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Review Article

Sudden unexpected death in epilepsy

Susan Duncan [a,*], Martin J. Brodie [b]

[a] Edinburgh and South East Scotland Epilepsy Service, Department of Clinical Neurosciences, Western General Hospital, Edinburgh, Scotland, UK
[b] Epilepsy Unit, Western Infirmary, Glasgow, Scotland, UK

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ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) has an incidence ranging between 0.09 and 9 per 1000 patient-years depending on the patient population and the study methodology. It is the commonest cause of death directly attributable to epilepsy, and occurs at or around the time of a seizure. The principal risk factor for SUDEP is poorly controlled generalized tonic–clonic seizures. Other risk factors include polytherapy, male sex, early age at onset of epilepsy, symptomatic etiology, and, possibly, treatment with lamotrigine. The mechanisms underlying SUDEP are poorly understood, but autonomic dysfunction, central apnea, cerebral depression, and cardiac arrthymias have all been described in animal models of SUDEP and during human seizures. Prevention of this fatal event should be aimed at optimizing control of seizures, including prompt referral for consideration of epilepsy surgery. All patients should be told about the risks of SUDEP and informed that complete seizure control appears to be the one proven way of preventing the phenomenon.

1. Introduction

Over the last 20 years the topic of sudden unexpected death in epilepsy (SUDEP) has attracted increasing attention not only from physicians and nurses who treat people with epilepsy, but from patient advocacy groups. The tragic consequences engender bewilderment in doctors asked to explain to relatives why their loved one has died, and anguish in bereaved families.

2. Epidemiology of sudden unexpected death in epilepsy

Sudden unexpected death in epilepsy can be defined as the sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death of a person with epilepsy with or without a seizure, excluding documented status epilepticus, and in whom postmortem examination does not reveal a structural or toxicological cause of death [1]. Although this definition has been widely adopted, it is purely descriptive and reflects our lack of understanding of the underlying pathophysiology of the phenomenon.

Over the years further refinements of the definition have been added. Cases fulfilling the above criteria fall into the category of "definite SUDEP." Sudden death in which there has been no postmortem examination, but for which no other compelling cause is evident, is designated "probable SUDEP." Lastly, a case in which SUDEP cannot be discounted because of limited data relating to the circumstances surrounding the death or because there was a credible competing cause is labeled "possible SUDEP" [2,3].

The reported incidence of SUDEP varies widely depending on the populations studied and the methods of ascertaining the cause of death [3]. Community-based studies are felt to give more representative statistics about the incidence of SUDEP. The majority, however, have been undertaken in tertiary care centers and specialist epilepsy clinics [4] (Table 1).

Ficker and colleagues performed a community-based retrospective analysis of all deaths in patients with epilepsy in Olmsted, MN, USA [5]. The rate of SUDEP was compared with death rates in the population aged 20–40 years to determine the standardized mortality ratio (SMR). Nine patients who died from SUDEP were identified, with an additional six being unclassified for lack of supportive data. SUDEP accounted for 8.6% of deaths in people aged 15–44, giving an incidence per 1000 patient-years of 0.35 and an SMR of 23.7 [95% confidence interval (CI): 7.7–55]. In an earlier study in 1984, 66 cases of SUDEP reported to the medical examiner of Cook County, IL, USA, and who had undergone postmortem examination, were reviewed [6]. This study reported several findings that have been echoed in subsequent studies. Forty percent of patients were found dead in bed. Several died in the emergency room after having been taken there after a seizure. All attempts at resuscitation proved futile. Postmortem examination showed cerebral lesions in 60%, which could account for the seizures, and antiepileptic drug (AED) levels were low in 68% of patients. The article was written before Nashef's definition [1] of SUDEP was published, but some of the factors identified have subsequently been confirmed, particularly the occurrence of death during sleep and within a short time of a witnessed seizure. The

* Corresponding author at: Edinburgh and South East Scotland Epilepsy Service, Department of Clinical Neurosciences, Western General Hospital, Edinburgh, Scotland, UK.
E-mail address: susan.duncan4@nhs.net (S. Duncan).

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Table 1
Key points raised in this article.

- Studies of SUDEP are heterogeneous in their methodology, which explains the divergent reports of incidence of the phenomenon ranging from 0 in 1000 to 10 in 1000 patient-years.
- Studies of patients referred for epilepsy surgery and those attending specialist epilepsy centers and clinics report incidences of epilepsy higher than those in the general population.
- Overall the incidence is reported to be between 0.1 and 2 per 1000 patient-years
- The cause of SUDEP is unknown. Various mechanisms have been proposed: central apnea, cardiac arrhythmia, autonomic dysfunction, seizure-induced metabolic changes, and alterations in cerebral autoregulation.
- Risk factors are early age at onset of epilepsy, frequent generalized tonic–clonic seizures, symptomatic epilepsy, male sex, antiepileptic drug polytherapy, and possibly lamotrigine.
- Evidence that poor adherence to AED regimens is a risk factor for SUDEP is contradictory.
- Because the cause of death is unclear, prevention remains a challenge. The abolition of generalized tonic–clonic seizures, wherever possible, should be a priority as the majority of witnessed cases of SUDEP occur during or shortly after seizures.

authors calculated a prevalence of SUDEP between 1 in 525 and 1 in 2100.

