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Association of Periodic and Rhythmic Electroencephalographic Patterns With Seizures in Critically Ill Patients

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IMPORTANCE Periodic and rhythmic electroencephalographic patterns have been associated with risk of seizures in critically ill patients. However, specific features that confer higher seizure risk remain unclear.

OBJECTIVE To analyze the association of distinct characteristics of periodic and rhythmic patterns with seizures.

DESIGN, SETTING, AND PARTICIPANTS We reviewed electroencephalographic recordings from 4772 critically ill adults in 3 academic medical centers from February 2013 to September 2015 and performed a multivariate analysis to determine features associated with seizures.

INTERVENTIONS Continuous electroencephalography.

MAIN OUTCOMES AND MEASURES Association of periodic and rhythmic patterns and specific characteristics, such as pattern frequency (hertz), Plus modifier, prevalence, and stimulation-induced patterns, and the risk for seizures.

RESULTS Of the 4772 patients included in our study, 2868 were men and 1904 were women. Lateralized periodic discharges (LPDs) had the highest association with seizures regardless of frequency and the association was greater when the Plus modifier was present (58%; odds ratio [OR], 2.00, $P < .001$). Generalized periodic discharges (GPDs) and lateralized rhythmic delta activity (LRDA) were associated with seizures in a frequency-dependent manner (1.5-2 Hz: GPDs, 24%,OR, 2.31, $P = .02$; LRDA, 24%, OR, 1.79, $P = .05$; $\geq$ 2 Hz: GPDs, 32%, OR, 3.30, $P < .001$; LRDA, 40%, OR, 3.98, $P < .001$) as was the association with Plus (GPDs, 28%, OR, 3.57, $P < .001$; LRDA, 40%, $P < .001$). There was no difference in seizure incidence in patients with generalized rhythmic delta activity compared with no periodic or rhythmic pattern (13%, OR, 1.18, $P = .26$). Higher prevalence of LPDs and GPDs also conferred increased seizure risk (37% frequent vs 45% abundant/continuous, OR, 1.64, $P = .03$ for difference; 8% rare/occasional vs 15% frequent, OR, 2.71, $P = .03$, vs 23% abundant/continuous, OR, 1.95, $P = .04$). Patterns associated with stimulation did not show an additional risk for seizures from the underlying pattern risk ($P > .10$).

CONCLUSIONS AND RELEVANCE In this study, LPDs, LRDA, and GPDs were associated with seizures while generalized rhythmic delta activity was not. Lateralized periodic discharges were associated with seizures at all frequencies with and without Plus modifier, but LRDA and GPDs were associated with seizures when the frequency was 1.5 Hz or faster or when associated with a Plus modifier. Increased pattern prevalence was associated with increased risk for seizures in LPDs and GPDs. Stimulus-induced patterns were not associated with such risk. These findings highlight the importance of detailed electroencephalographic interpretation using standardized nomenclature for seizure risk stratification and clinical decision making.

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Supplemental content

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Continuous electroencephalographic (cEEG) monitoring is a useful diagnostic tool for identifying seizures and other abnormalities in critically ill patients. Periodic and rhythmic patterns are frequently found in this population and some are known to be associated with seizures.[1-8] Standardized terminology has been developed and validated for identifying these patterns, including generalized and lateralized periodic discharges (GPDs and LPDs), generalized and lateralized rhythmic delta activity (GRDA and LRDA), and bilateral independent periodic discharges (BIPDs). A more detailed description of these patterns can be conferred by using various modifiers such as frequency, amplitude, Plus (superimposed fast, rhythmic, or sharp activity), whether the pattern is induced by stimulation, and the prevalence of the pattern[9] (**Table 1**).

The objective of this study was to analyze the association of distinct characteristics of periodic and rhythmic patterns with seizures. Previous studies have demonstrated an association between seizures in specific periodic or rhythmic patterns, but these studies are limited in generalizability because of their small sample sizes.[1-5,10-16] They also do not describe the specific features of these patterns that are associated with risk for seizures. To overcome these limitations, we used a large, multicenter database containing detailed descriptions of cEEG recordings and seizure incidence in critically ill patients. We hypothesized that lateralized patterns and patterns with increased frequency and Plus modifier would confer increased risk for seizures.

