Generalized Periodic Discharges and ‘Triphasic Waves’: A Blinded Evaluation of Inter-rater Agreement and Clinical Significance

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Abstract*Objectives:*

Generalized periodic discharges (GPDs) are associated with nonconvulsive seizures. Triphasic waves (TWs), a subtype of GPDs, have been described in relation to metabolic encephalopathy and not felt to be associated with seizures. We sought to establish the consistency of use of this descriptive term and its association with seizures.

Methods:

11 experts in continuous EEG monitoring scored 20 cEEG samples containing GPDs using Standardized Critical Care EEG Terminology. In the absence of patient information, the inter-rater agreement (IRA) for EEG descriptors including TWs was assessed along with raters' clinical EEG interpretation and compared with actual patient information.

Results:

The IRA for 'generalized' and 'periodic' was near-perfect ($\kappa=0.81$), but fair for 'triphasic' ($\kappa=0.33$). Patients with TWs were as likely to develop seizures as those without (25% vs 26%, *N.S.*) and surprisingly, patients with TWs were less likely to have toxic-metabolic encephalopathy than those without TWs (55% vs 79%, $p<0.01$).

Conclusions:

While IRA for the terms "generalized" and "periodic" is high, it is only fair for TWs. EEG interpreted as TWs presents similar risk for seizures as GPDs without triphasic appearance. GPDs are commonly associated with metabolic encephalopathy, but 'triphasic' appearance is not predictive.

Significance:

Conventional association of 'triphasic waves' with specific clinical conditions may lead to inaccurate EEG interpretation.

1. Introduction

Continuous EEG (cEEG) is an important tool that is frequently indicated in the management of critically ill patients (Brophy et al. 2012). Many of the abnormalities seen on cEEG do not meet criteria for electrographic seizures, but instead include a variety of rhythmic or periodic patterns such as generalized periodic discharges (GPDs). GPDs are associated with the development of nonconvulsive seizures and nonconvulsive status epilepticus (NCSz and NCSE) (Foreman et al. 2012). However, triphasic waves (TWs), a subset of GPDs described by their characteristic appearance, were first described in association with hepatic disease (Foley et al. 1950), and are not traditionally regarded as indicators of seizure risk (Boulanger et al. 2005) but rather a marker of metabolic encephalopathy.

Accurately distinguishing TWs from GPDs without triphasic morphology is difficult in clinical practice, particularly in comatose patients (Husain et al. 1999; Brenner 2002; Kaplan and Schlattman 2012). Multiple criteria have been proposed to differentiate TWs such as discharge duration, dominance of the second phase, symmetry, phase lag, attenuation with sleep or emergence with stimulation (Boulanger et al. 2005; Kaplan and Schlattman 2012). However, no criterion is specific (Fisch and Klass 1988; Husain et al. 1999; Sutter et al. 2013). Presence of phase lag and response to stimulation can be quite variable and other periodic or rhythmic discharges, including evolving electrographic seizures (Hirsch et al. 2004), can result from stimulation. Complicating these distinctions further, reports have described NCSz containing GPDs with triphasic morphology (Towne et al. 2000; Martínez-Rodríguez et al. 2001); benzodiazepines have been shown to abolish TWs (Fountain and Waldman 2001); and TWs may occur upon withdrawal of anesthetics used for the treatment of refractory SE (Bhatt et al. 2014).

Yet, clinicians often use these imprecise distinctions to make important treatment decisions which can result in inappropriate administration of potentially harmful anti-epileptic drugs to patients with metabolic encephalopathy or under-treatment of patients at risk for seizures.

EEG is largely interpreted subjectively. The inter-rater agreement (IRA) for the presence or absence of “epileptiform” abnormalities is only moderate, with over one-third of the variance in agreement accounted for merely by an individual’s perceptual threshold for judging an EEG to be abnormal (Gilbert et al. 2003). In the critically ill, patterns are frequently encountered that are periodic or rhythmic but how to classify them has been a source of uncertainty (Brenner 2005; Chong and Hirsch 2005; Claassen 2009). To provide consistency in interpretation, standardized terminology was developed by The American Clinical Neurophysiology Society (ACNS) and The Critical Care EEG Monitoring Research Consortium (CCEMRC) (Hirsch et al. 2005, 2013) which has been validated across a large cohort of raters (Gaspard et al. 2014). However, a systematic assessment of the association of GPDs with outcome and development of seizures based on the presence or absence of triphasic morphology has not been undertaken.

