Sudden unexpected death in epilepsy

S D Lhatoo, Y Langan, J W A S Sander

It has become increasingly clear that epilepsy can kill, not only through status epilepticus and accidents caused by seizures but through other mechanisms that cause sudden unexpected deaths. Sudden death is a real problem in the management of epilepsy and is now perhaps the commonest category of seizure-related death in patients with chronic epilepsy, often affecting young adults in this group. Sudden unexpected death in epilepsy (SUDEP) is defined as a sudden, unexpected, non-accidental death in an individual with epilepsy with or without evidence of a seizure having occurred (excluding documented status epilepticus) and where autopsy does not reveal an anatomical or toxicological cause of death. In 1910, Munson reported on mortality from the Craig Colony in New York which housed patients with intractable epilepsy and found that 99 out of 582 deaths were ‘sudden’. Though some of these were seizure related accidental deaths, he concluded that most had occurred in the midst of a seizure, noting that “these deaths occur very rapidly at times, seizures not infrequently take place silently”. Since then, there has been a somewhat reluctant acceptance of a small but significant risk of death directly attributable to seizures, and sudden death has appeared sporadically through the decades in several epilepsy mortality series as a category of death. With present day knowledge of an increased mortality in epilepsy, there has been renewed interest in the phenomenology of SUDEP and several studies have attempted to describe this enigma.

Epidemiological studies

It is clear from outcome studies of epilepsy that more than 70% of all patients with epilepsy enter lasting remission from the condition and up to 30% suffer chronic seizures that are difficult to control. Approximately 1 out of every 200 such patients with chronic epilepsy die suddenly and unexpectedly every year. But how common is this phenomenon in the community where the majority of patients do not have difficult, intractable epilepsy? The National GP Study of Epilepsy in the UK (NGPSE), which is an observational study of epilepsy in the community, has had only one confirmed SUDEP death in a prospective cohort of 564 patients with definite epilepsy followed up for approximately 8000 person years. The MRC Antiepileptic Drug Withdrawal Study had just two deaths attributable to SUDEP after 5000 person years of follow-up. These figures are reflective of the relative rarity of this phenomenon in patients who do not have chronic epilepsy, as in the NGPSE almost 70% of the cohort had achieved 5-year remission from seizures. Similarly, the MRC study population was in remission and there is strong evidence that SUDEP is mainly a problem in the patient with intractable epilepsy.

Case ascertainment methods to determine the exact incidence of SUDEP have varied in different studies, but can be broadly categorised into studies that have used death certificates and coroner’s registers, studies that have used treatment data, either medical surgical, or palliative, and those that have been based on data from epilepsy clinics or institutions. Coroner-based studies have shown incidences varying between 1:370 and 1:2100. Many of these studies, however, are flawed due to the fact that death certificates are notoriously unreliable; a large number do not accurately record the cause of death or the underlying conditions that could have contributed. In addition, the prevalent epilepsy population is used as denominator – a presumed figure prone to variation and inaccuracy. A recent case-control study found that annual incidence figures for SUDEP were 1.4 per 1000 patient years in both males and females. SUDEP incidence rates of up to 1:200 per year have been reported by studies based on tertiary epilepsy clinic data, and slightly higher figures have been reported from institutionalised patients who share features of seizure intractability with clinic subjects. These figures are probably close to the true incidence of SUDEP in patients with chronic epilepsy.
Several studies have used anti-epileptic drug therapy lists for case ascertainment. More recent studies have been based on newer anti-epileptic drug registers such as those on lamotrigine, gabapentin and tiagabine. Some studies based on surgical data have shown particularly high incidences of sudden death (up to 1:50 per year), especially in post-surgical patients where the operative procedure has not been successful in containing seizures, reflective of a group with particularly bad epilepsy. A more recent study of 791 patients who had received vagal nerve stimulation system implants (a seizure-reducing device that acts by stimulating the left vagal nerve), were followed up for 1335 person years and showed an incidence of definite or probable SUDEP of 4.5/1000 person years of follow-up. The high mortality and incidence figures in most of these studies may reflect the severe epilepsy suffered by patients in these study populations and is likely to indicate the increasingly high risk of SUDEP in patients with chronic epilepsy.