Key Points

Question What are the specific characteristics of periodic and rhythmic electroencephalographic patterns that confer risk for seizures?

Findings This multicenter cohort study of 4772 consecutive critically ill adult patients undergoing continuous electroencephalographic monitoring found that lateralized periodic discharges, lateralized rhythmic delta activity, and generalized periodic discharges were associated with seizures, but generalized rhythmic delta activity was not. High frequency and Plus modifier were associated with an additional risk in all patterns except generalized rhythmic delta activity; and increased pattern prevalence was associated with risk for seizures in lateralized periodic discharges and generalized periodic discharges.

Meaning A detailed electroencephalographic interpretation using standardized nomenclature can assist seizure risk stratification.

Methods

Using the Critical Care EEG Monitoring Research Consortium multicenter database,[17] we collected clinical and electroencephalographic (EEG) data from consecutive critically ill adult patients who underwent cEEG at Brigham and Women's Hospital, Emory University Hospital, and Yale University Hospital between February 2013 and September 2015. The study was approved by the institutional review boards of each participating center and informed consent was waived because the study was retrospective.

Data entry was performed by attending physicians who were either board certified or board eligible in clinical neurophysiology and clinical neurophysiology fellows with training and certification to use the American Clinical Neurophysiology Society (ACNS) Standardized Critical Care EEG Terminology.[9] Individuals were invited to review a training module available at the ACNS website. This was followed by a web-based certification test in which 37 EEG samples were presented. The participants were required to identify detailed EEG features of patterns and seizures from these examples.[18] The multicenter data set included demographic factors and the presence of any of the following periodic or rhythmic patterns: LPDs, GPDs, BIPDs, LRDA, and GRDA. Other EEG pattern features included prevalence, duration, typical frequency, number of phases, sharpness, amplitude, polarity, superimposed Plus, fluctuation or evolution, and whether the pattern was stimulus-induced. These terms have been well defined and accepted in previous studies.[9] The ACNS terminology does not focus on defining seizures but most practitioners adhere to a form of the Young et al criteria[19] or the nonconvulsive status epilepticus definition.[20] Previous studies have described seizures as convulsive and nonconvulsive, the latter being the most common in intensive care unit patients.[2,21] We considered seizures convulsive if the seizure description was coded in the database as tonic-clonic, tonic, clonic, bilateral convulsive, or myoclonic. We considered seizures nonconvulsive with clinical manifestations if descriptors such as *focal sensory*, *focal motor*, *complex partial*, *aphasia*, *atonic*, *absence*, *epileptic spasms*, *subtle*, *twitching*, *stiffening*, *oral automatism*, *altered mental status*, *gaze deviation*, *blinking*, *chewing*, *subtle head movements*, *behavioral arrest*, and *confusion* were used. Electrographic-only seizures were described if seizures were seen in the EEG with no associated clinical signs. Unknown was defined if the description was not available or was coded as unknown. A more detailed analysis of the interaction of medications, sedatives, paralytics, and other clinical variables with seizures is out of the scope of the present study.

To determine the consistency of data completion, we calculated the percentage of missing data in each of the fields of interest (eTable 1 in the Supplement). Pattern prevalence, typical frequency, and duration were entered reliably (≤30% missing data). There was moderate data completion (30%-50% missing data) for superimposed Plus activity, amplitude, sharpness, fluctuation/evolution, and whether a pattern was stimulus-induced. Polarity, sharpness, amplitude, and number of phases were not reported reliably (>50% missing data). We did not analyze pattern characteristics if more than 50% of the data were missing.

