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CORTICAL SPREADING DEPRESSION

First Report of Spreading Depolarization Correlates on Scalp EEG Confirmed with a Depth Electrode

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Spreading depolarizations (SDs) are pathologic waves in cerebral gray matter defined by the near complete breakdown of electrochemical membrane gradients, consequent silencing of electrical activity (spreading depression), and, in some cases, associated cytotoxic edema (CE) on magnetic resonance imaging (MRI) [1]. SDs are common in patients with traumatic brain injury [2] and represent a potential therapeutic target [3]. Typically monitored with invasive electrocorticography from subdural or depth electrodes [4], SDs can also be observed on scalp electroencephalography (EEG) in patients after hemicraniectomy [5, 6]. To date, SDs have not been evident on scalp EEG in those with intact skulls, perhaps due to strong spatial filtering effects [7]. Here, we present the first case of SD features observed on scalp EEG in association with delayed cerebral injury in a patient with an intact skull.

A 60-year-old woman presented after a fall down a flight of stairs. In the emergency department, she was intubated for a Glasgow Coma Scale score of 7 (eyes, 1; verbal, 1; motor, 5). Initial head computed tomography (Fig. 1a) demonstrated small right frontotemporal contusions, a small right subdural hematoma, a small left epidural hematoma, and scattered subarachnoid hemorrhage. Invasive multimodality monitoring was initiated through a right frontal quad-lumen bolt at approximately 21 h post trauma [8].

On initiation of monitoring, clusters of SDs were identified on the depth electrode (Fig. 2, row 1). Figure 3 shows a representative sample of two SDs along with concurrent multimodal monitoring data, including the regional cerebral blood flow (rCBF), brain tissue oxygen, intracranial pressure, cerebral perfusion pressure, and pressure reactivity index. Both pictured SDs were associated with a concomitant decrease in rCBF (Fig. 3, row 5), a pattern that was observed in most SDs with available rCBF data (70%). This is known as an inverse hemodynamic response and implies impaired cerebrovascular autoregulation [9]. The pressure reactivity index curve (Fig. 3, row 9) offers further evidence of impaired cerebrovascular autoregulation, as most measurements were greater than 0.25 [10]. The SDs were also associated with a depression of lower frequency vascular fluctuations (Fig. 3, row 4), a common vascular signature of SDs [9].

Overall, intracranial pressure was well controlled throughout the monitoring period. There was initially some mild brain tissue hypoxia (brain tissue oxygen 10–20 mm Hg) during the first 9 h of monitoring that resolved with augmenting cerebral perfusion pressure. The SDs were not specifically treated, but their frequency decreased over time with augmented perfusion. By 72 h post trauma, the SDs became rare and the patient began to follow commands. The bolt was explanted at 96 h post trauma and an MRI was obtained immediately after.

The MRI showed predominantly cortical CE in the right parietotemporal lobe, with no features typical of a contusion or other traumatic injury (Fig. 1b–e). Computed tomography angiography showed no evidence of proximal vasospasm or other relevant pathology. Ischemic stroke workup, including an echocardiogram, was unremarkable. Clinically, she initially had left hemineglect and disorientation, but this improved and she was discharged to a rehabilitation facility after 2 weeks. At 6 months post trauma, the patient complained of

