

Sudden unexpected death in epilepsy (SUDEP)

Introduction

Individuals with epilepsy have a mortality rate 2-3 times that of the general population.^{1,3} This increased mortality is attributable to both the underlying disease and epilepsy itself. The commonest seizure related death is sudden unexpected death (SUDEP), an event which recently has aroused great interest.

Definition

An agreed definition of SUDEP and classification of epilepsy related deaths has not been achieved. We propose the following definition: "...sudden unexpected, nontraumatic and nondrowning 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".⁴

In recent years in the UK an estimated 90% of sudden deaths have been referred to the coroner and proceed to postmortem examination but where this is not done, it is necessary to formulate, for the purposes of epidemiological studies, a definition which encompasses possible, probable and definite cases of SUDEP. An approach that has been adopted by various studies.⁵⁻⁷

Incidence studies

The incidence of SUDEP has been estimated by a number of investigators who have undertaken both population based and cohort studies and the results of these studies are summarised in tables 1 and 2.

Post-mortem findings

Whilst the definition of SUDEP includes the proviso that no anatomical or toxicological cause of death is found at post-mortem, there are nevertheless certain features which are commonly found at autopsy. This includes pulmonary oedema (deemed insufficient in itself to cause death) increased lung, liver and cardiac weights.⁸⁻¹⁰ In addition neuropathological findings have reported decreased brain weights⁸ and cerebral oedema^{8,11} with structural brain lesions being present in 27- 70% of cases.^{8,10-12}

Possible mechanisms

A variety of mechanisms have been proposed for sudden death in epilepsy including disturbances of respiration and cardiac conduction. Apnoea was a frequent finding in a study of ictal cardiorespiratory parameters at the telemetry unit of the National Hospital for Neurology and Neurosurgery,¹³ and this hypoventilation, which was primarily central in nature, occurred in the context of both generalised and partial seizures. Obstructive apnoea occurred less commonly in this study but it is likely that in the controlled environment of the telemetry unit, where nursing intervention is likely to minimise airway compromise, the contribution of intrinsic or extrinsic obstructive apnoea to SUDEP may be underestimated.

An important role for hypoventilation is also supported by an animal model in which chemically induced seizures in sheep can cause death in association with a precipitous drop in the partial pressure of oxygen which occurs along with a concomitant rise in pulmonary artery and left atrial pressures resulting in pulmonary oedema - a frequent finding and almost a pathologic hallmark for sudden death in epilepsy (see above¹⁵). In this animal model care was taken to ensure that airway patency was maintained.¹⁴

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Of further interest with respect to the role of apnoea in SUDEP are the findings of a study in a residential school for children with epilepsy and learning difficulties. The children were closely supervised by experienced staff while at school, including at night. No cases of SUDEP were witnessed during the period of the study suggesting that attention to the recovery of the individual following a seizure, and positioning or stimulating if necessary, may have a role in its prevention.¹⁶

The development of apnoea during a seizure does not exclude a role for cardiac arrhythmia in SUDEP. Clinical observations of seizures associated with severe cardiac arrhythmias have been reported, mainly involving sinus arrest and bradycardia with the majority of these cases having an epileptic focus located in the temporal lobes.¹⁷⁻²⁰

Bradyarrhythmias, often transient have also been noted to occur in the presence of apnoea¹³ and proposed mechanisms for this transient bradycardia include a direct effect of the seizure discharge or a response to apnoea mediated by the cardio-respiratory reflex.²¹ Sinus tachycardia is a common accompaniment to seizures²² but although malignant tacharrhythmias also occur the evidence suggests that this is an infrequent occurrence.²³ Experimentally Mameli and colleagues²⁴ found that various arrhythmias occurred during the paroxysmal discharge when hypothalamic partial epilepsy was induced in hemispherectomised rats, furthermore severe arrhythmias also occurred where there was a mesencephalic or rhombencephalic focus.^{25,26}

Prolongation of the QT interval has been postulated to occur in sudden death cases with some investigators finding some evidence of ictal prolongation of the QT and QTc intervals although not beyond the normal ranges.²⁷ It has already been noted that cases of prolonged QT syndrome may be misdiagnosed as epilepsy²⁸ and it remains to be

seen whether the same genetic predisposition may cause long QT syndrome and epilepsy in a subgroup of patients with idiopathic epilepsy and SUDEP. Autonomic dysfunction leading to an imbalance in cardiac autonomic control may also play a role in SUDEP²⁹ as investigators have shown reduced heart rate variability in those with epilepsy which may be related to the epilepsy itself, medication and medication withdrawal.³⁰⁻³²