Utilizing the ACNS Standardized Terminology, we sought to determine the IRA for the terms GPDs and ‘triphasic’ and to identify specific characteristics that define triphasic morphology. To assess the impact of patient history on the subjectivity of EEG interpretation, we asked EEG raters to make predictions about outcome and risk of seizures based on cEEG findings alone in the absence of any clinical information. We hypothesized that when blinded to clinical findings, GPDs described as ‘triphasic’ would not confer any difference in predictions of outcome or likelihood to develop seizures compared to GPDs without triphasic morphology.

2. Methods

2.1. Patients and clinical data acquisition

From July 2011 to July 2012, the cEEG recordings of all adults hospitalized at the New York-Presbyterian Hospital's Columbia University Medical Center were prospectively screened for the presence of GPDs. GPDs were defined as bilaterally synchronous, repetitive discharges of similar morphology with quantifiable inter-discharge intervals recurring at nearly regular intervals and without laterality (Foreman et al. 2012). GPDs with triphasic morphology (traditionally called TWs) were included. All initial screening was performed by clinical neurophysiology fellows and cEEG recordings identified as having GPDs were confirmed by the first author.

After the cEEG cohort was established, medical records were reviewed for clinical data and basic laboratory studies including sodium, blood urea nitrogen, creatinine, liver function test, and blood counts. Exam at the time of admission and cEEG initiation was determined retrospectively using chart information, and categorized into four groups: awake, alert but abnormal, lethargic or stuporous, and comatose (Claassen et al. 2004). Outcome at hospital discharge was reported as modified Rankin Score (mRS) and Glasgow Outcome Score (GOS), noting decision for withdrawal of care. Poor outcome was defined as death or severe disability (mRS 5-6 or GOS 4-5). A representative sample comprising 25% of the total cohort was chosen based on age and presenting diagnosis to reflect the entire cohort (n=20). Recordings were preferentially selected to minimize artifacts.

2.2. EEG acquisition and processing

cEEGs were recorded for clinical purposes using 21 electrodes placed according to the International 10-20 System by certified EEG technologists (Claassen et al. 2004). Two 30-minute segments of each cEEG recording were selected by the first author from the day that GPDs were first identified: one included a representative sample of background including the GPD pattern, and the second included any possible or definite seizure activity. From these two 30-minute segments, a single de-identified contiguous 120-second sample was selected specifically to include the best representation of the GPD pattern, along with any changes in state or equivocal patterns suspicious for electrographic seizures. Focal or unequivocal evolving seizures per ACNS Standardized Terminology (Hirsch et al. 2013) were not included.

cEEG samples were provided to raters via a cloud-based review software system, EEGNet (<http://eegnet.clemson.edu/>) (Halford et al. 2013). EEGNet is a novel Web-based JavaScript platform that allows individual users to access, annotate, and manipulate EEG files from any web-capable computer. Raters may scroll by 10-second epochs through the entire sample, adjust channel gain and montage, add or adjust filters, and mark segments with time calipers. Default filters were set with low-pass at 70Hz and high-pass at 0.5Hz. Detailed instructions were provided to each rater about how to adjust EEG viewing parameters.

2.3. Raters and inter-rater assessment

The Critical Care EEG Monitoring Research Consortium (CCEMRC) provides infrastructure to perform collaborative clinical EEG-based research. A requirement for participation in the consortium is documentation of competence using the ACNS Critical Care EEG Terminology by passing a certification exam (Hirsch et al. 2013). Raters were solicited from clinical neurophysiologists with active involvement in the CCEMRC who had acquired this certification.

Of the 15 volunteers who agreed to participate in the study, 11 completed the inter-rater assessment for all 20 patients.

Each rater was provided a link to a Web-based survey (SurveyMonkey, Palo Alto, CA). Raters were asked to complete one assessment per EEG sample for a total of 20 assessments. Clinical information (including age, presenting illness) was purposefully withheld. Raters were asked to describe the EEG using ACNS Standardized Terminology (Supplementary Web Survey) including localization, ‘plus’ component, variability, frequency, dominant phase, polarity of the dominant phase, sharpness, amplitude, and phase lag. Variability was defined by asking raters if ‘discharges appear to vary during the recording.’ Raters were provided a formal definition of ‘triphasic’ morphology as defined by the ACNS Terminology (Hirsch et al. 2013), and asked if the cEEG pattern would be considered ‘triphasic’. Finally, based solely on EEG findings, raters were asked to provide their clinical impression of the recordings and recommend management in a multiple choice format. Raters were also asked to complete two Likert-type questions regarding the likelihood that the patient would later develop seizures on subsequent cEEG or have poor outcome.

