High epileptiform discharge burden predicts delayed cerebral ischemia after subarachnoid hemorrhage


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Highlights

- Epileptiform discharges (ED) increase after subarachnoid hemorrhage during the high risk delayed cerebral ischemia (DCI) time-frame.
- Quantitative ED burden is higher in those who develop DCI compared to those who do not.
- ED burden can be used as a marker of DCI risk for automated prediction algorithm development.

Abstract

Objective: To investigate whether epileptiform discharge burden can identify those at risk for delayed cerebral ischemia (DCI) after subarachnoid hemorrhage (SAH).

Methods: Retrospective analysis of 113 moderate to severe grade SAH patients who had continuous EEG (cEEG) recordings during their hospitalization. We calculated the burden of epileptiform discharges (ED), measured as number of ED per hour.

Results: We find that many SAH patients have an increase in ED burden during the first 3–10 days following rupture, the major risk period for DCI. However, those who develop DCI have a significantly higher hourly burden from days 3.5–6 after SAH vs. those who do not. ED burden is higher in DCI patients when assessed in relation to the onset of DCI (area under the receiver operator curve 0.72). Finally, specific trends of ED burden over time, assessed by group-based trajectory analysis, also help stratify DCI risk.

Conclusions: These results suggest that ED burden is a useful parameter for identifying those at higher risk of developing DCI after SAH. The higher burden rate associated with DCI supports the theory of metabolic supply-demand mismatch which contributes to this complication.

Significance: ED burden is a novel biomarker for predicting those at high risk of DCI.

1. Introduction

Delayed cerebral ischemia (DCI) is a leading complication following aneurysmal subarachnoid hemorrhage (SAH) (Dupont et al., 2010; Rowland et al., 2012; Vergouwen et al., 2011). Progress in preventing DCI that leads to improved outcomes has stagnated, due in part to challenges identifying those at high risk early after ictus. Transcranial doppler remains the standard of care for DCI detection (Naqvi et al., 2013; Suarez et al., 2002), but has limited sensitivity and specificity (Carrera et al., 2009; Kumar et al., 2016), and poor time resolution in that they are typically performed once or twice daily. There is also growing evidence that large vessel vasospasm is only one of several causes of DCI (Dreier et al., 2013; 2009; Rowland et al., 2012; Woitzik et al., 2012). Thus, other diagnostic modalities are needed to more broadly monitor for impending DCI.

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Continuous EEG (cEEG) is increasingly used to monitor for early signs of DCI. Pathological low frequency spectral activity increases and higher frequency activity decreases hours to days prior (Claassen et al., 2005; 2004; Gollwitzer et al., 2015; Rots et al., 2016; Stuart et al., 2010; Vespa et al., 1997). Less is known about epileptiform abnormalities, which include sporadic epileptiform discharges (spikes and sharp waves), periodic discharges, and lateralized rhythmical delta activity (Sivaraju and Gilmore, 2016). We previously showed that late onset epileptiform discharges are associated with increased DCI risk (Kim et al., 2017; Rosenthal et al., 2018). We proposed that these abnormalities worsen metabolic supply-demand mismatch in an already injured brain leading to secondary ischemia. It is unknown whether specific features of these epileptiform abnormalities further inform DCI risk. Burden of seizures and frequency (per second) of periodic discharges have been linked to worsened neurologic outcomes (De Marchis et al., 2016; Vespa et al., 2016; Witsch et al., 2017). However, the association between burden of epileptiform discharges and DCI has not yet been characterized. Assessing features of these abnormalities, such as sporadic and periodic epileptiform discharge (ED) burden, by manually marking discharges in multi-day recordings is untenable. By utilizing automated detection of these ED (Scheuer et al., 2017) we investigated whether ED burden over time differentiates those who do vs do not develop DCI.

