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Review article

Triphasic waves: To treat or not to treat?

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ABSTRACT

Generalized periodic discharges (GPDs) with triphasic morphology (triphasic waves, TWs) are EEG waveforms that have been a frequent topic of research evaluating their etiology and clinical correlates. More specifically, prior studies have tried to better elucidate their implications regarding seizures to help guide decision making regarding empiric treatment and EEG monitoring and in spite of multiple studies, controversies remain due to disparate findings. In this review we discuss the historical views of TWs and their clinical and radiographic correlates, highlight the typical and atypical features of TWs, discuss the controversy related to the association between TWs and seizures, and propose an approach to their management.

1. Introduction

Generalized periodic discharges (GPDs) with triphasic morphology (triphasic waves, TWs) are EEG waveforms encountered in patients with altered sensorium and often in critically ill patients. Their appearance has led to studies regarding their association with encephalopathy and seizures, with some reporting a relationship with seizures and non-convulsive status epilepticus (NCSE) based on responses to empiric treatment with benzodiazepines and/or antiseizure medications (ASMs) and recommending trials of these medications when TWs are encountered (O'Rourke, et al., 2016; Foreman, 2021). Others suggest that *typical* TWs (to be defined later) are not ictal or interictal and are associated with toxic-metabolic and other encephalopathies, or structural abnormalities (Boulanger, et al., 2006; Fernández-Torre and Kaplan, 2021a). Though generalized periodic discharges (GPDs) have been included in the Salzburg criteria as being on the ictal-interictal continuum (IIC), a recent work suggests that they do not necessarily require prolonged EEG monitoring if their frequency is less than or equal to 2 Hertz (Struck, et al., 2017) which is the typical frequency of TWs (Fernández-Torre and Kaplan, 2021a). This is based on the validated 2HELPS2B scoring system which uses mainly EEG features, and clinical seizure history, to stratify risk of seizures and need for EEG monitoring (Struck, et al., 2017). Also, studies on TWs have mostly been performed in an era prior to development of monitoring and treatment algorithms in evaluating NCSE and IIC, and before imaging correlations with MRI, were prevalent (Sutter, et al., 2013a; Kaplan and Rossetti, 2011). Recent insights gained from studies of EEG source imaging and intracranial EEG in the ICU have shed light on the controversies on the origin of TWs though they still appear to support both ictogenic and non-ictogenic implications (Fernández-Torre, et al., 2024; Zafar, et al., 2021). In this review, we discuss the typical and atypical features of TWs and report on the association among TWs and seizures, treatment outcomes, and recent controversies. We present case examples that highlight the need for further studies of the implications and management approaches to TWs in specific clinical situations.

2. Defining TWs

TWs have been referred to since the 1950s, first as blunted spike and slow waves (Foley, et al., 1950). Later, Bickford and Butt coined the term "triphasic wave," and they were felt to be etiologically specific, and associated with hepatic encephalopathy (Fernández-Torre and Kaplan, 2021a; Bickford and Butt, 1955). There continues to be debate and discordance in the literature regarding their clinical correlates and

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Table 1
Comparison of typical and atypical features of triphasic waves.

	Typical triphasic waves	Atypical triphasic waves
Symmetry	Symmetrical or shifting asymmetry; may be asymmetrical depending on underlying structural abnormalities#	Consistently lateralized or asymmetrical, or focal/ multifocal negativity; maybe asymmetrical depending on underlying structural abnormalities as well as potential epileptogenicity#
Phases and Location	Triphasic or biphasic with prominent frontal/ frontocentral positivity	Triphasic or biphasic but prominent negativity as opposed to positivity
Frequency	$\leq$ 2 Hertz frequency	$>$ 2 Hertz frequency
State/Stimulus Dependence	Stimulus or state dependent, often resolve completely or becoming less frequent in sleep or drowsiness; may also be seen more frequently in sleep or drowsiness and less frequently in wakefulness	Continuous, without state or stimulus dependence
Presence of Absence of Lag	Anterior-posterior or posterior-anterior lag	No lag
Contour	Blunted	Spiky/sharp contour
Benzodiazepine responsiveness	May resolve with benzodiazepine; would not typically demonstrate clinical responsiveness to benzodiazepine	May resolve with benzodiazepine; may or may not demonstrate clinical responsiveness to benzodiazepine
Background	Background activity is present though slow	Slow or attenuated background
Dynamic or Monotonous	When present the waveforms have a similar appearance and are somewhat monotonous	When present the waveforms have dynamic appearance

*Adapted from Fernández-Torre and Kaplan[4].
#Case 1 in this manuscript demonstrates that asymmetry may arise from cortical dysfunction in 1 hemisphere which may impair the ability to project TWs which is not necessarily considered atypical; on the other hand if they are more prominent in the abnormal hemisphere this may suggest the potential for seizure.

implications (Fernández-Torre and Kaplan, 2021a) but over time, there has been a delineation between atypical and typical features (Fernández-Torre and Kaplan, 2021a; Sutter, et al., 2013b; Bicchi, et al., 2021). This differentiation is important clinically as atypical triphasic waves have a higher correlation with potential epileptogenicity, though the exact risk of seizures is not well defined (Fernández-Torre and Kaplan, 2021a; Kaya and Bingol, 2007; Kaplan and Sutter, 2015). Yet, the distinction between typical TWs and atypical TWs or GPDs without triphasic morphology is difficult even among experts (Foreman, 2021; Foreman, et al., 2016). This calls into question studies on this topic and what has been defined as a TW. The subsequent conclusions may explain the variation in reports on TWs.

Differentiating TWs from other periodic and epileptiform-appearing waveforms has been a subject of controversy which will be highlighted later in this manuscript. It has been suggested that TWs do not need to be differentiated from other GPDs and that they lie along the ictal-interictal continuum (IIC) and possibly represent nonconvulsive status epilepticus (NCSE) (Foreman, 2021). Previous studies in the literature demonstrated that periodic discharges can cause secondary brain injury due to their association with increased lactate and reduced glucose levels using micro dialysis techniques, as well as an increased risk of seizures on continuous EEG, though these studies do not mention findings relating specifically to TWs (Vespa, et al., 2016; Struck, et al., 2020). Further, there are some studies suggesting a higher incidence of seizures in critically ill patients when the EEG demonstrates TWs (O'Rourke, et al., 2016; Braksick, et al., 2016). However others have suggested lower rates of seizures (Boulanger, et al., 2006; Sutter, et al., 2013b). There are possible confounders including clinical history as well as the definition of TWs within these studies.

Many use the term "triphasic" loosely and applying the criteria strictly may improve the diagnostic yield and interrater reliability as well as clarify the possible association with seizures (Boulanger, et al., 2006). When looking at the illustrations and figures provided over the years of cases with "TWs," this loose attribution to some morphologies as being TWs becomes evident. The defining features of typical TWs may not be fully elucidated in a particular study (O'Rourke, et al., 2016). They include the following: stimulus or state dependence, lack of prominent 1st phase and frontal polar negativity, and a frequency up to but no more than 2 Hz, among others (Fernández-Torre and Kaplan, 2021a; Li, et al., 2017). (Table 1; Fig. 1) Many studies on TWs do not present diagrammatic examples in their manuscripts and therefore what they are defining as TWs cannot be confirmed regarding their typical or atypical nature (Kaplan and Birbeck, 2006). There are interesting examples in the literature of what has been termed as TWs when these samples actually demonstrate atypical features including asymmetry, sharp contour, and/or negativity that is more prominent than the typical positivity that is expected in the frontocentral head regions ((Blatt and Brenner, 1996; Braksick et al., 2016), Fig. 2). In some cases, both typical and atypical features can be seen in the same patient and this may be helpful in predicting a higher risk of seizures (Martínez-Rodríguez, et al., 2001) but is not typically presented in detail in many studies (Fernández-Torre and Kaplan, 2021a). It has also not been established as