A recent study which examined cardiac pathology in SUDEP cases found evidence of perivascular and interstitial fibrosis along with reversible myocyte vacuolisation. The control group, in whom such abnormalities were not detected, did not include individuals with epilepsy dying of other causes and thus the significance of these findings is unclear.³³ Opeskin and colleagues³⁴ performed detailed cardiac examination on ten SUDEP victims and ten controls, where there was no history of epilepsy and death was due to a non cardiac cause. They found no increase in morphological cardiac conduction system abnormalities in the SUDEP group and neither was there any difference in the level of coronary artery stenoses between the two groups. They qualify their findings by stating that subtle abnormalities of the conduction system were identified in some of the epilepsy related deaths which could have contributed to death by causing cardiac arrhythmia.

Case – control studies to date

Descriptive studies of SUDEP cohorts have reported potential risk factors which include youth, male sex, remote symptomatic

epilepsy, structural findings on neuropathology, severe epilepsy, alcohol abuse, abnormal EEG's with epileptiform changes and greater variations, mental handicap, psychotropic medication, African Americans, lack of compliance with treatment, abrupt medication changes, low antiepileptic drug levels and unwitnessed nocturnal seizures.³⁵ Case control studies are the way forward in further clarifying risk factors for SUDEP.

Nilsson and colleagues³⁶ have undertaken the first sizeable case control study. Fifty seven cases were identified of whom 91% had undergone PM examination and a number of conclusions can be drawn: The relative risk of SUDEP increased with increasing number of seizures/year. The estimated RR was 10.16(2.94-35.18) in those with more than 50 seizures/year compared with those who had two seizures/year and RR was 23.2(3.16-170.28) when those having any seizure were compared with those who were seizure free.

The risk of SUDEP increased with increasing number of concomitant AEDs 9.89 for three compared with monotherapy. This was a risk factor independent of seizure control as judged by seizure frequency. Seizure severity was not investigated. Other major risk factors were frequent changes of AED dosage compared with unchanged dosage 6.08(1.99-18.56). There was an 18 fold increase in RR associated with epilepsy in childhood compared with onset >45 years of age. The association between SUDEP risk and early onset of epilepsy and SUDEP risk and seizure frequency was weaker for women than men whereas the association between dosage change and increased risk was stronger in female patients. Male patients with localisation related epilepsy had a lower risk when compared to those with idiopathic epilepsy.

Walczak *et al*⁷ identified ten probable and ten definite SUDEP cases with the risk of SUDEP being increased by tonic clonic seizures [OR 7(2-24)], number of AEDs [OR 3.8(1.3-11)] when adjusted for the number of all seizures and mental retardation OR4.6(1.2-18).

Preliminary results have also been reported from a large case-control UK study of 154 SUDEP cases, of whom 21 were witnessed.³⁸ This is the largest case control study to date and all cases underwent post-mortem examination. Risk of SUDEP was greater if a generalised tonic clonic seizure occurred in the last 3 months (OR 10.3(5.6-19.2)) and with increasing number of antiepileptic drugs ever taken (OR4.3(2.1-8.90 for 4 AEDs when compared with 1-2). Those who had never had drug therapy were also at increased risk when compared with those who had taken 1-2 drugs (OR 11.6(4.3-39.4). Recent AED withdrawal i.e. in the last 3 months also increased the risk of SUDEP (OR 2.7(1.1-6.5). Taking carbamazepine appeared to be associated with an increased risk of SUDEP with the OR just achieving significance OR 2(1.1-3.6). The clinical significance of this observation, suggested previously^{39,40}, is not yet clear and causation should not be assumed as there are many possible interpretations. This study also investigated supervision. There was a decreased risk of SUDEP if the bedroom was

shared with someone capable of giving assistance (OR 0.38 (0.2-0.8) and if special precautions such as the use of listening devices were taken (OR 0.3 (0.1-0.86)).

Clinical implications

This possibility of sudden death should be considered whenever patient management strategies are considered. SUDEP is largely a seizure related phenomenon and the optimisation of seizure control is highly important in its prevention. Effective AED therapy is therefore of paramount importance in the prevention of these tragic deaths. The risk of SUDEP needs to be considered whenever decisions are made about changes, particularly withdrawal of AED therapy as this may increase the risk as a consequence of altered seizure control or severity as a result of changes in reflex function.

