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Etiology and prognostic significance of ictal EEG patterns in patients with non-convulsive seizures

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ABSTRACT

Objective. We aimed to study the ictal EEG patterns in patients with non-convulsive seizures (NCS) and their relationship with underlying etiology and patient outcome.

Methods. We conducted a retrospective review of EEG studies from patients undergoing continuous EEG (cEEG) monitoring for indication of altered mental status with a suspicion of NCS. Ictal EEG findings of NCS were categorized as three patterns: focal or generalized epileptiform discharges (EDs) at frequencies >2.5 Hz (Pattern 1); EDs at frequencies of ≤2.5 Hz or rhythmic activity >0.5 Hz with spatiotemporal evolution (Pattern 2); and EDs with ≤2.5 Hz with subtle clinical correlate during the ictal EEG or clinical and EEG improvement after a trial of IV anti-seizure drugs (Pattern 3). Patients with anoxic brain injury were excluded from the study. Associations between ictal EEG patterns and underlying etiology and their impact on in-hospital mortality was measured.

Results. Of 487 patients included in the study, NCS was recorded on cEEG monitoring in 57 (12%). The ictal EEG Pattern 2 was the most commonly seen ictal EEG finding in our cohort of patients with NCS (70%, *n*=40/57), followed by Pattern 3 (15%, *n*=9/57) and Pattern 1(14%, *n*=8/57). In patients with acute brain injury, Pattern 2 (67%, *n*=27/40) was a commonly seen ictal EEG finding, whereas Pattern 1 (62% *n*=5/8) was seen in patients with underlying acute medical illness. No statistically significant difference was found between ictal EEG patterns and underlying neurological versus medical etiologies (p=0.27) or in-hospital mortality (p=0.5).

Significance. Spatiotemporal evolution of epileptiform discharges at a lower frequency was the most commonly recorded ictal EEG pattern in our cohort. Further prospective studies with a larger sample size of patients with NCS may provide valuable clinical data that could be used to evaluate the etiologic correlate of the various ictal EEG patterns and their effect on outcome.

Key words: non-convulsive seizures, ictal EEG pattern, continuous EEG monitoring

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Non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) are increasingly recognized in the evaluation of patients with disturbances of consciousness in various clinical settings [1-3]. Continuous EEG monitoring (cEEG) has proven to be a very helpful tool in this scenario, considering the clinical manifestation of NCS can range from very subtle

muscle twitching to varying degrees of impaired consciousness. Various ictal and inter-ictal EEG patterns have been studied extensively in the evaluation and prognosis of patients with anoxic brain injury [4, 5]. However, the literature is limited on ictal EEG findings of NCS outside of anoxic brain injury as to whether a specific ictal pattern has any correlation with underlying etiology or could have any prognostic clinical value. In this study, we aimed to evaluate the relationship between various ictal EEG patterns of NCS and underlying etiologies and their effect on patient outcome. Clinical and EEG characteristics associated with NCS were also studied.

Methodology

We retrospectively analyzed the collected data on patients who underwent cEEG between January, 2019 to June, 2019 at The Ohio State University Wexner Medical Center. Patients undergoing cEEG monitoring for anoxic brain injury assessment were excluded.

EEG variables

EEG data collected included background activity, the presence of interictal epileptiform discharges (IEDs; spikes and sharp waves with or without slow wave complex), and the presence of rhythmic or periodic discharges. All EEG recordings were interpreted by a clinical electrophysiologist with special expertise in interpretation of critical care EEG. All EEG recordings were reviewed again by two independent board-certified clinical neurophysiologists to obtain the consensus on ictal EEG pattern. In some patients, more than one video-EEG monitoring session was performed, and the seizures were recorded during the second or third, and so on, monitoring session. In terms of ictal EEG findings for NCS, we accepted only the relevant video-EEG monitoring sessions and ignored previous ones.

The ictal EEG findings of NCS were classified using Salzburg criteria into three categories as:

- Pattern 1: focal or generalized epileptiform discharges at frequencies higher than 2.5 Hz (*figure 1A*).
- Pattern 2: Focal or generalized epileptiform discharges at frequencies of 2.5 Hz or lower or rhythmic activity higher than 0.5 Hz with spatiotemporal evolution defined as incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency above 1 Hz or change in location), or decrementing termination (voltage or frequency) (*figure 1B*).
- Pattern 3: Focal or generalized epileptiform discharges at frequencies of 2.5 Hz or lower or rhythmic activity higher than 0.5 Hz with subtle clinical correlate or clinical and EEG improvement after a trial of anti-seizure drug therapy (*figure 1C*).