2. Methods

2.1. Study population

We evaluated EEG reports and medical records from intensive care unit patients at a tertiary care center (Massachusetts General Hospital Neurosciences intensive care unit) who met study inclusion criteria between September 2011 and January 2015. Inclusion criteria were (previously published (Kim et al., 2017)): age ≥ 18 years; Hunt Hess 4–5 or Fisher grade 3 SAH; cEEG data was available lasting at least 24 hours; and cEEG monitoring was not discontinued more than 24 hours before any clinically diagnosed DCI events. We excluded one patient who developed status epilepticus (defined as ≥ 5 minutes of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures (Brophy et al., 2012)) because mechanisms of secondary brain injury in frank status epilepticus may be distinct. cEEG monitoring for ischemia detection was performed as part of routine clinical care which entailed recording within 48 hours of admission and continuing for 10 days, unless otherwise indicated. Retrospective collection and analysis of clinical data was performed under a protocol approved by the local institutional review board.

2.2. EEG recordings

Continuous EEG data was recorded using the International 10–20 scalp electrode placement (19 electrodes).

2.3. EEG ED identification

EEG data was processed using Persys 13 (Persyst Development Corporation, San Diego) spike detection software, which has been validated against interrater agreement amongst EEG technologists (Scheuer et al., 2017). ED burden was calculated as number of discharges (sporadic or periodic) detected per hour. We compared ED burden between those who did and did not develop DCI over time.

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, sedation, spike in intracranial pressure, re-rupture, hydrocephalus, 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, acquired at the discretion of the clinical team, that was not present on any neuroimaging done within the first 48 hours following early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment.”

As previously described (Kim et al., 2017), we used the above DCI definition and assessed patients via: “(1) prospective daily structured research coordinator interview with the clinical team, (2) independent medical record review by three of the authors (ESR, MBW, SFZ) blinded to cEEG findings, (3) consensus adjudication by the same three authors in cases of uncertainty or disagreement. If a patient experienced a DCI event at any point during hospitalization, this was documented, even if after cessation of cEEG recording. Patients with DCI events occurring > 24 hours after discontinuation of cEEG monitoring were excluded (see Study Population above).”

2.5. Data analysis

For data analysis we used Matlab (MathWorks; Natick, MA) and STATA (Statcorp, College Station, TX). To investigate the relationship between ED and DCI, we separated cases into those who did and did not develop DCI and calculated the mean frequencies and standard error of each group. We winsorized the data for outliers above and below the 5% limits of the population (Frey, 2018). For cumulative ED burden, each patient’s ED burden was summed progressively over each hour. When a patient was disconnected from EEG, the final recorded cumulative ED value was carried forward to day 15, to not alter the trajectory of the population average cumulative curve. Mean and standard error were calculated for hourly and cumulative ED burden and compared by t-test. Area under the receiver operator curves (AUC) were also calculated hourly. These calculations were made based on data aligned from day of SAH and relative to the day of DCI. Spline smoothing was applied with a parameter of 0.001. Sensitivity and specificity for all ROC curves were calculated based on the optimal threshold (i.e. threshold value with the highest Youden’s J value, J = sensitivity + specificity − 1). To generate comparisons relative to the day of DCI between DCI and non-DCI patients, we first identified each DCI patient and found their cEEG start time and DCI onset time. Then we searched all non-DCI patients to determine who had recordings during that same time frame. This process was repeated iteratively for each DCI patient, such that multiple controls were matched to each DCI patient and each non-DCI patient could be re-used to match multiple DCI patients. Finally, we used group-based trajectory modeling (Elmer et al., 2018; Nagin, 2014), to identify distinct polynomial trajectories of ED burden over time. We scaled hourly ED burden to 0 to 1 and fit our model using a beta distribution (Elmer et al., 2018). We assigned each patient to a single trajectory group based on the maximal posterior probability of group membership after all available data were modeled. We then determined if trajectory group membership was associated with DCI. 2-tailed Freeman Halton extension of Fisher’s exact test was used to test significance of group separation.
2.6. Data availability

Data are available upon request.

3. Results

We found 113 patients who met our inclusion criteria, 58 of whom developed DCI. Mean age of the total cohort is 56 ± 14 years old. And 79 of the patients (70%) were female. Seven patients had seizures on EEG. The median time to DCI was 6.5 ± 3.4 days.