2.4. Statistical Analysis

Statistical analysis was performed using commercially available statistical software (SPSS v. 21; IBM Corp, Armonk, NY). Univariate analyses of variables were carried out using χ^2 (or Fisher’s Exact test), Mann-Whitney U, or the Kruskal-Wallis test, where appropriate. Using significant variables from univariate analysis (Supplementary Table S1), logistic regressions were created to explore raters’ responses to survey questions. Spearman’s *rho* and the *phi* coefficient were used to correlate responses regarding seizures and poor outcome with actual outcome, respectively.

Inter-rater agreement (IRA) was evaluated using Gwet's agreement coefficient (AC1) for categorical variables. Ordinal variables, including Likert-type items, were evaluated using weighted Gwet's agreement coefficient (AC2). Fleiss' kappa, a measure of agreement for multiple raters, may be spuriously low despite high overall agreement based on the prevalence for a given variable. The AC1 statistic was developed to avoid this 'kappa paradox' (Gwet 2008). For both agreement coefficients, 95% confidence intervals (CI) were estimated using an adjusted bootstrap percentile interval (n=1000). Both AC1 and AC2, hereafter jointly referred to as *IRA*, are classified by range: 0-0.2, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, near-perfect agreement.

2.5. Standard protocol approvals, registrations, and patient consents

The prospective collection of patients with GPDs was approved by the Columbia University institutional review board. Consent was waived based on the observational nature of the study. The IRA study was part of the larger, multicenter CCEMRC for which approval was granted by the institutional review boards of each participating center.

3. Results

We prospectively identified 79 patients with GPDs (5.5%) out of a total of 1450 patients undergoing cEEG during the one-year study period of which 20 (25%) were selected for IRA assessment. There were no significant differences between the total GPD cohort and the IRA cohort (Supplementary Table S2). The mean age of the IRA cohort was 69+/-11 and 50% were women. The most common etiology was toxic-metabolic encephalopathy, many of whom were also septic, followed by cardiac arrest. One-quarter had non-anoxic acute brain injuries. The

median discharge GOS was 3 and mortality was 7/20 (35%), with all but one occurring after decision to withdraw care.

A total of 220 assessments were completed by 11 raters (see Figure 1 for a representative sample). The IRA for main terms ‘generalized’ and ‘periodic’ was 0.81 (Table 1). Half of the cEEG samples (10/20) were considered by all 11 raters to contain GPDs. cEEG samples *not* rated as GPDs were instead classified as the following: a) generalized rhythmic delta with sharp component (n=9); b) lateralized periodic discharges (n=3); c) brief ictal events (n=2); d) delta waves (n=2); e) bilateral independent periodic discharges (n=1). One rater commented that one pattern did not fulfill cycle length criteria (at least 6 discharges) to qualify as GPDs.

The IRA for the descriptor ‘triphasic’ was 0.33. Two samples were considered to have TWs by all 11 raters, one with toxic-metabolic encephalopathy and one with acute demyelinating encephalomyelitis, both of whom died. Neither had seizures recorded on cEEG. One sample was considered to have TWs by 10/11 raters which was recorded from a patient with aphasia following an elective cardiothoracic procedure. Subsequent cEEG demonstrated evolution of the initial pattern into frequent generalized electrographic seizures with resolution and clinical improvement after administration of midazolam.

Multivariate modeling demonstrated increased odds that GPDs would be characterized as ‘triphasic’ if an anterior-posterior lag or an increasing number of phases were present and decreased odds if the most dominant phase was the first phase or if the dominant phase was negative in polarity (Table 2). Over half of the EEGs judged to have TWs belonged to patients with toxic-metabolic encephalopathy (62/113 assessments, 55%) compared to more than three-quarters of the samples without TWs (67/85 assessments, 79%, $p<0.01$, Figure 2). Therefore,

GPDs were commonly associated with toxic-metabolic encephalopathy, particularly in the absence of triphasic morphology. Anterior-posterior (AP) or posterior-anterior (PA) phase lag was judged to be present in 47% (60/128) of EEGs from patients with toxic-metabolic encephalopathy compared with 60% (40/67) of those without toxic-metabolic encephalopathy (*N.S.*).

