

SUDDEN UNEXPECTED DEATH IN EPILEPSY

Hiba Arif¹ and Tariq Naseem²

¹The Neurological Institute, Columbia University; and ²Department of Surgery, Columbia-Presbyterian Medical Center, New York, NY, USA

Correspondence to: Hiba Arif MD, Research Fellow, The Neurological Institute, Columbia University, New York, NY 10027, USA. Email: harif@neuro.columbia.edu

Every year, about one in 1000 patients with chronic severe epilepsy will die suddenly, unexpectedly and without warning. Explanations are not forthcoming, even on post-mortem examination. This well recognized clinical phenomenon is known as SUDEP (Sudden Unexpected Death in Epilepsy). For the past century, clinical series of proportionate mortality in patients with epilepsy have suggested an unusually high rate of unexplained deaths in such patients. These observations have sparked debate and raised concerns regarding possible prevention, risk factors, and the ethical challenge of discussing this small but real prospect of death with patients who are living with epilepsy.

EPIDEMIOLOGY

SUDEP accounts for 7-17% of deaths among patients with epilepsy. The reported incidence spans a wide range - from 0.35 deaths per 1000 person-years in a population based cohort¹ to 6 deaths per 1000 person-years in a cohort with refractory epilepsy.² In a population based study, the risk of sudden unexplained death was 24 times higher than that seen in the general population.¹ Direct comparison of these and other studies is ill-advised, because the study populations, level of documentation, and definitions of SUDEP vary considerably across studies; the risk of SUDEP may also depend on the nature of the underlying population. The general population includes the entire spectrum of age and medical conditions; consequently, the proportion of deaths from SUDEP and the SUDEP mortality rate is lower. On the other hand, cohorts chosen from epilepsy clinics or epilepsy surgery series represent the other extreme of the patient spectrum. These consist of otherwise healthy, relatively young individuals who have fewer other reasons to die; hence, SUDEP achieves a greater prominence as a cause of death.³

MECHANISMS

Mechanisms leading to SUDEP remain largely unknown, though cardiac and pulmonary derangements have been hypothesized.^{4,5} There is some evidence to support EKG changes as the terminal event. Ictal EKG studies have found evidence of transient ictal conduction abnormalities and myocardial ischemia.^{5,6} Peri-ictal prolonged asystolic periods have been associated with SUDEP⁷, which directly implicates cardiac arrhythmias as the underlying cause of at least some cases of SUDEP. Central apnea has also been postulated as a cause. Since both cardiac and pulmonary mechanisms can account for SUDEP, the actual etiology is likely to be patient- and seizure-dependent.

RISK FACTORS

Earlier studies have suggested that male gender, cerebral lesions, developmental delay, a history of ongoing tonic-clonic seizures, and subtherapeutic anticonvulsant drug levels predominated in patients who died of SUDEP.^{8,9} Later studies yielded conflicting results, yet certain features have been consistent in most SUDEP series.^{2,10} It appears that patients with uncontrolled seizures are at the highest risk, and that patients with well controlled epilepsy (seizure-free), are not at increased risk. Seizure frequency may be related to risk of SUDEP, as patients with frequent seizures die more often than those with few seizures. Nonetheless, it is abundantly clear that even patients with rare seizures, experiencing as few as 1 per year, are at increased risk of dying. Seizure type also influences risk. Tonic-clonic seizures convey the greatest risk of SUDEP, though sudden death can certainly occur in the presence of other types of seizures (e.g., complex partial seizures).^{1,2,10,11} Concomitant neurological illness may also influence the risk of SUDEP. Mental retardation, which is a marker of brain dysfunction, appears to be a

significant risk factor, but recent series have not found structural lesions to be associated with SUDEP.¹⁰

Anticonvulsant medication may also relate to risk of SUDEP. Initially, low serum levels of anticonvulsant drugs were noted in autopsied cases,¹² which led to the notion that poor compliance may have precipitated seizures and subsequent death. Recent studies, however, have not been able to replicate these findings. Opeskin et al.¹¹ found no evidence for poor compliance with medical therapy or lower serum levels in patients who died of SUDEP, as compared with controls. While Nilsson et al. related less frequent therapeutic drug monitoring to a higher risk, SUDEP was not associated with suboptimal serum drug levels.¹² These authors also associated polytherapy, frequent dose changes, and high carbamazepine levels as risk factors for SUDEP. Most of these may be considered as markers of severe unstable epilepsy. It is still unclear whether high carbamazepine levels are a risk factor for SUDEP per se or represent some unidentified aspect of epilepsy. However, two recent studies^{10,12} have noted an association between polytherapy and SUDEP. Patients on multiple drugs appeared to have a higher SUDEP rate. It is unclear whether this reflects a risk conveyed by antiepileptic drugs or rather the presence of more severe epilepsy.