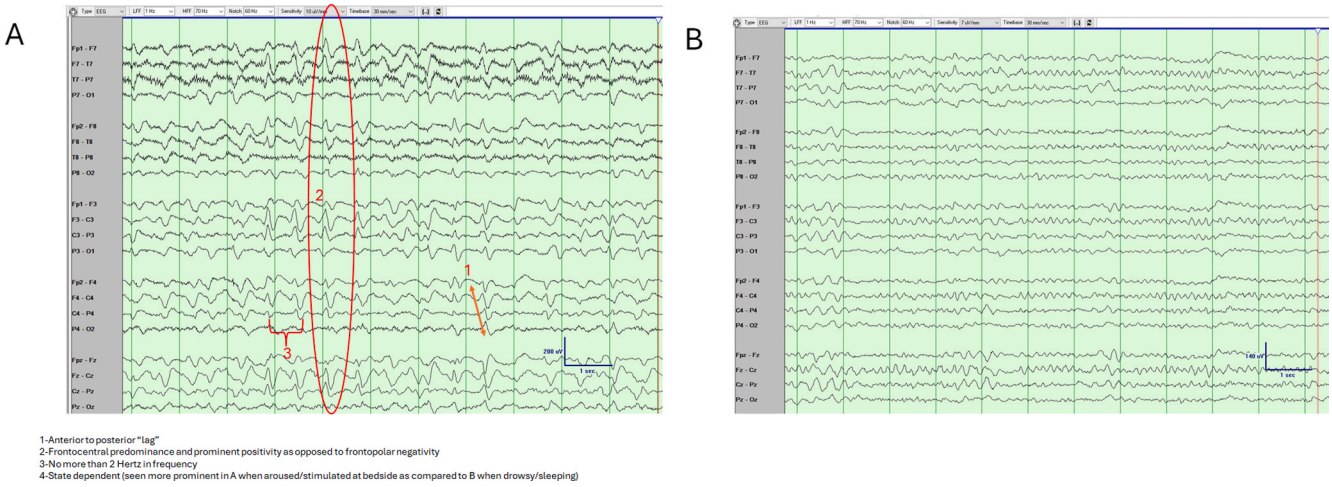

Fig. 1. Longitudinal bipolar montage when the patient is stimulated/aroused (A) showing more prominent TWs with typical features, and abolition of TWs (B) when the patient becomes drowsy and is falling asleep.

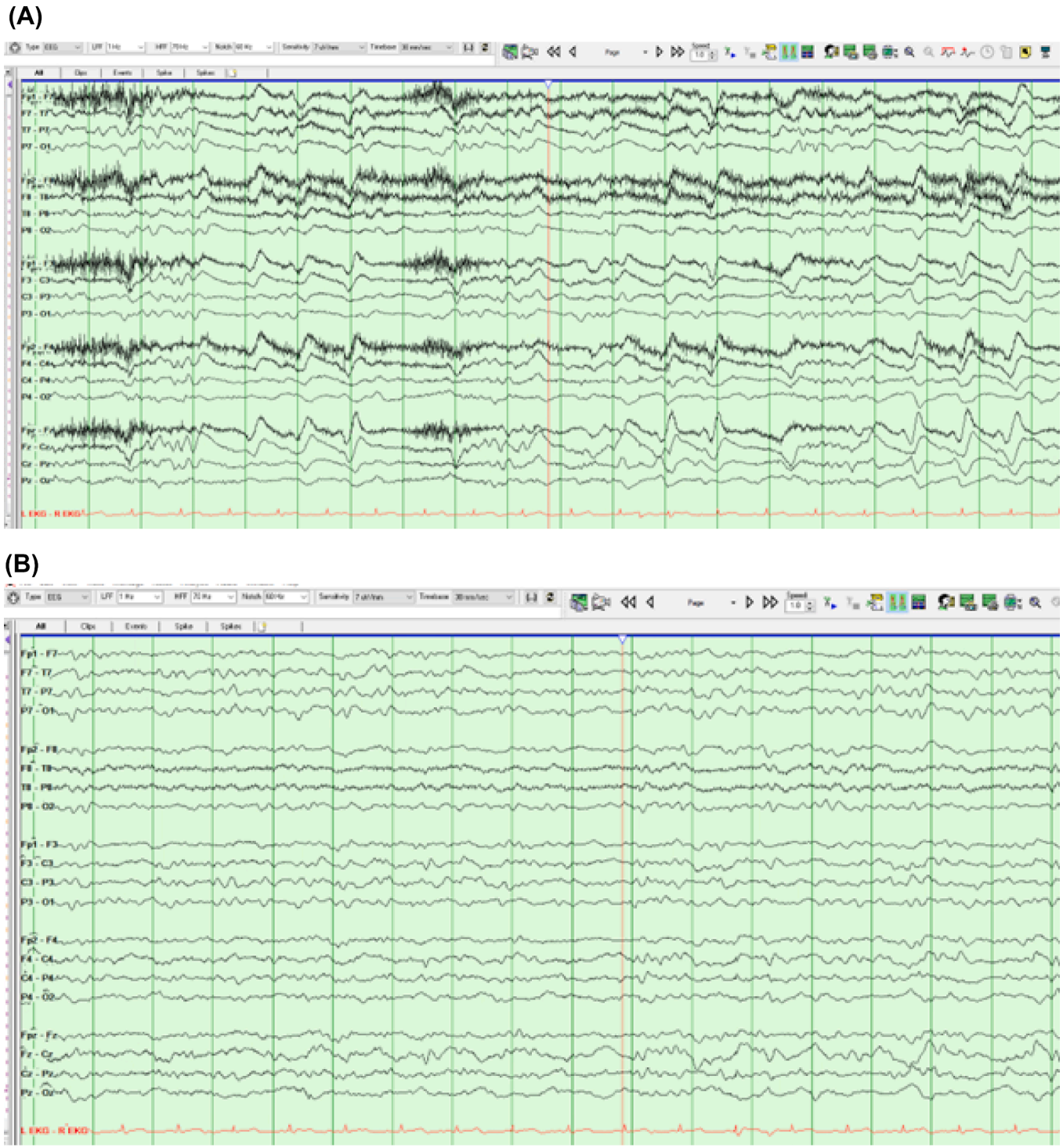

Fig. 2. (A-C). Example of EEG using longitudinal bipolar montage (A) with stimulation at the bedside showing symmetrical typical TWs with blunted morphology, maximal positivity in the frontocentral head regions as well as an anterior-posterior lag and frequency up to but no more than 2 Hz. In sleep (B) there is resolution of the triphasic waves but then they reappear with maximal arousal with both typical and atypical features including left more than right predominance (which may be related to the patient's history of right hemispheric subdural hematoma) (C).

to the degree and amount of atypia that still falls within "normal" when encountering TWs as not every TW may appear typical even in cases when the majority are typical such as in toxic-metabolic encephalopathy. Further, many of the studies are confounded in that the indication for ordering EEG as well as prior history of seizures are rarely reported (Braksick, et al., 2016). This key clinical detail can differentiate those that are at greater or lesser risk for seizures regardless of the EEG findings (Struck, et al., 2020). As in other cases of encephalopathy without TWs, there could be both encephalopathy and ictogenesis, and therefore one cannot prove causality based on association (Miller, et al., 1986). As noted above, more recent studies have suggested that any form of GPD of a frequency 2 Hz or lower does not warrant continuous EEG monitoring (Struck, et al., 2017; Struck, et al., 2020) which would be typical for triphasic waves. However, this may not apply to atypical