Raters' substantially agreed with each other in predicting which patients were likely to develop seizures on cEEG (IRA=0.78). However, this only weakly correlated with actual seizure development (Spearman's *Rho* 0.20, *p*=0.01). Both raters' perception and actual development of seizures during cEEG were independently associated with increasing sharpness of discharges (Table 2). The odds of developing seizures were increased if GPDs were varied or waxing and waning, higher amplitude, or contained superimposed fast frequencies. There was no difference in the likelihood of developing seizures based on the presence vs. absence of triphasic morphology (25% vs 26%, Figure 2; *Phi* 0.01, *N.S.*). There was no difference in the odds of developing seizures based on the presence of AP or PA lag (22% with lag had seizures vs 29% without lag, Figure 2; *N.S.*); similarly, 44% of samples from patients with seizures had lag documented vs. 53% from those without seizures (*N.S.*). None of the clinical variables, including age, presenting illness, and neurological exam were associated with the development of seizures during cEEG.

Raters were more likely to predict poor outcome in patients with low amplitude, discontinuous or suppression-burst background (Table 2). However, the clinical predictions based solely on EEG did not correlate with actual outcome (Spearman's *Rho* 0.08, *p*=0.26). EEG features that were correlated with actual outcome (death or severe disability at discharge) included invariant, i.e. "static" GPDs (Supplementary Figures S1-S3), superimposed faster frequencies, a low number

of phases (e.g. 1 phase rather than 3), anterior-posterior phase lag, and a lack of triphasic morphology. None of these characteristics independently influenced the raters' *perception* of outcome. Once both EEG and significant clinical variables were combined, all factors remained significant. Of samples judged to have TWs, only 36% were associated with poor outcome compared to 60% of those without triphasic morphology (Figure 2; ϕ -0.24, $p < 0.01$). A higher proportion of patients had poor outcome in the group of samples judged to have AP lag compared to those with either no phase lag or PA lag (61% vs 43% vs. 23%, respectively; $p < 0.01$). However, when phase lag was considered as a dichotomous variable (present or absent), there was no significant association with outcome ($p = 0.41$). Importantly, inter-rater agreement for phase lag was only "slight" ($\kappa = 0.23$).

4. Discussion

Discharges that were both 'generalized' and 'periodic' were reliably identified, while agreement on the term 'triphasic' was only fair despite the fact that raters were experienced in the interpretation of ICU EEG recordings and certified in the use of standardized Critical Care EEG Terminology. When GPDs with triphasic morphology were identified, odds that the raters would predict the development of seizures were lower. However, predictions based on EEG findings alone were not correlated with the actual development of seizures: patients in whom TWs were identified were no less likely to develop seizures. Furthermore, although GPDs in general were commonly associated with toxic- metabolic encephalopathy, only half of the samples noted to contain TWs were associated with any type of metabolic disturbance. This study provides evidence that the terms 'triphasic' and 'triphasic waves' may be unreliable and do not have a clear association with either seizures or toxic-metabolic encephalopathy. Perhaps more

importantly, the conventional association of ‘triphasic waves’ with specific clinical conditions may lead to inaccurate EEG interpretation and improper patient management.

The overall IRA for GPDs in this study was excellent (0.81), similar to the agreement demonstrated in a recent study which employed standardized ACNS Terminology and found an IRA of 0.89 for main term 1 (localization, e.g. generalized) and 0.80 for main term 2 (pattern, e.g. periodic) across 49 raters (Gaspard et al. 2014). However, there was only moderate agreement for ‘triphasic’ in that study (IRA=0.58) (Gaspard et al. 2014). In two prior studies, the IRA for TWs alone was also reported to be 0.81 and 0.84, although each study compared only two raters (Boulanger et al. 2005; Sutter and Kaplan 2014). Our study found only fair agreement with an IRA=0.33 across 11 raters. However, compared to recent study of ACNS Terminology, we used a larger set of prospectively-collected recordings containing GPDs (20 vs 6), longer EEG samples (120s vs 10-20s), and had the ability to manipulate montage, sensitivity, and filters via EEGNet (Halford et al. 2013). The lower agreement in our study may have resulted in part from variability in ‘triphasic’ characteristics from page to page within a given patient recording. Nonetheless, a ‘triphasic’ appearance independently influenced raters’ *perception* that a given patient was less likely to develop seizures consistent with conventional thought, but not supported by our results.