In a subsequent prospective study, the same group identified 60 cases of SUDEP [7]. Thirty-three percent of the patients were found dead in bed, 23% were found dead elsewhere in the home, and 38% had been witnessed to collapse with subsequent failure of attempts at resuscitation. One such case occurred after what was believed to be that individual's first ever seizure. All of these persons had experienced generalized tonic–clonic seizures (GTCS), but by no means had all of these patients, according to case records, had frequent seizures. Other risk factors included the presence of a structural abnormality in the brain, alcohol misuse, and poor AED compliance, with 61% of cases having subtherapeutic AED levels. Sixty-five percent of the patients who died from SUDEP were of African-American lineage. An Australian study using coroner's cases, which employed Nashef's criteria for SUDEP, identified 50 cases over a 21-month period in a population of 4 million in the state of Victoria in Australia [8]. They were matched with 50 controls who had died of other causes. The persons who died from SUDEP tended to be younger and were more likely to be found dead in bed with evidence of a terminal seizure. Interestingly, there was no evidence that AED polytherapy was a relevant risk factor.

In the United Kingdom, a cohort of 792 patients identified through the National General Practice Study of Epilepsy was followed for 11.8 years [9]. SMRs were higher than in the background populations of patients with remote and acute symptomatic epilepsy and those with neurological deficits. The risk in individuals with idiopathic generalized epilepsies, however, did not differ from that in the population at large. The study reported five deaths caused by epilepsy, one of which was SUDEP. The incidence of SUDEP was 0.09 per 1000 patient-years, and this study concluded that SUDEP was uncommon in community-based cohorts.

Case ascertainment has always been a challenge to neurologists studying SUDEP [10]. Examination of death certificates and coroners' cases are widely used, but there is evidence that SUDEP is an underused diagnosis for sudden death in people with epilepsy. Other methods have been tried. One study used the pharmacy prescriptions of 300,000 members of a health care organization in the US Northwest to identify people with epilepsy [11], and from there the numbers and causes of death were ascertained (Table 2). After patients taking AEDs were identified, case notes and death certificates were examined to confirm the diagnosis of epilepsy and to establish the likely cause of death. From 1977 to 1986, 43 deaths were identified. This study predated the publication of Nashef's definition, but the authors identified 11 patients whose deaths had been sudden and unexplained. Each was matched with 4 people with epilepsy for age and sex. Compared with 20% of the control group, 27% of the patients who died from SUDEP had statements in their records to the effect that in the preceding year their seizures had been poorly controlled. Thirty-six percent of the group who died from SUDEP had learning difficulties, as opposed to 10% of the control group. Given the date of the article, cerebral imaging was not available to the authors; however, it is not unreasonable to conclude that the SUDEP group probably had a higher incidence of structural brain abnormalities. The SUDEP group, however, had received a larger number of prescriptions during the preceding year, with 36% of this group collecting 10 or more scripts a year, as opposed to only 10% of the non-SUDEP group. This suggests their compliance was good, but perhaps also that their epilepsy was more severe than that of the controls. The authors calculated an overall risk of SUDEP of 1.3 per 1000 patient-years.

In a later study the same group used prescription data from a Canadian province to ascertain the incidence of SUDEP [12]. They identified 18 definite/probable and 21 possible cases, yielding an overall incidence of 1.35 per 1000 patient-years. They found male sex, use of psychotropic drugs, learning difficulties, and alcohol excess to be risk factors.

Studies undertaken in specialist epilepsy services have tended to quote incidences of SUDEP higher than those in community-based studies. Timmings and co-workers identified 14 cases in 7000 patient-years, or 2 per 1000 patient-years [13] (Table 2). Men were twice as likely to be affected as women, and SUDEP was associated with the use of more than two AEDs, GTCS, and monotherapy with carbamazepine. A retrospective study in a residential care setting reported an incidence of SUDEP of 3.4 per 1000 patient-years [14]. The same group reported an incidence of 5.9 per 1000 years in patients attending an outpatient clinic in a tertiary care center [15].

Another study conducted in a specialist epilepsy outpatient setting compared the actual and expected mortality in two cohorts (newly treated and refractory epilepsy) with expected mortality in the background population [16]. Their electronic patient list was matched with the national death registry held in the Registrar Office for Scotland. The number of deaths in the newly diagnosed cohort of 890 patients was significantly higher than expected at 93 versus 65.5, yielding an SMR of 1.42 (95% CI: 1.16–1.72). Among the patients who did not respond to treatment, the SMR was 2.54 (95 CI: 1.84–3.44, compared with 0.95 (95% CI: 0.68–1.29) in responders. A separate cohort of 2689 patients with chronic epilepsy had an SMR of 2.03 (95% CI: 1.83–2.26). Further investigation revealed 7 cases of probable SUDEP in the recently diagnosed cohort compared with 55 in the chronic epilepsy cohort ($P = 0.013$), confirming what many other studies have implied: SUDEP is a seizure-related phenomenon.

The highest incidence of SUDEP has been reported in patients awaiting epilepsy surgery and those who have had unsuccessful surgery. In one study of a cohort of 583 patients, there were 19 deaths after surgery, 10 of which satisfied the criteria for SUDEP [17]. Patients who had a recurrence of seizures after surgery were more likely to die (10.8 per 1000 patient-years) than those who became seizure free (0.85 per 1000 patient-years). All the deaths occurred in patients who had had temporal lobectomy. Side of resection did not appear to affect mortality. The overall incidence of SUDEP in this study was 6.3 per 1000 patient-years. An earlier study from six centers in Sweden reported the mortality in patients who had had epilepsy surgery, comparing them with a group who did not proceed to operation [18]. Overall, 651 surgical procedures were carried out in 596 patients, 14 of whom subsequently died; 6 of the 14 died from SUDEP, giving an incidence of 2.4 per 1000 patient-years. Seizure outcome at 2 years of follow-up did not appear to influence mortality. According to the