ORIGINAL ARTICLE

Sudden unexpected death in epilepsy: experience from a tertiary epilepsy centre in Cyprus with review of the literature

Papacostas SS

The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

Abstract

Background: Sudden unexpected death in epilepsy (SUDEP) affects 0.09-9.3 per 1,000 person-years depending on the population studied and constitutes the most common cause of death in people with epilepsy. The purpose of this study was to analyze epidemiological data of patients with SUDEP, identify possible risk factors in the population of a tertiary referral center and provide a review of the literature aiming to raise awareness of this phenomenon.

Methods: Data for this study originate from the records of the Cyprus Institute of Neurology and Genetics in Nicosia Cyprus. We performed a systematic review of patients with epilepsy who had died between 1997 and 2012 and identified those whose death circumstances met the definition of SUDEP. Information was collected regarding sex, age, type of seizures, anti-epileptic therapies, and circumstances of death. Ethical approval was obtained from the institutional medical ethics committee.

Results: Four hundred and forty four new patients were diagnosed with epilepsy among referrals to the epilepsy clinic and were followed to the end of the study period. Seven patients, six males, were identified who met criteria for SUDEP. The average age was 30 years. All patients had had either primary or secondary tonic-clonic seizures. Most were on polypharmacy, and two had Vagus Nerve Stimulation implanted. Most deaths were unwitnessed and nocturnal. The overall incidence rate for SUDEP in this population was 2.13 deaths/1000 person-years. Overall Cumulative Incidence (or lifetime risk) was calculated at 15.76 SUDEP deaths/1,000 patients.

Conclusions: In our series, SUDEP was primarily a nocturnal and unwitnessed event that affected primarily young males. Among both males and females patients, 36.8% of all deaths were due to SUDEP. The major risk factor identified was the occurrence of generalized tonic-clonic seizures signifying that every effort should be made to control this type of seizures. Hippokratia 2015; 19 (4): 338-343.

Keywords: SUDEP, epidemiology, epilepsy, case series, risk factors

Corresponding Author: Papacostas Savvas, MD, FAAN, Neurology Clinic B', The Cyprus Institute of Neurology and Genetics, 6 International Airport Road, 1683 Nicosia, Cyprus, tel: +35722358600, fax: +35722392786, e-mail: savvas@cing.ac.cy

Introduction

Mortality in people with epilepsy (PWE) is higher than the general population due partly to sudden unexpected death (SUDEP). A common definition of SUDEP is "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where postmortem examination does not reveal a cause for death"[1]. This definition differs from that of sudden death in general, because the latter includes deaths with and without an identified pathologic cause, whereas SUDEP refers to deaths without an identified pathologic or toxicological cause. However, most evidence suggests that the majority of SUDEP cases occur following terminal seizures, and result from functional pathogenic mechanisms[1].

The concept of SUDEP is not recent. In 1868, Bacon[2] wrote about "sudden death in a fit", whereas Spratling[3] referred to epilepsy as "a disease which destroys life suddenly and without warning through a single brief attack". Livingstone[4] however, claimed that "there is no reason why someone with epilepsy … should not live as long as he would if he did not have epilepsy". Recently, a consensus on a unified definition and a working classification was proposed along with nine recommendations[5]. The word "unexpected," instead of "unexplained," was proposed to be used in the term SUDEP; the term should be applied whether or not a terminal seizure is known to have occurred. The category "Possible SUDEP" should be used in cases with competing causes of death; the term "SUDEP Plus" should be used when evidence indicates that a pre-existing condition, known before or after autopsy, could have contributed to the death (e.g. long-QT syndrome with no documented primary ventricular arrhythmia leading to death or coronary insufficiency with no evidence of myocardial infarction). Death should have occurred within one hour from the onset of a known terminal event. Status epilepticus lasting more than 30 min should be an exclusion criterion for SUDEP. A specific category of SUDEP due to asphyxia should not be designated. Death occurring in

water but without circumstantial or autopsy evidence of submersion should be classified as "Possible SUDEP"; and the designation "Near-SUDEP" should include cases of cardiorespiratory arrest reversed by resuscitation and subsequent survival for more than one hour.

It should be emphasized that SUDEP is not a diagnosis of death but a clinical event which strikes immediately following convulsive seizures and remains a diagnosis of exclusion[6]. Against this background, we sought to identify the series of SUDEP that occurred in our Institution.

