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# The EEG Ictal–Interictal Continuum—A Metabolic Roar But a Whimper of a Functional Outcome

## Lateralized Periodic Discharges Frequency Correlates With Glucose Metabolism

Subramaniam T, Jain A, Hall LT, Cole AJ, Westover MB, Rosenthal ES, Struck AF. *Neurology*. 2019;92(7):e670-e674.

Objective: To investigate the correlation between characteristics of lateralized periodic discharges (LPDs) and glucose metabolism measured by (18)F-fluorodeoxyglucose (FDG)-positron emission tomography (PET). Methods: We retrospectively reviewed medical records to identify patients who underwent FDG-PET during electroencephalography (EEG) monitoring with LPDs present during the FDG uptake period. Two blinded board-certified neurophysiologists independently interpreted EEGs. (18)F-fluorodeoxyglucose uptake was measured using standardized uptake value (SUV). Structural images were fused with PET images to aid with localization of SUV. Two PET readers independently measured maximum SUV. Relative SUV values were obtained by normalization of the maximum SUV to the SUV of pons (SUVRpons). Lateralized periodic discharge frequency was analyzed both as a categorical variable and as a continuous measure. Other secondary variables included duration, amplitude, presence of structural lesion, and "plus" EEG features such as rhythmic or fast sharp activity. Results: Nine patients were identified and 7 had a structural etiology for LPDs. Analysis using frequency as a categorical variable and continuous variable showed an association between increased LPD frequency and increased ipsilateral SUVRpons ($P = .02$). Metabolism associated with LPDs (0.5 Hz as a baseline) increased by a median of 100% at 1 Hz and for frequencies $>1$ Hz increased by a median of 309%. There were no statistically significant differences in SUVRpons for other factors including duration ($P = .10$), amplitude ($P = .80$), structural etiology ($P = .55$), or "plus" features such as rhythmic or fast sharp activity ($P = .84$). Conclusions: Metabolic activity increases monotonically with LPD frequency. Lateralized periodic discharge frequency should be a measure of interest when developing neuroprotection strategies in critical neurologic illness.

## Continuous Electroencephalography After Moderate to Severe Traumatic Brain Injury

Lee H, Mizrahi MA, Hartings JA, Sharma S, Pahren L, Ngwenya LB, Moseley BD, Privitera M, Tortella FC, Foreman B. *Crit Care Med.* 2019;47(4):574-582.

Objectives: After traumatic brain injury, continuous electroencephalography is widely used to detect electrographic seizures. With the development of standardized continuous electroencephalography terminology, we aimed to describe the prevalence and burden of ictal–interictal patterns, including electrographic seizures after moderate to severe traumatic brain injury, and to correlate continuous electroencephalography features with functional outcome. Design: Post hoc analysis of the prospective, randomized controlled phase 2 multicenter INTREPID study (ClinicalTrials.gov: NCT00805818). Continuous electroencephalography was initiated upon admission to the intensive care unit. The primary outcome was the 3-month Glasgow Outcome Scale–Extended. Consensus electroencephalography reviews were performed by raters certified in standardized continuous electroencephalography terminology blinded to clinical data. Rhythmic, periodic, or ictal patterns were referred to as "ictal–interictal continuum"; severe ictal–interictal continuum was defined as greater than or equal to 1.5 Hz lateralized rhythmic delta activity or generalized periodic discharges and any lateralized periodic discharges or electrographic seizures. Setting: Twenty US level I trauma centers. PATIENTS: Patients with nonpenetrating traumatic brain injury and post-resuscitation Glasgow Coma Scale score of 4 to 12 were included. Interventions: None. Measurements and main results: Among 152 patients with continuous electroencephalography (age $= 34 \pm 14$ years; 88% male), 22 (14%) had severe ictal–interictal continuum including electrographic seizures in 4 (2.6%). Severe ictal–interictal continuum burden correlated with initial prognostic scores, including the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury ($r = 0.51$; $P = .01$) and Injury Severity Score ($r = 0.49$; $P = .01$), but not with functional outcome. After controlling clinical covariates, unfavorable outcome was independently associated with absence of posterior dominant rhythm (common odds

ratio, 3.38; 95% confidence interval, 1.30-9.09), absence of N2 sleep transients (3.69; 1.69-8.20), predominant delta activity (2.82; 1.32-6.10), and discontinuous background (5.33; 2.28-12.96) within the first 72 hours of monitoring. Conclusions: Severe ictal–interictal continuum patterns, including electrographic seizures, were associated with clinical markers of injury severity but not functional outcome in this prospective cohort of patients with moderate to severe traumatic brain injury. Importantly, continuous electroencephalography background features were independently associated with functional outcome and improved the area under the curve of existing, validated predictive models.

## Commentary

The ictal–interictal continuum (IIC) encompasses electroencephalography (EEG) patterns that neither meet the criteria for seizures nor are purely interictal. There is general agreement that these include rhythmic or periodic discharges between 1 and 2.5 Hz, particularly those that are ictal appearing or with fluctuating frequency patterns. The more destructive of these, periodic discharges, have been described for over 50 years. They range from the highly destructive ictal, in a continuum to the relatively benign interictal without implication for ongoing brain injury.[1] There is still a lack of consensus regarding the optimal approach to treating them. Periodic discharges confined to a single hemisphere and referred to historically as periodic lateralized epileptiform discharges or more recently as lateralized periodic discharges (LPDs)[2] have the highest association with clinical and electrographic seizures.[3] Certain morphological characteristics[4] and increasing frequencies of these discharges increase the strength of this association.[3]

Recent standardization of the electrographic characterization of these periodic discharges through the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology has allowed for more systematic studies of these patterns.[2] Of particular interest is whether these discharges, occupying what is described as the IIC,[5] are independently associated with poor clinical outcome.

