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Possible Cortical Spreading Depression Recorded Intraoperatively Following a Generalized Seizure: Illustrative Case

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Abstract

Background: We present a compelling case fitting the phenomenon of cortical spreading depression detected by intraoperative neurophysiological monitoring (IONM) following an intraoperative seizure during a craniotomy for revascularization. Cortical spreading depression (CSD, also called cortical spreading depolarization) is a pathophysiological phenomenon whereby a wave of depolarization is thought to propagate across the cerebral cortex, creating a brief period of relative neuronal inactivity. The relationship between CSD and seizures is unclear, although some literature has made a correlation between seizures and a cortical environment conducive to CSD. **Methods:** Intraoperative somatosensory evoked potentials (SSEPs) and electroencephalography (EEG) were monitored continuously during the craniotomy procedure utilizing standard montages. Electrophysiological data from pre-ictal, ictal, and post-ictal periods were recorded. **Results:** During the procedure, intraoperative EEG captured a generalized seizure followed by a stepwise decrease in somatosensory evoked potential cortical amplitudes, compelling for the phenomenon of CSD. The subsequent partial recovery of neuronal function was also captured electrophysiologically. **Discussion:** While CSD is considered controversial in some aspects, intraoperative neurophysiological monitoring allowed for the unique analysis of a case demonstrating a CSD-like phenomenon. To our knowledge, this is the first published example of this phenomenon in which intraoperative neurophysiological monitoring captured a seizure, along with a stepwise subsequent reduc-

tion in SSEP cortical amplitudes not explained by other variables.

Keywords

Cortical Spreading Depression, Electroencephalography, Intraoperative Neurophysiological Monitoring, Seizure

1. Introduction

Cortical spreading depression/depolarization (CSD) is a proposed pathophysiological phenomenon in which a wave of depolarization propagates across the cerebral cortex, creating a brief period of relative neuronal inactivity. First described by Leão in 1944 [1], electroencephalography (EEG) captured propagating relative attenuation in rabbits following particular patterns of cortical electrical stimulation. Several authors have noted this "spread of cortical depolarization" travels both horizontally across the superficial cortical layers and vertically into the deeper cortical layers [2] [3]. Several conditions are thought to be associated with CSD, including stroke, migraine aura, epilepsy [4], and concussion [5]. More recently, spreading depolarizations have been shown to be modifiable by antimigraine medications [6] or drugs which inhibit inter-astrocytic gap junction communication [7].

The relationship between CSD and seizures is unclear, although literature exists suggesting that seizures create a local environment conducive to CSD [8]. As CSD has been reported to occur both before and after seizures, it is unclear whether CSD facilitates seizures, interrupts them, or both [3] [8]. However, CSD has been implicated as a potential contributing factor towards postictal generalized EEG slowing [9] [10], suggesting a stronger association for the post-ictal period rather than the pre-ictal period.

Beniczky and colleagues [11] described reduced somatosensory evoked potential (SSEP) cortical amplitudes in a patient immediately following a seizure in the non-operative setting. They postulated the reduction may have been due to postictal cortical inhibition. Diaczun and Lüders [12] also reported an intraoperative neurophysiological study in which SSEP amplitudes were reduced *during* a clinical seizure (rather than after the seizure), although a specific pathological mechanism was not discussed.

The objective of this manuscript is to present a case compelling for the phenomenon of CSD, whereby IONM detected a stepwise SSEP cortical amplitude attenuation following an intraoperative seizure during a craniotomy for revascularization. Signals were monitored continuously during the procedure, recording electrophysiological data from the pre-ictal, ictal, and post-ictal periods. To our knowledge, this is the first published example of evolving signal changes consistent with the CSD phenomenon in which intraoperative monitoring captured the ictal event, subsequent reduction in SSEP amplitudes, and finally, relative improvement in neuronal function.