Materials and Methods

The data of this study originate from the records of the Cyprus Institute of Neurology and Genetics, a tertiary referral medical and academic center in Nicosia Cyprus, where patients with intractable and pharmacoresistant epilepsy are managed. We carried out a systematic review of patients with epilepsy who died between 1997 and 2012 and identified those whose death circumstances met the definition of SUDEP[1]. Information was collected regarding the sex, age, type of seizures, anti-epileptic therapies and circumstances of death. Data on this series are presented in tabular form (Table 1), and a review of the literature is provided aiming to raise awareness regarding SUDEP. Ethical approval was obtained from the institutional medical ethics committee. Statistical analyses were performed regarding the incidence, cumulative risk, and sex-specific characteristics.

Results

A total of 444 patients had been diagnosed with epilepsy and followed between 1997 and 2011. Of these, seven patients were identified who met the criteria of SUDEP, six men, and one woman, ranging in age from 18 to 55 years with a mean age of 30 years (Table 1). One patient had left-sided temporal lobe epilepsy (TLE), one had right-sided TLE, one had multifocal epilepsy with secondary generalization in the setting of mild static encephalopathy, three had frontal lobe epilepsy with secondary generalization, and one had idiopathic epilepsy with generalized tonic-clonic seizures (GTCS). Circumstances of death are described in the table. All but one (No. 3) were unwitnessed; of the unwitnessed cases, two (33.3%) were found dead in bed, three (50%) were found dead elsewhere in the home, and one (16.5%) was found dead outside the home on his boat. Death occurred in association with a witnessed generalized tonic-clonic seizure in one case; resuscitation was attempted unsuccessfully in this patient by family members. Two patients (Nos. 3 and 4) had vagus nerve stimulation in conjunction with their anti-epileptic therapy.

The overall incidence rate among our population was 2.13 SUDEP deaths/1,000 person-years, whereas the overall Cumulative Incidence (lifetime risk) was 15.76 SUDEP deaths/1,000 patients. Among both male and female patients, 36.8% of deaths were due to SUDEP. Regarding sex-specific characteristics the incidence rate was 0.68 SUDEP deaths/1000 person-years among females, and 3.30 SUDEP deaths/1000 person-years among male patients. Female-specific Cumulative Incidence (or lifetime risk) was 5.10 SUDEP deaths/1000 patients (1 SUDEP death/196 females). Male-specific Cumulative Incidence (or lifetime risk) was 24.19 SUDEP deaths/1000 patients (6 SUDEP death/248 males). Among females, 20% of all deaths were due to SUDEP whereas among males, 42.8% of all deaths were due to SUDEP pointing to a male preponderance.

Discussion

SUDEP incidence depends on the population studied and may vary by a factor of 100; In a US population-based study, Ficker[7] indicated an overall rate which was 20 times higher than expected. Unselected cohorts of incident epilepsy cases have low rates, between 0.09 to 35 per 1,000 person-years[8]. Incidence rates from 0.9 to 2.3 per 1,000 person-years[9,10] were observed in epilepsy populations, whereas in chronic refractory cases they ranged from 1.1 to 5.9 per 1,000 person-years[11,12]. The significance of seizures as a risk factor was demonstrated in epilepsy surgery candidates and in patients who continue to have seizures after surgery with rates between 6.3 to 9.3 per 1,000 person-years[13]. Moreover, in patients with chronic refractory epilepsy, SUDEP accounts for

Table 1: Circumstances of death of the seven patients who met the criteria of sudden unexpected death in epilepsy (SUDEP), identified from 444 patients that had been diagnosed with epilepsy and followed between 1997 and 2011 in the Cyprus Institute of Neurology and Genetics.