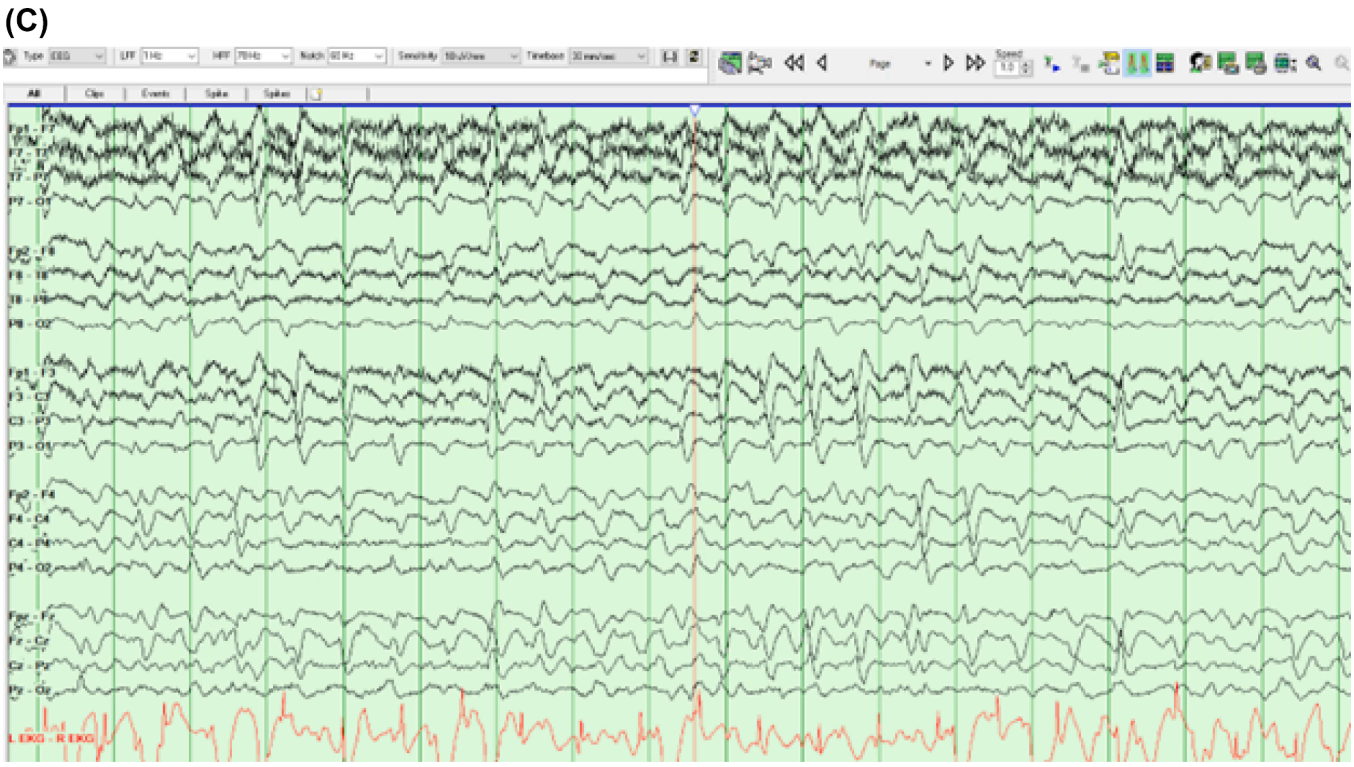

Fig. 2. (*continued*).

Table 2
Etiologies of Triphasic Waves.

Clinical
Hepatic failure/Hyperammonemia
Renal dysfunction
Hypothermia
Systemic or CNS infections
Intracranial hypertension
Angelman syndrome
Rett syndrome
Hashimoto encephalopathy/Thyroid disorders
Medications (levodopa, metrizamide, pentobarbital, naproxen, gadolinium, levetiracetam, baclofen, cefepime, ifosfamide, lithium, cefoperazone, pregabalin, ceftriaxone, aztreonam)
Alzheimer disease/Dementia
Hypoparathyroidism and other endocrinologic disorders
Radiographic
White matter lesions
*Brainstem or diencephalic lesions
*Acute ischemic stroke (cortical and subcortical)
*Acute intracranial hemorrhage (including all types)
*Hydrocephalus
*Traumatic Brain Injury
*Hypertensive emergency/posterior reversible leukoencephalopathy

*Confounded by presence of cerebral atrophy and/or white matter lesions.

TWs.

Regarding their relationship to activation or arousal, stimulus induced rhythmic, periodic, or ictal discharges (SIRPIDs) have previously been described as being associated with seizures (Braksick, et al., 2016; Hirsch, et al., 2004) though in the seminal study on SIRPIDs, TWs were not reported as the only type of SIRPID and therefore conclusions regarding their association with seizures cannot be made due to potential confounding variables also being present (Hirsch, et al., 2004). TWs have later been described as stimulus induced generalized periodic discharge plus rhythmicity (SI-GPD + R) or SI-GPDs+, with triphasic morphology, potentially on the IIC (Hirsch, et al., 2023). Recently, it has been suggested that other features should be considered regarding potential for seizures related to the presence of SIRPIDs and that these are not necessarily related to a higher risk of seizure detection on EEG monitoring in critically ill patients (Martinez, et al., 2023). Stimulus or reactive periodic patterns that are not continuous are thought to be less likely associated with IIC (Gélisse, et al., 2023) and state dependence of non-evolving discharges would be evidence arguing against potential ictogenicity (Gélisse, et al., 2024). Evolving SIRPIDs are more associated with potential ictogenesis and would themselves represent seizures depending on their duration (Hirsch, et al., 2004). A typical feature of TWs relates to their state or stimulus dependence and could further support a non-ictogenic potential (Fernández-Torre and Kaplan, 2021a) and one could consider that TWs themselves are not “ictal” given the