Supervision at night appears to protect against SUDEP. Indeed as the majority of these deaths are unwitnessed, attention to recovery following a seizure and positioning or stimulation as necessary may be important in SUDEP prevention. Every effort should be made to reduce avoidable seizures such as those related to specific trigger factors or to poor compliance with medication. It is thus important that patients be aware of the risks of their condition in order to make balanced decisions about treatment and lifestyle. Such discussion may be difficult and its nature and timing will vary from patient to patient dependent on assessment of individual risk. The issue of supervision at night may be particularly difficult to address, especially in the young adult.

Finally correct certification of epilepsy deaths is vital both for accurate data on SUDEP and other epilepsy related deaths and to allow for the monitoring of trends in mortality and the effectiveness of potential preventive measures discussed here.

References

- Zielinski JJ. *Epilepsy and mortality rate and cause of death*. *Epilepsia* 1974; 15: 191-201.
- Cockerell OC, Johnson AL, Sander JW, Hart YM, Goodridge DM, Shorvon SD. *Mortality from epilepsy: results from a prospective population-based study*. *Lancet* 1994; 344: 918-921.
- Nilsson L, Tomson T, Farahmand BY, Diwan V, Persson PG. *Cause-specific mortality in epilepsy: A cohort study of more than 9,000 patients once hospitalized for epilepsy*. *Epilepsia* 1997; 38: 1062-1068.
- Nashef L. *Sudden Unexpected Death in Epilepsy: Terminology and Definitions*. *Epilepsia* 1997; 38: S6-S8.
- Leestma JE, Annegers JF, Brodie MJ, *et al*. *Sudden unexplained death in epilepsy: observations from a large clinical development program*. *Epilepsia* 1997; 38: 47-55.
- Tennis P, Cole TB, Annegers JF, Leestma JE, McNutt M, Rajput A. *Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada*. *Epilepsia* 1995; 36: 29-36.
- Jick SS, Cole TB, Mesher MD, Tennis P, Jick H. *Sudden Unexplained Death in Young Persons with Primary Epilepsy*. *Pharmacoepidemiology and Drug safety* 1992; 1: 59-64.
- 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.

Table 1. Population based studies of SUDEP Incidence

Authors	Incidence rate	Study method
Terrence <i>et al</i> 1975	1:1100	Coroner
Leestma <i>et al</i> 1984	1:525-1:2000	Coroner
Leestma <i>et al</i> 1989	1:370-1:1100	Coroner
Langan <i>et al</i> 1996	1:680	Coroner
Ficker <i>et al</i> 1998	1:2850	Coroner
Jick <i>et al</i> 1992	1:770	>= 1 AED implies epilepsy
Tennis <i>et al</i> 1995	1:1850	
	(definite & probable cases)	>= 1 AED implies epilepsy
Derby <i>et al</i> 1996	1:680	
	(definite & probable cases)	>= 2 AEDs implies intractable epilepsy

Table 2. Cohort studies of SUDEP Incidence

Authors	Incidence rate	Study method
Lip & Brodie	1:200	Epilepsy clinic
Klenerman <i>et al</i> 1993	1:260	Epilepsy institution
Timmings <i>et al</i> 1993	1:500	Epilepsy clinic
Nashef <i>et al</i> 1995	1:200	Epilepsy clinic
Nashef <i>et al</i> 1995	1:300	Residential school
Dasheiff 1991	1:100	Epilepsy surgery programme
Sperling 1996	1:150	Epilepsy surgery programme
Hennessy <i>et al</i> 1999	1:450	Epilepsy surgery programme
Annegers <i>et al</i> 1998	1:220	Vagal nerve stimulation
Annegers <i>et al</i> 2000	1:588	Vagal nerve stimulation