A/A	Case	Sex	Age	Seizure Type	Location	AEDs	Timing
1	06/07/54	M	55	L TLE c 2 gen	Home	TPR, Venlafaxine, Mirtazapine	Nocturnal
2	13/10/82	F	29	R TLE c 2 gen	Home	VPA	Morning
3	25/01/90	M	18	MF c 2 gen	Beach	VPA, LTG, TPR, **VNS**	Daytime
4	11/10/86	M	25	L Frontal c 2 gen	Bed	Clobazam, OXC, LEV, **VNS**	Nocturnal
5	26/01/68	M	29	L Frontal c 2 gen	Home	Clonazepam, LTG, CBZ	Nocturnal
6	27/11/87	M	22	NFLE c 2 gen	Bed	(CBZ) Non-compliant	Nocturnal
7	02/06/59	M	35	1 GTC	Boat	VPA, TPR	Daytime

M: male, F: female, AEDs: antiepileptic drugs, TLE: temporal lobe epilepsy, MF: multifocal epilepsy, Frontal: frontal lobe epilepsy, GTC: epilepsy with generalized tonic-clonic seizures, TPR: Topiramate , VPA: Valproate , LTG: Lamotrigine, VNS: vagus nerve stimulation, OXC: Oxcarbazepine, LEV: Levetiracetam, CBZ: Carbamazepine.

10-50% of all deaths and is the leading cause of premature death[14]. The high proportion of SUDEP among our patients probably reflects the relatively young age of our epileptic cohort (average age =41.3 years) and the consequent small number of deaths. In addition, our population mainly consists of intractable cases that were referred in order to undergo a presurgical evaluation or other specialized interventions. Among females, 20% of all deaths were due to SUDEP whereas, among males, 42.8% of all deaths were due to SUDEP pointing to a male preponderance in agreement with other studies.

SUDEP is mostly an unwitnessed event, but there is often circumstantial evidence suggesting that an epileptic seizure did or could have occurred[6]. Among the few witnessed events, habitual seizures were observed, presumed epileptic[6]. Langhan et al in 2000 reported 15 cases in whom SUDEP was preceded by a seizure in 80%, as did 9/12 cases that Kloster and colleagues reported[14]. Seizures seem to resolve before death in all observed cases, and the mechanism appeared to be a respiratory arrest (obstructive or central) in the majority[6].

Supervision, therefore, becomes a putative protective factor, and this is corroborated by several studies[15,16], especially in residential settings which allow close supervision at night, and SUDEP incidence is reported to be low. In fact, in one such study SUDEP occurred during school recess but not during term time[16]. A supervisor may stimulate a person, whose breathing is compromised following a seizure, restoring proper cardiorespiratory function[17] and potentially preventing SUDEP. This becomes significant considering the fact that many such cases are found in the prone position and have unwitnessed deaths during sleep[14]. Six of our seven patients had an unwitnessed death.

In order to elucidate SUDEP risk factors further, the International League Against Epilepsy (ILAE) appointed a Task Force[15] which pooled data from four major case-control studies. Their review included 289 cases and 958 controls with epilepsy and the analysis revealed SUDEP risk 1.4 times higher in males compared to females; moreover, age at onset and duration of epilepsy correlated with SUDEP risk as follows: it was 1.7 times higher in those whose epilepsy begun before 16 years of age compared with those who had onset between ages 16 to 60; risk doubled if epilepsy was present for more than 15 years. Notably, the frequency of GTCS emerged as the most important risk factor for SUDEP as compared to those without GTCS. An odds ratio of 2.94 was estimated for patients having one or two GTCS per year; it was increased to 8.28 in those having three to 12 GTCS per year. A 9.06 odds ratio was associated with a frequency between 13-50 GTCS per year; and 50 or more GTCS per year were associated with an odds ratio of 14.51. In addition, patients on antiepileptic drug (AED) polytherapy, implying intractability, had triple the risk that those on monotherapy. The combination of GTCS frequency with polytherapy had the highest risk[15]. The number and type of AEDs or their combinations had not shown increased risk once the authors adjusted their analysis for GTCS[15]. GTCS frequency remained strongly associated with an increased risk for SUDEP. In our series all patients had GTCS either primary or secondarily generalized. Thus, decreasing GTCS frequency should be one of the main strategies in the attempt to prevent SUDEP[13].

Nocturnal seizures are an independent SUDEP risk factor, therefore, night supervision becomes a key preventive measure. Lambert's study[16] revealed that SUDEP occurred during sleep in 58% of his sample whilst in 86% it occurred as a non-witnessed event; When it occurred during sleep, it was usually unobserved [odds ratio (OR) 4.4, 95% confidence interval (CI) 1.6–12]. Moreover, patients whose SUDEP happened while they were asleep, had more chances to exhibit habitual nocturnal seizures compared to those whose SUDEP was not related to sleep (OR 3.6, 95% CI 1.4–9.4). Moreover, patients with habitual nocturnal seizures had a greater chance of dying than controls who remained alive (OR 3.9, 95% CI 2.5–6.0). Four of our seven patients died at night.