PREVENTION

At the present time, there are no clear guidelines for the prevention of SUDEP. Based on the review of risk factors above, aggressive seizure control and emphasis on compliance would appear to be logical recommendations. In a case-control study, Nilsson and associates identified frequent changes in anti-epileptic drug (AED) regimens as a risk factor for SUDEP.¹³ Most SUDEP cases occur during sleep. One retrospective, non-randomized study found that patients who sleep with someone else in the room or have nocturnal monitoring devices are less likely to be SUDEP victims.¹⁴ It may also be reasonable to avoid AEDs that are known to affect the cardiac conduction system in patients judged to be at increased risk of SUDEP. As shown in a recent study by Rugg-Gunn et al.,⁷ implanting permanent pacemakers after detection of cardiac arrhythmias by subcutaneous loop recorders can help prevent the consequences of bradyarrhythmias that could otherwise lead to SUDEP. The use of implantable loop recorders is not without its caveats: it is possible that such strategies may be overused, patients may experience excessive anxiety about a condition that might or might not be preventable, and potential false positives could lead to unnecessary pacemaker insertion. Thus, these findings need to be replicated before these devices can be used for the routine care of patients with epilepsy.

PHYSICIAN VERSUS PATIENT - TO TELL OR NOT TO TELL?

There are differences of opinion regarding if and when SUDEP should be discussed with patients. Although all patients and families should be aware of the dangers of seizures and the importance of medication compliance, we recommend concentrating on discussion of seizure-related injuries and deaths that are clearly preventable, such as those associated with outdoor activities, driving, swimming or bathing alone, bicycling on busy roads, working at heights, or other risky behaviors. An extended discussion of SUDEP with every patient does not seem reasonable or warranted, given that SUDEP is not common, and that only a subgroup of epilepsy patients are at relatively high risk. A commonsense approach is required. The potential of adverse psychological and other effects as a consequence of overemphasizing SUDEP, especially in children and young adults, such as increased supervision and limitation of activities, should be borne in mind. A reasonable and judicious practice is to provide all patients with comprehensive information on epilepsy and its consequences, including SUDEP, but to discuss it directly only if asked, if patients are non-compliant, if there is a family history of sudden death, or as part of the decision-making process regarding epilepsy surgery. Although there is evidence that successful epilepsy surgery is associated with a lower risk of SUDEP and longer life expectancy^{15,16}, some studies have shown little difference between preoperative and postoperative mortality^{17,18}. If only seizure-free patients are considered, mortality does appear to be decreased postoperatively^{16,18}. It is also possible that differences in survival between operated and non-operated groups of patients with intractable epilepsy could be due, at least in part, to preoperative biological differences between cured and non-cured patients. For example, autonomic dysfunction appears to be more common in patients who fail surgery¹⁹, and it has been hypothesized that insular involvement could explain both surgical failure and a predisposition to SUDEP²⁰.

CONCLUSION

Patients with chronic epilepsy are faced with a small but real risk of sudden unexplained death. Many of these patients are young and otherwise healthy, and have little other reason to die. Until the risk factors and mechanisms behind SUDEP are elucidated in greater detail, prevention must focus on aggressive measures to ensure compliance with medication. Reducing seizure frequency must be the prime goal, since even infrequent seizures can cause death.

REFERENCES

1. Ficker DM. Sudden unexplained death and injury in epilepsy. *Epilepsia* 2000; 41 Suppl 2: S7-12
2. Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. *Ann Neurol* 1999; 46: 45-50
3. Sperling MR. Sudden Unexplained Death in Epilepsy. *Epilepsy Curr* 2001; 1: 21-3
4. So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. *Epilepsia* 2000; 41: 1494-7
5. Lathers C, Schraeder P, Boggs J. Sudden unexplained death and autonomic dysfunction. *Epilepsy: A comprehensive textbook*. Philadelphia: Lippincott-Raven Press 1997; p. 1943-55
6. Nei M, Ho RT, Sperling MR. EKG abnormalities during partial seizures in refractory epilepsy. *Epilepsia* 2000; 41: 542-8
7. Rugg-Gunn FJ, Simister RJ, Squirrell M, Holdright DR, Duncan JS. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. *Lancet* 2004; 364: 2212-9
8. Leestma JE, Kalelkar MB, Teas SS, Jay GW, Hughes JR. Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia* 1984; 25: 84-8
9. Leestma JE, Walczak T, Hughes JR, Kalelkar MB, Teas SS. A prospective study on sudden unexpected death in epilepsy. *Ann Neurol* 1989; 26: 195-203
10. Walczak TS, Leppik IE, D'Amelio M, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. *Neurology* 2001; 56: 519-25
11. Opekin K, Thomas A, Berkovic SF. Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy? *Epilepsy Res* 2000; 40: 17-24
12. Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. *Epilepsia* 2001; 42: 667-73
13. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet* 1999; 353: 888-93
14. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005; 64: 1131-3
15. Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. Mortality after epilepsy surgery. *Epilepsia* 2005; Suppl 11: 49-53
16. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* 2002; 43: 170-4
17. Stavem K, Guldvog B. Long-term survival after epilepsy surgery compared with matched epilepsy controls and the general population. *Epilepsy Res* 2005; 63: 67-75
18. Nilsson L, Ahlbom A, Farahmand BY, Tomson T. Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia* 2003; 44: 575-81
19. Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. *Neurology* 2005; 65:1021-5
20. Ryvlin P, Montavon A, Kahane P. The impact of epilepsy surgery on mortality. *Epileptic Disord* 2005; 7 Suppl 1: 39-46