Several previous studies provide clues to the possible mechanisms tying these patterns to brain injury. In a study utilizing intracranial EEGs and microdialysis of patients with traumatic brain injury (TBI), periodic discharges were associated with elevated lactate/pyruvate ratios, suggesting a "metabolic crisis," predominated by impaired oxidative metabolism,[6] presumably due to increased metabolic demand that outstrips supply. Multiple studies have demonstrated that LPDs are associated with increased metabolism as demonstrated by increased glucose utilization on fluorodeoxyglucose positron emission tomography (PET). The lack of clinical symptoms with some of these LPDs has suggested that they may represent relatively benign phenomena. However, at least one study has implied that the anatomical location at an eloquent cortical region is in fact what differentiates symptomatic from asymptomatic LPDs.[7]

Two recent studies both illuminate and blur what we know—or thought we knew—regarding the patterns of the IIC. Subramaniam et al build on the concept of the link between LPDs and hypermetabolism by providing evidence of a robust dose response between the frequency of the discharges and degree of hypermetabolism. In a small retrospective study, they analyzed all patients with LPDs on continuous EEG monitoring who underwent a PET scan. Lateralized periodic discharge frequency was associated with metabolic activity in the same hemisphere, though not necessarily strictly in a superficial cortical region. Patients with LPDs discharging at 1 Hz and $>1$ Hz had FDG update that was 100% and 309% higher, respectively, than patients whose LPDs discharged at $<1$ Hz. The inference is that LPDs (particularly, presumably, with higher frequencies) should be more aggressively treated.

The strength of the study is that within their population, the effect size is substantial and, despite their small sample size, is quite convincing. There are several problems with this study that limit its generalizability. Firstly, the sample size is truly small, consisting of a total of 9 patients. As a retrospective study, it is virtually guaranteed that there was selection bias. Patients who underwent continuous EEG likely underwent PET scans because of suspicion that the LPDs were potentially highly epileptiform. Even a single patient whose study did not conform to the expected association between LPD frequency and increased metabolism may have resulted in nonsignificance of their main results. It is not stated at which time point of the patient's admission, in relation to the EEG, the PET scan was obtained, thus making the relationship between the 2 parameters more tenuous. The choice of parameters, while convenient for this population, does not necessarily examine the frequency changes of greatest interest, as other studies have suggested that an increase in risk of both seizures and potential hypoxic injury occurs at frequencies above 1.5 to 2 Hz.[3,8] There are certainly examples in the literature where LPDs at $\sim 1$ Hz are associated with clear hypometabolism,[9] thus raising the likelihood that the underlying pathophysiology of LPDs is heterogeneous, and do not necessarily result in the final pathway of increasing tissue metabolism, and by extension, ischemia, inflammation, or other features of the "metabolic crisis."

Nonetheless, within these significant limitations, it would seem reasonable that patients with LPDs with higher frequency discharges should raise alarm. The hope is that a change in intervention would result in an improvement in clinical outcome. However, in this respect, definitive evidence remains elusive.

Lee et al report a post hoc analysis of a large multicenter study of 155 patients with moderate to severe TBI who also obtained continuous EEG monitoring. Their goal was to determine what continuous EEG features were predictive of

long-term functional outcome. Ictal–interictal continuum patterns were categorized as severe versus nonsevere, and the burden of the IIC was estimated by the frequency of the IIC pattern multiplied by its duration. Approximately half of patients had patterns that were consistent with IIC, and about 15% had severe IIC. Outcome was evaluated at 3 months by the Glasgow Outcome Scale–Extended. The severity of the IIC was associated with the TBI severity measure. However, although functional outcome was associated with characteristics of EEG baseline and the presence of stage 2 sleep, it was not associated with either the severity or burden of IIC patterns.

This is the largest, most comprehensive study of patients with TBI and continuous EEG, correcting for known determinants of functional outcome; the results appear quite robust. The evaluation of both background and IIC on EEG was performed using standardized terminology. The fact that only approximately 60% of patients in this cohort obtained EEGs again leads to questions of selection bias, and indeed, the patients with more TBI were more likely to have obtained cEEG. If all patients were included, a significant univariate association with IIC may have been detected, though it is still doubtful whether it would have remained significant after accounting for other background cEEG features. It is also possible that cognitive changes more subtle than can be evaluated by their measure of functional outcome are associated.

Although no association between IIC patterns and functional outcome was found in this study, it is important to recall that this relationship has been demonstrated in other conditions such as subarachnoid hemorrhage[10]—though again, this has not been universally replicated.[11] Clearly more research is needed in determining the effect of IIC patterns. What is apparent, though, is that the mechanisms that produce IIC patterns are heterogeneous, and their effects likely dependent on the underlying neurological insult. Unfortunately, this does not allow treatment to be organized into simple principles based on data, and a large degree of individualized patient management algorithms may be necessary, as evidenced by several recent helpful guides.[12-14]

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