SUDEP probably results from a combination of different mechanisms in different individuals[6]. Most research has focused on the physiological consequences of the hypoventilation associated with seizures (central and/or obstructive) as well as cardiac dysrhythmia. Animal studies using sheep suggested a primary respiratory cause. In one such study[17] five out of 13 sheep died acutely following the onset of a seizure. Those that died exhibited a greater degree of hypoventilation and peak left atrial and pulmonary artery pressure, as well as extravascular edema compared to survivors. In another sheep study of experimental status epilepticus[18], there was a rapid fall in pO_2 and rise in pCO_2 concentrations before death in the animals that died compared with those that survived. In yet a third study Johnston[19] noted the occurrence of central and obstructive apnea, in the absence of significant cardiac dysrhythmias concluding that hypoventilation, originating mainly in the central nervous system, was the culprit of the deaths observed. Likewise, in audiogenic mice, which tend to die following seizures induced by sound stimuli, the phenomenon was totally prevented when they were placed in an environment augmented with oxygen, signifying the importance of respiratory dysfunction as a cause of death[20].

Central apnea was also noted to occur in people with epilepsy, sometimes with peripheral respiratory obstruction components[21]. Reported cases of SUDEP or near-SUDEP while undergoing video electroencephalography (EEG) monitoring suggest the sequence of events that occur; usually a partial-onset, often secondarily generalized, seizure in most of which a lethal interruption or generalized suppression of EEG activity was noted followed by cardiorespiratory changes (central nervous system shut down). Five of our seven patients had partial-onset seizures, all with secondary generalization. Such findings point to a profound central inhibition and possibly explain the central respiratory hypoventilation that occurs. In most cases, apnea and hypoventilation were thought to be the primary cause of death[22-29].

Lhatoo and colleagues[30] reported significantly longer postictal EEG flattening following convulsive

seizures in ten cases with SUDEP compared to 30 controls. The Mortality in Epilepsy Monitoring Unit Study (MORTEMUS)[31] was a review of SUDEP and near-SUDEP cases which took place while undergoing video-EEG telemetry. SUDEP in this study usually followed an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by GTCS, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnea and cardiac arrest.

Cardiac and autonomic changes during seizures have also been considered to be risk factors for SUDEP as it is known that patients with drug-resistant epilepsy can develop subtle cardiac dysfunctions[32,33] or changes in autonomic myocardial control[34-37]. Such a supposition, however, was not corroborated in a small controlled study, which failed to detect differences in the variability of interictal heart rate between seven patients who subsequently had SUDEP and seven controls with epilepsy who did not die[38]. The evidence for ictally-induced changes is more convincing nonetheless. In two studies[39,40] conducted on patients undergoing video-EEG monitoring, ictal asystole occurred in an estimated 0.27-0.40% of cases. Of the ten seizures recorded all were complex partial; eight arose out of the temporal and two out of the frontal lobe.

Rossetti[41] reported the interesting case of drop attacks in a patient with significant improvement following implantation of a demand pacemaker. Cerebral stimulation of insular, orbitofrontal and anterior temporal lobe regions was reported to cause ictal bradyarrhythmia[42] suggesting that seizures may interfere with proper heart function through brain areas that affect cardiac rate, rhythm, output and QT duration, causing prolongation and increased risk for torsade de pointes arrhythmia[43]; moreover, the autonomic control centers of the brain including the hypothalamus and the amygdala are functionally connected with these structures suggesting putative mechanisms by which seizures may alter cardiac function. It is known that heart rate variability can decrease during or after seizures possibly leading to cardiac arrhythmias some of which could, in susceptible individuals, prove fatal. Neurotransmitter and catecholamine surges may also contribute to occurrences of arrhythmias[34,44].