To account for potential day-to-day fluctuations, a pattern was recorded as present if it occurred any time during an individual EEG monitoring session. An EEG monitoring session was defined as contiguous EEG recordings without interruption for longer than 24 hours. The number of patients who underwent EEG monitoring was lower than the total number of EEG monitoring sessions (**Table 2**). Total EEG monitoring sessions were analyzed instead of total patients to account for individuals who may have undergone repeated EEG monitoring many days or months later, with different risk profiles for

Table 1. American Clinical Neurophysiology Society Standardized Critical Care Electroencephalographic Terminology

Name	Definition
Main Term	
I (Location)	
Generalized	Refers to any bilateral, bisynchronous, or symmetric pattern, even if it has a restricted field (ie bifrontal).
Lateralized	Unilateral and bilateral synchronous but asymmetric; includes focal, regional, and hemispheric patterns.
Bilateral independent	The presence of 2 independent (asynchronous) lateralized patterns, 1 in each hemisphere.
Multifocal	Refers to the presence of at least 3 independent lateralized patterns with at least 1 in each hemisphere.
II (Patterns)	
Periodic discharges	Repetition of a waveform with relatively uniform morphology and duration with a quantifiable interdischarge interval between consecutive waveforms and recurrence of the waveform at nearly regular intervals. Applies only to single discharges, not bursts (which have no more than 3 phases and last ≤0.5 s).
Rhythmic delta activity	Repetition of a waveform with relatively uniform morphology and duration, and without an interval between consecutive waveforms.
Spike-wave or Sharp-wave	Polyspike, spike, or sharp wave consistently followed by a slow wave in a regularly repeating and alternating pattern, with a consistent relationship between the spike component and the slow wave and with no interval between a spike-wave complex and the next.
Modifiers[a]	
Frequency	Rate/s.
Plus; periodic discharges: +F/+R/+FR; rhythmic delta activity: +F/+S/+FS	Additional features that render the pattern more ictal-appearing than the usual term without the plus. They include superimposed fast or rhythmic delta activity for periodic discharges and superimposed fast activity or frequent intermixed sharp waves or spikes for rhythmic activity.
Stimulus-induced	Reproducibly caused by an alerting stimulus, with or without clinical alerting.
Prevalence	Specified percentage of record or epoch that includes the pattern.

Abbreviations: F, superimposed fast activity; FR, superimposed fast and rhythmic activity; FS, superimposed fast and sharp waves or spikes; R, superimposed rhythmic or quasirhythmic delta activity; S, superimposed sharp waves or spikes, sharply contoured.

[a] This includes modifiers relevant for this article only. For further details, see Hirsch et al.[9]

seizures. Because pattern frequency may fluctuate within a given monitoring session, we selected the maximal recorded frequency for any given pattern within that session.

The data were analyzed using the open source statistical package R (R Foundation for Statistical Computing).[22] Differences in patient age and duration of EEG monitoring sessions were calculated using the Kruskal-Wallis rank sum test. Several multivariate logistic regression models were estimated, controlling for age, sex, institution, and diagnosis. In these models, patients with specific periodic or rhythmic patterns were compared with patients without these patterns while controlling for all other major patterns to evaluate an association between the pattern and seizure occurrence. For all the models, the estimated odds ratios and 95% CIs were presented. Adjusted *P* values to control false discovery rate were calculated using the method described by Benjamini et al.[23] For statistical significance, a certainty level of α = .05 was used. The interquartile range was used to measure variability in the patient sessions.[24]

Results

Patient Population

A total of 4772 patients underwent cEEG for a total of 5742 sessions across 3 centers during the study. The median time between sessions was 25.3 hours and an interquartile range of 18.0 to 46.9 hours. Most patients were recorded for more than 12 hours. The incidence of seizures and periodic or rhythmic patterns was similar among the 3 centers as well as primary neurological diagnoses (Table 2). The percentage of male patients ranged between 47.6% and 51.6% and the median patient age was between 59 and 63 years. We identified 2344 sessions (41%) with at least 1 type of periodic or rhythmic pattern. Seizures were documented in 719 sessions (12.5%), of which 530 (74%) also had a periodic or rhythmic pattern. There were 3427 sessions with no periodic or rhythmic patterns in which 202 patients had seizures (6%). There were 1739 seizures recorded in which 183 (10.5%) were convulsive, 471 (27.1%) nonconvulsive with clinical manifestations, 865 (49.7%) electrographic only, and 220 (12.7%) unknown/unclassified.

