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# Effect of epileptiform abnormality burden on neurologic outcome and antiepileptic drug management after subarachnoid hemorrhage

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## HIGHLIGHTS

- Higher epileptiform abnormality burden is associated with worse outcomes in subarachnoid hemorrhage.
- Epileptiform abnormalities are frequently treated with anti-epileptic drugs.
- Prospective studies are needed to delineate the clinical risks and benefits of treatment.

## ABSTRACT

*Objective:* To quantify the burden of epileptiform abnormalities (EAs) including seizures, periodic and rhythmic activity, and sporadic discharges in patients with aneurysmal subarachnoid hemorrhage (aSAH), and assess the effect of EA burden and treatment on outcomes.
*Methods:* Retrospective analysis of 136 high-grade aSAH patients. EAs were defined using the American Clinical Neurophysiology Society nomenclature. Burden was defined as prevalence of <1%, 1–9%, 10–49%, 50–89%, and >90% for each 18–24 hour epoch. Our outcome measure was 3-month Glasgow Outcome Score.
*Results:* 47.8% patients had EAs. After adjusting for clinical covariates EA burden on first day of recording and maximum daily burden were associated with worse outcomes. Patients with higher EA burden were more likely to be treated with anti-epileptic drugs (AEDs) beyond the standard prophylactic protocol. There was no difference in outcomes between patients continued on AEDs beyond standard prophylaxis compared to those who were not.
*Conclusions:* Higher burden of EAs in aSAH independently predicts worse outcome. Although nearly half of these patients received treatment, our data suggest current AED management practices may not influence outcome.
*Significance:* EA burden predicts worse outcomes and may serve as a target for prospective interventional controlled studies to directly assess the impact of AEDs, and create evidence-based treatment protocols.


*Abbreviations:* AED, anti-epileptic drugs; ACNS, American Clinical Neurophysiology Society; APACHE II, Acute Physiology and Chronic Health Evaluation II; aSAH, aneurysmal subarachnoid hemorrhage; BID, bis in die; BIPDs, bilateral independent periodic discharges; cEEG, continuous electroencephalogram; DCI, delayed cerebral ischemia; EAs, Epileptiform abnormalities; EEG, electroencephalogram; GOS, glasgow outcome score; GRDA, generalized rhythmic delta activity; GPDs, generalized periodic discharges; HAI, hospital acquired infection; HAP, hospital acquired pneumonia; HH, Hunt and Hess; IIC, ictal-interictal continuum; LPDs, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; NMDA, N-methyl-D-aspartate; SHOP, Subarachnoid Hemorrhage Outcomes Project.

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## 1. Introduction

Epileptiform abnormalities (EAs) including seizures, periodic and rhythmic patterns, and sporadic discharges are seen in electroencephalogram (EEG) recordings in up to 20% percent of patients with aneurysmal subarachnoid hemorrhage (aSAH) (Claassen et al., 2006). The presence of periodic discharges and seizures has been linked to worse functional and cognitive outcomes (Claassen et al., 2006; De Marchis et al., 2016). Nevertheless, there is limited and conflicting data on how the burden and subtype of EAs influence outcome in patients with aSAH (Crepeau et al., 2013).

With the publication of consensus recommendations and increased application of continuous electroencephalogram (cEEG) monitoring in critically ill patients, the diagnosis of seizures and other EAs is increasing (Sutter et al., 2011; Claassen et al., 2013; Ney et al., 2013). In a large series of critically ill mechanically ventilated patients in the US, use of cEEG increased by 33% per year on average, and the number of hospitals using cEEG doubled between 2005 and 2009 (Ney et al., 2013). Anti-epileptic drugs (AEDs) are frequently prescribed not only for seizures but also for other EAs, despite absence of data on clinical response to treatment or effect of treatment on short and long-term neurologic outcomes (Sivaraju and Gilmore, 2016).

The primary objective of our study is to investigate the dose-response relationship between epileptiform abnormalities and outcomes in patients with aneurysmal subarachnoid hemorrhage. Our secondary objective is to define AED prescription practices, and assess whether our data provide evidence that treatment improves outcomes.

## 2. Materials and methods

### 2.1. Study design

This is a retrospective cohort study of patients from the MGH aneurysmal subarachnoid hemorrhage (aSAH) database admitted between September 2011 and February 2016. The study was conducted under a protocol approved by the Institutional Review Board. Informed consent was not required for this retrospective study. The aSAH database includes patients with high grade aSAH ($\geq$Hunt and Hess 3 and $\geq$Fisher 3) or who undergo continuous EEG or multimodality monitoring. All patients with age >18 years, an identified aneurysm, and continuous EEG monitoring for >18 hours were included. We excluded non-aneurysmal SAH, including SAH caused by trauma or other vascular malformations. Presence of aneurysms was confirmed by computed tomography and conventional angiography.