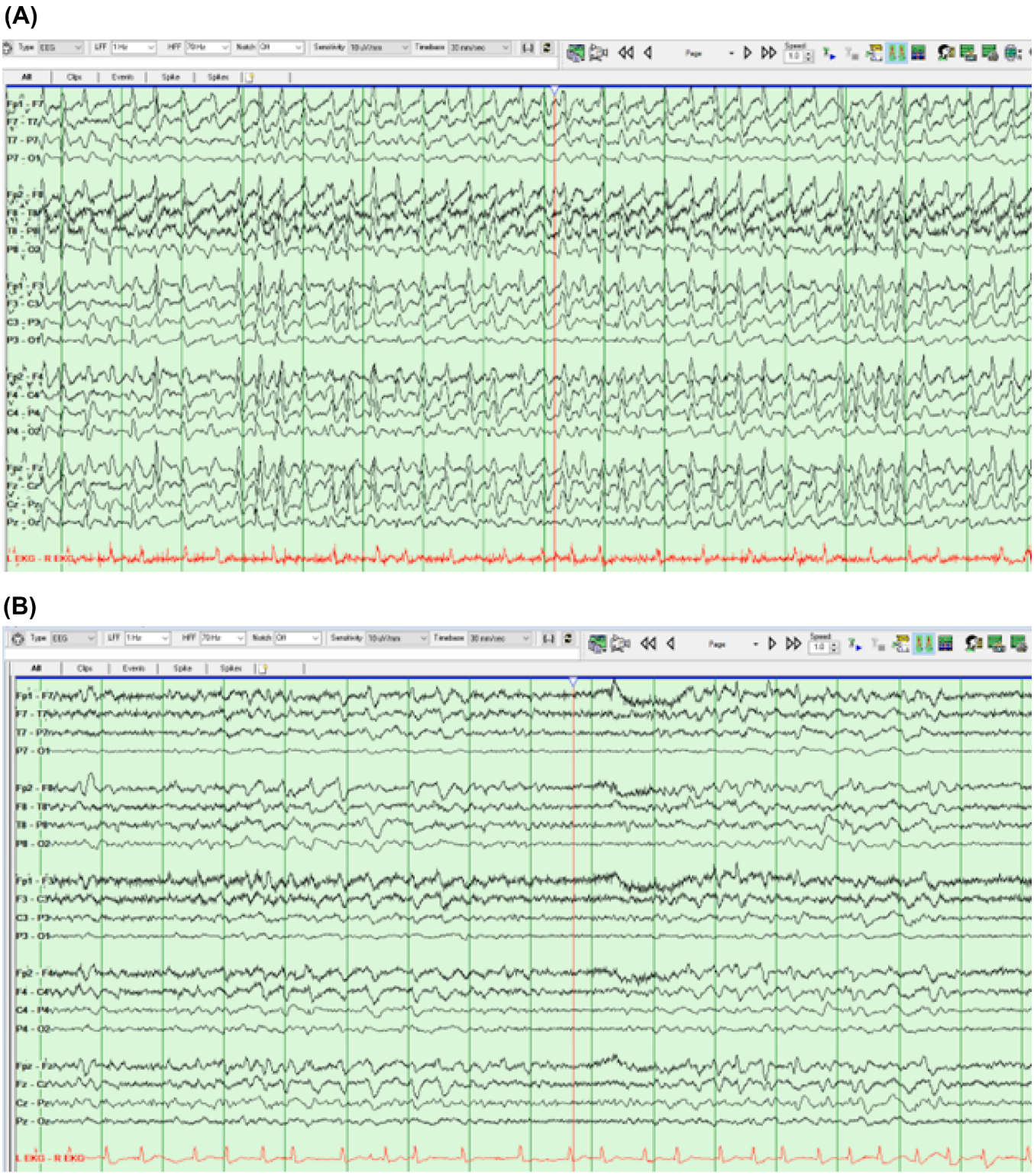

Fig. 3. (A-C). EEG using longitudinal bipolar montage (A) shows GPDs with atypical features for triphasic waves (TWs) with maximal negativity in the frontal polar regions as well as a frequency of discharges up to 3 Hertz without alteration of state or stimulation. This would be diagnostic of nonconvulsive status epilepticus (NCSE). At this point the patient was unable to answer to her name, respond verbally or follow commands. The patient was treated with 2 mg of intravenous lorazepam with immediate improvement in mental status during which time the patient was able to follow simple commands and count 2 fingers as well as say her name. EEG (B) above following administration of lorazepam and during clinical improvement demonstrates resolution of the previously seen atypical periodic discharges and NCSE with improved background EEG and typical TWs with an anterior-posterior gradient and a blunted morphology with maximal positivity in the frontocentral head regions. Later in the recording during drowsiness/sleep the EEG (C) demonstrated resolution of the triphasic waves.

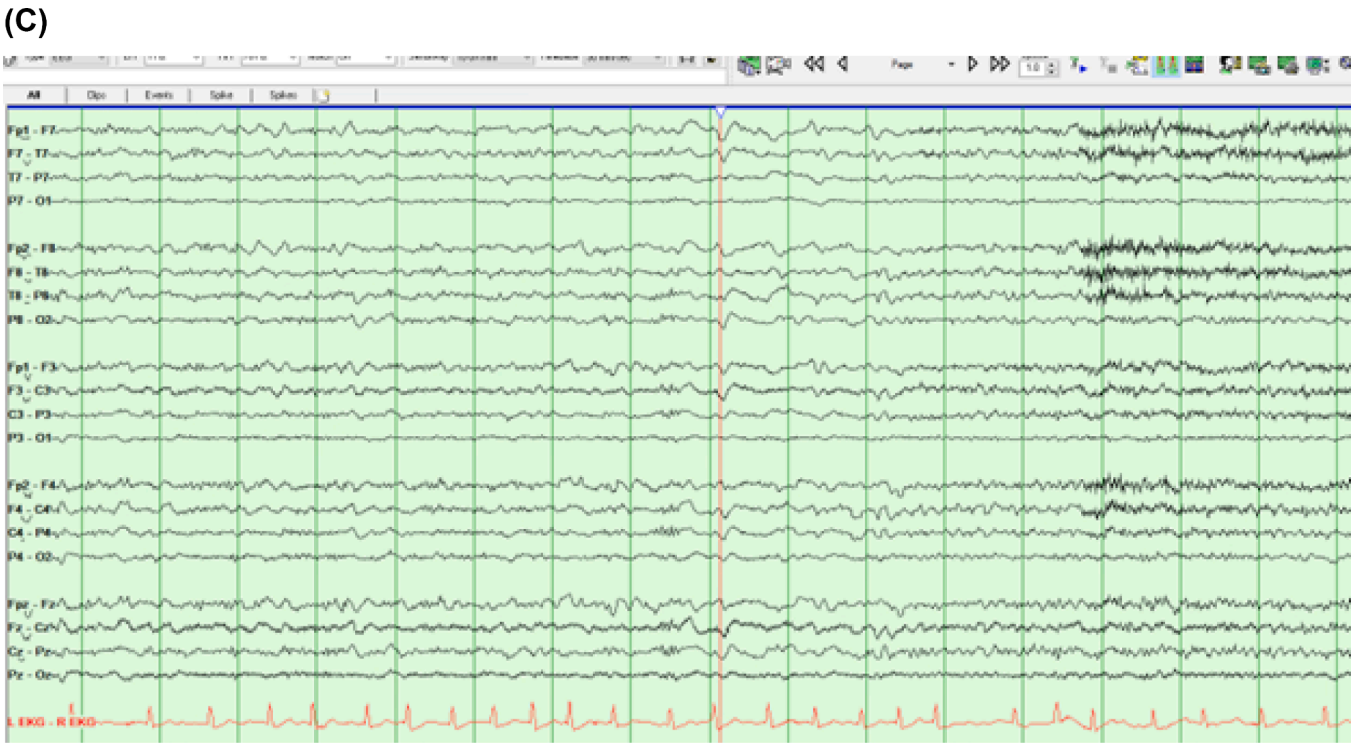

Fig. 3. (*continued*).

lack of evolution. Additionally, TWs typically abate with deep sleep and with maximal stimulation and are present in drowsiness and submaximal arousal (Gélisse, et al., 2023). This may explain the "responsiveness" to sedatives and benzodiazepines as TWs can resolve with sleep induction from these medications (Elliott, et al., 1974). Another example of state dependence of some GPDs would be that they can be abolished by improved wakefulness with the use of amphetamines in CJD (Elliott, et al., 1974).

3. Clinical, structural and radiographic correlates of TWs

There have been several different clinical conditions associated with TWs on EEG; typically toxic, metabolic, infectious or neurodegenerative, and multiple concomitant conditions described and therefore making a determination of etiology is challenging (Fernández-Torre and Kaplan, 2021b). The classic cause described was hepatic failure, which was the first associated clinical condition (Fernández-Torre and Kaplan, 2021a; Bickford and Bitt, 1955). However, renal dysfunction/failure has been found to be a common precipitant and may predict worse outcomes (Sutter, et al., 2013b). Other conditions associated with TWs include hypothermia, systemic and CNS infections, intracranial hypertension, Angelman syndrome, Hashimoto encephalopathy, thyroid disorders, sepsis, medications, and Alzheimer disease (Fernández-Torre and Kaplan, 2021a; Freund, et al., 2024).

Many older studies regarding TWs did not include MRI or source localization technology that is now readily available. TWs have been demonstrated to be associated with subcortical white matter dysfunction, likely leading to defects within thalamocortical connections (Zafar, et al., 2021; Sutter and Kaplan, 2014; Freund, et al., 2021; Kotchetkov, et al., 2021). Focal brainstem or diencephalic lesions may also cause TWs (Fernández-Torre and Kaplan, 2021a; Fernández-Torre and Kaplan, 2021b; Aguglia, et al., 1990). The specific localization of their origin is likely midline deep gray/thalamic or white matter structures (Zafar, et al., 2021). This relationship to white matter disease and subcortical lesions (Freund, et al., 2021) calls into question the association with ictogenesis. TWs can arise in the absence of metabolic or acute CNS disturbances with only white matter disease being present on imaging (Kotchetkov, et al., 2021). Other imaging abnormalities have been described regarding their relationship to TWs, including acute ischemic stroke, intracranial hemorrhage including subarachnoid hemorrhage, hydrocephalus, brain tumors and CNS malignancies (Sutter, et al., 2013a; Blatt and Brenner, 1996; Fernández-Torre and Kaplan, 2021b; Sutter and Kaplan, 2014; Freund, et al., 2021; Kotchetkov, et al., 2021; Aguglia, et al., 1990). However, many of these patients had concomitant cerebral atrophy and/or white matter changes which confounds these associations (Sutter and Kaplan, 2014). When evaluating ictal correlates of periodic waveforms, functional and metabolic imaging (FDG-PET and CT Perfusion) can aid the neurophysiologist in the decision making, where FDG-PET hypermetabolism or CT Perfusion hyper-perfusion may warrant treatment (Husari et al., 2023; Akbik et al., 2020; Gugger et al., 2020).