Periodic or Rhythmic Patterns and Their Association With Seizures

Plus Modifier

Regardless of consideration of frequency or Plus, LPDs, LRDA, GPDs, and BIPDs were associated with seizures while GRDA was not (**Table 3**). Compared with EEG sessions with no rhythmic or periodic pattern present, LPDs and LRDA without Plus were associated with seizure risk, which increased when a Plus modifier was present (Table 3). Generalized periodic discharges with Plus modifier were associated with seizures but GPDs without Plus were not. There was a trend toward BIPDs with Plus being associated with seizures while GRDA was not, regardless of whether a Plus modifier was present. There was also an additional risk of seizures when a particular pattern contained a Plus modifier compared with the same pattern without a modifier: LPDs with Plus vs without (odds ratio, 2.00, 95% CI, 1.44-2.78, $P < .001$) and GPDs with Plus vs without (odds ratio, 2.66, 95% CI, 1.59-4.41, $P < .001$). Although the odds ratio for seizures was higher in patients with LRDA Plus compared with LRDA alone, it failed to meet statistical significance (odds ratio, 1.85, 95% CI, 1.07-3.23, $P = .06$). The presence of a Plus modifier did not confer any difference in seizure risk for patients with GRDA ($P = .25$, 95% CI, 0.38-1.15). There were no significant changes in these findings when patients were Plus and were not coded or left blank (not applicable, data not shown).

Pattern Frequency

To determine whether pattern frequency conferred particular risk for seizures, we divided each pattern into 4 frequency bands—less than 1.5 Hz, 1.5 to less than 2 Hz, greater than or

Table 2. Baseline Characteristics

Characteristic	No. (%) Emory	BWH	Yale	Total
Total patients	1710	1597	1465	4772
Sessions	1968	1930	1844	5742
Patients with patterns	791 (46)	655 (41)	573 (39)	2019
Sessions with patterns	886 (45)	759 (39)	699 (38)	2344
Patients with seizures	249 (15)	204 (13)	201 (14)	654
Sessions with seizures	267 (14)	228 (12)	224 (12)	719
Patients with patterns and seizures	194 (11)	146 (9)	153 (10)	493
Sessions with patterns and seizures	201 (10)	160 (8)	169 (9)	530
Median session duration, h	30	24.2	24	25.3
Mean session duration, h	45.6	41.5	37.1	41.3
Range of session duration, h/d (minimum-maximum range)	0.0-678.8 (0.00-28.28)	0.0-688.3 (0.00-28.68)	0.0-478.9 (0.00-19.95)	0.0-688.3 (0.00-28.68)
IQR, variability, d	0.81-2.16	0.82-1.94	0.61-1.83	0.75-1.95
Age/sex				
Median age	59	62	63	61
Male	936 (47.6)	996 (51.6)	936 (50.8)	2868 (49.9)
Primary diagnosis				
Seizure	554 (28.2)	292 (15.1)	381(20.7)	1227 (21.4)
Status epilepticus	117 (5.9)	51 (2.6)	63 (3.4)	231 (4.0)
Stroke	107 (5.4)	110 (5.7)	81 (4.4)	298 (5.2)
SAH	179 (9.1)	85 (4.4)	122 (6.6)	386 (6.7)
SDH	57 (2.9)	121 (6.3)	67 (3.6)	245 (4.3)
ICH	122 (6.2)	148 (7.7)	163 (8.8)	433 (7.5)
IVH	15 (0.8)	8 (0.4)	27 (1.5)	50 (0.9)
Traumatic brain injury	7 (0.4)	63 (3.3)	48 (2.6)	118 (4.3)
Altered mental status	490 (24.9)	393 (20.4)	413 (22.4)	1296 (22.6)
Hydrocephalus	8 (0.4)	13 (0.7)	7 (0.4)	28 (0.5)
Infection	16 (0.8)	44 (2.3)	26 (1.4)	86 (1.5)
Inflammation	6 (0.3)	20 (1.0)	12 (0.7)	38 (0.7)
Neoplasm	103 (5.2)	267 (13.8)	82 (4.4)	452 (7.9)
Hypoxic ischemic encephalopathy	65 (3.3)	163 (8.4)	151 (8.2)	379 (6.6)
Metabolic encephalopathy	64 (3.3)	21 (1.1)	95 (5.2)	180 (3.1)
Other	58 (2.9)	131 (6.8)	106 (5.7)	295 (5.1)