Non-convulsive status epilepticus was defined as an ongoing or intermittent seizure activity without convulsions, without recovery of consciousness between the seizures, and lasting for more than 10 minutes.

Clinical variables

Patients' demographic (age, gender) and clinical characteristics were recorded, including history of epilepsy, presence of structural lesion on brain imaging (*e.g.* tumor, stroke), and SOFA (sequential organ failure assessment) score at the initiation of cEEG monitoring. Neurological states were defined as comatose or non-comatose (awake or stuporous state).

Etiologies for altered mentation were classified as:

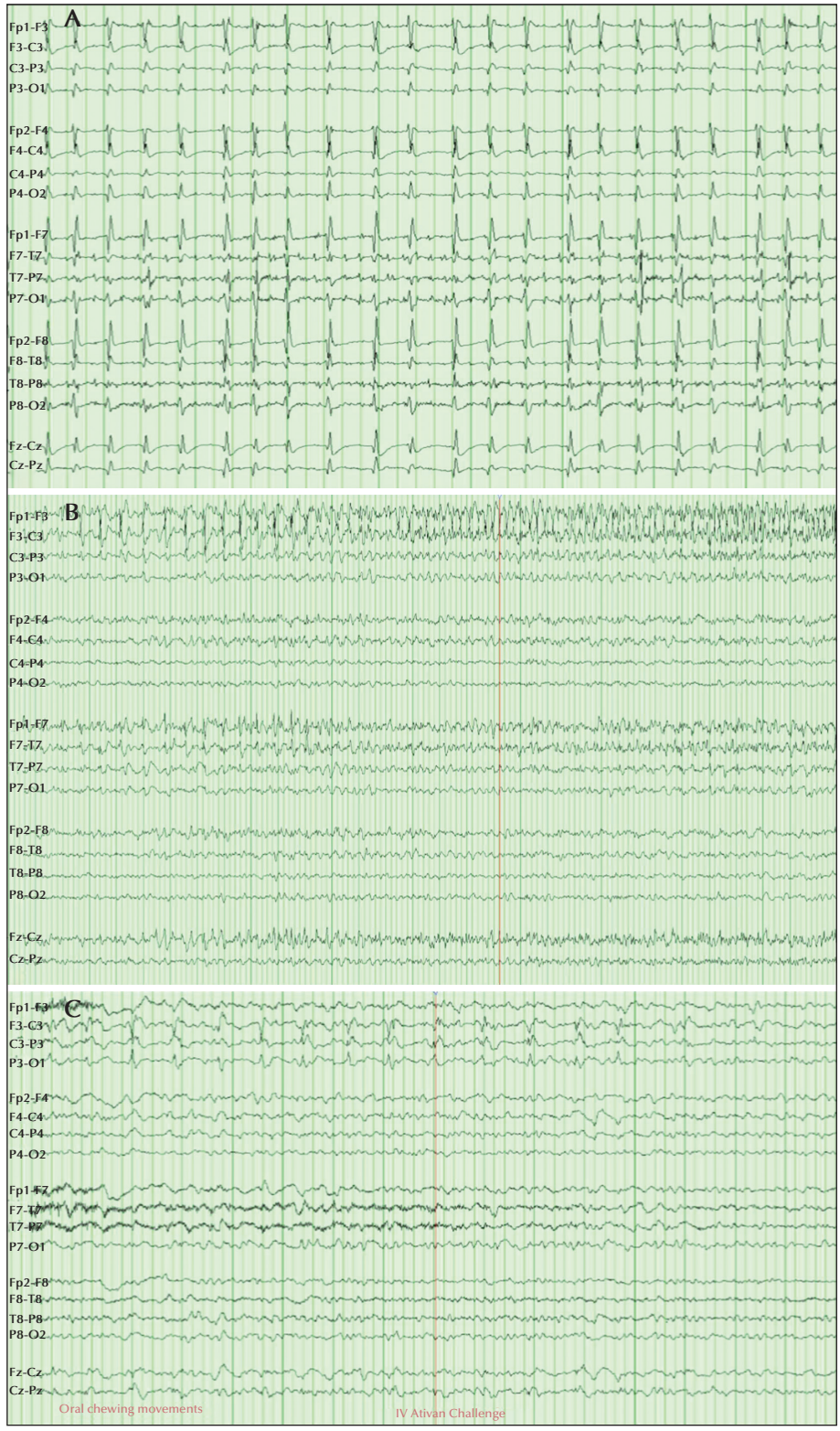
- acute brain injury which included intracranial infection (meningitis, encephalitis and brain abscess), subdural hematoma, subarachnoid or intracerebral hemorrhage, ischemic stroke, and traumatic head injury;
- and acute medical illness which included sepsis, metabolic disturbances/organ failure, and drug related. Patients who met the criteria for both categories were included in the group of acute brain injury.

