



ARTICLE OF THE MONTH

Movement on the Ictal Interictal Continuum

Witsch J, Frey HP, Schmidt JM, Velazquez A, Falo CM, Reznik M, Roh D, Agarwal S, Park S, Connolly ES, Claassen J. Electroencephalographic Periodic Discharges and Frequency-Dependent Brain Tissue Hypoxia in Acute Brain Injury. *JAMA Neurol.* 2017 Mar 1;74(3):301-309. PMID: 28097330

We are welcoming you to the April 2018 installment of SNACC's Article of the Month. This month's selection addresses a topic in the field of neuroscience and discusses the relevance of periodic discharges seen on EEG in the intensive care setting.

The article was selected and expert commentary was provided by Jeffrey Kennedy, MD. Dr. Kennedy is an assistant professor of neurology at University of California Davis School of Medicine. He is an epileptologist and neurophysiologist whose research interests include the use of ICU EEG monitoring and understanding the basic cortical and autonomic neurophysiology of seizures.

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~ Nina Schloemerkerper, MD, Adrian Pichurko, MD, and Oana Maties, MD

Commentary

Jeffrey Kennedy, MD

Over the past few decades, continuous EEG monitoring (cEEG) has become routinely incorporated into the evaluation of patients admitted to neurologic intensive care units, detecting seizures in 10-48% of patients, a high proportion of which are nonconvulsive and only identified with cEEG.¹ The rate of seizure detection is primarily influenced by the diagnosis leading to neurological ICU admission and level of arousal.¹ Seizures and status epilepticus are associated with worse prognosis and functional outcome.²⁻⁴

cEEG frequently reveals periodic and rhythmic patterns, such as periodic discharges (PDs), which do not meet the criteria required to be classified as seizures.⁵ They are often referred to as lying on an ictal interictal continuum. When faced with these findings of indeterminate significance, many clinicians treat patients with a trial of short acting benzodiazepines and/or administer antiseizure medications. However, there may not be clear clinical improvement or sustained resolution of the EEG pattern.⁶ Seeking evidence to determine if these patterns are associated with physiology similar to seizures, contributing to depressed level of consciousness, or contributing to cerebral injury, clinicians may obtain further studies. These include neuron specific enolase and glial fibrillary acidic protein analysis or performing MRI or functional imaging to support considerations for more aggressive treatments of the underlying brain injury and antiseizure therapies.

Investigators have begun utilizing intracranial depth EEG electrodes (dEEG) and performing multimodality monitoring (MMM) of cerebral physiology to facilitate early recognition of pathological changes. MMM includes techniques such as intracranial pressure (ICP), cerebral perfusion pressure (CPP), regional cerebral blood flow (CBF), partial pressure in interstitial oxygen (PbtO₂), jugular venous oximetry, and microdialysis measurements of brain metabolism.⁷ Animal models and studies of patients with severe traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), have demonstrated measurable changes during seizures including reduced PbtO₂, elevation in ICP, microdialysis metabolic crisis, and delayed increase in CBF.^{8,9} Detection of these fluctuations may provide physicians with a more definitive indication to treat patients and reduce secondary brain injury. However, unexplained MMM changes are common⁹ and therefore challenging to guide treatment.

To evaluate seizures and periodic discharges occurring on cEEG and dEEG and their association with metabolic crises, Vespa *et al.*¹⁰ evaluated 34 consecutive severe TBI patients with cEEG, dEEG and MMM including microdialysis. Seizures and PDs occurred in 61% of patients, 42.9% of which were seen only on dEEG. MMM demonstrated a significant association of metabolic crisis (elevated lactate/pyruvate ratio and decreased extracellular glucose) occurring with seizures and PDs when compared to patients without these discharges, implicating a pathologic physiology in both seizures and PDs.

In this study, Witsch *et al.*¹¹ investigated the association of seizures, PDs, and MMM in 90 consecutive patients with high grade spontaneous subarachnoid hemorrhage utilizing cEEG, dEEG, and MMM (ICP, PbtO₂, and regional CBF). The authors hypothesized that ictal interictal continuum patterns (PDs) cause tissue hypoxia which may lead to additional brain injury. They also tested hypotheses that higher frequencies of PDs and PDs with larger detected fields (generalized vs lateralized) are associated with more significant metabolic stress.

Fifty-three patients (59%) were found to have PDs, 40% of which were only seen on dEEG. Twenty-eight patients (31%) had seizures, 68% of which were only seen on dEEG. The authors evaluated MMM findings associated with PDs, finding a significant decrease in brain tissue oxygenation (PbtO₂) if the PD frequency was greater than 2.0 Hz. The investigators observed that PbtO₂ began to decrease approximately five minutes before the onset of PDs of at least 2.0 Hz and significantly decreased five-ten minutes after the onset of PDs. No difference in PbtO₂ was detected when comparing lateralized and generalized PDs of 2.0 Hz or greater. They also reported a trend of increasing CBF corresponding with increasing frequency of PDs until 2.0 Hz. No statistically significant change in ICP or CPP was observed. The authors hypothesized that CBF increased as compensation for physiologic stress and oxygen demand until PDs increased beyond 2.0 Hz, indicating a potential threshold. This study provides evidence that periodic discharges with frequencies greater than 2.0 Hz are associated with pathophysiologic changes similar to those in seizures, and potentially having more clinical significance than those with less than 2.0 Hz. Additional studies are needed to determine if higher frequency periodic discharges pose higher risks and if there is more benefit from therapeutic intervention.

These studies provide insight into the significance of ictal interictal continuum patterns, linking PDs to dEEG seizures and pathophysiologic cerebral metabolism. Additional studies may demonstrate if they are symptomatic of brain injuries and if they contribute to metabolic demand and worsening injury. Further studies are required to determine if these can be considered reliable biomarkers of evolving brain injury and indicators for treatment intervention directed toward the underlying brain injury and antiseizure medications to reduce injury and improve outcomes.

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