9. Earnest MP, Thomas GE, Eden RA, Hossack KF. *The sudden unexplained death syndrome in epilepsy: demographic, clinical, and post-mortem features.* *Epilepsia* 1992; 33: 310-316.
10. Hirsch CS, Martin DL. *Unexpected death in young epileptics.* *Neurology* 1971; 21: 682-690.
11. Vickery BG. *Mortality in a Consecutive Cohort of 248 Adolescents who underwent diagnostic evaluation for Epilepsy Surgery.* *Epilepsia* 1997; 38: S67-S69.
12. Thom M. *Neuropathologic Findings in Postmortem Studies of Sudden Death in Epilepsy.* *Epilepsia* 1997; 38: S32-S34.
13. 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.
14. 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.
15. Johnston SC, Darragh TM, Simon RP. *Postictal pulmonary edema requires pulmonary vascular pressure increases.* *Epilepsia* 1996; 42: 432.
16. Nashef L, Fish DR, Garner S, Sander JW, Shorvon SD. *Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty.* *Epilepsia* 1995; 36: 1187-1194.
17. Howell SJ, Blumhardt LD. *Cardiac asystole associated with epileptic seizures: a case report with simultaneous EEG and ECG.* *J Neurol Neurosurg Psychiatry* 1989; 52: 795-798.
18. Fincham RW, Shivapour ET, Leis AA, Martins JB. *Ictal bradycardia with syncope: A case report.* *Neurology* 1992; 42: 2222-2223.
19. Dasheiff RM, Dickinson LJ. *Sudden unexpected death of epileptic patient due to cardiac arrhythmia after seizure.* *Arch Neurol* 1986; 43: 194-196.
20. Jallon P. *Epilepsie et coeur.* *Rev Neurol* 1997; 153: 173-184.
21. Spyer KM. *Central nervous control of the cardiovascular system.* In: Bannister R, Mathias CJ, eds. *Autonomic Failure*, 3rd ed. 1998: 55-77.
22. Blumhardt LD, Smith PEM, Owen L. *Electrocardiographic accompaniments of temporal lobe epileptic seizures.* *Lancet* 1986; 1: 1051-1056.
23. Keilson MJ, Hauser A, Magrill JP, Goldman M. *ECG abnormalities in patients with epilepsy.* *Neurology* 1987; 37: 1624-1626.
24. Mameli P, Mameli O, Tolu E, et al. *Neurogenic myocardial arrhythmias in experimental focal epilepsy.* *Epilepsia* 1988; 29: 74-82.
25. Mameli O, Mameli P, Tolu E, et al. *Analysis of central cardioarrhythmogenic triggers in experimental epilepsy.* *Epilepsy Res* 1990; 7: 210-218.
26. Mameli O, Melis F, Giraudi D, et al. *The brainstem cardioarrhythmogenic triggers and their possible role in sudden epileptic death.* *Epilepsy Res* 1993; 15: 171-178.
27. Tavernor SJ, Brown SW, Tavernor RME, Gifford C. *Electrocardiograph QT lengthening associated with epileptiform EEG discharges - A role in sudden unexplained death in epilepsy?* *Seizure* 1996; 1: 79-83.
28. Ballardie FW, Murphy RP, Davis J. *Epilepsy: a presentation of the Romano Ward syndrome.* *British Medical Journal* 1983; 24: 896-897.
29. Schraeder PL, Lathers CM. *Paroxysmal autonomic dysfunction, epileptogenic activity and sudden death.* *Epilepsy Res* 1989; 3: 55-62.
30. Hennessy MJ, Tighe M, Polkey CD, Nashef L. *Sudden withdrawal of carbamazepine increases cardiac sympathetic activity in sleep.* *Neurology* 2001; 57: 1650-1654.
31. Massetani R, Strata G, Galli R, et al. *Alteration of cardiac function in patients with temporal lobe epilepsy: different roles of EEG-ECG monitoring and spectral analysis of RR variability.* *Epilepsia* 1997; 38: 363-369.
32. Tomson T, Kennebeck G. *Arrhythmia, Heart Rate Variability and Antiepileptic drugs.* *Epilepsia* 1997; 38: S48-S51.
33. Natelson BH, Suarez RV, Terrence CF, Turizo R. *Patients with epilepsy who die suddenly have cardiac disease.* *Arch Neurol* 1998; 55: 857-860.
34. Opeskin K, Thomas A, Berkovic S.F. *Does cardiac conduction pathology contribute to sudden unexpected death in epilepsy.* *Epilepsy Res* 2000; 40: 17-24.
35. Shorvon S. *Risk factors for sudden unexpected death in epilepsy.* *Epilepsia* 1997; 38(Suppl 11): S20-S22.
36. Nilsson L, Farahmand BY, Persson P, Thiblin I, Tomson T. *Risk factors for sudden unexpected death in epilepsy: a case control study.* *Lancet* 1999; 353: 888-893.
37. Walczak T, Leppik IE, D'Amelio M, et al. *Incidence and risk factors in sudden unexpected death in epilepsy.* *Neurology* 2001; 56: 519-525 (Abstract)
38. Langan Y. *Prevention of sudden unexpected death in epilepsy.* Thesis 2002.
39. Timmings PL. *Sudden unexpected death in epilepsy: Is carbamazepine implicated?* *Seizure* 1998; 7: 289-291.
40. Nilsson L, Bergman U, Diwan W, 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: 667-673.

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