3.1. Hourly ED burden after SAH

ED burden was significantly higher in patients with DCI compared to those without DCI. Temporal raster plots show ED burden of each patient from the day of SAH with darker shading corresponding to higher frequencies (Fig. 1a). The ED detection algorithm detected at least one ED during recording in all patients. The median duration (±standard deviation) of recordings across all patients was 7 (±3.1) days with a median start time of 2 (±1.8) days post-SAH. The mean ED burden was significantly higher in DCI vs non-DCI patients from day 3.5 to day 6 (black bars; t-test, p = 0.05) after SAH (Fig. 1b). Evaluating AUC generated each hour after SAH, we found the maximum AUC within the first 6 days of SAH to range from 0.61–0.62 at 3.5–5.3 days after SAH. The optimum threshold sensitivity and specificity were 0.6 and 0.7, respectively.

3.2. Cumulative ED burden after SAH

The AUCs calculated above were based on treating each hour independently but did not consider any prior ED burden information about a patient. A simplified way to investigate whether prior ED burden history further discriminates DCI from non-DCI groups, we calculated cumulative ED frequencies additively (Fig. 2a). Within the first 5 days after subarachnoid hemorrhage, the peak AUC of cumulative ED burden was 0.61 and occurred at day 4.8, with an optimum threshold sensitivity of 0.66 and specificity of 0.60. Within the first 10 days, peak AUC was 0.68, occurring at day 9.6 (Fig. 2b), with a sensitivity of 0.73 and specificity of 0.54.

3.3. ED burden aligned to time of DCI

We also investigated whether ED burden differs in the days leading up to DCI. We aligned the data of all DCI patients to the date of DCI diagnosis. A temporal raster plot of each DCI patient aligned relative to the time of DCI (DCI = day 0) is shown in Fig. 3A. Our control-matching process for comparison to DCI patients aligned to their DCI onset yielded 935 controls (see Methods). We found a higher ED burden in DCI patients prior to DCI onset (Fig. 3B). AUC assessments at each hour prior to DCI yielded the highest AUC of 0.72 within 5 days prior to DCI based on the spline smoothed curve. This AUC was similar between –4.4 and –3.3 days prior to DCI onset, based on this curve (Fig. 3C). Sensitivity and specificity were 0.74 and 0.70, respectively. AUC for ED burden beyond 5 days prior to DCI were high, but the number of patients with late DCI who recorded at these times points is low as reflected by the increased variance.

3.4. ED burden trajectories over time for DCI discrimination

Given the heterogeneity in ED burden patterns in individual patients, we sought to determine if there are groups of DCI patients who follow particular trajectories in discharge burden over time, and whether these trajectories are associated with DCI risk. Using group-based trajectory analysis, we found that a 3-group model best fit the data (Fig. 4a). Based on these trajectories we calculated the probability of developing DCI based upon group membership (Fig. 4b). In group 3, 79% of patients developed DCI, whereas in group 1, only 37% developed DCI and in group 2 52% had DCI. The differences in group membership related to DCI outcome was significant (p = 0.011).

4. Discussion

Our data demonstrate that automated, quantitative ED burden calculations can differentiate patients who do and do not develop DCI. Curve separation occurs around Day 3, corresponding to the beginning time period of DCI risk. Mean ED burden is significantly higher in DCI patients from day 3.5 to 6, with moderate discrimination. Interestingly, even non-DCI patients have increased ED burden during the peak DCI window of days 3–14. This may suggest a continuum of neuronal dysregulation that tips toward clinical deterioration beyond a certain threshold. As previously published (Kim et al., 2017), we propose that epileptiform abnormalities contribute to supply–demand mismatch and may contribute to the development of DCI. These data suggest that not only presence of EDs, but their burden confer increased DCI risk. In our previous model of DCI (Kim et al., 2017), we focused on daily presence of EA and determined the first occurrence of each subtype in DCI and non-DCI patients. This method allowed us to differentiate between groups at day 6. Our current model allows us to detect earlier, starting day 3.5. Our results are also complementary to our prior multi-state model (Rosenthal et al., 2018) and functional outcomes prediction model (Zafar et al., 2018), by assessing for continuous, automated feature analysis rather than dependence on manual reporting of EEG abnormalities. This continuous assessment allowed us to include patients with shorter EEG durations (24–72 hours) compared to prior Rosenthal et al. study (>72 hours). Of note, the burden definition used here is separate than the ACNS definition for burden (Hirsch et al., 2013) used in our prior paper, because here the ED detection algorithm allowed for automated, hourly assessment of ED rates compared to a single daily assessment of burden.

