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Epileptiform abnormalities predict delayed cerebral ischemia in subarachnoid hemorrhage

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HIGHLIGHTS

- Ictal-interictal continuum abnormalities (IICAs) are common after subarachnoid hemorrhage (SAH).
- IICAs are associated with higher risk for delayed cerebral ischemia (DCI), especially if they emerge late in the acute period after SAH.
- Quantification of IICA features may assist in the development of an algorithm to predict DCI risk.

ABSTRACT

Objective: To identify whether abnormal neural activity, in the form of epileptiform discharges and rhythmic or periodic activity, which we term here ictal-interictal continuum abnormalities (IICAs), are associated with delayed cerebral ischemia (DCI).
Methods: Retrospective analysis of continuous electroencephalography (cEEG) reports and medical records from 124 patients with moderate to severe grade subarachnoid hemorrhage (SAH). We identified daily occurrence of seizures and IICAs. Using survival analysis methods, we estimated the cumulative probability of IICA onset time for patients with and without delayed cerebral ischemia (DCI).
Results: Our data suggest the presence of IICAs indeed increases the risk of developing DCI, especially when they begin several days after the onset of SAH. We found that all IICA types except generalized rhythmic delta activity occur more commonly in patients who develop DCI. In particular, IICAs that begin later in hospitalization correlate with increased risk of DCI.
Conclusions: IICAs represent a new marker for identifying early patients at increased risk for DCI. Moreover, IICAs might contribute mechanistically to DCI and therefore represent a new potential target for intervention to prevent secondary cerebral injury following SAH.
Significance: These findings imply that IICAs may be a novel marker for predicting those at higher risk for DCI development.

1. Introduction

Subarachnoid hemorrhage (SAH) patients are at risk for early and late post-hemorrhage complications, including seizures, rebleeding and delayed cerebral ischemia. Among these, delayed cerebral ischemia (DCI) is the primary source of long-term neurologic disability (Hijdra et al., 1986; Roos et al., 2000; Dupont et al., 2010; Vergouwen et al., 2011; Rowland et al., 2012; Sánchez-Porras et al., 2013). Until recently most believed that DCI is caused by vasospasm of large cerebral arteries (Rowland et al., 2012). Consequently, transcranial doppler (TCD) monitoring to detect signs of vasospasm has been the chief modality for predicting DCI (Suarez et al., 2002; Naqvi et al., 2013).

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However, increasing evidence shows that vasospasm alone predicts DCI poorly, and that other factors contribute to its development (Dreier et al., 2009, 2013a; Rowland et al., 2012; Woitzik et al., 2012). The post-SAH injured brain is often in a state of metabolic crises, in which a tenuous balance of low metabolic reserve coexists with increased metabolic demand (Macdonald, 2014; Chung et al., 2016). If this increased demand can be met, then further injury may be avoided; otherwise, secondary brain injury ensues. We term this framework for understanding secondary brain injury the "metabolic supply–demand mismatch hypothesis for DCI".

Seizures and to an even greater extent cortical spreading depolarizations (CSDs) increase metabolic demand (Dreier et al., 2013b). To meet this increased energy demand, cerebral blood flow in the healthy brain typically increases. However, this neurovascular coupling can be disturbed in the injured brain. In a rat model of SAH, CSDs are capable of causing a severe ischemic (inverse neurovascular) response that spreads together with the depolarization wave in brain tissue, a phenomenon known as spreading ischemia (Dreier et al., 1998). Spreading ischemia can aggravate the degree of ischemia already present in the injured brain (Shin et al., 2006; Strong et al., 2007; Bere et al., 2014), or can start from a relatively normal level of cerebral blood flow (Dreier et al., 1998). There are a number of different patterns and hybrid phenomena between CSDs and electrographic seizures (see for example, Fig. 1 in Fabricius et al. or Fig. 2 in Dreier et al. (2012)), and in animals epileptiform activity is capable of triggering CSDs (Koroleva and Bures, 1983). Recent studies have shown that the reverse phenomenon can also be observed such that CSDs can trigger epileptiform discharges, possibly via facilitating synchrony (Eickhoff et al., 2014). The foregoing discussion highlights a series of complex links from CSD and (although less well studied) epileptiform abnormalities to secondary brain injury following SAH (Dreier et al., 2009; Claassen et al., 2013).

Continuous electroencephalography (cEEG) is increasingly used to monitor for early signs of DCI. Several groups have found that pathological low frequency activity increases and normal higher frequency activity decreases hours to days before DCI (Claassen et al., 2004a, 2005; Stuart et al., 2010; Foreman and Claassen, 2012; Gollwitzer et al., 2015). Seizures occur in approximately 10–15% of SAH cases, and recent studies suggest that longer or more frequent seizures lead to worse outcomes (Claassen et al., 2013; De Marchis et al., 2016).