Statistical analysis

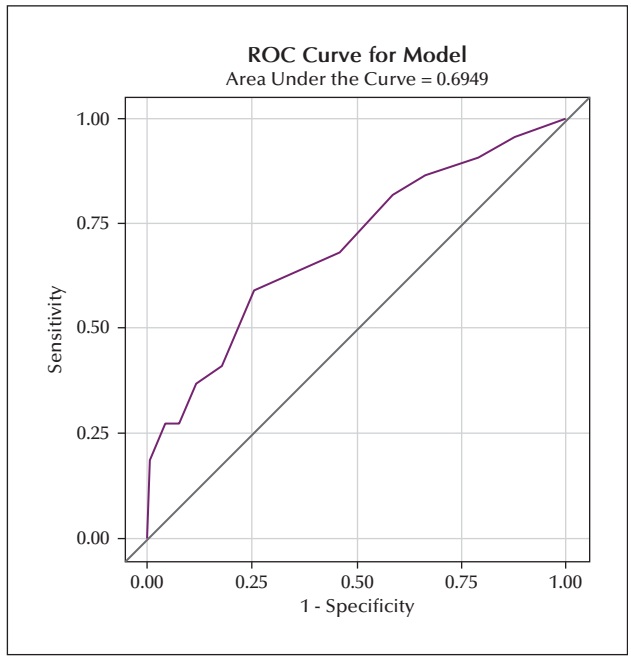
Univariate logistic regression models were used to examine the association with NCS recorded on cEEG. Odds ratios (OR) and 95% confidence intervals (CI) were reported. For counts less than 5, the Fisher exact test was performed. The Chi-square or fisher exact test were performed to examine the relationship between categorical variables and ictal EEG patterns. The Wilcoxon rank sum test was used to examine the difference in SOFA scale among ictal EEG patterns. A 2-sided significance level of α=0.05 was used for all tests. All analyses were carried out in SAS version 9.2 (SAS institute, Cary, NC).

Results

Among 487 patients included in the study, a total of 57 (11.7%) patients had NCS and 20 (4.1%) had NCSE recorded on cEEG monitoring; 61.4% (35/57) of NCS cases were reported in patients with acute brain injury. A SOFA score of 7.23 ($\pm$ 4.1) was found to be associated with NCS (OR: 1.234, CI: 1.092-1.395) in patients with acute medical illness with the ROC curve showing an AUC value of 0.69 (*figure 2*). No significant association was seen between SOFA score and NCS in patients



■ **Figure 1.** (A) Pattern 1: generalized epileptiform discharges >2.5 Hz. (B) Pattern 2: repetitive ED <2.5 Hz over left frontal region with evolution into sharply contoured faster frequencies. (C) Pattern 3: LPDs over the left central-parietal region correlating with subtle oral chewing movements. EEG and clinical improvement was noted after IV Ativan challenge.



■ **Figure 2.** ROC curve of SOFA score as a predictor of NCS in patients with acute medical illness.

with acute brain injury (OR: 1.053, CI: 0.958-1.156). Among EEG variables, the presence of interictal epileptiform discharges (IEDs) (OR: 1.847; $p<0.0001$) and lateralized periodic discharges (LPDs) (OR: 5.563; $p<0.0001$) on cEEG were associated with NCS in our cohort. These results based on univariate regression analysis are summarized in *table 1*.