This is in contrast to more focal/regional/hemispheric periodic discharges such as lateralized (LPDs) or bilateral independent periodic discharges (BIPDs) which are more frequently associated with structural etiologies and cortical dysfunction that could predispose to seizures or represent ictal patterns (Li, et al., 2017; Freund et al., 2018; Freund and Kaplan, 2018). See (Table 2).

4. Treatment of TWs and association with seizures

There are only a few studies assessing the impact of medical intervention on patients with TWs on EEG. In general, GPDs are thought to be less associated with NCSE and seizures (Chong and Hirsch, 2005) than LPDs, especially at slower and more typical TW discharge frequencies (Struck, et al., 2017). Further, TWs can be abolished with benzodiazepines even when arising from nonepileptic metabolic causes, usually without improvement in the level of consciousness (Chong and Hirsch, 2005; Fountain and Waldman, 2001). Also, one must consider that overaggressive treatment may do harm particularly in the elderly (Litt, et al., 1998) who would be at higher risk for TWs given concomitant white matter disease (Kotchetkov, et al., 2021). Previous reports of an association between TWs and encephalopathy demonstrate no evidence

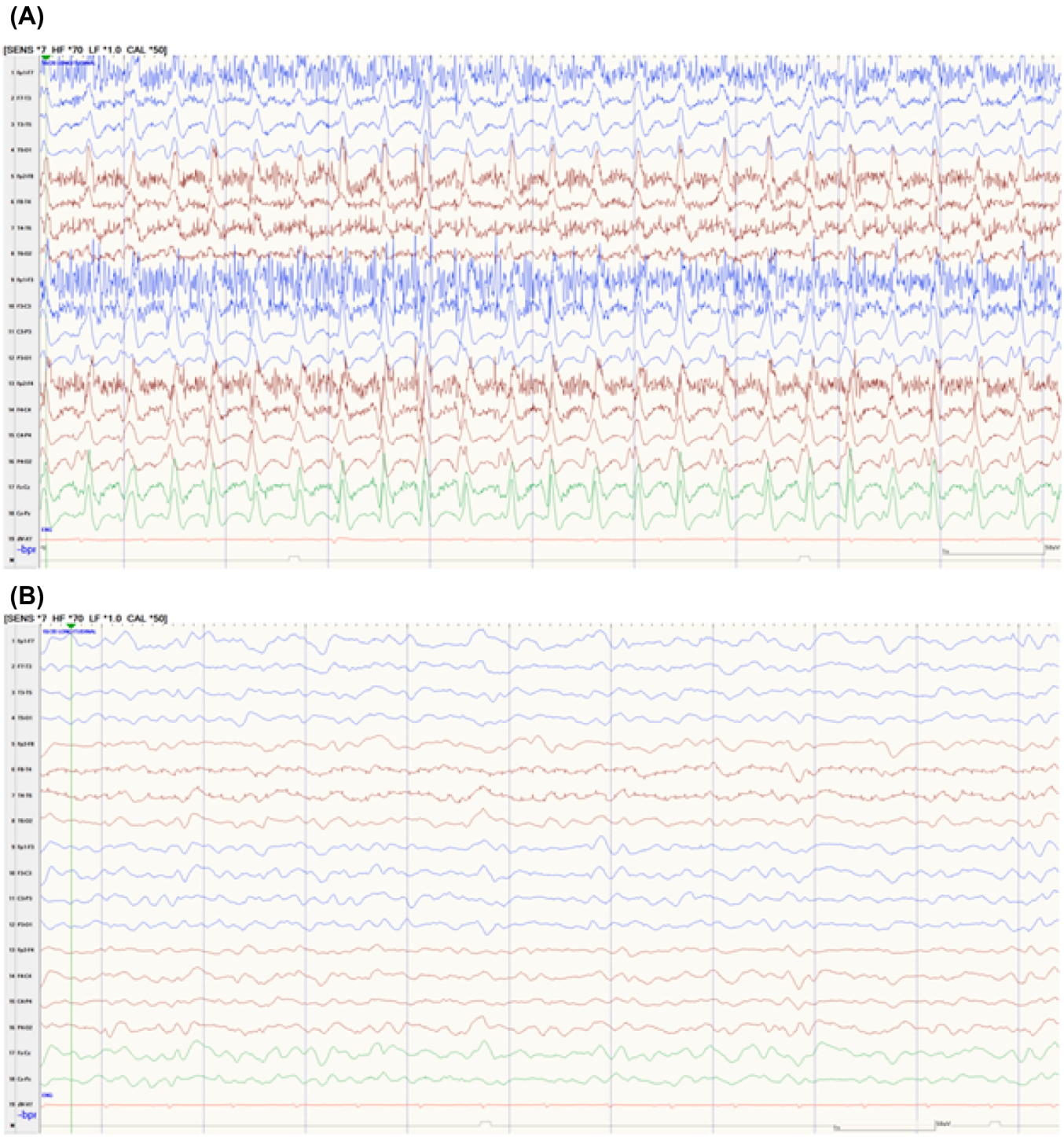

Fig. 4. (A-G): EEG using longitudinal bipolar montage (A) shows atypical triphasic waveforms with a prominent negativity in the frontal polar region bilaterally and a frequency of 2–3 Hertz. The patient received 500 mg intravenous levetiracetam and EEG demonstrates resolution of these waveforms (B) though the patient was also less stimulated and drowsy at this time. Trend analysis demonstrates rhythmic lower frequency activity in the left greater than right hemisphere (C). One hour later the discharges recur with stimulation (D). The patient received 200 mg intravenous load of lacosamide with persistence of the stimulus induced discharges and similarly demonstrated resolution of the discharges with reduced alertness (E and F). Treatment was not further escalated due to persistence of the discharges and their association with arousal and stimulation, and cefepime was withheld and changed to a different antibiotic. Two days after discontinuing cefepime the EEG during stimulation in the most alert state (G) appeared normalized and there was also clinical improvement seen over this time.

of seizures or need for initiation of antiseizure medications (ASMs) (Scherokman, 1980). Conversely, TWs may also be seen with coincident evidence of potential ictogenicity on EEG, including LPDs, BIPDs (Jacome, 1983), and intermittent epileptiform discharges (Blatt and Brenner, 1996) all of which are independently associated with seizures. Other authors have clearly reported atypical features of TWs encountered that were associated with seizures (Kaya and Bingol, 2007; Yasuda, et al., 1988). There are reports of clinical and EEG improvement