2. Illustrative Case

A 47-year-old, right-hand dominant woman was brought to the operating room for surgical management of moyamoya disease. Earlier in the year, she suffered an ischemic stroke affecting the left cerebral hemisphere, manifesting clinically as right hemiparesis and aphasia. She had no history of epilepsy or seizures before or after her infarct. Brain MRI studies at the time revealed multifocal acute infarctions in the left middle cerebral artery (MCA) territory. Subsequent CT angiography revealed occlusion of the distal left internal carotid artery and stenosis of the right internal carotid artery. The left MCA and anterior cerebral arteries (ACA) were occluded, resulting in lenticulostriate collaterals reconstituting the MCA branches on that side, consistent with Moyamoya disease. The right-sided MCA and ACA were noted to be of normal caliber. On surgical referral following the infarction, the patient had persistent mild right hemiparesis and hyperreflexia, with a slow gait aided by the use of a cane. Surgical intervention was recommended, and the patient agreed. The operative plan included revascularization by left superficial temporal to middle cerebral artery (STA-MCA) bypass, with possible encephalo-dural-myo-synangiosis, and left parietal dural inversion.

3. Methods: Intraoperative Neurophysiological Monitoring

Intraoperative neurophysiological monitoring (IONM) was performed using the Cadwell 32-channel Cascade Surgical Studio system. Monitoring modalities consisted of median and tibial nerve SSEPs, transcranial motor evoked potentials (tcMEPs), 10-channel EEG, and neuromuscular junction monitoring with train of four (TOF). A master's-level, CNIM-certified IONM technologist was physically present in the operating room, with professional oversight and interpretation of the IONM data provided in real-time by an online clinical neurophysiology fellowship-trained neurologist.

For EEG and cortical SSEP recording, subdermal needle electrodes were placed according to the International 10 - 20 System except where slight adjustments in placement were required to accommodate the surgical field. For upper extremity SSEP stimulation, surface-stimulating electrodes were placed over the median nerve at each wrist. For lower extremity SSEP stimulation, subdermal needles were placed at the tibial nerve near each medial malleolus (per the monitoring company's standard practice). A minimum of 150 - 200 sweeps was acquired and averaged for each waveform at each stimulus site. Recording electrodes consisted of subdermal needle electrodes which were placed to obtain the following channels: (C4'-Fpz), (C3'-Fpz), (Cv5-Fpz), (EPL-EPR), (CZ-Fpz), (CZ-C4'), (CZ-C3'), (C3'-C4'), and (C4'-C3'). A ten-channel EEG was recorded in an anterior-to-posterior bipolar montage with one MCA-derived channel and filter settings from 1 - 70 Hz. The display gain was set at 75 μV/Div and the sweep speed at 1000 ms/Div for a total sweep of 10 seconds per page. TcMEPs were produced by supramaximal stimulation from C3 and C4 scalp electrodes

and were recorded from the bilateral deltoids, extensor carpi radialis, abductor pollicis brevis, vastus lateralis, tibialis anterior, and abductor hallucis. Ipsilateral muscles were added to the tcMEP recording montage on each side to account for "crossover" effects that can indicate stimulation of subcortical structures.

4. Results

4.1. Baseline Intraoperative Neuromonitoring

Baseline SSEPs demonstrated reproducible median and tibial SSEP cortical responses with amplitudes in the 1.0 to 1.6 μV range and best seen in the contralateral midline channels (Figure 1). Bilateral median nerve cervical ("subcortical") responses were monitorable, however, tibial nerve cervical responses were not. TcMEPs were well-formed and reliable in the upper and lower extremities on the control side, but only a small foot response was obtainable upon stimulation of the operative side at baseline, presumably related to the patient's preoperative deficits. Due to the limited utility of the tcMEP data, they are not shown herein. The EEG was mostly continuous at baseline (also shown in Figure 1).

4.2. Anesthesia

Propofol was used for anesthesia, with the initial rate at 130 mcg/kg/min, ranging between 120 and 180 mcg/kg/min during the procedure. No neuromuscular blockade was used, as train-of-four testing demonstrated four full twitches without fade.