Abbreviations: BWH, Brigham and Women's Hospital; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, interventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

equal to 2 Hz, and frequency not recorded—and evaluated the association with seizures (**Table 4**). Lateralized periodic discharges were associated with seizures at any frequency with seizure risk greatest at higher frequencies. The risk of seizures was also frequency-dependent for LRDA and GPDs, but only frequencies of 1.5 Hz or greater were associated with seizures. Generalized rhythmic delta activity was not associated with seizures at any frequency. The sample size was too small to study the effect of individual frequencies for BIPDs.

Given the paucity of patterns classified at higher frequencies (≥2.5 Hz), we hypothesized that these patterns were not being recorded as periodic or rhythmic patterns but instead were considered electrographic seizures. To test this hypothesis, we compared frequency bands of various periodic and rhythmic patterns with the minimum and maximum frequency of any electrographic seizures recorded during the same sessions as the patterns (eTable 2 in the Supplement). Although there is often an overlap between pattern frequency and minimum seizure frequency, there was little overlap with maximum seizure frequency. Therefore, it is unlikely that patterns with frequencies in the 2- to 3-Hz range were being recorded as electrographic seizures instead of a periodic or rhythmic pattern.

Pattern Prevalence

To determine the influence of pattern prevalence on seizure risk, each pattern was divided into the following categories according to ACNS Standardized Critical Care EEG Terminology[9]: rare/occasional (up to 9% of the recording), frequent (10%-49% of the recording), and abundant/continuous (50%-89% of the recording). There was a positive correlation between increasing prevalence and incidence of seizures for GPDs (rare/occasional vs frequent and frequent vs abundant/

Table 3. Periodic/Rhythmic Patterns and Seizures With and Without Plus Modifier

Pattern	No. of Sessions Without Seizures	No. of Sessions With Seizures	Odds Ratio (95% CI)[a]	FDR-Adjusted *P* Value[a,b]	Odds Ratio Controlled for Frequency (95% CI)[c]	FDR-Adjusted *P* Value (Controlled for Frequency)[b,c]
GRDA without Plus	644 (87)	96 (13)	1.27 (0.97-1.65)	.14	1.38 (0.98-1.91)	.11
GRDA with Plus	161 (86)	26 (14)	0.86 (0.51-1.40)	.62	0.94 (0.52-1.63)	.86
GPDs without Plus[d]	461 (88)	61 (12)	1.13 (0.81-1.55)	.55	0.98 (0.68-1.38)	.92
GPDs with Plus[d]	125 (72)	49 (28)	3.00 (1.94-4.56)	<.001	2.11 (1.23-3.56)	.02
LRDA without Plus	219 (78)	62 (22)	1.93 (1.35-2.71)	.001	1.46 (0.87-2.37)	.23
LRDA with Plus	78 (60)	51 (40)	3.57 (2.25-5.63)	<.001	3.12 (1.77-5.44)	<.001
LPDs without Plus[d]	326 (64)	183 (36)	6.68 (5.30-8.42)	<.001	6.53 (5.15-8.28)	<.001
LPDs with Plus[d]	123 (42)	170 (58)	13.35 (9.99-17.89)	<.001	12.66 (9.09-17.67)	<.001
BIPDs without Plus	77 (75)	26 (25)	1.59 (0.90-2.72)	.17	1.66 (0.94-2.85)	.14
BIPDs with Plus	11 (58)	8 (42)	3.27 (0.99-10.30)	.09	3.38 (1.00-10.77)	.09

Abbreviations: BIPDs, bilateral independent periodic discharges; FDR, false discovery rate; GPDs, generalized periodic discharges; GRDA, generalized rhythmic delta activity; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity.

[a] The odds ratios compare patients with patterns vs patients without patterns and are adjusted for age, sex, site, and diagnoses.

[b] The *P* values were adjusted using the FDR to adjust for multiple comparisons.

[c] Odds ratios and *P* values were additionally adjusted for frequency to control for confounding risk.

