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The Underappreciated But Potentially Lethal Role of Brainstem Dysfunction in Epilepsy

Association of Peri-Ictal Brainstem Posturing With Seizure Severity and Breathing Compromise in Patients With Generalized Convulsive Seizures

Vilella L, Lacuey N, Hampson JP, et al. *Neurology*. 2021;96(3):e352-e365. doi:10.1212/WNL.0000000000011274

Objective: To analyze the association between peri-ictal brainstem posturing semiologies with postictal generalized electroencephalographic suppression (PGES) and breathing dysfunction in generalized convulsive seizures (GCS). Methods: In this prospective, multicenter analysis of GCS, ictal brainstem semiology was classified as (1) decerebration (bilateral symmetric tonic arm extension), (2) decortication (bilateral symmetric tonic arm flexion only), (3) hemi-decerebration (unilateral tonic arm extension with contralateral flexion), and (4) absence of ictal tonic phase. Postictal posturing was also assessed. Respiration was monitored with thoracoabdominal belts, video, and pulse oximetry. Results: Two hundred ninety-five seizures (180 patients) were analyzed. Ictal decerebration was observed in 122 (41.4%) of 295, decortication in 47 (15.9%) of 295, and hemi-decerebration in 28 (9.5%) of 295 seizures. Tonic phase was absent in 98 (33.2%) of 295 seizures. Postictal posturing occurred in 18 (6.1%) of 295 seizures. Postictal generalized electroencephalographic suppression risk increased with ictal decerebration (odds ratio [OR]: 14.79, 95% CI: 6.18-35.39, $P < .001$), decortication (OR: 11.26, 95% CI: 2.96-42.93, $P < .001$), or hemi-decerebration (OR: 48.56, 95% CI: 6.07-388.78, $P < .001$). Ictal decerebration was associated with longer PGES ($P = .011$). Postictal posturing was associated with postconvulsive central apnea (PCCA; $P = .004$), longer hypoxemia ($P < .001$), and Spo2 recovery ($P = .035$). Conclusions: Ictal brainstem semiology is associated with increased PGES risk. Ictal decerebration is associated with longer PGES. Postictal posturing is associated with a 6-fold increased risk of PCCA, longer hypoxemia, and Spo2 recovery. Peri-ictal brainstem posturing may be a surrogate biomarker for GCS severity identifiable without in-hospital monitoring. Classification of evidence: This study provides Class III evidence that peri-ictal brainstem posturing is associated with the GCS with more prolonged PGES and more severe breathing dysfunction.

Commentary

Drug-resistant epilepsy is associated with a lifetime mortality ratio of 2 to 3 times the general population, and sudden unexpected death in epilepsy (SUDEP) is the most tragic outcome in this disorder. Young people are among those at the highest risk of succumbing to SUDEP, particularly individuals with a history of frequent generalized seizures. The mechanisms of SUDEP are poorly understood but have been hypothesized to involve brainstem pathophysiology.[1] It is possible that both lower and upper brainstem dysfunction during seizures may contribute to this phenomenon, leading to respiratory arrest as well as impairments in ascending arousal systems, respectively. Although some animal studies of seizures have supported this hypothesis, brainstem involvement during seizures has not been studied in humans.

In the highlighted study by Vilella and colleagues, the authors sought to indirectly relate presumed brainstem involvement during generalized seizures with clinical factors that might predispose to SUDEP in adult epilepsy patients.[2] Data were collected from 295 generalized seizures in 180 patients undergoing video-electroencephalogram (EEG) monitoring at multiple epilepsy monitoring units (EMUs), with approximately half of seizures captured during wakefulness and half during sleep. Approximately 16% of patients had a generalized epilepsy subtype, while most had presumed focal or multifocal onset, with temporal lobe localization being most common. Investigators correlated tonic seizure phase and postictal semiology with cardiorespiratory measures including hypoxemia, SpO_2 recovery, and central apnea, as well as postictal generalized electroencephalographic suppression (PGES) on EEG. Notably, in the Mortality in Epilepsy Monitoring Unit Study, PGES and cardiorespiratory instability were observed in all monitored cases of SUDEP.[3]

The investigators found that brainstem posturing (decerebrate, decorticate, hemi-decerebrate), which was present in two-thirds of seizures, was significantly associated with the

presence and duration of PGES. The longest episodes of PGES were seen in seizures with ictal decerebration, and the shortest episodes were observed during events associated with hemidecerebration, but no clear differences in PGES patterns were noted between seizures occurring during wakefulness versus sleep. Also, the duration of tonic posturing was associated with hypoxemia duration and SpO_2 recovery, and postictal posturing was also associated with longer hypoxemia and SpO_2 recovery, as well as a markedly increased risk of post-convulsive central apnea. Prior work by the authors demonstrated that post-convulsive central apnea may represent an important biomarker of SUDEP.[4] Based on the presently highlighted results, the authors conclude that brainstem semiology is related to seizure severity markers such as PGES and peri-ictal breathing dysfunction, with a clear relationship between semiologic severity and these measures of neurologic and respiratory compromise.

Overall, the findings of Vilella and colleagues provide a compelling suggestion that brainstem posturing during and following generalized seizures is associated with clinical factors that may increase SUDEP risk. The authors acknowledge that a limitation of the study is that these conclusions can only be indirectly presumed. SUDEP outcomes were not included in this patient population, and tonic posturing is not a direct indication of brainstem influence of seizure activity. Nevertheless, the case for brainstem involvement in epilepsy and its potential relationship to SUDEP has been supported by various human and animal studies.

In rodent models of temporal lobe epilepsy, limbic seizure activity has been shown to spread to subcortical arousal centers, including brainstem serotonergic nuclei, which may contribute to suppression of neocortical activity and behavior.[5] Also, human neuroimaging studies have demonstrated brainstem atrophy and network disruption in focal epilepsy patients which may affect both caudal respiratory centers and rostral arousal networks.[6,7] It is possible that SUDEP involves not only seizure-induced hypoventilation, potentially influenced by the spread of seizure spread from amygdala to the brainstem,[8] but also a subsequent failure of normal arousability from hypercapnia, which requires the brainstem ascending reticular activating system. Continued mechanistic studies in animal models and neuroimaging investigations of human patients focusing on the potential contributions of brainstem dysfunction to SUDEP will be critical moving forward.

There are several practical clinical considerations relevant to the findings of Vilella and colleagues. Respiratory monitoring is not routinely utilized in many EMUs, but SUDEP and near-SUDEP events have occurred in the hospital setting. Antiseizure medication wean increases the likelihood of generalized seizures, which may be less common in a patient's natural setting.[9] Recently in our own EMU, a patient undergoing intracranial stereotactic EEG monitoring experienced a near-SUDEP event in conjunction with a severe generalized seizure, characterized by prolonged PGES, postictal apnea, and hypoxia.[10] Therefore, respiratory monitoring with a respiratory belt and continuous pulse oximetry should be more strongly considered in the EMU setting.

Given that generalized seizures with tonic brainstem posturing may convey the highest risk for PGES and apnea, providers should consider additional SUDEP counseling and precautions for patients who demonstrate this seizure semiology. Finally, given that epilepsy surgery has been shown to reduce risk of SUDEP and mortality in patients with drug-resistant focal epilepsy, referral to a tertiary epilepsy center for surgical evaluation should be expeditiously pursued in these individuals, particularly in those who have generalized seizures. SUDEP is a truly catastrophic consequence of epilepsy, so "all hands on deck" are needed for innovative research, mitigation policies, and patient education.

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