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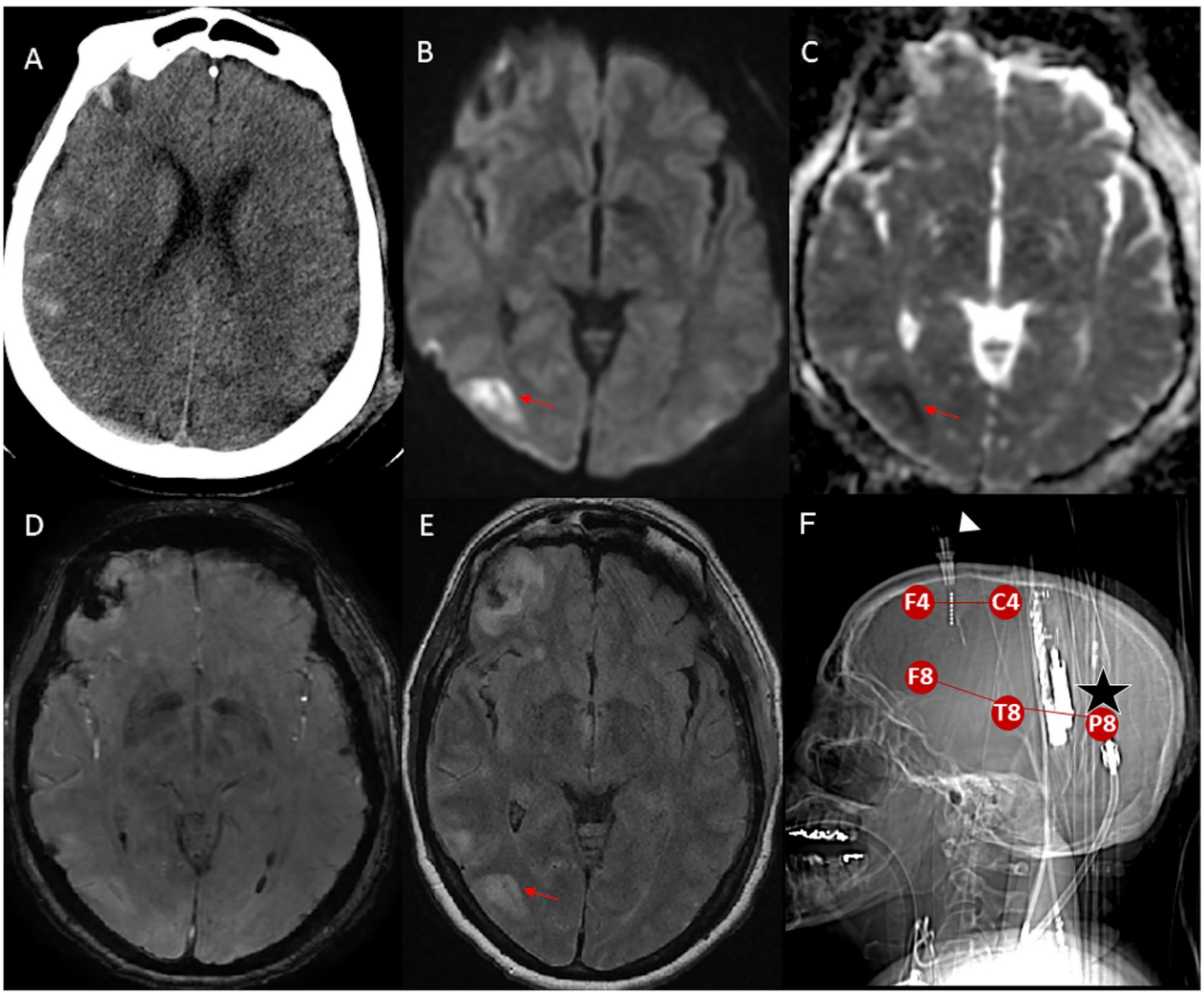

Fig. 1 Relevant neuroimaging. **a**, Representative slice of admission head CT, showing scattered subarachnoid hemorrhage, a posterior subdural hematoma, and a frontal contusion. **b, c,** Diffusion-weighted and apparent diffusion coefficient images from 96 h post trauma, showing a region of restricted diffusion in a region without pathology on the initial CT, consistent with cytotoxic edema (red arrow). **d,** A representative susceptibility-weighted image is shown that demonstrates absence of any hemorrhage that could be confounding interpretation of diffusion restriction. **e,** T2 fluid attenuated inversion recovery image shows early changes in the region of cytotoxic edema (red arrow). **f,** Relevant EEG electrode locations overlaid on CT scout image. Note the location of the multimodal monitoring bolt (white arrowhead) between the F4 and C4 electrodes, and the approximate location of the cytotoxic edema (black star). CT, computed tomography, EEG, electroencephalography (Color figure online)

cognitive impairment and depression but was independent in her activities of daily living. No follow-up imaging was obtained.