We previously demonstrated a strong association between NCSz and GPDs (Foreman et al. 2012). One-quarter of patients with GPDs in this study developed NCSz, similar to the 27% in our prior retrospective cohort. We found that GPDs with triphasic morphology were *no less likely* to develop seizures than those without triphasic morphology. In prior case-control series of patients with isolated TWs, nearly 15% were excluded for seizures or SE (Sutter and Kaplan 2014), and in another study comparing TWs with generalized NCSE, 4% of those with TWs had

seizures within 24 hours (Boulanger et al. 2005). Therefore, some GPDs with triphasic morphology are clearly associated with seizures. We also found that ‘plus’ features and sharpness had independent associations with development of seizures with IRA for these terms ranging from moderate to substantial, respectively. This data provides a valuable assessment of which EEG characteristics might be used to objectively guide predictions about clinical outcomes.

This study prospectively identified GPDs in 5.5% of hospitalized patients, which mirrors our previous work showing an incidence of 4.5% (Foreman et al. 2012). The proportion of patients in coma (55%) was also comparable (Foreman et al. 2012). The 35% mortality in this series is similar to our prior series as well (41%) (Foreman et al. 2012) although higher than studies that have exclusively evaluated ‘triphasic’ GPDs (15%) (Sutter and Kaplan 2014). We found that GPDs described as having triphasic morphology are associated with increased odds of a good outcome. Paradoxically, an AP phase lag (but not PA) was associated with increased odds for having a *poor* outcome, despite this term being described closely in patients with TWs.

However, agreement for either phase lag category was fair ($\kappa = 0.23$), and when comparing AP and PA lag combined vs. no lag, there was no longer any association with outcome, suggesting that this association requires confirmation before giving it meaningful significance.

For now, the presence of lag does not appear to be associated with metabolic encephalopathy or risk of developing seizures. Superimposed faster frequencies were the only feature that increased the odds for both the development of seizures and a poor outcome. Although the plus modifier has been described in close association with seizures (Fitzpatrick and Lowry 2007), this term has not previously been established as a potential marker for poor clinical outcome.

This study does not specifically address the particularly difficult issue of how to approach GPDs after cardiac arrest. A history of cardiac arrest is reported in 10-17% of patients with GPDs or TWs (Fisch and Klass 1988; Boulanger et al. 2005; Foreman et al. 2012). In this study, cardiac arrest was seen in one-third of cases. GPDs after cardiac arrest may reflect neuronal injury, metabolic dysfunction, or the interplay of the two. Raters for this study predicted that low-amplitude, discontinuous, or suppression-burst background would be associated with poor outcome, consistent with prior studies evaluating EEG findings after cardiac arrest (Wijdicks et al. 2006; Cloostermans et al. 2012). However, the actual outcome of death or significant disability was most strongly associated with GPDs lacking variability, regardless of underlying etiology (Supplementary Figures S1-S3). Since recent studies have identified the absence of background reactivity as a predictor of poor outcome after cardiac arrest (Rossetti et al. 2010; Crepeau et al. 2013), there may be a common pathophysiology linking the absence of variability or reactivity to poor outcome regardless of the primary neurological insult.

Although the term “triphasic” only achieved fair IRA, we designed the study to compare individual rater perceptions with actual clinical outcomes rather than using a ‘gold standard’ in order to avoid this bias. A single author was responsible for choosing each EEG sample (B.F.) which may create selection bias. However, comparing EEG recordings that were selected for analysis to the unselected prospectively identified cohort, there were no significant clinical differences. Based on our short cEEG sample length and the blinded nature of the study, we felt that clinical EEG reports were the most accurate determinant of which patient recordings contained electrographic seizures. Therefore, the identification of electrographic seizures was not subject to inter-rater assessment. The lack of information regarding AED administration and its potential impact on the incidence of seizures is an additional confounder. Therefore, we

selected cEEG samples from the first day GPDs were visualized in order to minimize the potential effect of adding AEDs on subsequent days. It remains possible that patients with GPDs with a triphasic morphology were less likely to receive AED treatment resulting in seizures that could have been prevented. The effect of AED administration on GPDs may provide additional understanding of their clinical relevance and systematic study is warranted. Efforts have begun in exploring such effects in the cardiac arrest population. (Clinicaltrials.gov Identifier NCT02056236).