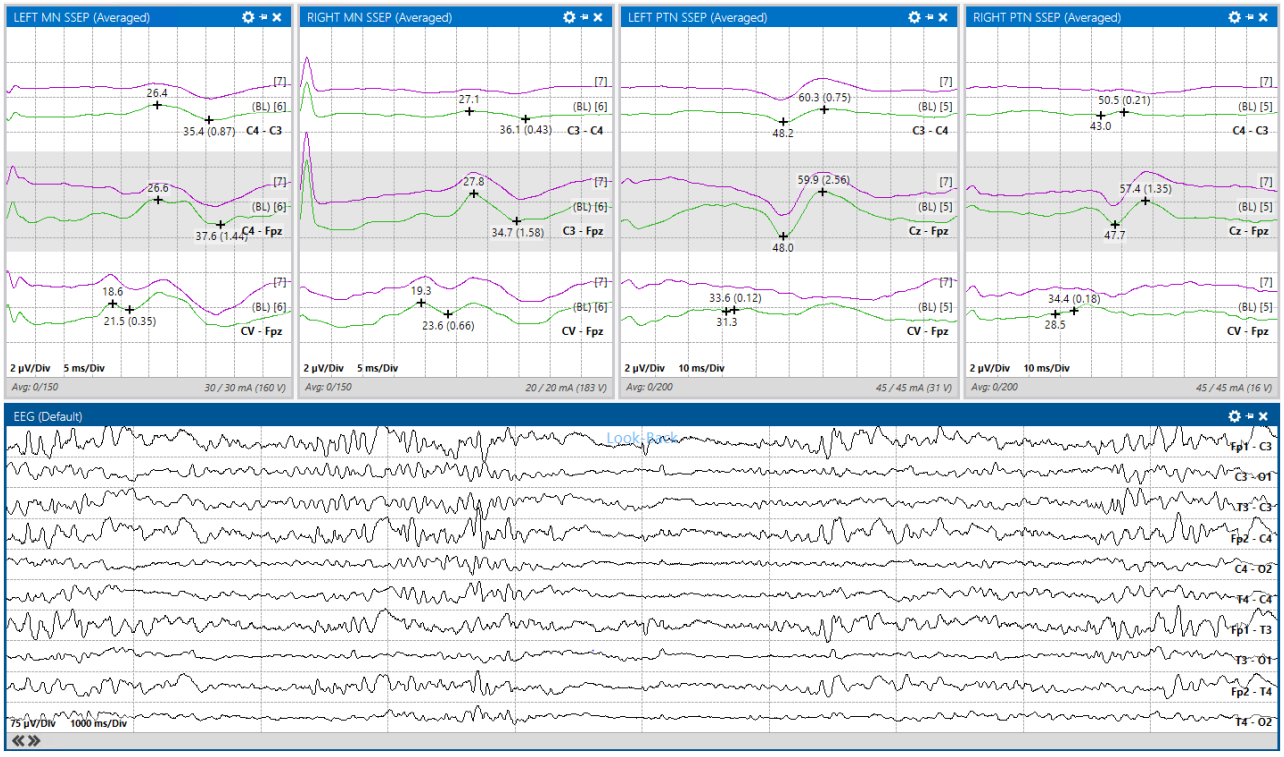


Figure 1. Baseline SSEPs and EEG.