SUDEP may also result from genetic factors through mechanisms that cause channelopathies. Abnormal ion channels may be co-expressed in both heart and brain resulting in pathological interplay leading to seizures and cardiac arrhythmias. This is corroborated by animal studies which reveal the co-expression of epilepsy in a mouse model of human long QT mutations[45]. Glasscock et al[46] suggested that the KCNQ gene in knockout mice may confer susceptibility to SUDEP. A family has been reported by Hindocha et al[47], with two members dying of SUDEP, which harbored an SCN1A mutation. Other candidate mutations for SUDEP were reported by Tu et al[48], detected on SCN5A or KCNH2 genes. Langan et al, hypothesized an overlap between SUDEP, cardiac syncope, sudden infant death syndrome, intrauterine death, and premature sudden cardiac death[49]. In addition, Aurlien[50] and colleagues reported a SUDEP case with a missense mutation in the LQTS-associated gene on SCN5A coding for the cardiac sodium channel suggesting another putative mechanism.

Every attempt should be made to achieve SUDEP risk reduction. To that effect, drug treatment to reduce GTCS should also, theoretically, decrease SUDEP risk. Studies have shown that AED treatment, mono or polytherapy, confers neuroprotection compared to no treatment; in the ILAE Task Force pooled analysis[15], a protective, albeit not significant trend was noted even on a single AED therapy compared to no treatment. However, in another controlled study[49] lack of treatment was associated with a SUDEP risk that was 21.7 times higher compared with patients on treatment. Frequent AED changes, perhaps indicating more difficult to control seizures, appear to increase this risk; one controlled study showed a relative risk of 6.08 in those individuals with multiple changes in treatment regiments per year compared to those on stable dosages[51], whereas poor compliance with antiepileptic treatment has been reported to increase this risk[49]. Whereas AED polytherapy was reported to increase the risk of SUDEP in several case-control studies[10,49,52,53] the association may not be necessarily causal and may reflect, again, more severe epilepsy. In fact, Ryvlin[54] reported that adjunctive AED treatment may reduce the risk of SUDEP more than seven-fold in patients with uncontrolled seizures.

There have been concerns that some AEDs, especially carbamazepine, and lamotrigine, might increase the risk of SUDEP either due to their mechanism of action[55], or their effects on cardiac conduction[56,57]. However, such putative associations could not be confirmed by the ILAE Task Force pooled analysis[15], and SUDEP risk was decreased by about 80% in patients who were assigned additional AED therapy compared to patients given placebo[58].

Serotonin (5-HTT) should be mentioned with respect to its role in respiration, antiepileptic effects[59], and putative protective potential[60]. The raphe nucleus controls respiration centrally, and may be involved in the respiratory dysfunction observed postictally and possibly be linked etiologically to SUDEP[61]. A link may thus exist between epilepsy, serotonin, and respiration through a polymorphism in the 5-HTT gene leading to genetic susceptibility in certain individuals[6]. In animal models Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has shown a protective effect in reducing ictal respiratory arrest[60]. Desaturation of oxygen was detected significantly less frequently postictally in patients receiving SSRIs[22] suggesting a possible neuroprotective and SUDEP preventive role.

Another preventive strategy would involve careful selection of candidates for surgical control of their epilepsy. SUDEP incidence rates after surgical treatment of epilepsy range from 1.8 to 4.0 per 1,000 patient-years in various studies[62-66] which are lower than those reported in surgical pharmacoresistant candidates. Even though SUDEP can occur after epilepsy surgery, it appears in patients who continue to have seizures following surgery, whereas in most series published, it has not been

reported in seizure-free postoperative patients[35,38,62,64,67,68]. However Persson et al[35], have suggested that firm conclusions regarding postoperative SUDEP rates cannot be established since there may be intrinsic differences between successful and unsuccessful postoperative patients in terms of their medical characteristics and responses to therapy. Other risk factors reported included right-sided resections in mesial temporal sclerosis (MTS) [standard mortality ratio (SMR) 3.33, 95% CI 1.39-8.00], men with MTS (SMR 3.12, 95% CI 1.56–6.25), and men with non-specific lesions[69] (SMR 2.68, 95% CI 1.00–7.09). In our series, one patient was awaiting surgery.

Concern was raised regarding vagus nerve stimulation (VNS) therapy and its potential to induce bradycardia or cardiac arrest. Ardesch[70] recommended greater caution to avoid asystole if bradycardia was induced during the VNS device insertion. There is evidence that VNS can exacerbate obstructive and central sleep apnea[71,72]. However, in a review of 1819 individuals (funded in part by the device manufacturers), totaling 3,176.3 person-years following implantation, 25 deaths had occurred suggesting, according to the authors, that there were no differences from the rates reported in other epileptic populations[11]. Two of our patients had VNS implanted.

