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Sudden unexpected death in epilepsy

癲癇症患者的突然意外死亡

Sudden unexpected death in epilepsy is the most common category of seizure-related death for patients who develop chronic epilepsy, accounting for up to 17% of epilepsy deaths. Sudden unexpected death in epilepsy 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. Incidence rates range between 0.35 and 2.70 per 1000 person-years in the population-based studies and between 1.50 and 9.30 per 1000 person-years in selected cohorts. Seizure frequency appears to be an important factor in sudden unexpected death in epilepsy, although the exact pathogenetic mechanisms involved are unclear.

突然意外死亡是慢性癲癇症患者最常見的與癲癇有關的致命類型，佔癲癇症死亡的17%。癲癇症患者的突然意外死亡定義為癲癇症患者，不論有沒有癲癇發作跡象，發生突然的、意料之外的非意外事故死亡(不包括檔案記載的癲癇)，且屍體解剖沒有顯示出解剖學或毒物學死因。按普通人口比例研究顯示，病症的發生率介乎每千人年0.35至2.70之間，而選擇人口的發生率則為每千人年1.50至9.30之間。儘管準確的致病機制尚未清楚，癲癇發作的頻率似乎是癲癇症突然意外死亡的一個重要因素。

Introduction

Mortality is significantly increased in patients with epilepsy to twice or thrice that of the general population.[1] Sudden unexpected death in epilepsy (SUDEP) is the most common category of seizure-related death for patients who develop chronic epilepsy, accounting for up to 17% of epilepsy deaths.[2] Sudden unexpected death in epilepsy 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.[3] In 1910, Munson reported on mortality in patients with intractable epilepsy and found that 99 of 582 deaths were 'sudden', noting that "these deaths occur very rapidly at times—seizures not infrequently take place silently".[4] Since then, sudden death has appeared only sporadically throughout the decades, as a category of death in some epilepsy mortality series,[5] and it is only in the past 2 decades that there has been renewed interest in the phenomenology of SUDEP.

Epidemiological studies

The Table lists the incidence rates of SUDEP in community-based studies of epilepsy and in more selected cohorts with epilepsy.[6-18] These range between 0.35 and 2.70 per 1000 person-years in population-based studies and between 1.50 and 9.30 per 1000 person-years in selected cohorts.

Sudden unexpected death in epilepsy is infrequently encountered in the general population compared with patients attending hospital with chronic epilepsy. For example, in the National General Practice Study of Epilepsy (NGPSE) in the UK, there was only one confirmed SUDEP death in a prospective cohort of 564 patients with definite epilepsy followed up for approximately 8000 person-years.[19] The Medical Research Council (MRC) Antiepileptic Drug Withdrawal Study showed only two deaths attributable to SUDEP after

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Table. Studies of incidence of sudden unexpected death in epilepsy

Authors	Population studied	Incidence per 1000 person-years
Community-based studies		
Terrence et al,[6] 1975	Autopsy records	0.90
Leestma et al,[7] 1989	Prospective, medical examiner records	0.90-2.70
Jick et al,[8] 1992	Death certificates and autopsy records	1.30
Tennis et al,[9] 1995	Death certificates and autopsy records	0.50-1.40
Ficker et al,[10] 1998	Review of all deaths in Rochester	0.35
Selected cohorts		
Dasheiff,[11] 1991	Referrals for epilepsy surgery	9.30
Lip and Brodie,[12] 1992	Epilepsy clinic	4.90
Timmings,[13] 1993	Epilepsy clinic	2.00
Nashef et al,[14] 1995	Learning disabilities	3.40
Nashef et al,[15] 1995	Tertiary referral clinic	5.90
Leestma et al,[16] 1997	Refractory seizures when taking lamotrigine	3.50
Nilsson et al,[17] 1999	Based on hospital admissions	1.50
Annegers et al,[18] 1998	Patients with vagus nerve stimulator implants	4.50

5000 person-years of follow-up.[20] This is reflective of the relatively mild epilepsy of patients in these studies; patients in the MRC study, for example, were in 2-year remission from seizures at enrolment.