SDs have been established as a marker and mechanism for development of secondary cortical injury, including delayed CE after aneurysmal subarachnoid hemorrhage [11–13]. Mechanistically, SDs can cause ionic shifts and ischemia that can lead to CE [1, 13, 14]. As the CE in our patient was potentially related to SDs, we retrospectively examined the scalp EEG to determine whether the SDs were also found more posteriorly (Fig. 1f). As shown in Fig. 2, we observed episodic depressions of high-frequency scalp activity in the frontal and temporal channels that corresponded with the incidence and timing of SDs recorded in the ipsilateral frontal depth electrode. These episodic depressions were observed as far back as the P8 electrode (not

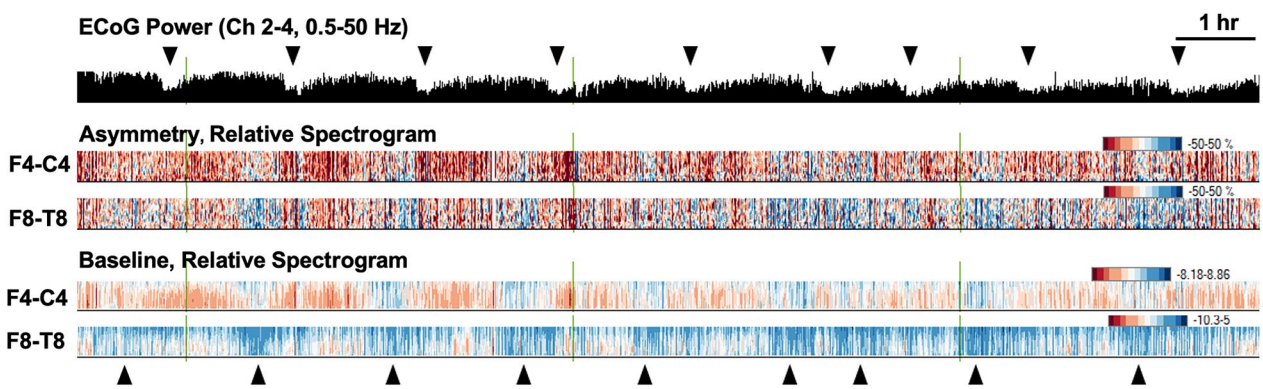

Fig. 2 Spreading depolarizations in depth ECoG and scalp EEG. This figure demonstrates depth electrode (ECoG) and quantitative scalp EEG data spanning a 12-h period from post trauma day 2 to post trauma day 3. Data were captured by the bedside Component Neuromonitoring System (CNS) (Moberg Research Inc, Ambler, PA) using a full-band Advanced Amplifier (Moberg Research Inc). Scalp EEG was recorded using Natus AC-coupled amplifier (Natus Neuro, San Diego, CA) and patched into the bedside CNS. Quantitative EEG was calculated using Persyst (P14; Persyst Inc, Prescott, AZ) and propriety Artifact Reduction was applied prior to analysis. For all rows, time is on the *y*-axis. The top trace in black shows power of bipolar ECoG channel 2–4 (0.5–50 Hz). Regularly occurring depressions are seen (arrowheads) and correspond to DC shifts of SD (not shown; see Fig. 3). Asymmetry Relative Spectrograms quantify the laterality of the EEG delta activity (0–4 Hz) for the F4-C4 and F8-T8 channels. There is periodic right-sided slowing (dark blue) corresponding with the depressions observed on the depth electrode. Baseline Relative Spectrograms show the delta frequency band (0–4 Hz) compared with a baseline value selected from the same channels after resolution of SDs approximately 80 h post injury. These spectra demonstrate changes in the delta frequency band (arrowheads), which are consistent with depressions that precede those detected on the depth electrode. DC, direct current, EEG, electroencephalography (Color figure online)

shown). The depressions on scalp EEG occurred before the SDs at the frontal depth electrode, which could suggest that the SDs originated posteriorly.