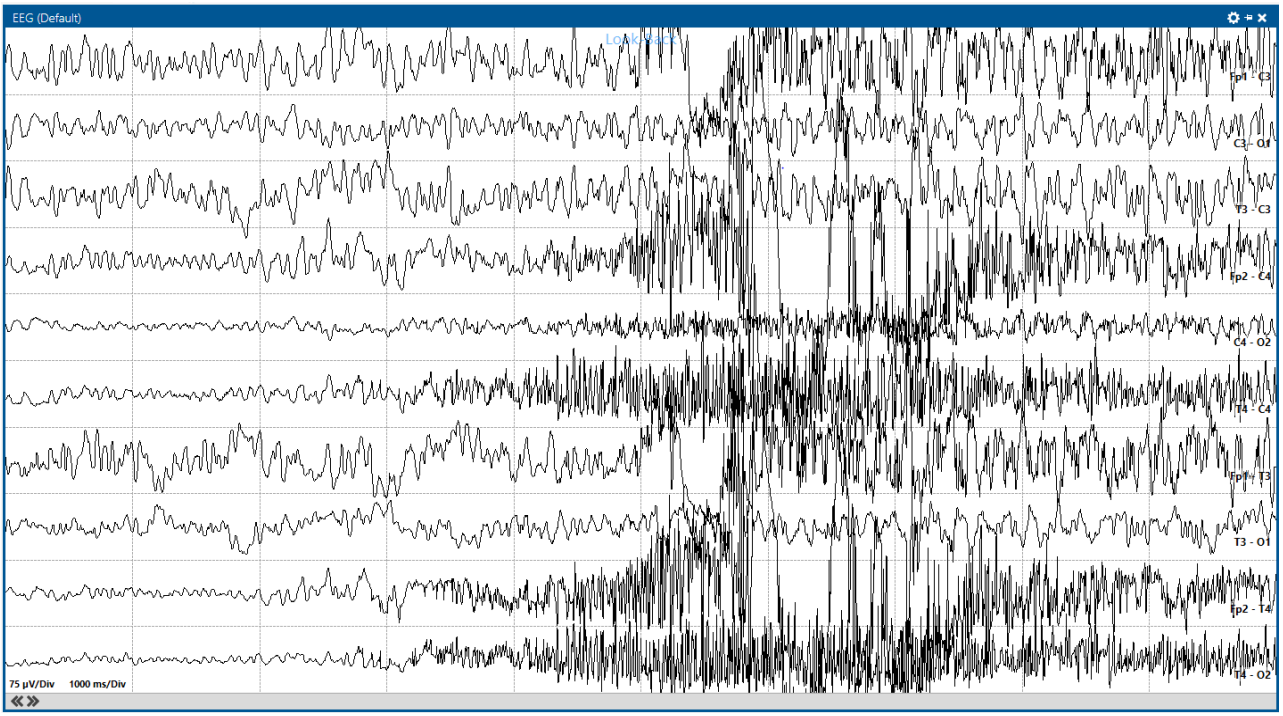


Figure 2. Seizure onset.