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 coroners' registers,[6,7,21,22] studies that have used treatment data such as medical,[8,9,16,23] surgical,[11,24,25] or palliative,[18] and those that have been based on data from epilepsy clinics or institutions.[12-14,26] 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 as a large number do not accurately record the cause of death or the underlying conditions that could have contributed to death.[27] In addition, the prevalent population with epilepsy is used as a denominator—a presumed figure prone to variation and inaccuracy.[27] A recent case-control study found that annual incidence figures for SUDEP were 1.4 per 1000 person-years in males as well as females[17] although case ascertainment here was based on death certificates and underestimation was likely.

Sudden unexpected death in epilepsy incidence rates of up to 1:200 per year have been reported by studies based on tertiary epilepsy clinic data,[15] and slightly higher figures have been reported from institutionalised patients who share features of seizure intractability with clinic patients.[26] These figures are probably close to the true incidence of SUDEP in patients with chronic epilepsy.[14]

Several studies have used antiepileptic drug therapy lists for case ascertainment.[8,9,23] More recent studies have been based on newer antiepileptic drug registers such as those for lamotrigine,[16] gabapentin,[28] and tiagabine.[29] Some studies based on surgical data have shown a particularly high incidence of sudden death (up to 1:50 per year), especially for postsurgical patients where the operative procedure has not been successful in containing seizures—reflective of a group with particularly bad epilepsy.[11] 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 1 in 222 person-years of follow-up.[18] The high mortality and incidence figures in most of these studies may reflect the severe epilepsy suffered by patients in these study populations and are likely to indicate the increasingly high risk of SUDEP in patients with chronic epilepsy.

Risk factors

Seizure status

Recent studies have made it clear that the majority of cases of SUDEP were strongly temporally related to seizure episodes and witnessed deaths invariably occur during or soon after a seizure.[30-32] Fewer than half of all cases of SUDEP were witnessed but circumstantial evidence of a generalised tonic-clonic seizure having occurred was often found in the form of superficial injuries, a bitten tongue, incontinence, or characteristic postures.[7,15,31]

The frequency of seizures is therefore likely to be important in determining risk for SUDEP. It is well documented, however, that sudden deaths can occur with the first-ever or second-ever seizure, in the absence of status epilepticus. In one study of 66 cases in a medical examiner series, 11% of the cases of SUDEP had occurred after a first or second known seizure.[21] Similarly, SUDEP can occur in patients with active epilepsy who have infrequent seizures.

Several studies have now established, however, that increased seizure frequency directly correlates with increased SUDEP incidence. A case-control study in Sweden of 57 cases of SUDEP aged between 15 and 70 years found seizure frequency to be the strongest predisposing factor. The relative risk of SUDEP increased with the number of seizures per year (10.16; 95% confidence interval [CI], 2.94-35.18) in patients with more than 50 seizures per year in comparison to patients with two or fewer seizures per year.[17] The three controls used for each patient with SUDEP were patients with epilepsy from the same hospital

population and it was found that fewer cases (1.8%) than controls (31.6%) were seizure-free during the last year of comparison. The relative risk associated with having any seizure compared with being seizure-free was 23.0 (95% CI, 16.00-170.28). Although CIs are wide for many of the relative risk estimates provided in this study, it is the only comprehensive case-control study published to date.

Another important study from the US that analysed 11 cases of SUDEP in a surgical cohort followed for 10 years (median, 3.31 years) found that all of these deaths occurred in the 194 patients with postoperative seizure recurrence whilst none occurred in the 199 patients with no post-operative recurrence.[33] Standardised mortality ratio (SMR) or ratio of observed to expected deaths in the former group was 4.69 (95% CI, 2.33-7.87) whereas the SMR in the seizure-free group was no different from that of the general population (0; 95% CI, 0-1.8). This study suggests that seizure frequency is singularly important in determining risk for SUDEP. There is a small possibility, however, that biological factors related to the different seizure disorders treated by these different procedures may have contributed to the findings.