Shorvon and Tomson[6] suggested the following measures to reduce the risk of SUDEP in clinical practice: control of GTCS with optimum treatment, compliance and lifestyle adjustments (e.g., use of alcoholic beverages, sleep habits); slowly and gradually changing AEDs; nighttime supervision for those patients at high risk; caution with AEDs, which may potentially cause adverse cardiorespiratory effects; attention to ictal warning signs such as prolonged GTCS, marked cyanosis, severe bradycardia or apnea, marked atonia, and EEG suppression postictally; supervision after a seizure until full consciousness is restored; and counseling of selected patients on the risks. Further research is warranted in order to delineate the mechanism of SUDEP precisely and to devise and implement effective preventive measures. Patients in our series had characteristics similar to those identified in larger studies elsewhere. Finally, the physician should assess the appropriate population and the critical time at which to facilitate a discussion about SUDEP. Kroner et al[73] reported that approximately half the patients and their caregivers believed that knowledge regarding SUDEP would influence their epilepsy management; in that respect, they recommend that health care providers need to educate those at high risk about preventative measures as well as help alleviate fears among those at minimal or no risk.

Conclusions

SUDEP remains a significant factor for mortality in people with epilepsy. As in most series reported, our patients had GTCS, most had nocturnal seizures, all but one were male and the average age was 30 years. The majority of deaths were unwitnessed. Therefore, our strategies to reduce or prevent SUDEP should include measures to control seizures, medically, surgically or with other interventions, monitoring of selected cases at risk especially at night, and further research to ascertain the factors which lead to SUDEP so that better preventive strategies are developed.

Conflict of interest

The author reports no conflict of interest in reporting this study.

Acknowledgements

The author wishes to thank Dr. Christiana Demetriou for carrying out statistical analysis of the data; also, Mrs. Elena Polycarpou for her assistance in the preparation of the manuscript.

References

1. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia. 1997; 38: S6-S8.
2. Bacon GM. On the modes of death in epilepsy. Lancet Neurol. 1868; 1: 555-556.
3. Spratling WP. Prognosis. Epilepsy and Its Treatment (1904). W.B. Sanders, Philadelphia, 1904, 304.
4. Livingstone S. Living with epileptic seizures. Charles C Thomas Pub Ltd, Springfield, IL, 1963, 143-163.
5. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012; 53: 227-233.
6. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet. 2011; 378: 2028-2038.
7. Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology. 1998; 51: 1270-1274.
8. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Ann Neurol. 2001; 49: 336-344.
9. Mohanraj R, Norrie J, Stephen LJ, Kelly K, Hitiris N, Brodie MJ. Mortality in adults with newly diagnosed and chronic epilepsy: a retrospective comparative study. Lancet Neurol. 2006; 5: 481-487.
10. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology. 2001; 56: 519-525.
11. Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia. 2000; 41: 549-553.
12. Vlooswijk MC, Majoie HJ, De Krom MC, Tan IY, Aldenkamp AP. SUDEP in the Netherlands: a retrospective study in a tertiary referral center. Seizure. 2007; 16: 153-159.
13. Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. Mortality after epilepsy surgery. Epilepsia. 2005; 46 Suppl 11: 49-53.
14. Kloster R, Engelskjøn T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. J Neurol Neurosurg Psychiatry. 1999; 67: 439-444.
15. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al; ILAE Commission on Epidemiology (Subcommission on Mortality). Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia. 2012; 53: 249-252.
16. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. Epilepsia. 2012; 53: 253-257.
17. Johnston SC, Horn JK, Valente J, Simon RP. The role of hypoventilation in a sheep model of epileptic sudden death. Ann Neurol. 1995; 37: 531-537.
18. Johnston SC, Darragh TM, Simon RP. Postictal pulmonary edema requires pulmonary vascular pressure increases. Epilepsia. 1996; 37: 428-432.
19. Johnston SC, Siedenberg R, Min JK, Jerome EH, Laxer KD. Central apnea and acute cardiac ischemia in a sheep model of epileptic sudden death. Ann Neurol. 1997; 42: 588-594.
20. Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. Epilepsia. 2004; 45: 993-996.
21. Nashef L, Walker F, Allen P, Sander JW, Shorvon SD, Fish DR. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. J Neurol Neurosurg Psychiatry. 1996; 60: 297-300.