By calculating cumulative ED burden, we utilize historical information about ED burden at each progressive time point. However, this approach did not significantly improve performance compared to independent performance calculations. This is likely due to the initial fluctuations in ED rates soon after SAH and the large spread in cumulative ED frequencies of individuals. Further work is needed to explore other time integrating methods which may improve DCI prediction.

We also investigated whether ED burden changes precede DCI. Our results show that discharge burden of DCI patients is elevated prior to DCI. Within the five-day window prior to DCI, the maximal AUC occurred 4 days prior to DCI. These results are consistent with prior studies suggesting that epileptiform abnormalities are notable 2–4 days prior to DCI onset (Rosenthal et al., 2018). One possible explanation for this observation is that brain physiology is altered long before any clinical or radiographic evidence of DCI. This time separation presents an opportunity to trial new therapies or earlier implementation of existing ones, within a time window of reversible tissue injury.

Additionally, we observe that our patient cohort could be classified into three patterns of ED burden over time. Using group-based trajectory analysis, we identified three distinct patterns among these varied trajectories. This type of modeling has not previously been applied in SAH patients, but has shown value in cardiac arrest prognostication (Elmer et al., 2016). We show that SAH...
patients can be described by three trajectory patterns over time and that belonging to either group 1 or 3 confers different DCI risk. An important direction for future work is to perform real-time evaluation of which trajectory group each patient belongs, dynamically updated based on accumulating data, for prospective assessment of how trajectory group belonging influences the probability of DCI, which is a more recently developed approach using GBTM (Elmer et al., 2019).

Overall, we found that most patients with SAH have increased ED burden 3–10 days after SAH, regardless of DCI status. This raises questions about why this timeframe is particularly injury prone. Perhaps patients with high ED burden reach a “tipping point” of

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**Fig. 1.** Epileptiform discharge (ED) burden is higher in patients with delayed cerebral ischemia (DCI) compared to non-DCI patients. 

a) Swimmer plots of hourly ED burden (gray color scale) of individual patients (rows) with DCI (left) and without DCI (right) across time after subarachnoid hemorrhage (SAH). Gray color scale: white to black, range: 5–95% max ED burden, respectively. Purple shading corresponds to duration of EEG collection. 

b) Winsorized mean and standard error of DCI (red) and non-DCI (blue) patients for each hour, with an overlaying spline smoothed curve. Bars above the mean curves indicated statistical significance (t-test of p < 0.05 for ≥2 hours). 

c) AUC of ED burden prediction calculated for each hour after SAH (black), with an overlaying spline smoothed curve. Maximum AUC of 0.62 found at 3.5–5.3 days after SAH.
decompensation, resulting in DCL. While SAH causes some direct neural injury, it also triggers a cascade of other processes, such as cortical spreading depression, inflammation, vasospasm and abnormal neural activity leading to metabolic supply–demand mismatch (Kim et al., 2017). There is evidence that seizures and other interictal patterns can increase metabolic demand (Vespa et al., 2016; Witsch et al., 2017). This study cannot definitively determine whether high ED burden directly contributes to injury or is simply a marker of worsening metabolic supply–demand mismatch. However, it supports the hypothesis that prolonged abnormal neural activity over time could contribute to worsened injury after SAH, similar to the concept of the penumbra to ischemia threshold where prolonged mild reductions in cerebral blood lead to infarction.