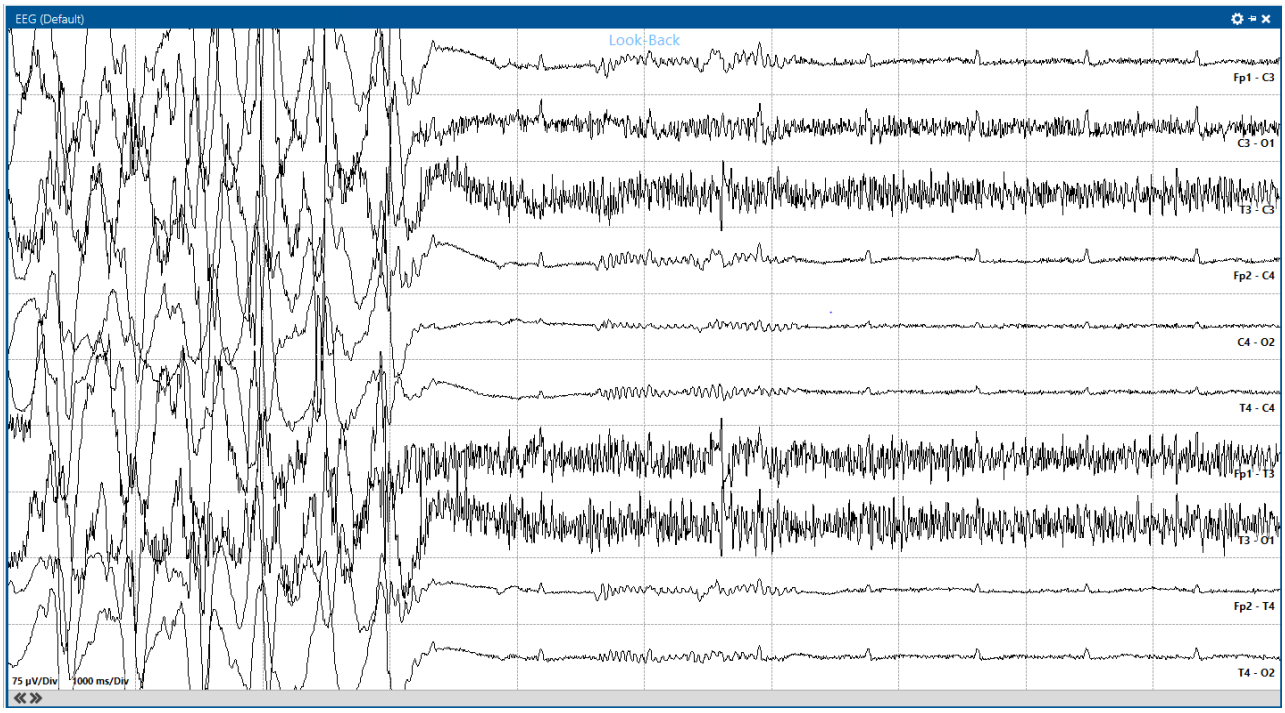


Figure 3. Termination of seizure activity following cold saline irrigation.

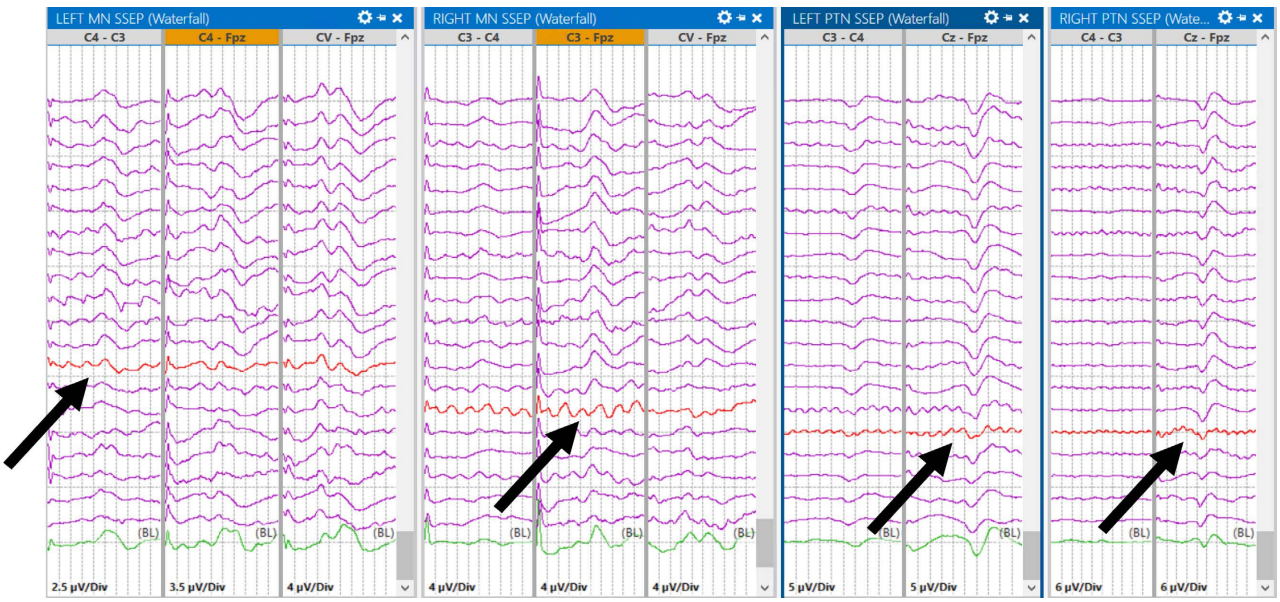
4.3. Monitoring and Clinical Course

The patient appeared clinically stable through the vascular anastomoses. Confirmatory imaging included indocyanine green angiography and Doppler ultrasound of the superficial temporal artery. Several minutes after the imaging, the