[d] The statistically significant difference for Plus vs no Plus for GPDs and LPDs was FDR-adjusted *P* < .001. Seizures were seen in 202 of 3427 sessions (6%) of patients with no patterns.

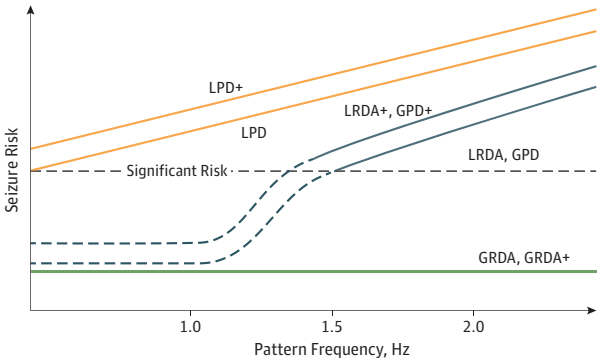
Table 4. Effect of Specific Frequencies on Association With Seizures

Pattern	No (%)		Odds Ratio (95% CI)	FDR-Adjusted *P* Value	Odds Ratio (Plus-Controlled)[a]	FDR-Adjusted *P* Value[a]
	Sessions Without Seizures	Sessions With Seizures				
GRDA						
<1.5 Hz	297 (87)	45 (13)	1.34 (0.91-1.93)	.20	1.47 (0.99-2.15)	.10
1.5 to 2 Hz	248 (88)	35 (12)	0.97 (0.62-1.47)	.92	1.05 (0.66-1.64)	.86
≥2 Hz	137 (84)	26 (16)	1.31 (0.78-2.12)	.38	1.44 (0.85-2.37)	.25
Not recorded	123 (88)	16 (12)	1.11 (0.59-1.96)	.79	1.18 (0.63-2.10)	.65
Any frequency	805 (87)	122 (13)	1.18 (0.93-1.50)	.26		
GPDs						
<1.5 Hz	345 (86)	55 (14)	1.35 (0.94-1.91)	.17	1.12 (0.74-1.64)	.65
1.5 to 2 Hz	65 (76)	20 (24)	2.31 (1.25-4.11)	.02	1.72 (0.86-3.29)	.19
≥ 2 Hz	54 (68)	25 (32)	3.30 (1.79-5.87)	<.001	2.30 (1.14-4.46)	.04
Not recorded	122 (92)	10 (8)	0.73 (0.34-1.41)	.47	0.68 (0.31-1.34)	.38
Any frequency	586 (84)	110 (16)	1.53 (1.17-1.99)	.005	NA	NA
LRDA						
<1.5 Hz	101 (83)	21 (17)	1.56 (0.87-2.66)	.20	1.10 (0.57-2.02)	.81
1.5 to 2 Hz	106 (76)	34 (24)	1.79 (1.08-2.89)	.05	1.36 (0.77-2.33)	.37
≥2 Hz	61 (60)	40 (40)	3.98 (2.41-6.50)	<.001	3.43 (2.03-5.70)	<.001
Not recorded	29 (62)	18 (38)	2.86 (1.36-5.89)	.02	2.28 (1.03-4.89)	.08
Any frequency	297 (72)	113 (28)	2.36 (1.78-3.13)	<.001	NA	NA
LPDs						
<1.5 Hz	325 (60)	220 (40)	7.55 (6.03-9.46)	<.001	6.20 (4.82-7.97)	<.001
1.5 to 2 Hz	58 (50)	59 (50)	10.89 (7.09-16.76)	<.001	6.42 (3.89-10.54)	<.001
≥2 Hz	20 (34)	38 (66)	16.40 (8.97-30.64)	<.001	10.60 (5.54-20.62)	<.001
Not recorded	46 (56)	36 (44)	4.93 (5.80-15.82)	<.001	8.41 (5.03-13.93)	<.001
Any frequency	449 (56)	353 (44)	8.61 (7.08-10.49)	<.001	6.53 (5.15-8.28)	<.001
BIPDs						
Any frequency	88 (72)	34 (28)	1.83 (1.12-3.03)	.04		

Abbreviations: BIPDs, bilateral independent periodic discharges; FDR, false discovery rate; GPDs, generalized periodic discharges; GRDA, generalized rhythmic delta activity; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; NA, not applicable.