### 2.2. Clinical covariates

Demographic and clinical variables were abstracted from the electronic health record. Clinical covariates included the Hunt and Hess (HH) and Fisher scores, admission Acute Physiology and Chronic Health Evaluation II (APACHE II) score, aneurysm treatment modality, occurrence of re-bleed, treatment with AEDs, use and duration of mechanical ventilation and duration of ICU stay. Per institutional protocol, AED prophylaxis was continued until the aneurysm was secured or for 7 days post craniotomy. Unless contraindicated, levetiracetam was the prophylactic AED of choice. Patients were coded as having been treated with AEDs if they were continued for longer than the protocol standard. In addition, we recorded time points at which AED doses were either escalated or decreased. Primary indications for AED continuation were: clinical seizures, and/or scalp or depth seizures, periodic and rhythmic patterns or sporadic discharges, at the treating physicians discretion. Additional or alternate AEDs, frequently phenytoin and lacosamide, were used for refractory seizures or other persistent EAs at the treating physician's discretion. Routine prophylactic dose for levetiracetam was 500 mg BID. If treatment was escalated, standard levetiracetam dose ranged from 750 mg BID to a maximum of 2000 mg BID. The typical loading dose for phenytoin was 20 mg/kg, and maintenance dose was titrated to a phenytoin level of 10–20 ug/ml. If given as a load, the typical loading dose for lacosamide was 400 mg, and maintenance dose was 100–200 mg BID.

Delayed complications that we studied included delayed cerebral ischemia (DCI) and hospital acquired infections (HAI), including hospital acquired pneumonia (HAP). Two neurologists independently determined whether each patient developed DCI, defined using published consensus guidelines (Vergouwen et al., 2010). Inter-rater agreement of independent review was excellent (95.83%) for overall agreement on the presence or absence of any delayed ischemic events (Zafar et al., 2016). Any disagreements were further adjudicated following a published protocol (Zafar et al., 2016). HAIs were confirmed by positive cultures or radiographic and clinical evidence of a respiratory tract infection.

### 2.3. cEEG protocol and EEG features

The institutional protocol recommends 10 days of cEEG monitoring for ischemia detection in high grade ($\geq$HH3F3) patients. Additionally, patients with suspected subclinical seizures underwent cEEG monitoring for variable duration as indicated. All cEEG recordings were obtained using 21 electrodes and the conventional International 10–20 system. Raw EEG data was reviewed and reported by 2 clinical neurophysiologists per institutional protocol. EEG reports were updated at least twice daily. A board certified neurologist and clinical neurophysiologist (SFZ) with certification in the American Clinical Neurophysiology Society EEG terminology exam administered by the Critical Care EEG Monitoring Research Consortium (Hirsch et al., 2013) reviewed all the EEG reports for abstraction and independently reviewed raw cEEG data to confirm appropriate designation of EAs. This reviewer was blinded to outcomes at the time of EEG review.

Epileptiform abnormalities (EAs) were defined as seizures, periodic and rhythmic patterns and sporadic discharges. Periodic and rhythmic patterns, and sporadic discharges were defined using the American Clinical Neurophysiology Society (ACNS) nomenclature (Hirsch et al., 2013). The ACNS recognizes the following EEG patterns: lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), generalized periodic discharges (GPDs), lateralized rhythmic delta activity (LRDA), generalized rhythmic delta activity (GRDA), and sporadic discharges. Electrographic seizures were defined as spikes, sharp waves, sharp-slow wave complexes, or rhythmic activity lasting at least 10 seconds at a frequency of 3 Hz or more, or patterns with lower frequencies with evolution in frequency, morphology, or location (De Marchis et al., 2016).

### 2.4. EA Burden: per epoch, and overall exposure

Burden of EAs in any single 18–24 hour epoch was quantified based on the fraction of time during the epoch occupied by the pattern, using ACNS terminology: *rare*: <1%, *occasional*: 1–9%, *frequent*: 10–49%, *abundant*: 50–89%, *continuous*: $\geq$90% (Hirsch et al., 2013). For each 18–24 h epoch of recording, we recorded EA pattern types and burden.

The overall EA exposure or burden over the entire course of cEEG monitoring does not have a standardized definition. We therefore examined three alternative formulations as quantitative markers of the overall EA burden for each patient: