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Commentary on stimulus-induced arousal with transient electroencephalographic improvement distinguishes nonictal from ictal generalized periodic discharges

Marcus C. Ng[1], **Sahar Zafar**[2], **Brandon Foreman**[3], **Jennifer Kim**[4], **Aaron F. Struck**[5], **M. Brandon Westover**[6]

[1]Section of Neurology, University of Manitoba, Winnipeg, Manitoba, Canada

[2]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Neurology Department, University of Cincinnati, Cincinnati, Ohio, USA

[4]School of Medicine, Yale University, New Haven, Connecticut, USA

[5]University of Wisconsin-Madison, Madison, Wisconsin, USA

[6]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Here we critique recent arguments proposing to distinguish ictal from non-ictal generalized periodic discharges (GPDs) based on etiology and stimulation response, arguing that these are unreliable. We advocate for an empirical approach to GPDs: describe objectively, interpret through medication trials, and base further treatment on response. We call for evidence-based approaches considering meaningful clinical outcomes.

Keywords

encephalopathy; GPD; NCSE

We appreciate the critical review by Gélisse et al.[1] and their efforts to classify generalized periodic discharges (GPDs) into ictal and nonictal categories. However, we would like to draw critical attention to some aspects of their arguments.

Gélisse et al. argue for three main claims:

1. GPDs fall into two categories: ictal and nonictal.
2. Ictal GPDs are a form of nonconvulsive status epilepticus (NCSE), whereas nonictal GPDs arise from toxic–metabolic, respiratory, septic, or other multifactorial encephalopathies distinct from NCSE.

Correspondence: M. Brandon Westover, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. bwestove@bidmc.harvard.edu.

3. Ictal and nonictal GPDs can be distinguished based on their responsiveness to state changes and stimulation.

First, an issue with Claim 1 is that Gélisse et al. do not clearly define the terms “ictal” and “NCSE.” Although they consider “ictal” GPDs a form of NCSE by definition, they do not clarify what NCSE entails. The authors reference the Salzburg criteria,[2] which define GPDs as NCSE if they meet specific conditions: GPD frequency > 2.5 Hz, clear spatiotemporal evolution, or empirical evidence of improvement with antiseizure medication (ASM). Yet, Gélisse et al. suggest that ictal GPDs and nonictal GPDs can be distinguished without empirical treatment, even in the absence of clear spatiotemporal evolution and when discharge frequency is <2.5 Hz. Unfortunately, this leaves “ictal” and “NCSE” undefined.

It appears that the only way to salvage Claim 1 of Gélisse et al. is to adopt the Salzburg criteria definition for NCSE, so that “ictal GPDs” are defined as those fulfilling these criteria, including GPDs with triphasic morphology. In short, for challenging cases where discharges are <2.5 Hz with no clear spatiotemporal evolution, diagnosis should rely on treatment responsiveness.

Second, Claim 2 by Gélisse et al. makes a “mistake of category” by associating GPDs with specific etiologies like toxic–metabolic, respiratory, or septic factors, without considering their treatment response. The dichotomy between NCSE and toxic–metabolic encephalopathy (TME), including encephalopathy due to sepsis or respiratory failure, is false. NCSE is defined by electroencephalography (EEG) and clinical response to ASM, regardless of the underlying cause, whereas TME refers to etiology. It is possible, for example, to diagnose NCSE due to TME, as metabolic derangements, sepsis, respiratory failure, and toxic exposures can cause seizures and NCSE.[3–10]

Third, the classification of GPDs based solely on their etiology or EEG characteristics is known to be unreliable. Recent studies suggest that GPDs, even those with triphasic morphology traditionally associated with metabolic encephalopathy, often respond to ASM. For example, O’Rourke et al. found that a significant proportion of patients with unexplained encephalopathy and triphasic waves showed EEG and clinical improvement with benzodiazepines or nonsedating ASM.[11] Importantly, there were no significant metabolic differences between responders and nonresponders. These findings suggest that a substantial proportion of patients with GPDs, including those with triphasic morphology, may meet the Salzburg criteria for NCSE based on treatment response. These findings highlight the difficulty in predicting treatment response based on metabolic profiles alone or EEG alone, underscoring the importance of empiric treatment trials in diagnosing NCSE.