This is the first report demonstrating scalp EEG correlates of SDs in a patient with an intact skull. Such EEG correlates are easily identified in patients with hemicraniectomy and have been used to guide clinical care at our institution but have not been apparent in nonoperative cases using standard EEG visualization and analysis [7]. In the present case, identification of SD correlates was facilitated by visual analysis of quantitative EEG examined in 12-h blocks. Although it is labor intensive, visual analysis of long blocks of compressed data is critical to identifying SDs on scalp EEG, as spreading depressions develop gradually (interquartile range 8–15 min) and are prolonged (interquartile range 16–33 min). Further study of this approach will be needed to determine whether it can be developed for routine use in noninvasive SD detection.

Our report also highlights the occurrence of SD-associated impaired neurovascular coupling. In the setting of normal cerebrovascular autoregulation, SDs typically evoke a vasodilatory response resulting in a near doubling of rCBF. However, our patient demonstrated an inverse hemodynamic response to SDs, known as spreading ischemia [15], that occurs when impaired autoregulation is present [9, 16]. Spreading ischemia can prolong the recovery from a depolarization and puts the tissue at risk for CE and permanent neuronal injury [14, 17]. In this case, although the rCBF did not reach the ischemic threshold of subcortical white matter [18], the depth of the inverse responses was modulated by improvements in cerebral hemodynamics, suggesting tissue at risk for ischemia. Further, because the rCBF can only measure perfusion in the region of the monitor, the degree of ischemia near the identified CE is unknown.

In conclusion, our case provides a compelling link between SDs and secondary brain injury. The cortical pattern of CE has been previously identified in patients with traumatic brain injury who have a suspected link to SD, although SD monitoring was not performed in prior work [19, 20]. In our case, it is possible that the SDs were provoked by the scattered subarachnoid hemorrhage or the subdural hematoma near the CE [21]; although we cannot prove that the SDs caused the observed CE, this case highlights the importance of SDs as a marker of secondary brain injury.