The ictal EEG Pattern 2 was the most commonly seen ictal EEG finding in patients with NCS (70.1%, *n*=40/57), followed by Pattern 3 (15.7%, *n*=9/57) and Pattern 1 (14.0%, *n*=8/57). A small group of patients had more than one studied ictal EEG pattern (12.2%, *n*=7/57); only the most frequent ictal pattern was included in our final analysis. In patients with acute brain injury, Pattern 2 (67.5%, *n*=27/40) was the most commonly seen ictal EEG finding, whereas for patients with underlying acute medical illness, Pattern 1 (62.5%, *n*=5/8) was more common. There was no statistical significant difference between underlying neurological versus medical etiologies ($p=0.27$) and the studied ictal patterns. Additionally, we found no statistically significant association between these patterns and in-hospital mortality or SOFA score (summarized in *table 2*).

Discussion

In this large single-center retrospective study of 487 hospitalized patients, we looked at the ictal EEG findings of non-convulsive seizures and classified these into three patterns as per the Salzburg criteria [6, 7]. We found that the ictal EEG Pattern 2, characterized as spatiotemporal evolution of epileptiform discharges at lower frequencies, was the most commonly recorded ictal pattern of NCS. In a similar study by Granner *et al.* [8], EEG patterns were evaluated and essentially classified similarly to those of our criteria; the authors noted that the majority of NCS were associated with discharge at less than 3 Hz. Another study by Gosavi *et al.* reported that 67.3% (37/55) of ictal EEG patterns in NCSE were regional, followed by generalized (18%) and multiregional (14.5%) [9]. They also reported that the ictal onset frequency in their series was evenly distributed across the cut-off of 8 Hz. None of these studies correlated these findings to etiology.

To the best of our knowledge, our study is the first of its kind that has evaluated the relationship of ictal patterns of NCS, using the Salzburg criteria, with underlying etiology and in-hospital mortality. Although we did not find a statistically significant association between the ictal patterns and underlying etiology, there was a trend for Pattern 2 to be associated with underlying acute brain injury. Additionally, our findings showed that there was no significant difference between the ictal patterns and underlying in-hospital mortality. This may be attributed to reported zero mortality among the groups with ictal Patterns 1 and 3. There was a comparable 10% in-hospital mortality between patients with or without NCS. These findings are likely a result of a low incidence of NCS in our cohort. Further studies with a larger sample of cases of non-convulsive seizures are needed to evaluate this further.

In our cohort of patients who underwent cEEG, NCS was recorded in 11.7% and NCSE in 4.1%. Similarly, in a large multicenter cohort study by Rodriguez Ruiz *et al.*, in which a total of 4,772 critically ill adult patients underwent cEEG, a comparable incidence of NCS was also reported [10]. However, in earlier literature reports, NCS or NCSE was seen in approximately 5-19% of patients with an incidence that varied based on the study population. NCS or NCSE is seen in 5% of patients with altered mental status presenting to the emergency department, but is reported in 9.8% of inpatient emergent EEGs [11, 12]. This number can increase to 14% in patients undergoing cEEG following convulsive status epilepticus [13]. Another study by Hirsch *et al.* has shown that nearly 19% of critically ill patients undergoing cEEG have subclinical seizures [14]. In our cohort of patients, we found a similar incidence of NCS but lower incidence of NCSE since we included all the patients who underwent cEEG

▼ **Table 1.** Clinical and EEG variables associated with NCS.

Variables	level	NCS=No (*n*=430)	NCS= Yes (*n*=57)	OR (95% CI)[a]	*p* value[b]
Sex	Female	206 (52.1)	24 (57.9)	1.000	0.41
	Male	224 (47.9)	33 (42.1)	1.124 (0.850, 1.487)	
History of epilepsy	No	357 (83.0)	44 (77.2)	1.000	0.28
	Yes	73 (17.0)	13 (22.8)	1.202 (0.861, 1.679)	
Structural lesion	No	179 (41.7)	21 (36.8)	1.000	0.482
	Yes	250 (58.3)	36 (63.2)	1.108 (0.833, 1.474)	
Clinical exam	Non-comatose	311 (72.5)	37 (64.9)	1.000	0.234
	Comatose	118 (27.5)	20 (35.1)	1.194 (0.892, 1.598)	
Etiology group	Acute Brain Injury	213 (49.8)	35 (61.4)	1.000	0.101
	Acute Medical illness	215 (50.2)	22 (38.6)	0.789 (0.595, 1.047)	
Organ failure	No	201 (46.7)	23 (40.4)	1.000	0.363
	Yes	229 (53.3)	34 (59.6)	1.139 (0.860, 1.509)	
Presence of IEDs	No	375 (87.2)	38 (66.7)	1.000	<0.001
	Yes	55 (12.8)	19 (33.3)	1.847 (1.355, 2.517)	
Presence of Periodic discharges	No	356 (82.8)	24 (42.1)	1.000	<0.001
	LPDs	21 (4.9)	26 (45.6)	18.365 (9.045, 37.287)	
	GPDs	53 (12.3)	7 (12.3)	1.959 (0.805, 4.771)	
Presence of LRDA	No	421 (98.1)	54 (94.7)	1.000	0.121
	Yes	8 (1.9)	3 (5.3)	1.710 (0.868, 3.370)	