5. Conclusions

This study concludes that the EEG descriptor ‘triphase waves’ is clinically ambiguous and is not reliable for the prediction of seizures or the presence of a toxic-metabolic encephalopathy.

GPDs, with or without a triphasic morphology, are associated with electrographic seizures and therefore cEEG is indicated in these patients, with careful consideration of potential treatment based on the particular clinical context. More research is needed to clarify which cEEG features *objectively* correlate with specific clinical findings, in order to optimize management of these critically ill patients.

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Figure Legends

Figure 1. Example of a generalized periodic discharge pattern judged to have triphasic appearance with good inter-rater agreement.

Ten-second EEG example from a 57 y/o man who presented after a cardiac arrest (as viewed in the EEGNet web interface, <http://eegnet.clemson.edu/>) (Halford et al. 2013). High-frequency filter: 70Hz, Low-frequency filter: 0.5Hz, Notch filter: Off. Note variability in morphology, along with wide complex, sharply contoured triphasic morphology (shown in box). This patient developed nonconvulsive status epilepticus and was treated with midazolam. He was eventually discharged with good outcome (GOS 2).

All 11 reviewers classified this pattern as both generalized and periodic; 9 of 11 rated the pattern as triphasic and 8 of 11 classified the pattern as also falling along the ictal-interictal continuum. 7 of 11 reported no lag, 1 of 11 reported anterior-posterior phase lag, and 3 of 11 reported posterior-anterior phase lag. The median frequency was 1.5 Hz (IQR 1-2). Six raters felt seizures were very likely to develop and the other 5 felt seizures were possible. Eight opted for treatment with either a benzodiazepine trial or initiation of a quick acting anti-epileptic drug. 3 of 11 felt a poor outcome was likely, and 7 felt a poor outcome was possible.

Figure 2. Relationship between triphasic waves and clinical outcomes (%).

* $p < 0.01$.

but with severe functional disability (GOS 3). Overall, 10 of 11 reviewers classified this pattern as both generalized and periodic; 8 of these 10 rated the pattern as not triphasic.

Table 1. Survey Questions and Inter-rater Agreement.

Survey Question (abbrev.)	Proportion of Rater Agreement (%)	Chance Agreement (%)	Items*	IRA**	CI
Are GPDs present?	83	9	20	0.81	0.70-0.91
Localizing Features: Frontal, Occipital, Midline/Central, or Generalized, not otherwise specified?	67	15	10	0.61	0.47-0.75
Is there a (+) component?	65	20	9	0.56	0.42-0.69
Variability (do discharges appear to vary during the recording?)	50	23	9	0.36	0.26-0.47
Discharge Frequency?	98	71	8	0.92†	0.89-0.96
Number of Phases?	94	51	7	0.87†	0.67-0.93
Dominant Phase?	56	17	9	0.47	0.37-0.56
Polarity of Dominant Phase?	53	19	9	0.42	0.33-0.55
Sharpness of sharpest phase?	91	56	10	0.80†	0.71-0.87
Average absolute amplitude?	94	53	8	0.88†	0.84-0.91
Relative amplitude?	77	27	10	0.69	0.47-0.84
Discharge Lag?	46	31	8	0.23	0.13-0.34
Were these GPDs triphasic?	66	49	10	0.33	0.18-0.51
Were seizures present during the epoch?	80	12	10	0.78	0.61-0.90
Was the background continuous?	59	17	10	0.50	0.33-0.66
What was the dominant background frequency?	95	64	5	0.85†	0.77-0.93
What was the average background amplitude?	88	42	5	0.80†	0.62-0.89
Clinically, would you: Remove EEG leads? Observe EEG? Benzodiazepine trial? AED? Suppress the pattern?	36	17	10	0.24	0.19-0.30
Clinically, is this pattern: Purely metabolic? Metabolic with higher risk for seizures? Ictal-Interictal? Likely ictal?	40	23	10	0.22	0.15-0.27
Do you think this patient will go on to develop seizures, clinically or on EEG?	93	68	10	0.78†	0.64-0.83
Do you think this patient will leave the hospital with a poor outcome (minimally conscious, vegetative, or dead)?	93	64	10	0.79†	0.61-0.85

AEDs = Antiepileptic Drugs; CI = Confidence Interval; EEG = electroencephalogram; GPDs = Generalized Periodic Discharges; IRA = Inter-rater Agreement

*n=10 cases were considered to be GPDs by all 11 raters.