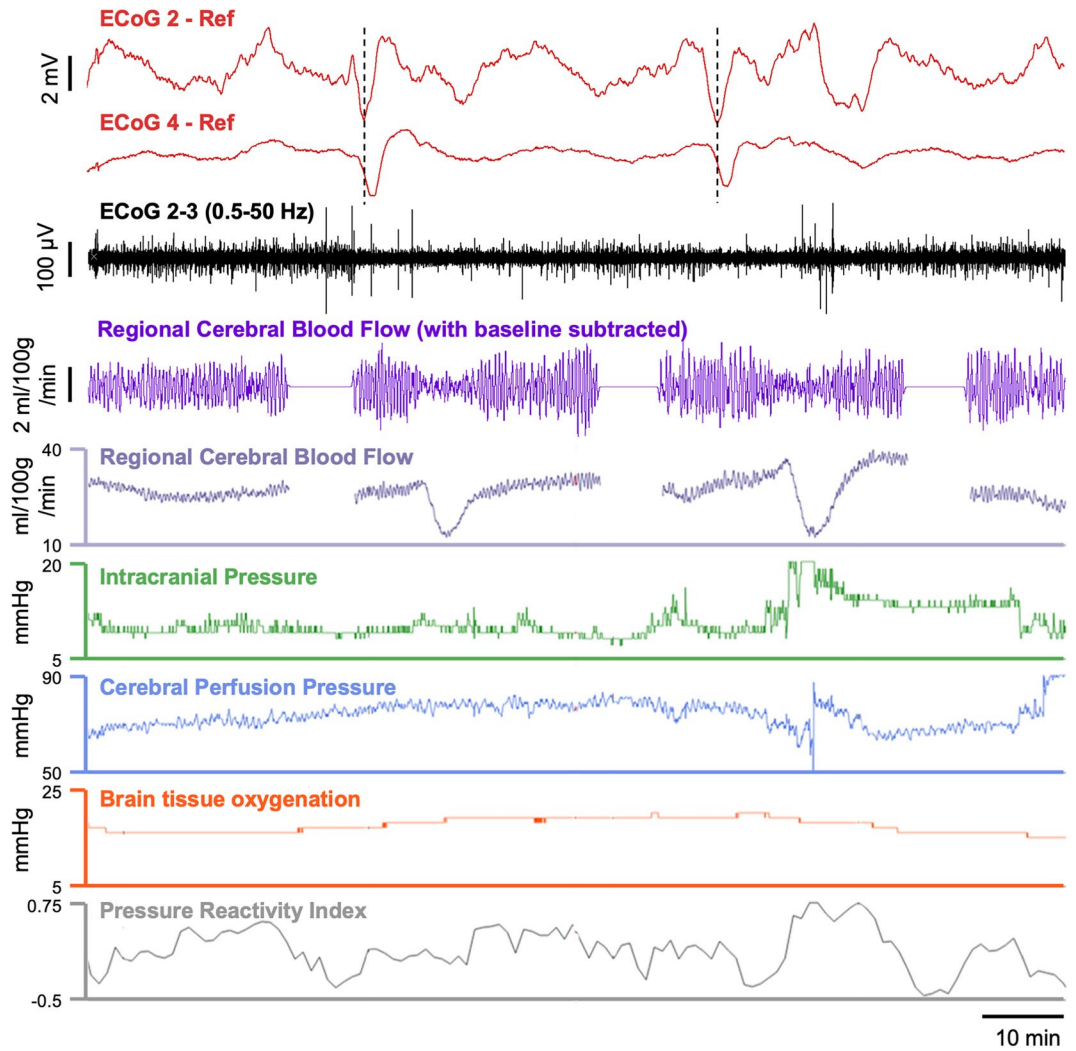

Fig. 3 Inverse hemodynamic response of SDs. Monitoring included intracranial pressure (ICP) and brain tissue oxygen ($P_{bt}O_2$) through a Raumedic PTO (Raumedic Inc, Mills River, NC), a Spencer depth electrode (Ad-Tech Medical, Racine, WI), and a Bowman Perfusion Monitor (Hemedex Inc, Waltham, MA). Top traces (red) of direct current (DC) electrocorticography (ECoG) show the negative DC shifts of SDs with slight time delay between electrodes 2 and 4. Raw signals were corrected for baseline drift by subtraction of the 30-min moving average and then low-pass filtered at 0.1 Hz. High-frequency bipolar ECoG (0.5–50 Hz; black) of channel 2–3 shows the depressions corresponding to the two SDs. The top purple trace shows the rCBF signal after removing the baseline by subtracting the 45-s moving average. This reveals the low-frequency vascular fluctuations (LFVFs) that become depressed during both SDs. Because LFVFs are driven by electrical activity due to neurovascular coupling, their depression is a vascular manifestation of spreading depression. The lavender trace shows the raw rCBF signal with inverse neurovascular coupling to the SDs, with transient blood flow decreases from 30 to 12 ml/100 g/min. ICP (green), CPP (blue), $P_{bt}O_2$ (orange), and the pressure reactivity index (PRx) (gray) are also shown. Throughout this period, there is relatively well controlled ICP and adequate CPP, whereas $P_{bt}O_2$ is 15–20 mm Hg and the PRx is frequently elevated to greater than 0.25, indicating autoregulatory dysfunction. CPP, cerebral perfusion pressure, rCBF, regional cerebral blood flow, SDs, spreading depolarizations (Color figure online)

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Author Contributions
All authors listed meet criteria for authorship, specifically each author contributed to the following: (1) the conception/design of the study, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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Conflict of interest
Dr. Robinson has nothing to disclose. Dr. Hartings has nothing to disclose. Dr. Foreman has nothing to disclose.

Ethical Approval
This case its associated imaging/data were obtained through a study approved by the local institutional review board, with a waiver from informed consent.

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