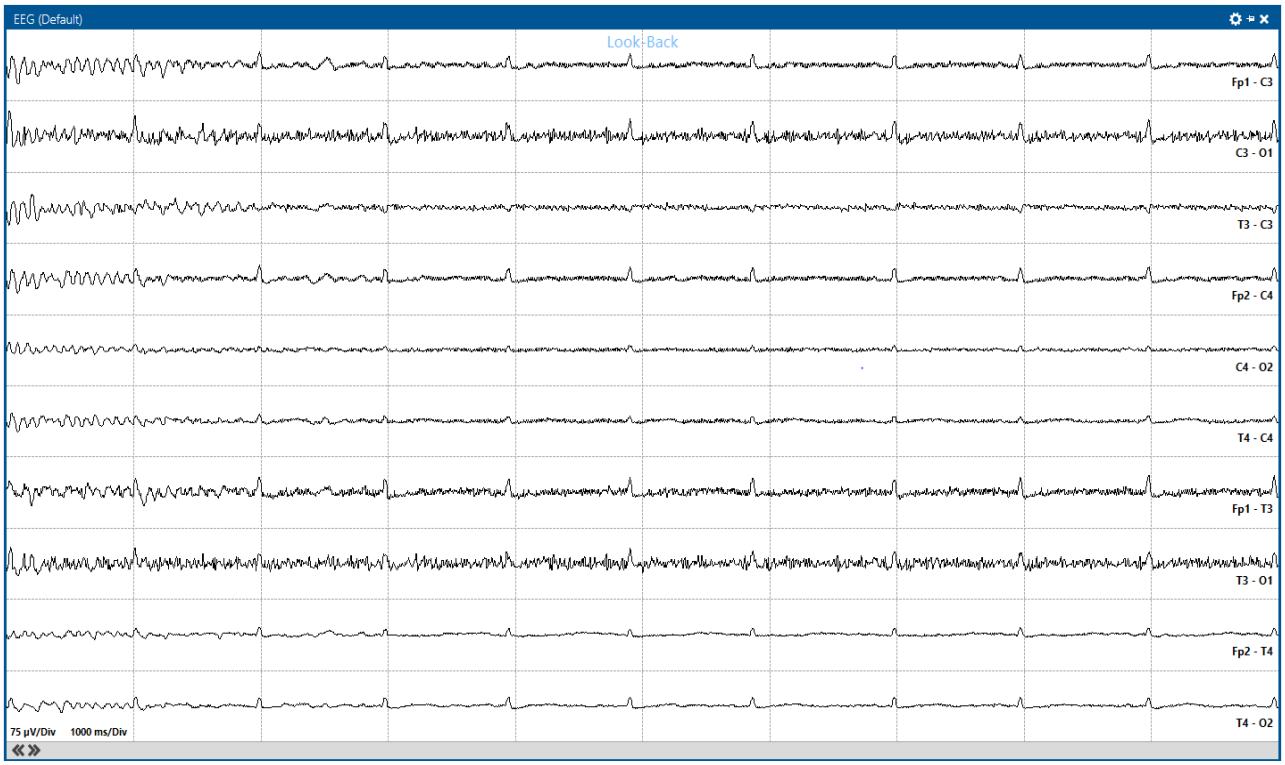
patient suffered a brief generalized convulsion which was quickly aborted with cold saline irrigation. Additionally, 1000 mg of intravenous levetiracetam was given. The onset of the generalized epileptic activity is shown in Figure 2. Electrographic seizure activity continued for approximately one-and-a-half minutes, with the termination of the seizure shown in Figure 3. The final propofol bolus was given 45 minutes prior to the seizure, and no additional boluses were provided in response to the seizure. The propofol rate remained in the 120 to 150 mcg/kg/min range from the time of the seizure until closure.

By three minutes post-seizure, the left median *cortical* SSEP amplitude had declined to under 0.9 μV, while the right median nerve SSEP response remained within normal variation from baseline. By ten minutes post-seizure, the median cortical SSEP responses were reduced bilaterally by over 50% from baseline, and the left tibial cortical SSEP amplitude also showed a modest amplitude reduction. During this time, the median nerve *cervical* SSEP responses remained consistent with baseline, suggesting that whatever was occurring was restricted to the cortex. A waterfall view of the stepwise cortical SSEP changes is shown in Figure 4(a) and demonstrates 1) the left median cortical amplitudes dampening first, followed by 2) the right median cortical amplitude, and finally, 3) the bilateral tibial SSEP cortical amplitudes. Post-ictal EEG suppression is shown in Figure 4(b). The black arrows in Figure 4 demonstrate this post-ictal stepwise progression of SSEP amplitude changes over many minutes.