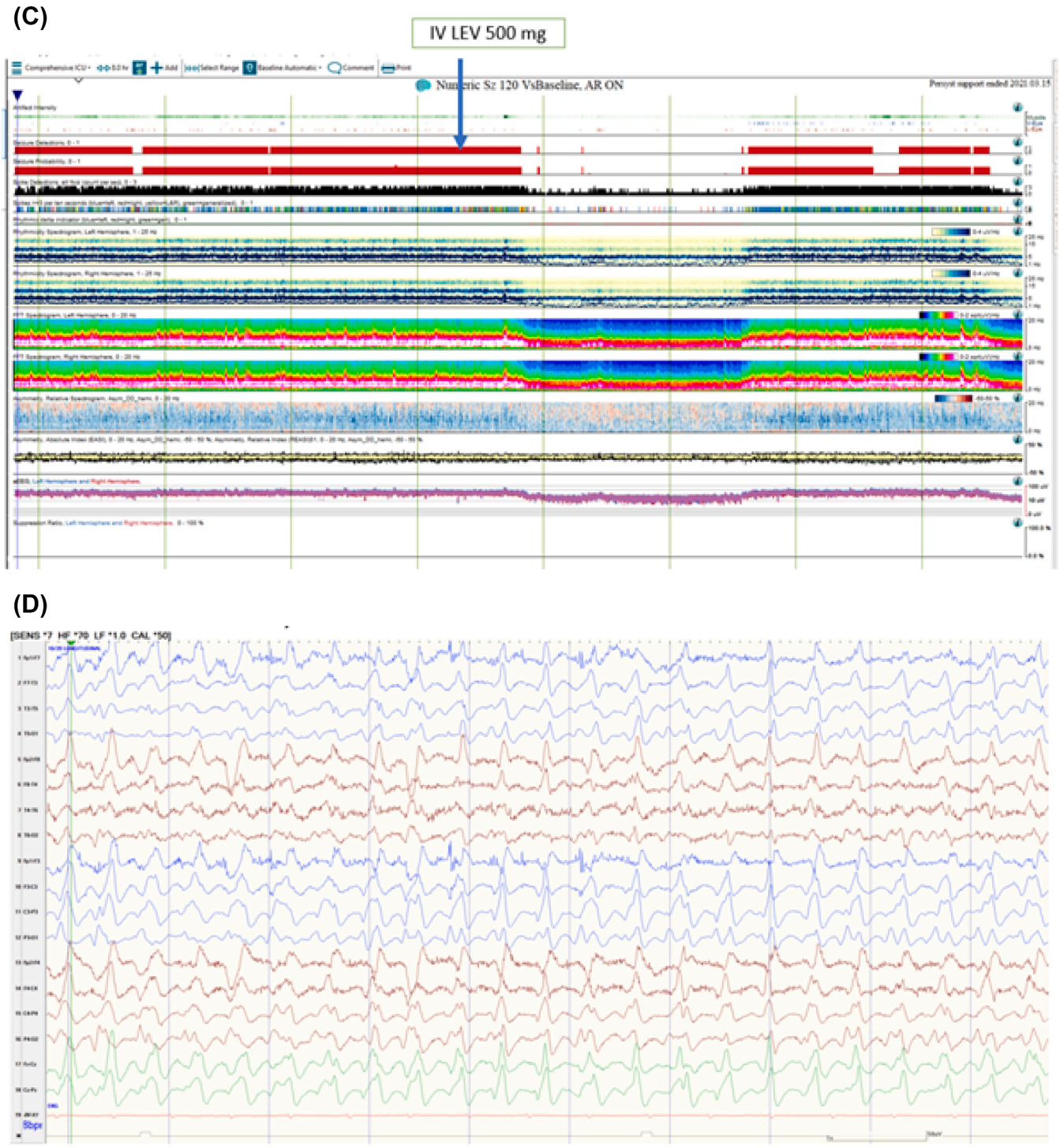

Fig. 4. (*continued*).

with ASM/benzodiazepine intervention though with the majority of the clinical responses being delayed (O'Rourke, et al., 2016). This delay may raise the possibility that the pattern seen on EEG may not have represented NCSE though a severe concomitant encephalopathy as that seen with TWs could cloud the picture regarding the expected clinical response to medication intervention in the patients with NCSE (Kaplan and Birbeck, 2006). Others demonstrate that treatment with benzodiazepines for presumed NCSE may improve concomitant atypical epileptiform activity with persistence of TWs suggesting they are not potentially ictogenic (Kaplan and Birbeck, 2006). More recently a paper based upon expert opinion proposed clinical responsiveness in cases of presumed NCSE that could be delayed up to 24 h after treatment (Leitinger, et al., 2023). However, it would be difficult to differentiate medical responsiveness from an improvement in a metabolic encephalopathy over a 24 h period. This difficulty in differentiating NCSE from encephalopathy when encountering periodic discharges is further supported by a model that TWs and NCSE EEG patterns in patients with toxic-metabolic encephalopathy are produced by similar mechanisms, differing in severity and potential for seizures (Ligtenstein et al., 2021). This could be considered a "continuum" itself, with slower GPDs and triphasic morphology being lower risk for seizures as opposed to GPDs with faster frequency and without typical TW appearance (Fernández-

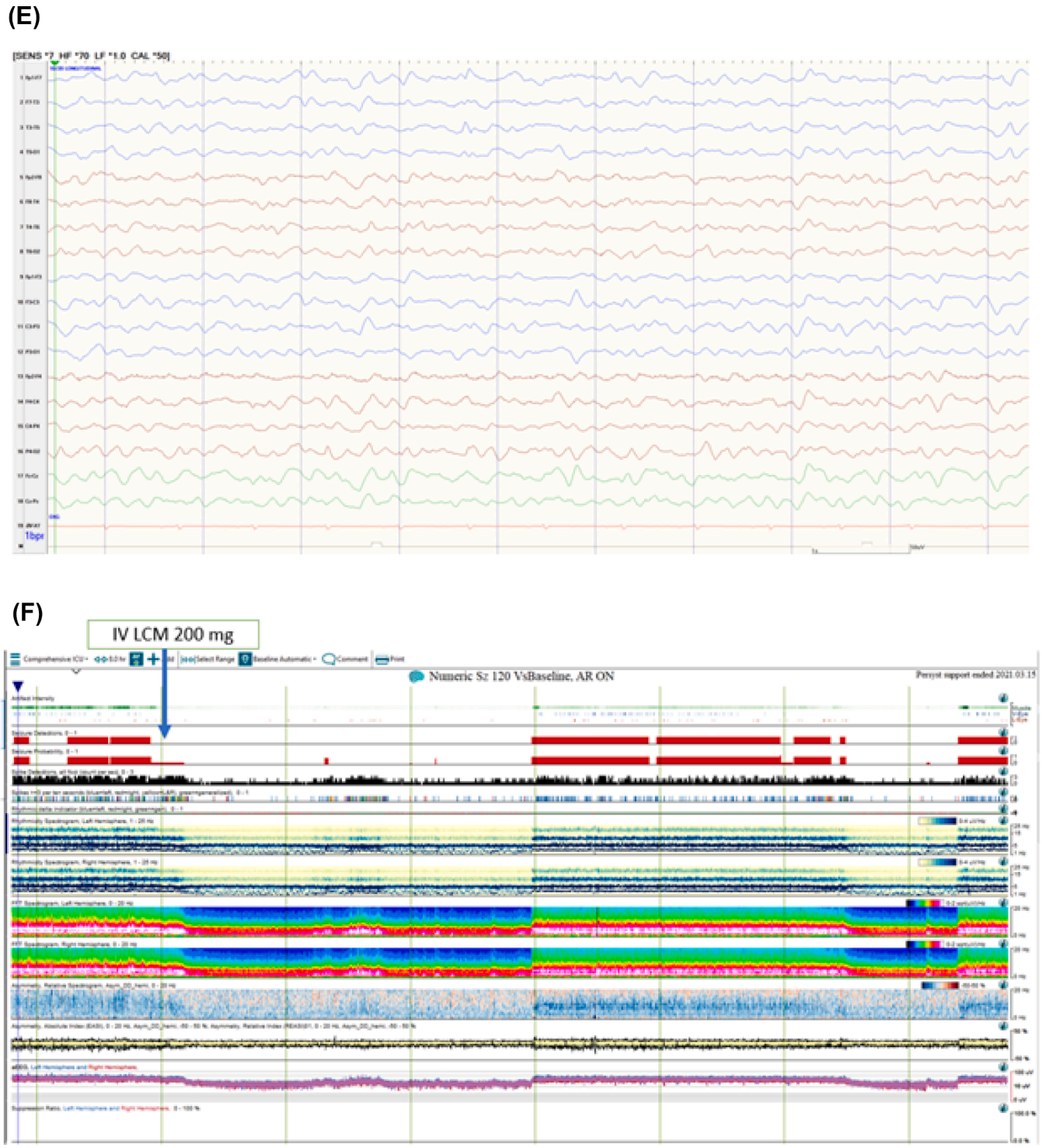

Fig. 4. (*continued*).

Torre and Kaplan, 2021a; Struck, et al., 2020).