22. Bateman LM, Spitz M, Seyal M. Ictal hypoventilation contributes to cardiac arrhythmia and SUDEP: report on two deaths in video-EEG-monitored patients. Epilepsia. 2010; 51: 916-920.
23. Bird JM, Dembny KAT, Sandeman D, Butler S. Sudden Unexplained Death in Epilepsy: An Intracranially Monitored Case. Epilepsia. 1997; 38: S52-S56.
24. Dasheiff RM, Dickinson LJ. Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure. Arch Neurol. 1986; 43: 194-196.
25. Espinosa PS, Lee JW, Tedrow UB, Bromfield EB, Dworetzky BA. Sudden unexpected near death in epilepsy: malignant arrhythmia from a partial seizure. Neurology. 2009; 72: 1702-1703.
26. Lee HW, Hong SB, Tae WS, Seo DW, Kim SE. Partial seizures manifesting as apnea only in an adult. Epilepsia. 1999; 40: 1828-1831.
27. McLean BN, Wimalaratna S. Sudden death in epilepsy recorded in ambulatory EEG. J Neurol Neurosurg Psychiatry. 2007; 78: 1395-1397.
28. So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. Epilepsia. 2000; 41: 1494-1497.
29. Thomas P, Landré E, Suisse G, Breloin J, Dolisi C, Chatel M. Syncope anoxo-ischémique par dyspnée obstructive au cours d'une crise partielle complexe temporale droite. Epilepsies. 1996; 8: 339-346.
30. Lhatoo SD, Faulkner HJ, Dembny K, Trippick K, Johnson C, Bird JM. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol. 2010; 68: 787-796.
31. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013; 12: 966-977.
32. Natelson BH, Suarez RV, Terrence CF, Turizo R. Patients with epilepsy who die suddenly have cardiac disease. Arch Neurol. 1998; 55: 857-860.
33. Opeskin K, Thomas A, Berkovic SF. Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy? Epilepsy Res. 2000; 40: 17-24.
34. Adjei P. Autonomic dysfunction in epilepsy. PhD Thesis, University College London, 2010.
35. Persson H, Kumlien E, Ericson M, Tomson T. Preoperative heart rate variability in relation to surgery outcome in refractory epilepsy. Neurology. 2005; 65: 1021-1025.
36. Ronkainen E, Ansakorpi H, Huikuri HV, Myllylä VV, Isojärvi JI, Korpelainen JT. Suppressed circadian heart rate dynamics in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 2005; 76: 1382-1386.
37. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res. 1998; 30: 77-83.
38. Surges R, Henneberger C, Adjei P, Scott CA, Sander JW, Walker MC. Do alterations in inter-ictal heart rate variability predict sudden unexpected death in epilepsy? Epilepsy Res. 2009; 87: 277-280.
39. Rocamora R, Kurthen M, Lickfett L, Von Oertzen J, Elger CE. Cardiac asystole in epilepsy: clinical and neurophysiologic features. Epilepsia. 2003; 44: 179-185.
40. Schuele SU, Bermeo AC, Alexopoulos AV, Locatelli ER, Burgess RC, Dinner DS, et al. Video-electrographic and clinical features in patients with ictal asystole. Neurology. 2007; 69: 434-441.
41. Rossetti AO, Dworetzky BA, Madsen JR, Golub O, Beckman JA, Bromfield EB. Ictal asystole with convulsive syncope mimicking secondary generalisation: a depth electrode study. J Neurol Neurosurg Psychiatry. 2005; 76: 885-887.
42. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992; 42: 1727-1732.
43. Oppenheimer S. Cerebrogenic cardiac arrhythmias: cortical lateralization and clinical significance. Clin Auton Res. 2006; 16: 6-11.
44. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. Neurology. 1984; 34: 255-257.
45. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. Sci Transl Med. 2009; 1: 2ra6.
46. Glasscock E, Yoo JW, Chen TT, Klassen TL, Noebels JL. Kv1.1 potassium channel deficiency reveals brain-driven cardiac dysfunction as a candidate mechanism for sudden unexplained death in epilepsy. J Neurosci. 2010; 30: 5167-5175.