**Risk factors**

**SEIZURE STATUS**

It is obvious from most studies that seizure control or the lack thereof, is vitally important in the mortality statistics of SUDEP and incidence figures are considerably higher in cohorts of patients with refractory and chronic seizures (hospital or clinic based) as compared to studies that are more community based. One surgical study found a particularly high incidence of SUDEP in patients unsuccessfully treated surgically for their epilepsy, with mortality approaching 1:50, in contrast to 1:150 when both pre- and post-surgical candidates were analysed together. In contrast, the NGPSE and MRC Drug Withdrawal studies, which both have large numbers of patients with mild epilepsy, have shown very low incidence figures for sudden death. It is important to note, however, that there have been reports of patients dying suddenly during their first-ever or second-ever seizure, though these are obviously uncommon occurrences. A recent case-control study showed that the relative risk of SUDEP increased with number of seizures per year (10.16; 95%CI=2.94–35.18), appearing substantially higher in patients with more than 50 seizures per year than in patients with two or less seizures per year.

**AGE, SEX AND RACE**

Patients with epilepsy within the 20 to 40 year age group appear to suffer higher mortality from this entity, and this has been a consistent finding in many studies. However, this does not mean that other age groups are immune and studies in children as well as older patients with epilepsy have shown significant mortality due to SUDEP. Apart from one study of children with epilepsy in a residential school, most studies have shown a male preponderance. One study found a higher incidence of sudden death in the African American population but this could reflect the higher incidence of epilepsy in this group.

**MEDICATION**

Non-compliance with prescribed anti-epileptic medication has been implicated in the occurrence of sudden death and several patients have been found to have low sub-therapeutic serum levels of anti-epileptic drugs. The significance of drug levels, however, is arguable as patients with well-controlled epilepsy can have low drug levels and vice versa. Conversely, there are reported instances of patients experiencing sudden arrhythmic deaths due possibly to the cardiac side-effects of carbamezepine, though this is obviously not the case in the majority of SUDEP cases. The above-mentioned case-control study showed that patients on three anti-epileptic drugs were more likely to suffer SUDEP than patients on monotherapy, although it could be argued that patients with bad epilepsy are more likely to be prescribed polytherapy and the increased mortality reflects on refractory epilepsy rather than drug therapy.

### Table: The incidence of SUDEP in different populations

<table>
<thead>
<tr>
<th>Population studied</th>
<th>Annual incidence in population studied</th>
<th>Incidence in person years</th>
<th>Type of epilepsy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy surgery patients</td>
<td>1 in 150</td>
<td>—</td>
<td>Chronic</td>
<td>Severe epilepsy</td>
</tr>
<tr>
<td>Epilepsy clinic patients</td>
<td>1 in 200</td>
<td>—</td>
<td>Chronic</td>
<td>Moderate to severe epilepsy</td>
</tr>
<tr>
<td>Patients from coroners' lists</td>
<td>1 in 1100</td>
<td>1 in 8000</td>
<td>All</td>
<td>Mild, moderate and severe epilepsy</td>
</tr>
<tr>
<td>Patients from community based studies of epilepsy</td>
<td>1.4 in 1000</td>
<td>—</td>
<td>All</td>
<td>Mild, moderate and severe epilepsy</td>
</tr>
</tbody>
</table>

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**Possible pathogenetic mechanisms of SUDEP**

- cardiovascular
- central hypoventilation
- combined mechanisms

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<th>Box 2</th>
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**Neurological status**

A higher incidence of SUDEP has been found in patients with neurological deficits and learning difficulties. This may be attributed to the severity of epilepsy that is usually present in these patient groups and the higher all-cause mortality generally found in such patients.