monitoring for various indications, which ranged from evaluation of spells in healthy patients to an assessment of comatose and critically ill ICU patients. However, a similar lower frequency of NCSE was reported by Gosavi *et al*. [9] and Haffey *et al*. [15].

We found that lateralized periodic discharges (LPDs) and IEDs were significantly associated with NCS. These findings have been seen in other studies, such as those of Rodriguez Ruiz *et al*. and Singh *et al*. [10, 16, 17]. Our findings also indicate that a higher SOFA score was

▼ **Table 2.** Summary of study results.

	Ictal EEG pattern						
Variable	**Pattern 1: (*n*=8)**	**Pattern 2: (*n*=40)**	**Pattern 3: (*n*=9)**	**Overall *p* value**	**Pattern 1 vs 2**	**Pattern 1 vs. 3**	**Pattern 2 vs. 3**
Etiology				0.28	0.131	0.637	0.7
Acute brain injury	3 (37.5%)	27 (67.5%)	5 (55.5%)				
Acute medical illness	5 (62.5%)	13 (32.5%)	4 (44.5%)				
SOFA scale	6.25 ± 3.24	5.05 ± 3.92	7.67 ± 4.18	0.145	0.31	0.466	0.069
In-hospital mortality				0.51	0.571	1.0	0.576
No	8 (100%)	34 (85%)	9 (100%)				
Yes	0 (0%)	6 (15%)	0 (0%)				

associated with NCS in patients with underlying acute medical illness. Severe organ failure is generally associated with inflammatory cytokine release, causing blood brain barrier disruption and secondary brain dysfunction [18, 20], which could potentially lead to seizure generation in critically ill patients. Interestingly, studies by Tummala *et al*. [18] in critically ill cancer patients and Hirsch *et al*. [19] in patients with sepsis reported a lower SOFA score in patients with NCS. In our study, we did not subtract GCS (Glasgow coma scale) from the total SOFA score which may have had some influence regarding the neurological component on total SOFA score. Hence, more data with prospective studies is needed to determine this association and develop a predication model for NCS in critically ill patients.

Our study has several limitations based on its retrospective methodology. We excluded patients with anoxic brain injury from our analysis due to the uncertainty of the clinical significance of NCS in this population which may explain the lower incidence of ictal Pattern 1. The lower incidence of Pattern 3 may be due to the difficulty in determining the timing of administration of antiseizure medications and subsequent clinical improvement in conjunction with the use of EEG. Additionally, due to the small sample size, we dichotomized our etiologies and were therefore unable to determine associations with specific etiologies within these groups. We did not quantify seizure burden which has been reported to have a negative impact on outcome [20]. Lastly, the effect of treatment on EEG cannot be excluded and may have influenced the ultimate rate of EEG findings and prevalence of NCS. Since the completion of this study, ACNS Critical Care EEG Terminology was revised in 2021 which now includes a criterion for NCSE that we did not implement.

Conclusion

Spatiotemporal evolution of epileptiform discharges was the most commonly recorded ictal EEG pattern in our cohort. We did not find any significant association between studied ictal EEG patterns and underlying etiology, however, further prospective studies with a larger sample size of patients with NCS may provide valuable clinical data that could be used to evaluate the etiologic correlate of the various ictal EEG patterns and their effect on patient outcome. ■

Disclosures.
None of the authors have any conflict of interest to declare.

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