UNRAVELING THE SECRETS OF SUDDEN DEATH IN EPILEPSY: IS IT POSSIBLE?

EEG and ECG in Sudden Unexplained Death in Epilepsy

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PURPOSE: Sudden unexpected death in epilepsy (SUDEP) is a major cause of mortality for patients with epilepsy. Cardiac factors may be involved and were evaluated in this study.

METHODS: EEG and ECG data for 21 patients with definite ($n = 6$) or probable ($n = 15$) SUDEP were compared with data from a group of 43 patients with refractory partial epilepsy. ECG abnormalities and heart rate (HR) changes were correlated with clinical data.

RESULTS: Fourteen patients died in their sleep; two were awake. Ictal maximal HR (90 seizures from 16 of 21 patients) was significantly higher in SUDEP (mean, 149 beats/min, BPM) than in comparison patients (mean, 126 BPM; $P < 0.001$). Greater increases in HR were associated with seizures arising from sleep (78 BPM increase) than from wakefulness (47 BPM; $P < 0.001$) in SUDEP, as compared with the non-SUDEP group (52 BPM in sleep, 43 BPM in wakefulness; $P = 0.27$). Ictal cardiac repolarization and rhythm abnormalities occurred in 56% of SUDEP (including two atrial fibrillation, two ventricular premature depolarizations, two marked sinus arrhythmia, two atrial premature depolarizations, one junctional escape, one ST-segment elevation), and 39% of comparison patients ($P = 0.39$). No specific seizure onset (laterality or lobe) was associated with SUDEP.

CONCLUSIONS: This study reveals, for the first time, evidence of increased autonomic stimulation (as measured by HR) associated with seizures, particularly in sleep, in patients with SUDEP, as compared with a clinically similar group of patients with refractory epilepsy.

COMMENTARY

Multiple investigators have tried to identify the mechanisms mediating sudden death in epilepsy (SUDEP), but to date, they remain unknown. Johnston et al. (1,2) developed an experimental model for sudden death after seizures through the chemical induction of seizures in sheep. These authors identified ictal-induced central hypoventilation, high pulmonary vascular pressures, and pulmonary edema in the animals that died. By using video-EEG-telemetry studies, Nashef et al. (3) found seizure-induced central apnea in 10 of 17 patients with epilepsy, and bradycardia in 4 of these 10 patients. Cardiac arrhythmias also have been proposed as a potential mechanism leading to SUDEP, including tachycardia, bradycardia, and asystole (4–7).

The advent of video-EEG (V-EEG) monitoring studies has provided clinicians and investigators with an ideal setting in which to study potential cardiac and respiratory abnormalities. Indeed, using ictal data collected in the course of V-EEG, Nei et al. were able to demonstrate ictal tachycardia of greater severity in seizures occurring during sleep among patients who eventually had SUDEP compared with controls (8). Control patients were not free of cardiac abnormalities, however, as ictal-induced cardiac rhythm abnormalities and repolarization disturbances were as frequent in SUDEP as in control patients.

Unfortunately, the authors failed to extend their analyses to abnormalities of the heart rate variability (HRV), a measure of sympathovagal imbalance (i.e., either heightened sympathetic activity, decreased parasympathetic regulation, or both), which has been found to be a risk factor for sudden death and ventricular arrhythmias in nonepilepsy patients with cardiovascular disease (9,10). For example, patients with low HRV, defined as a standard deviation of normal R-R intervals more than 50 msec, were 5.3 times more likely to die during a 31-month follow-up period than were patients with normal HRV (11). These data are applicable to SUDEP patients, given that postmortem myocardial abnormalities have been reported in SUDEP. For example, in the study of Nei et al., in one of two patients who had microscopic examination of the myocardium, diffuse myocardial injury was noted.

The following variables have been associated with the occurrence of SUDEP: (a) uncontrolled and frequent seizures (although patients with rare seizures are not necessarily spared SUDEP); (b) generalized tonic–clonic seizures (although patients with complex partial seizures also can have SUDEP); (c) mental retardation; (d) low antiepileptic drug serum concentration at the time of death; and (e) seizures during sleep (6,7,11–16). A definite pathogenic role for these variables is yet to be established.

Determining the actual pathogenic role played in SUDEP, by all the potential variables cited earlier, requires the prospective collection of data in a large number of patients. Such an undertaking can be achieved only in multicenter studies organized and sponsored by a governmental agency, such as the National Institutes of Health, with the establishment of national (or international) SUDEP registry. Walczak et al. (16) carried out this type of a study on a small scale when they collected prospective data from three epilepsy programs, enrolling 4,578 patients, whom they followed up prospectively for 16,463 patient-years; among these patients, only 28 patients died of definite, probable, or possible SUDEP. This finding of so few patients with SUDEP clearly demonstrates the need to include a large number of epilepsy centers from the United States (and abroad), if we are to collect meaningful data that could lead to the identification of risk factors and actual mechanisms of SUDEP.

In population-based studies, the risk of sudden unexpected death was found to be 24 to 40 times higher in patients with epilepsy than in the general population (17), accounting for 7% to 17% of deaths among the general population with epilepsy and up to 50% among patients with refractory epilepsy. Yet these ominous statistics continue to elude patients, families, and clinicians alike. Educating patients and the medical community on the existence of SUDEP is a necessary step to minimizing its occurrence. Seizure freedom after epilepsy surgery reduces the risk of sudden death to that of the general population (15). Furthermore, this type of information will most likely lead clinicians to become less complacent about persistent seizures and motivate patients and their families to seek more effective therapies capable of increasing the possibility of seizure freedom. An elevation in conscious awareness of SUDEP also will result in an earlier recognition of refractory epilepsy so that patients do not have to wait 15 to 20 years before they can be considered for curative treatments like epilepsy surgery.

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