neuroimaging on the understanding GPDs has been limited thus far. One study evaluated 21 critically ill pediatric patients with GPDs. Findings included abnormalities in the white matter, gray matter, deep gray matter nuclei, hemorrhagic lesions, and leptomeningeal enhancement. Another study noted that subcortical lesions were most common but were often associated with cortical lesions. Generalized periodic discharges with tricpheric morphology are associated with white matter changes and cortical or subcortical atrophy. It seems that the underlying etiology has more of an influence on the imaging findings than the presence of GPDs. The lesions do not seem to have a discriminatory pattern in association with GPDs.
TREATMENT

As a general rule, the value for treating GPDs remains unclear. If the cells are irreparably damaged because of ischemia, they are unlikely to benefit from the use of ASD. However, if there are abnormal excitatory pathways occurring in functioning cells, then ASD may prove beneficial. Differentiating between these two states is challenging, and the various characteristics of the GPDs discussed above are used to determine which state the GPDs represent.

Generalized periodic discharge patterns that are considered definite NCSE should be treated with ASDs. Additionally, ASDs should be considered when patterns consistent with possible NCSE are noted. The GPD score discussed above can assist with this determination. Treatment of other patterns remains much more controversial. Some have advocated for aggressively treating all GPD patterns as NCSE. Others have suggested more restraint, noting that GPD likely represent an injured brain that may not respond to treatment with ASDs. Additionally, drugs used to treat GPDs may themselves cause hepatic and renal injury, possibly worsening the metabolic encephalopathy causing the GPDs. There is general agreement that success of treatment depends more on the underlying etiology than on the electrographic seizure pattern.

Generalized periodic discharge patterns in the setting of anoxic encephalopathy represent a particularly challenging scenario. Whereas the underlying etiology of the GPDs is suggestive of a poor prognosis, if the patient is thought to be in NCSE and there are features of the EEG that suggest a favorable prognosis, treatment should be considered. A higher GPD frequency, higher background continuity, and lower discharge periodicity are suggestive of a better outcome. A currently ongoing clinical trial is exploring whether treatment of NCSE after cardiac arrest (anoxic encephalopathy) is beneficial. Included in the EEG patterns that qualify as NCSE is GPDs. Data from this trial will shed light on the value of treating GPDs in at least this patient population.

PROGNOSIS

EEG has long been used to help prognosticate outcomes in critically ill patients. The patterns that have usually been associated with poor outcome are an isoelectric EEG, spontaneous burst suppression, electrographic seizures, and periodic complexes (including GPDs). In one study, only 36% of patients with GPDs were alive at the time of discharge. In this study, patients were more likely to survive if they were younger, had seizures in addition to GPDs, and had a higher inter-GPD interval amplitude (33 vs. 18 μV). However, a more recent study noted that after controlling for age, etiology, and the level of consciousness, GPDs were not an independent marker for poor prognosis.

Etiology of the underlying condition is often considered a more important prognostic marker than the GPDs. Etiology-specific prognosis is discussed below.

FIG. 5. Generalized periodic discharges for a 61-year-old man undergoing ascending aorta surgery with hypothermic circulatory arrest. At the time of this EEG, the patient’s nasopharyngeal temperature was 24.5°C. Notice the generalized periodic discharges occurring at long intervals with suppression of the background EEG. With rewarming the generalized periodic discharges resolved and normal background activity returned.
Anoxic Encephalopathy

In anoxic encephalopathy, GPDs often lack variability and complexity and have a very predictable pattern. They are an early indicator of poor prognosis in patients whose EEGs have little background variability and a low inter-GPD amplitude.8–35 Several studies have noted that persistent GPDs are a marker of fatal outcomes.10,25,33,36 Even in the era of therapeutic hypothermia, the presence of GPDs or other periodic discharges after rewarming continues to be suggestive of poor prognosis in patients with anoxic encephalopathy.37,38

Toxic/Metabolic Encephalopathy

Patients with GPDs because of toxic/metabolic encephalopathy tend to have a more favorable prognosis than those with GPDs because of anoxic encephalopathy. Despite this, in one study, only 33% of patients with toxic/metabolic encephalopathy were alive at discharge (compared with 11% of those with anoxic encephalopathy).9 However, outcomes in these patients are highly dependent on the underlying cause of the toxic/metabolic encephalopathy.32

As discussed previously, GPDs with triphasic morphology are often seen in patients with toxic/metabolic encephalopathy. Mortality in these patients has been reported as high as 20%, and in one study, the etiology of these GPDs did not appear to be predictive of outcome.5

Infections

There is little data on the prognostic significance of GPD when seen in cases of infections. The available literature suggests that when GPD are seen in patients with infections of the central nervous system CNS, prognosis is poor. In one series, GPDs classified as periodic, short-interval, diffuse discharge (including patients with CJD) had a mortality of approximately 50%, while GPDs classified as periodic, long-interval, diffuse discharge, including patients with subacute sclerosis panencephalitis, had a mortality of approximately 20%.6 However, this study evaluated only routine EEGs, and mortality was evaluated in the first month. Long-term outcome of patients with CJD and subacute sclerosis panencephalitis is poor, regardless of the EEG pattern. In children, GPDs are often associated with central nervous system infections. In a study of children with GPDs, 43% of children who survived had central nervous system infections.19

Acute Neurologic Injury

A few studies have specifically reported outcomes of patients noted to have GPDs caused by acute neurologic injuries, other than anoxic encephalopathy and NCSE. More patients with acute neurologic injuries and GPDs (56%) had a favorable outcome in one study compared with those with toxic/metabolic encephalopathy (33%) and anoxic encephalopathy (11%) and GPDs.8

Nonconvulsive Status Epilepticus

Somewhat conflicting results have been reported in patients with GPDs and NCSE. One study noted that 50% of patients with GPDs and NCSE died, while 71% of those with GPDs without NCSE died.8 A larger study noted that GPDs and NCSE were an independent predictor of worse outcome.7 More data are needed to determine the additional risk posed by GPDs in patients in NCSE.

Hypothermia

Generalized periodic discharges reported in hypothermia induced for surgery are reversible with rewarming. Between 20°C and 30°C, burst suppression appears, followed by periodic discharges. These discharges can be GPDs, LPDs, bilateral independent periodic discharges or multifocal periodic discharges. As the temperatures approaches 30°C, the EEG becomes continuous.22,24 Barring complications from the surgery, patients with hypothermia-induced GPDs make a full recovery.

There is much evidence yet to be gathered in understanding GPDs and how to best manage them. The variety of injurious afflicions to the brain that cause GPDs may originate from sources such as ischemia and anoxic encephalopathy to toxic/metabolic derangements and infections. Nonconvulsive status epilepticus is a common accompaniment of GPDs. Neuroimaging shows that subcortical lesions are often seen with GPDs, but cortical lesions may also sometimes occur. When and how aggressively GPDs should be treated remains a topic of great debate. The underlying condition, state of the patient, and morbidity of treatment must be considered in all treatment decisions. Addressing the underlying etiology and any reversible causes are the chief considerations in treating GPDs.

Studies evaluating the pathophysiology, correlation with neuroimaging, and the long-term prognosis of treating GPDs are needed to help fill the gaps in knowledge. As the terminology and the definitions have broadened over the years for what we currently call GPDs, it is telling that clinical neurophysiologists are more willing to admit the limited understanding we have of these waveforms.

REFERENCES