The etiology may or may not necessarily impact the risk of seizures, such as that seen with cefepime, but would dictate management and possibly impact the response to treatment in spite of the EEG pattern representing NCSE (Freund, et al., 2024; Husari, et al., 2022). Specifically, discontinuation of the offending drug would be indicated but given the time needed to clear the effects of medications, initiation of a benzodiazepine and/or ASM in the short term would be recommended if there is concern for NCSE based on clinical and/or EEG features besides the TWs. However, as demonstrated in our case presentations to follow, clinical responsiveness may or may not lag considerably behind EEG improvement, with time needed for the drug to be cleared.

5. Recent controversy related to TWs and seizure risk

A recently published paper has sparked some controversy regarding TWs (Fernández-Torre, et al., 2024). In patients with acute brain injury, simultaneous scalp EEG and intracranial depth electrode recordings were performed. The study found that in some patients with acute brain injury, scalp EEGs showed triphasic waves, while depth electrodes

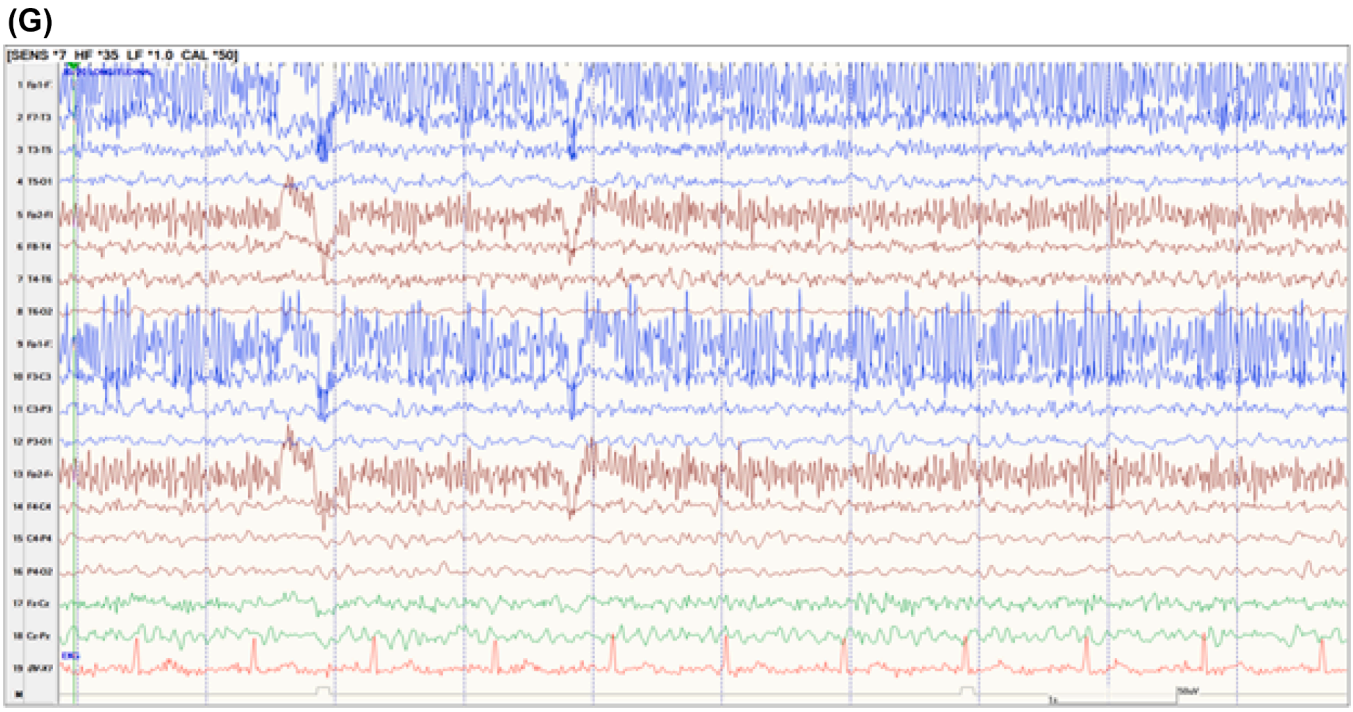

Fig. 4. (*continued*).

revealed epileptiform discharges. This observation led to the hypothesis of an association between depth electrode epileptiform patterns and TWs. However, another plausible explanation could be that patients exhibit a combination of encephalopathy, reflected by TWs on scalp EEG, and focal seizures detected by depth EEG without corresponding scalp EEG abnormalities in acute brain injury with a similar etiology but different manifestations (encephalopathy and ictogenicity). In light of this study, when abundant GPDs with triphasic morphology are present in patients with acute brain injury, especially in the absence of severe metabolic disorders or potentially neurotoxic medications, a trial of benzodiazepines to assess the regression of TWs and clinical improvement may be justified. In these cases, it is crucial to obtain a continuous EEG or follow-up routine EEG to evaluate both EEG and clinical improvements.

Given the lack of clarity and more recent studies suggesting that GPDs at a frequency of 2 Hz or below did not require EEG monitoring due to a low incidence of seizures (Struck, et al., 2020), we present cases below of typical and atypical TWs and clinical approach their management, as well as outcome from cEEG and clinical follow up. We highlight the importance of typical triphasic features including stimulus dependence in determining potential for seizures, the frequency of the discharges (with the possibility that even those between 2–2.5 Hertz could represent NCSE), as well as a clear inciting cause such as the use of medications that can affect the appearance and response to treatment of these waveforms, and their association with nonconvulsive seizures and NCSE.

6. Case examples

6.1. Case 1: A case of typical and atypical TWs in an encephalopathic patient

A 42-year-old man with a history of prior right frontoparietal convexity subdural hematoma, nonischemic cardiomyopathy with a pacemaker and Automatic Implantable Cardioverter-Defibrillator, nonalcoholic steatohepatosis, obesity and type 2 diabetes presents as a hospital transfer with altered mental status in the setting of acute hypoxic respiratory failure and heart failure following a recent orthotopic heart transplant. CT head showed watershed infarctions bilaterally with hemorrhagic conversion. EEG was ordered for evaluation of altered mental status (Fig. 2A-C).

The patient was monitored with continuous video EEG for 25 h with no seizures and his mental status significantly improved over the next day with extubation occurring the day after discontinuation of the continuous EEG. He did not demonstrate any clinical seizures during his hospitalization and was discharged on day 12 of his admission. This case illustrates the co-occurrence of both typical and atypical features of triphasic waves.

6.2. Case 2: Nonconvulsive status epilepticus (NCSE) due to cefepime that is responsive to medical intervention

A 78-year-old woman with a history of chronic kidney failure status post transplantation in 2013 currently on immunosuppressive therapy, atrial fibrillation on anticoagulation, with altered mental status and sepsis due to polymicrobial urinary tract infection and bacteremia. The patient's mental status had worsened over time in the setting of treatment with cefepime. Given the concern for NCSE, EEG was ordered (Fig. 3A-C).

Cefepime was discontinued immediately after the EEG was obtained. The patient was monitored on continuous EEG for 36 h after resolution of nonconvulsive status epilepticus without EEG seizure or atypical periodic discharges recurring and with sustained clinical improvement.