** Inter-rater agreement (see Methods). The level of agreement was classified as: 0-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, almost perfect agreement.

†Indicates an ordinal variable for which the quadratic-weighted AC2 is reported. All others are considered nominal and Gwet's AC1 is reported.

Table 2. Multivariate Analysis of Specific cEEG Characteristics and Impact on Seizures, Outcome, and Triphasic Morphology.

<i>Variable</i>		<i>Raters' Blinded Prediction</i>		<i>Actual Outcome</i>		
Seizures during cEEG	Predictor	OR	CI	Predictor	OR	CI
	Triphasic Appearance	0.25	0.14-0.42	<i>Triphasic Appearance</i>	<i>0.98</i>	<i>0.44-2.17</i>
	<i>Invariant GPDs</i>	<i>1.63</i>	<i>0.96-3.06</i>	Invariant GPDs	0.31	0.08-0.83
	↑ Sharpness	1.91	1.30-2.77	↑ Sharpness	2.50	1.37-5.57
	<i>↑ Discharge Amplitude</i>	<i>1.43</i>	<i>0.92-2.39</i>	↑ Discharge Amplitude*	2.74	1.43-6.22
	<i>Superimposed FAST activity (+F)</i>	<i>1.36</i>	<i>0.49-4.32</i>	Superimposed FAST activity (+F)	3.25	1.02-12.00
GOS 4-5 (Death or Unresponsive Wakefulness)**	↑ Sharpness	1.73	1.13-2.90	<i>↑ Sharpness</i>	<i>0.77</i>	<i>0.37-1.32</i>
	↓ Background amplitude	3.35	1.47-8.58	<i>↓ Background amplitude</i>	<i>0.40</i>	<i>0.10-1.06</i>
	Background: Discontinuous	3.52	1.36-10.50	<i>Background: Discontinuous</i>	<i>0.70</i>	<i>0.18-2.35</i>
	Background: Suppression-Burst	9.67	2.47-61.72	<i>Background: Suppression-Burst</i>	<i>3.02</i>	<i>0.41-34.85</i>
	<i>Triphasic Appearance</i>	<i>0.58</i>	<i>0.22-1.28</i>	Triphasic Appearance	0.27	0.07-0.70
	<i>↑ Number of Phases</i>	<i>0.86</i>	<i>0.43-1.52</i>	↑ Number of Phases	0.39	0.15-0.77
	<i>Superimposed FAST activity (+F)</i>	<i>0.47</i>	<i>0.13-1.55</i>	Superimposed FAST activity (+F)	5.39	1.73-35.60
	<i>Invariant GPDs</i>	<i>1.57</i>	<i>0.64-4.06</i>	Invariant GPDs	6.34	2.56-25.76
	<i>Anterior-Posterior Lag</i>	<i>0.98</i>	<i>0.42-2.40</i>	Anterior-Posterior Lag	7.90	3.15-34.37
<i>Variable</i>		<i>Characteristics Raters Associated with Triphasic Morphology</i>				
Triphasic Morphology	Predictor	OR	CI			
	Dominant 1 st Phase	0.03	0.00-0.35			
	Negative Polarity of Dominant Phase	0.09	0.02-0.22			
	Anterior-Posterior Lag	3.61	1.19-16.50			
	↑ Number of Phases	4.51	1.01-25.8			

cEEG = Continuous Electroencephalography; CI = Confidence Interval; GOS = Glasgow Outcome Score; GPDs = Generalized Periodic Discharges; OR = Odds Ratio

*After controlling for age ($p < 0.01$; OR 0.89 CI 0.83-0.92) and male gender ($p < 0.01$; OR 0.06 CI 0.01-0.16), discharge amplitude was no longer statistically significant predictors of developing seizures.

** After controlling for age ($p = 0.46$), male gender ($p = 0.05$; OR 30.8 95% CI 0.92-14.50), and serum ALT ($p = 0.01$; OR 1.002 95% CI 1.001-1.004), all terms remained significant.