[a] Odds ratios and *P* values were additionally adjusted for plus to control for confounding risk using FDR.

Figure. Model of Pattern Characteristics and Seizure Risk



Rhythmic and periodic patterns and their association with seizures. The y-axis depicts risk for seizures and the x-axis depicts electroencephalographic pattern frequency. Bilateral independent periodic discharges with Plus were not included but were found to be associated with seizures; however, the sample size was too small to draw firm conclusions. GPDs indicates generalized periodic discharges; GPDs+, generalized periodic discharges with Plus; GRDA+, generalized rhythmic delta activity with Plus; LPDs, lateralized periodic discharges; LPDs+, lateralized periodic discharges with Plus; LRDA, lateralized rhythmic delta activity; LRDA+, lateralized rhythmic delta activity with Plus.

continuous, 95% CI, 1.31-5.81 and 95% CI, 1.14-3.40, respectively) and LPDs (frequent vs abundant/continuous; 95% CI, 1.13-2.41) (all $P < .05$) (eTable 3 in the Supplement).

Stimulus-Induced Patterns

We analyzed whether seizure risk changed if a particular pattern was induced by stimulation. We did not detect a significant difference in the incidence of seizures when comparing spontaneously appearing patterns with the same type of pattern that emerged before stimulation (eTable 4 in the Supplement). However, this may be caused by sample size. Although the number of sessions of patients with stimulation-induced pattern was adequate (range, 21-127), the number of sessions of patients with stimulation-induced pattern and seizures was small (range, 6-30).

Discussion

This study demonstrates the association between periodic and rhythmic patterns and seizures in critically ill patients, including which patterns are dependent on specific features (**Figure**). Specifically, LPDs were highly associated with seizures regardless of whether particular features were present, and seizure risk increased with higher frequencies, Plus modifier, and higher pattern prevalence. Similarly, LRDA was also highly associated with seizures with increased risk when Plus was present, and a frequency-dependent association was seen at 1.5 Hz and higher. Generalized periodic discharges only confer seizure risk at frequencies of 1.5 Hz and faster when associated with a Plus modifier and at higher pattern prevalence. Comparing all sessions with BIPDs with sessions with no patterns revealed a trend toward association with seizures, but the small sample size did not allow for analysis of specific features. There was also an association between increasing pattern prevalence and risk of seizures for GPDs and LPDs. Most of the seizures were nonconvulsive, similar to previous studies.[1-3] Finally, there was no association between GRDA and seizures regardless of pattern characteristics.

These findings are concordant with previous studies. Chatrian et al[8] reported seizures in 88% of their participants with periodic lateralized epileptiform discharges (PLEDs) and acute focal lesions or history of chronic focal epilepsy. Similarly, Snodgrass et al[25] reported seizures in 126 of 147 patients (86%) with PLEDs on routine EEG. In 2002, García-Morales et al[5] reported focal seizures in 50% of patients with PLEDs. It is important to note that most of these older studies were based on routine EEGs. Our study also supports Gaspard et al[1] who demonstrated that LRDA was highly associated with seizures at an incidence similar to LPDs. That study reported that 17 of 27 patients (62%) with LRDA had seizures, while 57% of patients with LPDs experienced seizures. They also showed a trend toward increased risk of seizures when the LRDA was associated with superimposed spikes/sharps.

To our knowledge, the clinical significance of periodic or rhythmic patterns associated with admixed fast, rhythmic, or sharp activity (the Plus modifiers) has not been extensively explored in prior studies. Reiher et al[12] were the first to describe "PLEDs Plus" as typical PLEDs (termed *PLEDs Proper*) with superimposed fast activity. They found PLEDs Plus was more frequently associated with seizures and status epilepticus than PLEDs proper. Our study provides evidence that periodic and rhythmic patterns associated with Plus (as defined by the ACNS Standardized Critical Care EEG Terminology as superimposed fast, rhythmic, or sharp activity[9]) confers an additional risk for seizures in patients with LPDs, LRDA, and GPDs.