6.3. Case 3: A patient with cefepime induced neurotoxicity with SIRPIDS up to 3 Hertz but no response to antiseizure medications

An 84-year-old female with a history of heart failure and epilepsy on levetiracetam was admitted with uro-sepsis and an acute kidney injury. The patient received intravenous cefepime 1 g every 12 h for sepsis. CT head showed periventricular and subcortical white matter hypoattenuation likely secondary to microvascular ischemic changes as well as a focal hypodensity in the left midbrain compatible with a chronic lacunar infarct. EEG was ordered to rule out seizures as a cause of her persistent

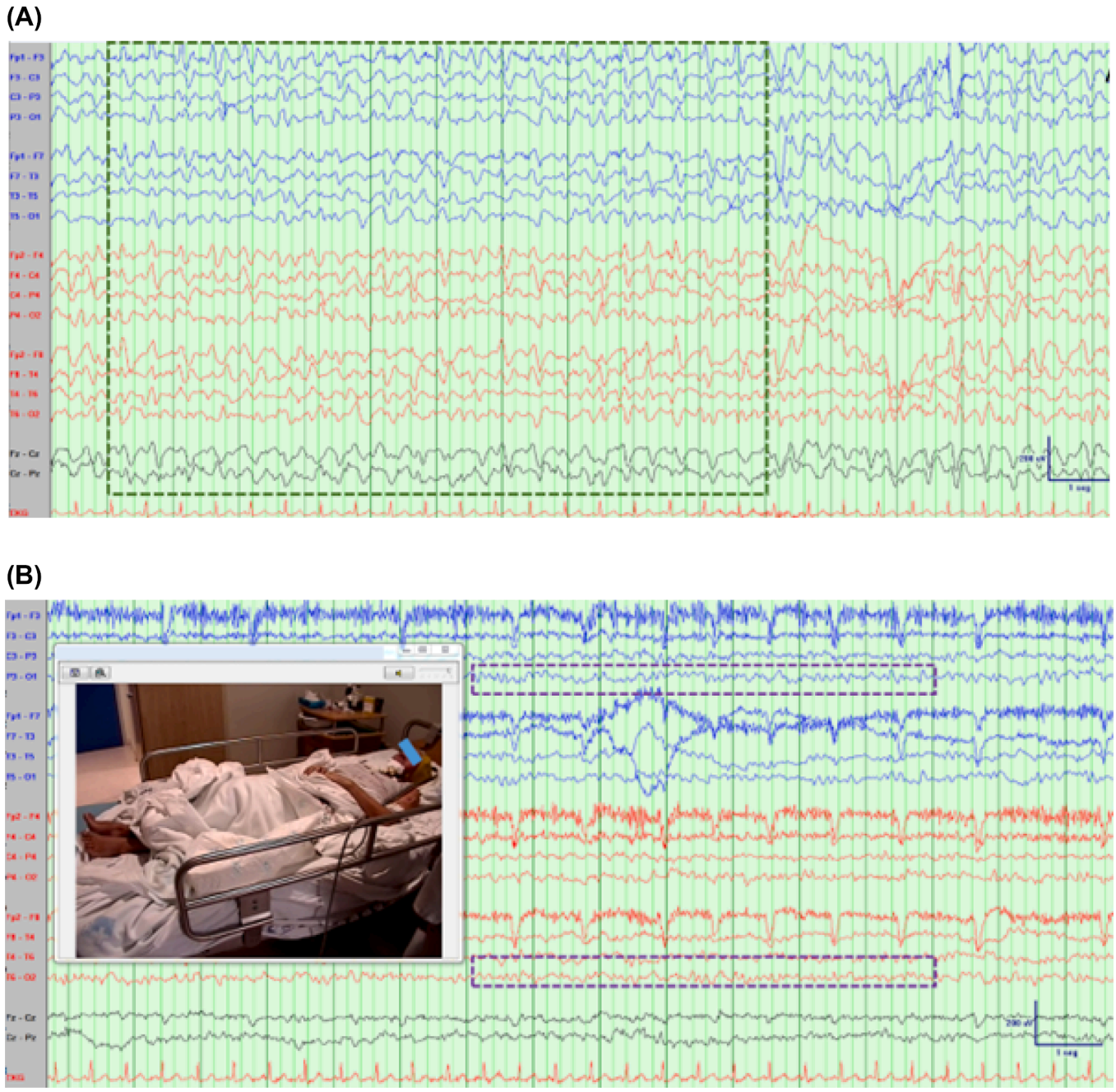

Fig. 5. (A and B): EEG using longitudinal bipolar montage and left hemisphere in blue and right hemisphere in red, background demonstrates typical triphasic waves (TWs) being no more than 2.5 Hertz (A). The patient received 5 mg IV diazepam. Immediately after the infusion, the patient responded normally to the examiner's questions and stated that she previously felt confused but did not know why. EEG using longitudinal bipolar montage with image included, also showed abolition of the TWs with recovery of a posterior alpha activity and resolution of the periodic pattern (B). The clinical response and improvement in the EEG background supports the diagnosis of generalized nonconvulsive status epilepticus in spite of the discharges being no more than 2.5 Hertz. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

altered mentation (Fig. 4A-G).

This case illustrates the challenges in managing patients with atypical TWs. Despite the high frequency periodic pattern and the atypical features of TWs, the patient had no clinical response to IV ASM in spite of improvement in the EEG background following treatment. This may have had more to do with state dependence and medication effects of cefepime regarding the TWs, and further highlights that NCSE due to cefepime may be at higher frequency and further study is needed to determine if a higher threshold is warranted regarding the diagnosis of NCSE.

6.4. Case 4. Cefepime induced neurotoxicity with triphasic waves up to 2.5 Hertz but responsive to medication intervention

This patient was admitted for allogeneic bone marrow transplantation and on day 20 developed neurological deterioration with dysphasia, drowsiness and disorientation. She was on treatment with cefepime, tacrolimus and methylprednisolone. EEG was ordered to investigate the nature of her abrupt neurologic change (Fig. 5A and B).

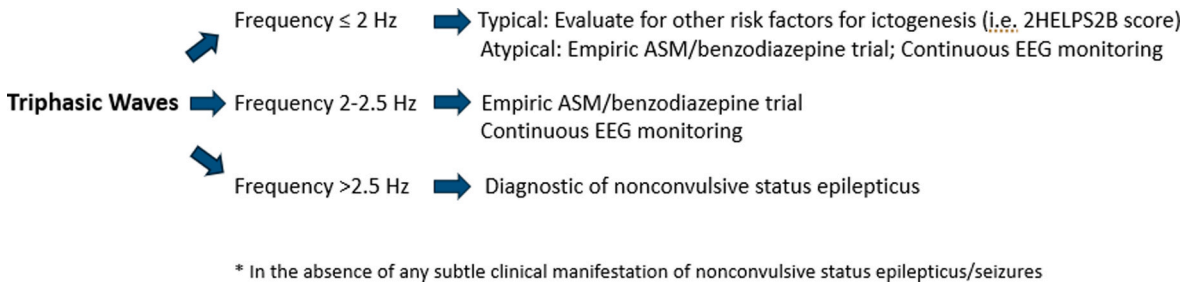

Fig. 6. Proposed diagnostic and treatment algorithm for TWs.

7. Conclusion

TWs are waveforms commonly encountered during inpatient EEG monitoring in critically ill patients and their significance regarding a higher risk of seizures is still debated. Based on the current literature available, typical TWs have not definitively been shown to be related to a higher risk of seizures. However, in certain clinical situations more aggressive approach is appropriate, including in cases of acute brain injury and when the frequency of discharges approaches 2-2.5 Hertz. One must consider clinical and concomitant electrographic data available in the evaluation of patients with altered mental status including a clinical history of seizures and EEG indicators of a higher risk of seizures (Struck, et al., 2017) as well as the presence of neurotoxic medications that can increase the risk of TWs that may impact the responsiveness to medical intervention. Functional imaging may also help guide treatment when periodic patterns are seen. A proposed approach to diagnosis and treatment is included in this manuscript (Fig. 6). When encountering TWs, with typical features as described in this manuscript without further clinical or electrographic evidence suggesting seizures, one should be wary of overtreating patients with potentially sedating medications given the risk of worsening an encephalopathy and hence outcomes, particularly in elderly patients. Further prospective studies are needed with the newly developed monitoring and diagnostic tools available to clinicians to better understand the prognostic significance of TWs regarding the risk of future seizures as well as to evaluate the clinical and electrographic features that would warrant more aggressive intervention, continuous EEG monitoring and empiric medical and antiseizure treatment.

CRediT authorship contribution statement

Brin E. Freund: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Khalil S. Husari:** Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. **José L. Fernández-Torre:** Data curation, Resources, Visualization, Writing – review & editing. **Philippe Gélisse:** Resources, Visualization, Writing – review & editing. **Peter W. Kaplan:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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