Final SSEP data, shown in Figure 5, was collected 52 minutes post-seizure. The median nerve cortical SSEP amplitudes remained reduced throughout the remainder of the procedure, while the tibial nerve SSEP amplitudes had returned to within normal variation from baseline. Final EEG data, also shown in Figure 5, had improved from the post-seizure suppression, with poorly modulated, mixed frequencies present.



(a)



(b)

Figure 4. Suppression data. Panel (a) shows the waterfall view of SSEPs demonstrating temporal progression of SSEP changes following the generalized seizure. Spreading SSEP changes are highlighted in red. Panel (b) shows post-seizure EEG suppression.

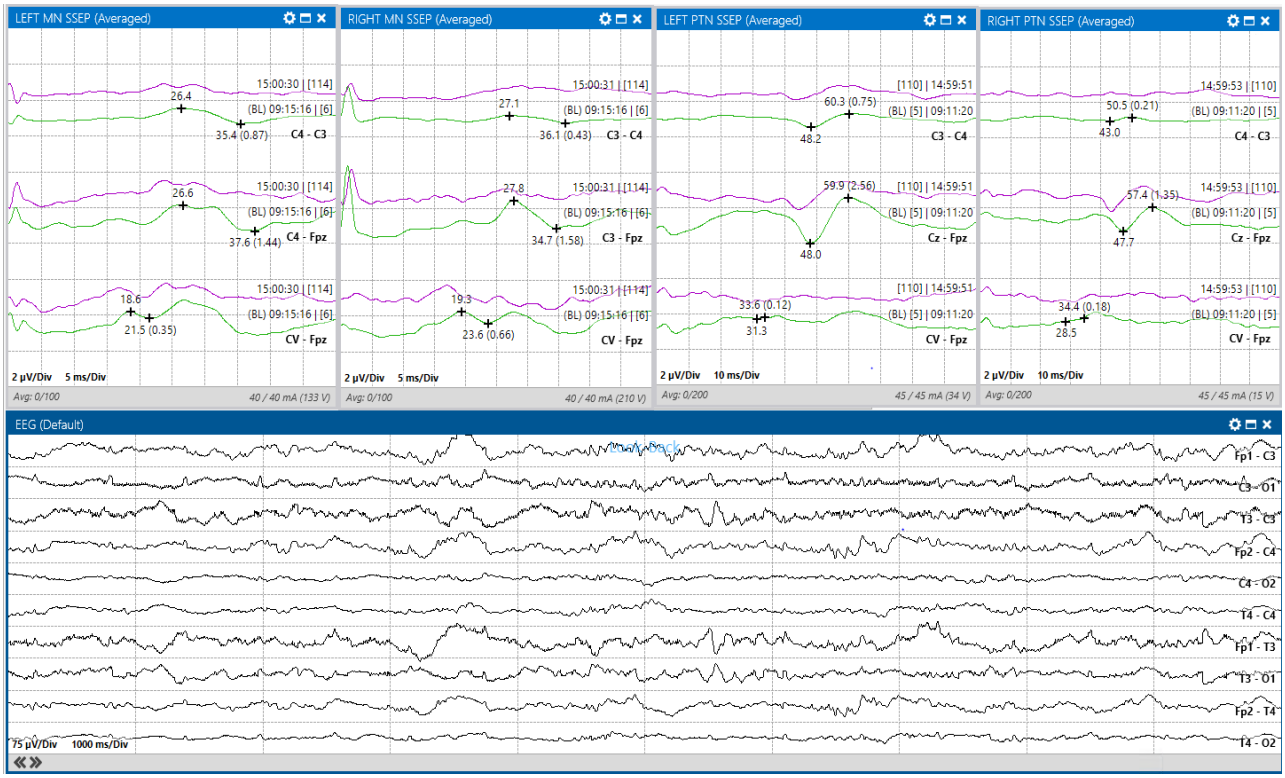


Figure 5. Final SSEP and EEG data.