Less is known about ictal-interictal continuum abnormalities (IICAs), which include sporadic epileptiform discharges (spikes and sharp waves), periodic epileptiform discharges, and rhythmic patterns (Sivaraju and Gilmore, 2016). IIICAs share some features with seizures and are common in all types of acute brain injury, including ischemic stroke, but their significance is less clear (de Curtis and Avanzini, 2001; Claassen et al., 2004a; Chong and Hirsch, 2005; Staley et al., 2011; Maciel and Gilmore, 2016). Critically ill patients with periodic discharges tend to have poorer outcomes in some studies, though not consistently (Pohlmann-Eden et al., 1996; Claassen et al., 2006; Ong et al., 2012; Crepeau et al., 2013; Punia et al., 2015). The presence of early epileptiform abnormalities makes subsequent electrographic seizures more likely (Shafi et al., 2012; Westover et al., 2015). However, the time course of epileptiform abnormalities and its impact on secondary neuronal injury has yet to be explored.

Evidence suggests that lateralized periodic discharges (LPDs) originate from the peri-lesional zone (Schwartz et al., 1973). Indirect observations indicate that LPDs increase local cerebral blood flow and cause focal hypermetabolism on PET imaging and microdialysis recordings of lactate/pyruvate ratios (Theodore et al., 1983; Pohlmann-Eden et al., 1996; Struck et al., 2016; Vespa et al., 2016). These studies suggest that, like CSDs, abnormal neural activity is metabolically taxing.

In light of these observations, we hypothesize that IICAs are associated with increased risk of DCI in SAH patients, perhaps via increased metabolic stress (directly or indirectly, e.g. via triggering CSDs) on the injured brain. Two testable predictions of this hypothesis are that IICAs will be more common in SAH patients with DCI, and that IICAs will generally precede DCI. To test these predictions, we compared the prevalence and time-course of IICAs in patients with and without DCI.

2. Methods

2.1. Study population

We evaluated EEG reports and medical records from 124 consecutive ICU patients at a tertiary care center (Massachusetts General Hospital Neurosciences ICU) who met study inclusion criteria between September 2011 and January 2015. Inclusion criteria were: age $\geqslant$18 years; Hunt Hess 4–5 or Fisher group 3 non-traumatic SAH; continuous EEG data (cEEG) was available lasting at least 24 h; and cEEG monitoring had not been discontinued more than 24 h before any clinically diagnosed DCI events. We excluded patients who developed status epilepticus (convulsive or non-convulsive). EEG monitoring for ischemia detection was performed as part of a clinical protocol in all Hunt Hess 4–5 and Fisher group 3 patients as part of routine medical care. The recommended protocol was to begin recording within 48 h of admission and continue for 10 days, although clinicians were allowed to override the recommended duration if they felt it would interfere with clinical care. In practice, the median duration (±standard deviation) of recordings was 7 (±3.1) days with a median start date of 2 (±1.8) days post-SAH. Retrospective collection and analysis of clinical data was performed under a protocol approved by the local institutional review board.

2.2. EEG recordings

cEEG data was recorded using conventional 10–20 scalp electrode placement.

2.3. EEG report review

Interictal continuum abnormalities were classified according to standardized, validated nomenclature (Mani et al., 2012; Hirsch et al., 2013) as: seizures, sporadic epileptiform discharges (EDs), lateralized or generalized periodic discharges (LPDs and GPDs), lateralized or generalized rhythmic delta activity (LRDA and GRDA). The presence or absence of these abnormalities on each day as documented in the daily clinical EEG reports was tallied for each patient with "day of bleed" marked as day 0.

2.4. DCI classification

DCI events were diagnosed according to an international consensus definition (Vergouwen et al., 2010) as either (1) new focal neurologic deficits and/or decrease in the Glasgow Coma Scale of at least 2 points, persisting for a minimum of one hour, not explained by other causes (e.g. complications of a procedure, spike in intracranial pressure, re-rupture, hydrocephalus, seizures, systemic or metabolic abnormalities) by means of clinical assessment, imaging or laboratory data, or (2) the presence of cerebral infarction on CT or MRI imaging of the brain that was not present on any neuroimaging done within the first 48 h following early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment.

DCI diagnoses using this definition were determined using a multi-step process of (1) prospective daily structured research coordinator interview with the clinical team, (2) independent med-