47. Hindocha N, Nashef L, Elmslie F, Birch R, Zuberi S, Al-Chalabi A, et al. Two cases of sudden unexpected death in epilepsy in a GEFS+ family with an SCN1A mutation. Epilepsia. 2008; 49: 360-365.
48. Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathol. 2011; 21: 201-208.
49. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology. 2005; 64: 1131-1133.
50. Aurlien D, Leren TP, Taubøll E, Gjerstad L. New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. Seizure. 2009; 18: 158-160.
51. 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: 888-893.
52. Beran RG, Weber S, Sungaran R, Venn N, Hung A. Review of the legal obligations of the doctor to discuss Sudden Unexplained Death in Epilepsy (SUDEP)--a cohort controlled comparative cross-matched study in an outpatient epilepsy clinic. Seizure. 2004; 13: 523-528.
53. McKee JR, Bodfish JW. Sudden unexpected death in epilepsy in adults with mental retardation. Am J Ment Retard. 2000; 105: 229-235.
54. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011; 10: 961-968.
55. Timmings PL. Sudden unexpected death in epilepsy: a local audit. Seizure. 1993; 2: 287-290.
56. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res. 2003; 57: 69-75.
57. Surges R, Taggart P, Sander JW, Walker MC. Too long or too short? New insights into abnormal cardiac repolarization in people with chronic epilepsy and its potential role in sudden unexpected death. Epilepsia. 2010; 51: 738-744.
58. Ryvlin P, Rheims S. Increased risk of SUDEP among epileptic patients receiving placebo in randomised controlled trials. Epilepsia. 2009; 50: 223.
59. Favale E, Rubino V, Mainardi P, Lunardi G, Albano C. Anticonvulsant effect of fluoxetine in humans. Neurology. 1995; 45: 1926-1927.
60. Tupal S, Faingold CL. Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. Epilepsia. 2006; 47: 21-26.
61. Richter DW, Manzke T, Wilken B, Ponimaskin E. Serotonin receptors: guardians of stable breathing. Trends Mol Med. 2003; 9: 542-548.
62. Bell GS, Sinha S, Tisi Jd, Stephani C, Scott CA, Harkness WF, et al. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? J Neurol Neurosurg Psychiatry. 2010; 81: 716-718.
63. Hennessy MJ, Langan Y, Elwes RD, Binnie CD, Polkey CE, Nashef L. A study of mortality after temporal lobe epilepsy surgery. Neurology. 1999; 53: 1276-1283.
64. Nilsson L, Ahlbom A, Farahmand BY, Tomson T. Mortality in a population-based cohort of epilepsy surgery patients. Epilepsia. 2003; 44: 575-581.
65. Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. Epilepsia. 2002; 43: 170-174.
66. Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. Ann Neurol. 1999; 46: 45-50.
67. Jehi L. Sudden death in epilepsy, surgery, and seizure outcomes: the interface between heart and brain. Cleve Clin J Med. 2010; 77 Suppl 3: S51-S55.
68. Salanova V, Markand O, Worth R. Temporal lobe epilepsy: analysis of failures and the role of reoperation. Acta Neurol Scand. 2005; 111: 126-133.
69. Seymour N, Granbichler CA, Polkey CE, Nashef L. Mortality after temporal lobe epilepsy surgery. Epilepsia. 2012; 53: 267-271.
70. Ardesch JJ, Buschman HP, van der Burgh PH, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Cardiac responses of vagus nerve stimulation: intraoperative bradycardia and subsequent chronic stimulation. Clin Neurol Neurosurg. 2007; 109: 849-852.
71. Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. Neurology. 2000; 55: 1450-1454.
72. Papacostas SS, Myrianthopoulou P, Dietis A, Papathanasiou ES. Induction of central-type sleep apnea by vagus nerve stimulation. Electromyogr Clin Neurophysiol. 2007; 47: 61-63.
73. Kroner BL, Wright C, Friedman D, Macher K, Preiss L, Misajon J, et al. Characteristics of epilepsy patients and caregivers who either have or have not heard of SUDEP. Epilepsia. 2014; 55: 1486-1494.