Our study has limitations. First, ED detection algorithms are imperfect. While we used the most commonly available ED detection algorithm, developed using epilepsy monitoring unit data (Scheuer et al., 2017), there are limitations in its performance (Westover et al., 2017). Namely, false positive spike detections are a common issue for many algorithms (Ver Hoef et al., 2010; Scheuer et al., 2017). However, since we used the same algorithm across all patients and compared over time, we believe the type and rate of false detections are likely to be common across patients and the impact of these false positive detections is thereby somewhat mitigated. The relative comparisons both within and across patients is significant. However, it is possible that our assumption is incorrect and that the false detection rates for the algorithm used are somehow higher in the DCL patients than non-DCL patients. Thus, it is important for future studies could compare DCL prediction based on other ED detection algorithms (e.g. Jing et al., 2020). Second, while group-based trajectory modeling provides a method to assess subgroups of patients and their data over time, trajectory group membership is assigned probabilistically and updated as new data become available. We assigned group membership based on the final highest probability of group membership after all available data were modeled and did not explore its performance over time. Further work is needed to determine its predictive value in a real-time predictive setting. Finally, we focused on only one quantitative feature of EEG, which limits our overall performance in predicting DCL. While it is a common approach to assess the value of single features (Claassen et al., 2004; Kim et al., 2017; Vespa et al., 1997) in DCL prediction, future prediction algorithms should incorporate multiple EEG parameters, such as quantitative ED morphologic features which have been shown to be important for source localization (Wong, 1996; 1991; Wong and Wong, 1991), other epileptiform patterns (periodic discharges, lateralized rhythmic delta activity, etc.) and spectral features (Claassen et al., 2004; Gollwitzer et al., 2015; Rots

Fig. 2. Cumulative epileptiform discharge (ED) burden after subarachnoid hemorrhage (SAH). a) Winsorized mean and standard error of delayed cerebral ischemia (DCL; red) and non-DCL (blue) patients for each cumulative hour. Bars above the mean curves indicate statistical significance (t-test of p < 0.05 for ≥ 2 hours). b) AUC of cumulative ED burden prediction of each cumulative hour after SAH (black). Maximum AUC within 5 days is 0.61 (day 4.8) and within 10 days of SAH is 0.68 (day 9.6).
Fig. 3. Epileptiform discharge (ED) burden is higher in patients with delayed cerebral ischemia (DCI) prior to their DCI onset. a) Swimmer plots of hourly ED burden (gray color scale) of individual patients (rows) with DCI aligned to their onset of DCI (time 0). Gray color scale: white to black, range: 5–95% max ED burden, respectively. Purple shading corresponds to duration of EEG collection. b) Winsorized mean and standard error of DCI (red) and non-DCI (blue) patients for each hour prior to the onset of their DCI, with an overlaying spline smoothed curve. Control patients were matched based on available EEG recordings during the same time frame as each individual DCI patient. Bars above the mean curves indicated statistical significance (t-test of \( p < 0.05 \) for \( >2 \) hours). c) AUC of rated burden prediction calculated for each hour prior to DCI onset, with an overlaying spline smoothed curve. Within 5 days of DCI, maximum AUC of 0.72 found at -3.3 days prior to DCI onset.
We did not evaluate the effects of anti-seizure medications on the presence or burden of ED, which is an important future investigation. Further integration of other modalities, including transcranial doppler, radiology and clinical variables could a more powerful multimodal prediction algorithm for DCI. While our focus here was on DCI prediction, similar methods could be applied in future studies of other SAH outcomes, such as long-term functional status.

5. Conclusions

Our data support the hypothesis that a higher burden of discharges identifies patients at increased risk for DCI. This study provides novel data to suggest that quantitative assessments of these abnormalities can quantify DCI risk. Despite being a single feature analysis, the ability to discriminate among groups was substantial. This provides the basis for future exploration of which epileptiform discharge features, in combination with other EEG features, best predict DCI.

Author Contribution Statement

JAK and MBW conceived of the presented idea. JAK performed the computations and drafted the manuscript. MBW supervised the project. WLZ verified the analytical methods. JE assisted with all group-based trajectory analyses. JJ, MG and VMJ assisted with data collection and processing. MBW, SFZ and ER performed DCI adjudication. All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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