



Generalized Postictal EEG Background Suppression: A Marker of SUDEP Risk

An Electroclinical Case-Control Study of Sudden Unexpected Death in Epilepsy.

Lhatoo, SD, Faulkner, HJ, Dembny, K, Trippick, K, Johnson, C, Bird, JM. *Ann Neurol* 2010;68(6):787–796.

OBJECTIVE: Sudden unexpected death in epilepsy (SUDEP) accounts for approximately 1 in 5 deaths in patients with epilepsy, but its cause remains unexplained. A recorded seizure resulting in death in our center appeared to suggest that postictal generalized electroencephalographic (EEG) suppression (PGES) and apnea are implicated in SUDEP. Our objective was to determine the association between PGES, as a possible identifiable EEG marker of profound postictal cerebral dysfunction, and SUDEP. **METHODS:** We studied 10 adult patients from our video-telemetry database who had 30 documented epileptic seizures during video-EEG recording and who later died of SUDEP. They were compared with 30 matching live controls with 92 epileptic seizures taken from the same database. Clinical and EEG findings were analyzed. **RESULTS:** PGES was seen in 15/30 (50%) case and 35/92 (38%) control seizures. A Mann-Whitney U test showed that PGES was significantly longer in the generalized motor seizures of the SUDEP group ($p < 0.001$). After adjustment for variables, odds ratio analysis of all seizures indicated significantly elevated odds of SUDEP with PGES durations of >50 seconds ($p < 0.05$). Beyond 80 seconds, the odds were quadrupled ($p < 0.005$). After adjustment for variables, for each 1-second increase in duration of PGES, the odds of SUDEP increased by a factor of 1.7% ($p < 0.005$). **INTERPRETATION:** Prolonged PGES (>50 seconds) appears to identify refractory epilepsy patients who are at risk of SUDEP. Risk of SUDEP may be increased in direct proportion to duration of PGES. Profound postictal cerebral dysfunction, possibly leading to central apnea, may be a pathogenetic mechanism for SUDEP.

Commentary

Although epilepsy-related mortality and sudden unexplained death in epilepsy (SUDEP) have been recognized for centuries, our understanding of the pathophysiology remains limited. For patients with epilepsy, an increased standardized mortality of two to three times has been reported, with multiple factors accounting for this risk, including accidental death and deaths secondary to the underlying etiology for seizures (e.g., stroke, tumor) (1). The incidence of SUDEP varies between studies and patient populations but ranges from 0.09 and 0.35 per 1,000 person years in the general epilepsy population to between 6.3 and 9.3 per 1,000 person years in treatment resistant epilepsy (TRE) who have failed epilepsy surgery (2).

Efforts to understand SUDEP are limited by both its relatively infrequent occurrence and the limited number of direct observations during or preceding the patient's death. Although a number of studies have, largely retrospectively, identified risk factors associated with SUDEP, methodologic issues limit comparisons between studies and the generalizability to broader populations with epilepsy (e.g., definition of

SUDEP and choice of control population) (2). A review of ten case-controlled studies utilizing living patients with epilepsy as controls identified several common risk factors, including poor seizure control, longer duration of epilepsy, and younger age at onset of seizures (2). Effects of antiepileptic drug (AED) therapy varied between studies. Polytherapy was associated with an increased risk of SUDEP in four studies, two studies identified carbamazepine as an independent risk, and one study identified absence of treatment with AEDs as a significant SUDEP risk (2–4).

Although these data provide a potential method for identifying higher risk populations, they provide only limited insights into the underlying pathophysiology. Most theories on SUDEP focus on either cardiac or pulmonary mechanisms, although specific physiologic biomarkers of susceptibility to SUDEP remain elusive. In two cases undergoing scalp EEG monitoring, SUDEP was preceded by profound postictal generalized EEG suppression (PGES) (5, 6).

Lhatoo et al. investigated the risk of SUDEP relative to the duration of PGES, studying ten definite SUDEP patients (from 1997–2009) with at least one prior seizure in the video EEG monitoring unit along with 30 consecutive patients who had undergone monitoring prior to March 2009. All patients had TRE. EEG and clinical data were reviewed by two blinded teams. PGES was defined as a generalized absence of background activity above 10 μV beginning within 30 seconds



of cessation of the ictal discharge. A total of 31 seizures in the SUDEP group and 92 seizures in the control group were analyzed.