In 2004, Hirsch et al[11] described rhythmic and periodic patterns that are induced by stimulation (termed *stimulus induced rhythmic*, *periodic*, or *ictal discharges*) and demonstrated an association with seizures in 50% of patients. Smaller series have verified the association of stimulus-induced rhythmic, periodic, or ictal discharges and seizures.[13,26] However, a key unanswered question is whether stimulus-induced patterns are more or less associated with seizures than the spontaneous appearance of the periodic or rhythmic pattern. In this study, there was no significant difference in the incidence of seizures when patterns were stimulus-induced compared with spontaneously occurring patterns, but this finding is limited because of the small number of patients with stimulus-induced patterns. Further studies should be performed to find better characterizations.

We described the influence of pattern frequency on seizure risk. After controlling for other variables, such as the Plus modifiers, we found that seizure risk is only linked to frequency for some patterns. In patients with GPDs and LRDA, frequencies of 1.5 Hz or more were highly associated with seizures, but there was no association less than 1.5 Hz. In a recent study by Foreman et al,[3] GPDs were found to be highly

associated with focal and generalized nonconvulsive seizures in critically ill patients (46.4% and 66.1%, respectively), but that study did not evaluate individual frequencies. Our study suggests that the association between GPDs and seizures is primarily seen at higher frequencies. Patients with LPDs were the only group in which seizure risk was high regardless of frequency, but there was still a frequency-dependent increase in seizure risk.

Finally, this study provides important information about GRDA. Generalized rhythmic delta activity was not associated with seizures, even when associated with Plus, stimulation induction, increasing frequencies, or prevalence. Before the standardized EEG classification system was published by ACNS, GRDA was largely known as frontal intermittent rhythmic delta activity, initially described by Cobb[27] in 1945. This pattern has been associated with numerous brain pathologies such as metabolic impairment (most common), midline brain lesions, subcortical lesions, Creutzfeldt-Jakob disease, diffuse Lewy body disease, and epilepsy.[28] In a study of frontal intermittent rhythmic delta activity in routine EEGs of patients with chronic epilepsy, this pattern was found only in 2%,[29] which is consistent with our finding of no association between GRDA and seizures.

There was an association between BIPDs and seizures in our data set. De la Paz and Brenner[30] described seizures in 78% of 18 patients with BIPDs during an acute illness. Snodgrass et al[25] described BIPDs in 10% of 147 patients with clinical diagnosis of cardiac arrest, central nervous system infections, and chronic epilepsy, including 4 patients following status epilepticus. Our cohort suggests that BIPDs may confer an increased association with seizures, but detailed characterization of this group was limited because of the small sample size.

We found that increasing pattern prevalence increases the risk for seizures in LPDs and GPDs. This may influence clinical practice because it suggests that each pattern's burden within a record is an important determinant of the risk for seizures. Furthermore, it supports cEEG use in the intensive care unit because it provides increased sampling to estimate pattern prevalence.

Limitations

This study has several limitations. First, the retrospective nature of the study introduces selection bias toward patients in whom clinicians had reason to order cEEG and may not accurately reflect the true frequency of various patterns and seizures than if the study was performed in all patients. Second, the small sample size of patients with BIPDs and stimulation-induced patterns limits the interpretation of our findings in these patients. Third, this study does not account for interactions between multiple EEG patterns when they occur together or when 1 pattern evolves to another. Fourth, we did not account for potential effects of antiepileptic medications or sedatives on the incidence of these patterns and seizures, which will be studied separately. Fifth, there were substantial missing data elements in this cohort because this database was primarily used for clinical reporting rather than research purposes. However, we do not feel that this affects our conclusions regarding periodic and rhythmic patterns because no systematic biases were found.

Conclusions

This study represents a large multicenter retrospective analysis of periodic and rhythmic patterns and their effect on seizure risk. The data support increased seizure risk in association with LPDs, LRDA, and GPDs and emphasize the importance of standardized identification and classification of these patterns and their specific features. Knowledge of these specific features can help physicians judge which patients should be monitored and treated more aggressively instead of indiscriminately monitoring or treating all patients who present with periodic/rhythmic patterns. Furthermore, it will provide a more cost-effective use of EEG monitoring resources.

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