5. Discussion

CSD remains an elusive phenomenon in the non-operative clinical realm. Intraoperatively, however, IONM allowed a unique opportunity to electrophysiologically observe a phenomenon fitting the CSD description - something not previously studied or published. Although post-ictal suppression of evoked potential amplitudes would be expected following the electrical storm of a generalized seizure, these effects would be expected to be global rather than stepwise, in a way that mirrors the diffuse post-ictal EEG suppression following a generalized event. This did not happen in our case. Rather, a clear, stepwise amplitude loss was observed instead, with SSEP signal recovery lagging behind EEG recovery. This temporal relationship of the electroclinical seizure, followed by the stepwise amplitude attenuation of the SSEPs, fits more with the proposed phenomenon of CSD than it does with global post-ictal suppression.

The pathophysiology of CSD was thought to be related to a disturbance in ion homeostasis. Extracellular potassium has been postulated as a critical event in CSD initiation [13]. A recent study suggested CSD initiation can be inhibited by blockage of NMDA glutamate receptors or voltage-gated calcium channels [14]. Evidence from cortical sampling showed a redistribution of ion concentrations in the intra- and extracellular environments [8]. This bioelectric change could be attributed to vascular disturbance or possible ischemia, which may explain the difference in recovery time in our data. As the EEG tends to predominantly reflect cortical changes while the SSEP pathway also includes subcortical sensory fibers, the latter may be slower to recover than the former. An electro-clinical analogy can be seen in the prolonged post-ictal state where the immediate relative voltage attenuation is typically shorter (lasting from seconds to a few minutes) than the aftercoming slow activity (lasting several minutes to even hours [15]; a phenomenon reflecting a longer recovery time of the partially cortical differentiated pathways from the subcortical structures.

Levetiracetam, a modulator of synaptic vesicle release [16], was administered as a one-time intravenous injection to our patient following seizure onset. While it is theoretically possible that this medication could cause SSEP amplitude attenuation, any pharmacological effect would be expected to dampen responses in a global fashion rather than the stepwise progression we observed over several minutes [17]. The temporal progression of the SSEP changes in our case is not consistent with a medication effect.

We believe this case is compelling evidence for the intraoperative presence of a CSD-like phenomenon. The timing of the SSEP changes relative to a generalized seizure with post-ictal EEG suppression near the end of the case, the selective amplitude dampening of cortical SSEPs with relative cervical sparing, and the stepwise progression of the SSEP changes (rather than diffuse changes as would be seen with post-ictal suppression or medication effect) are highly suggestive of a propagating wave of depolarization/depression limited to the cerebral cortex. Continuous intraoperative neurophysiologic monitoring allows the

real-time electrophysiologic observation of an event fitting the CSD description, and may prove useful for future qualification and quantification of such events, which have proven elusive in the clinical setting. We recognize that our situation was not optimal for recording a CSD-like event, as this was a routine intraoperative neurophysiologic study collected in the operating room with widely available equipment, parameter settings, and electrodes. Even under these sub-optimal CSD recording conditions, we recorded a series of events resembling CSD. One issue is that this phenomenon is rare and our case report is just a beginning—however as IONM is becoming more ubiquitous, more opportunities to capture and quantify these events are possible which may help our understanding of the complex cortical circuitry following abnormal electrical events of the brain.

This report describes a single case study, which the authors recognize does not have the generalizability of larger clinical studies. Additional reports of similar intraoperative findings may shed important light on the frequency of such events. Additionally, this single study cannot definitively prove a cause-and-effect relationship or fully explain the complex relationship between CSD and seizures.

6. Summary

In conclusion, postictal attenuation of SSEP amplitudes was observed intraoperatively, and these changes may be consistent with the phenomenon of cortical spreading depression. Recognizing these changes is important, so that they are not mistakenly attributed to some other cause such as a surgical event, in which case a false alert could lead to unnecessary surgical intervention, alteration, or even the abortion of the procedure. Also, the recognition of an ictal and subsequent CSD-like intraoperative pattern may help in prioritizing treatment urgency, directing treatment options, and understanding better the likelihood of temporal recovery. Further investigation is needed to determine if these patients may show signs of postoperative cognitive difficulties, slower recovery in general, or should be monitored postoperatively for subsequent seizure(s) or even development of epilepsy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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