**Other**

Alcohol abuse has also been implicated in some patients, as have psychotropic drugs. Recent head injuries have also been mentioned as a possible risk factor.

**Circumstances of death**

There is considerable evidence that the majority of sudden deaths in epilepsy are seizure related and circumstantial evidence of a generalised tonic–clonic seizure having occurred is often found in the form of superficial injuries, a bitten tongue or characteristic postures. This is strongly borne out by witnessed accounts of sudden death, one of which occurred during direct observation at a telemetry unit. However, less than half of sudden deaths in epilepsy are witnessed and it is yet unclear whether all such deaths are due to seizures.

**Autopsy findings**

Autopsy findings, by definition, should not indicate an anatomical or toxicological cause of death, though this does not necessarily imply that no abnormalities are found on post-mortem examination. Pulmonary oedema is often found, although this is usually of insufficient severity to be an attributable cause of death. Similarly, increased liver, cardiac and brain weights are also found. Some studies have found brain lesions on autopsy that could have caused seizures in those cases. A recent study noted the presence of interstitial cardiac fibrosis in patients who had epilepsy-related sudden deaths.

**Pathogenetic mechanisms**

Seizure activity remains central in the various hypotheses that have been put forward to explain the pathogenetic mechanisms that underlie sudden death. These studies can be broadly categorised into those that have looked at cardiovascular causes and those that have emphasised the role of central hypoventilation during seizures.

Various rhythm abnormalities have been implicated in SUDEP, but although autonomic disturbances are common enough observations in the fitting, hospitalised patient, there is no convincing evidence that malignant tachyarrhythmias cause significant mortality in epilepsy. There are case reports, however, of significant bradyarrhythmias and sinus arrest occurring in patients with temporal lobe epilepsy, suggesting that these could be a cause of death. Significant ST segment changes and QTc interval prolongations have been observed with epileptiform electroencephalogram (EEG) discharges in patients with chronic epilepsy, although the investigators also found that this prolongation remained within normal limits in almost all cases. Intrinsic cardiac disease has been implicated and in one recent study a significant number of patients were found to have interstitial cardiac fibrosis, though whether this is directly related to a mechanism of death is debatable. The influence of cardio-active anti-epileptic drugs too, remains speculative.

In an interesting study where seizures were chemically induced in sheep, central hypoventilation was found to be a mechanism of death. Endogenous opioids that may be released during seizures have been implicated in the causation of this central hypoventilation and could well account for the suppression of respiratory drive. In another study on anaesthetised and ventilated animals, elevated left atrial and pulmonary vascular pressures were found – a possible mechanism for the pulmonary oedema found in patients who have died from SUDEP, though why this should happen in the first place is unclear.

In another study, transient bradyarrhythmias were found to occur in association with apnoea and a change in respiratory pattern in patients experiencing seizures, suggesting that both cardiovascular as well as central mechanisms are important and that cardiorespiratory brainstem reflexes may play a role in SUDEP. In summary, however, although there are several postulates, the true mechanism of sudden death remains unclear.

**Conclusion**

Seizure control is likely to be an important issue in SUDEP and evidence from many studies strongly suggests an important role played by uncontrolled...
Sudden death in epilepsy

There is no doubt that the traditional emphases on drug compliance, minimisation of potential seizure precipitants, and referral of appropriate patients to epilepsy specialist units are as important as ever. Although the incidence of SUDEP in community-based populations is much lower, its occurrence is often devastating to relatives, carers and physicians. In patients with chronic epilepsy, where the incidence is considerably higher, the role of adequate supervision is equally important, especially amongst children and the institutionalised.

As newer anti-epileptics appear on the market and the provision of both curative and palliative surgery for intractable epilepsy becomes more established, the incidence of this often tragic complication will hopefully lessen. The role of further studies examining the risk factors involved in SUDEP in this cannot be under emphasised and detailed studies such as a case-control study presently underway at this centre, should be encouraged.
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