Fourth, Claims 1 and 2 by Gélisse et al. rest on the problematic assumptions that the cause of GPDs can be reliably determined, and that ictal GPDs/NCSE can be distinguished from nonictal GPDs/non-NCSE based on EEG alone. However, patients often present with multiple metabolic abnormalities and brain injuries, complicating attribution of brain activity abnormalities to a single cause.[6,8,11–13] Furthermore, experts are known to be unreliable in diagnosing NCSE based on EEG alone. GPDs with triphasic morphology, previously thought to indicate TME, do not exclude NCSE, as shown by Foreman et al.,[14] who found

that experts could not agree on diagnosing NCSE when blinded to clinical information, nor could they predict whether the final diagnosis would be NCSE.

Finally, Claim 3 by Gélisse et al. is problematic. They compare NCSE in critically ill patients to absence status epilepticus (ASE), which is not appropriate. ASE typically occurs in ambulatory patients, has a genetic origin, and does not appear to cause neuronal injury, unlike NCSE in critical illness, which arises in the context of acute brain injury or severe metabolic derangements and can cause neuronal injury. Although Gélisse et al. make an exception for atypical ASE in which there is brain damage from preexisting developmental–epileptic encephalopathy and in which seizures may respond to stimulation, we argue that NCSE is more like atypical ASE than typical ASE; therefore, responsiveness to stimulation is not a reliable criterion to differentiate between metabolic and epileptiform abnormalities. Moreover, epileptic activity outside of atypical ASE can also be influenced by state changes and external stimuli. This is routinely observed in epilepsy outside the intensive care unit (ICU), where sleep states modulate the brain's propensity for epileptiform activity. For instance, epileptiform discharges are suppressed during rapid eye movement (REM) sleep and are more frequent during non-REM sleep.[15–18] It is further known that the same stimulus can both trigger and abort reflex seizures in the same patient.[19] Landau–Kleffner syndrome and the associated EEG pattern of electrical status epilepticus in sleep demonstrate canonical examples of state-dependent electrographic activity that results in reversible neurological deficits.[20] In critical care EEG, stimulus-induced generalized periodic discharges, rhythmic and periodic patterns, and even seizures are common. Conversely, the current American Clinical Neurophysiology's Standardized Critical Care EEG terminology also has a designation of "ST" for when epileptiform patterns are "stimulus-terminated."[21] Hence, responsiveness to stimulation is not a failsafe criterion to differentiate between metabolic and epileptiform abnormalities.

Ultimately, a fundamental challenge with current debates about how to define NCSE is that they are largely semantic, a form of "armchair philosophy." It is time for our field to move beyond these theoretical arguments to focus on empirical evidence. We should anchor our terminology in meaningful outcomes: clinical outcomes such as functional or cognitive disability, mechanistic outcomes such as tissue oxygen levels or local blood flow, imaging outcomes that demonstrate neuronal injury or metabolic markers of ischemia, or shorter term outcomes like improvement in levels of arousal or neurological deficits in response to treatment with ASM and resolution of GPDs. Recent pilot studies have begun to make progress in these directions, providing evidence for this approach. Witsch et al.[22] demonstrated that higher frequency periodic discharges (PDs; ≥2.0 Hz) in patients with acute brain injury were associated with decreased brain tissue oxygenation, potentially leading to additional brain damage. Similarly, Vespa et al.[23] found that both seizures and PDs in traumatic brain injury patients were linked to metabolic crisis, as evidenced by lower brain glucose levels and higher lactate/pyruvate ratios during epileptiform activity. These findings underscore the potential harm of GPDs and support the need for careful monitoring and possibly intervention in patients exhibiting these EEG patterns. In the related pattern of lateralized periodic discharges, it was found that frequency of discharges—not etiology—correlated most with increased glucose metabolism as measured by fluorodeoxyglucose positron emission tomography, again highlighting the need for an empiric basis for

determining whether a pattern is potentially causing secondary damage to the brain.[24] The concept of something being ictal or not remains best defined as electrographic and clinical improvement secondary to ASM.[25]

We advocate for a threefold separation approach to GPDs[26]:

1. Agnostically describe GPDs,
2. Interpret GPDs as ictal or nonictal through an ASM trial, and
3. Prescribe treatment based on trial response.

This empirical approach aligns with recommendations for addressing ICU patterns and treatment responses in suspected status epilepticus, avoiding the pitfalls of problematic and debatable responsiveness criteria.

In conclusion, it is our hope that moving beyond semantic arguments and focusing on empirical, patient-focused approaches will lead to what all of us want for our patients: more meaningful advances in clinical care and better understanding of these clinical entities.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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