Although no significant difference was seen across all seizure types, a longer PGES duration was found in SUDEP cases compared with controls ($p < 0.001$) for generalized motor seizures. Linear regression identified age, gender, and the age at onset of seizures as significant factors for SUDEP. For all seizure types, PGES >50 seconds in duration were associated with an increased risk of SUDEP. After adjusting for age, gender, and age at onset, the odds ratio (OR) for >50 seconds was 5.22 and for >90 seconds the OR was 23.46. A similar increased risk was seen when only generalized motor seizures were analyzed, with durations >20 seconds (OR 12.99) showing an increased risk.

These findings suggest for each 1-second increase in the duration of PGES, the odds of SUDEP increase by 1.7%. The mechanism by which PGES starts and ultimately resolves is not understood nor is the relationship between PGES and SUDEP. A recent review hypothesized a role for dysfunction of the serotonin system following seizures that could blunt both respiratory drive and arousal responses to hypercapnea following a seizure (7). Thus, the PGES seen in some patients could reflect a broader disruption of cortical and subcortical brain functions that, in turn, predisposes them to SUDEP. However, one cannot discount the potential role of cardiac dysrhythmia in SUDEP; dysrhythmia and asystole have long been reported during and following seizures, and a recent study utilizing a mouse model with dominant human LQT1 mutations exhibited a phenotype of seizures and malignant cardiac arrhythmia (8).

In the supplementary materials, Lhatoo et al. report the case of a 39-year-old man who died during presurgical video-EEG evaluation. This case of SUDEP following a tonic-clonic seizure illustrates the complex interplay between cardiac, respiratory, and electrographic findings. In this case, sinus bradycardia was noted 2 seconds prior to the electrographic cessation of the seizure (ECS), and asystole occurred 15 seconds following the ECS. Subsequent ventricular escape rhythms and then asystole were seen, ultimately returning to a sinus rhythm 82 seconds following ECS. Significant muscle artifact obscured the EEG following ECS, but PGES was clearly seen 25 seconds after ECS (10 seconds after onset of asystole). Respirations remained regular (every 2–3 seconds) until 32 seconds following ECS, at which time a 91-second apnea was observed followed by continued regular respirations every 4 to 5 seconds. PGES never resolved, and the patient's final respiratory effort was seen 479 seconds after ECS; the final cardiac P wave was 527 seconds after ECS.

Although this study is limited by the small sample of patients and seizures in the SUDEP group, these data demonstrate a significant, quantifiable measure of SUDEP risk. Ultimately, the most important step is to identify not only risk

factors and predictors, but mechanisms by which SUDEP risk can be mitigated. In a review of 583 patients following epilepsy surgery, mortality was significantly reduced in patients who were seizure free following surgery; SUDEP accounted for 10 of the 19 deaths (9) reviewed. Beyond measures to control and eliminate seizures, existing data suggest that observation (e.g., bed partner) or monitoring (e.g., seizure alarms) at night may be protective against SUDEP (3).

Although this study raises many questions, it is an important step toward understanding and ultimately preventing SUDEP. These data provide a potential risk-stratification based upon postictal EEG data in addition to clinical factors. Confirmation of these findings in a larger sample of patients and seizures is important; however, these data do support a careful evaluation of not only the ictal, but also the postictal EEG, for all seizures with documentation of prolonged PGES.

For all patients, regardless of the presence/absence of PGES, complete control of seizures should remain the primary goal of treatment. For patients with significant PGES, particularly in patients with evolution to tonic-clonic seizures, the role of further intervention (e.g., listening devices or monitoring of cardiac or respiratory status) is unclear and will largely be based upon both physician and patient/family preferences until further data are available. Only through prospective studies linking clinical, cardiac, respiratory, and electrophysiology data can the pathophysiology be further elucidated, thereby providing a path to future effective interventions.

by Chad Carlson, MD

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