One surgical study found a particularly high incidence of SUDEP in patients with epilepsy who were unsuccessfully treated with surgery, with a mortality rate approaching 1:50 in contrast with 1:150 when both presurgical and postsurgical candidates were analysed together.[24] In contrast, the NGPSE and MRC Antiepileptic Drug Withdrawal Study, both of which had large numbers of patients with infrequent seizures, have shown very low incidence figures for sudden death.

Age, sex, and race

Patients with epilepsy within the 20 to 40 years age-group appear to experience the highest SUDEP mortality and this has been a consistent finding in many studies.[7,13,21] Patients of all ages can be affected, however, and a recent study described 27 paediatric deaths that represented a crude SUDEP incidence rate of 2 per 10 000 person-years, the youngest of whom was a 7-month-old child with developmental delay.[34] The Swedish case-control study found that, in men, there was an up to 18-fold increase in the relative risk with onset of epilepsy in childhood or adolescence compared with onset after the age of 45 years.[17] Seizure frequency did not appear to influence this finding.

Most studies, apart from one study of children with epilepsy in a residential school, have shown a male preponderance.[7,12,13,15] 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.[7]

Seizure type

Sudden unexpected death in epilepsy is not restricted to a particular seizure type. Most SUDEP series report generalised tonic-clonic seizures in the majority of patients although deaths in patients with complex partial seizures alone have also been reported. The Swedish case-control study classified patients as having generalised idiopathic, localisation-related symptomatic, localisation-related cryptogenic, and undetermined epilepsy, and found that the only significant correlation was one of decreased risk in male patients with localisation-related symptomatic epilepsy. This is in contrast with previous reports suggesting higher mortality rates with remote symptomatic epilepsy[35] and idiopathic epilepsy.[23] Differences in classification and a lack of standardisation in methodologies probably account for the lack of consensus at the present time, and the role of seizure type is therefore not exactly clear.[17]

Antiepileptic medication

The role of medication in SUDEP is not yet fully understood. Since seizure control appears to be of vital importance, it is most likely that the patients most at risk of SUDEP due to frequent seizures will also be those receiving polytherapy with high doses of antiepileptic drugs. Thus, the association of polytherapy and high drug doses with SUDEP may just be an example of their surrogacy for poor seizure control. Equally, however, some commonly used drugs are arrhythmogenic and others are capable of producing respiratory depression.

Non-compliance with prescribed antiepileptic medication has been implicated in the occurrence of sudden death and several patients have been found to have subtherapeutic serum levels of antiepileptic drugs.[7,21,25,36] One study found no difference in compliance in 44 cases and controls derived from a coroner's register.[37] The significance of drug levels, however, is arguable since patients with well-controlled epilepsy can have low drug levels and vice versa—postmortem drug level analysis may therefore be unreliable. Conversely, high carbamazepine levels have been associated with a relative risk of SUDEP of 9.5 (95% CI, 1.4-66.0) compared with patients with normal target range levels.[38] There are reported instances of patients experiencing sudden arrhythmic deaths possibly due to the cardiac side-effects of carbamazepine,[39] although this is obviously not the situation for the majority of cases of SUDEP. It has been suggested that patients who had no therapeutic drug monitoring were more likely to experience SUDEP, although drug monitoring may simply reflect a group of patients who have difficult-to-treat epilepsy for whom frequent dose manipulation and drug interactions are more common.[38]

The Swedish case-control study showed that patients taking two (2.69; 95% CI, 1.28-5.65) or three (9.89; 95% CI, 3.2-30.6) antiepileptic drugs were significantly more likely to experience SUDEP than patients receiving monotherapy. Patients taking three drugs were 10-fold more likely to have SUDEP than those receiving monotherapy.[17] Interestingly, when controlled for seizure frequency, the relative risks of polytherapy did not greatly alter, suggesting that polytherapy may not just be a surrogate marker for

epilepsy severity, but may contribute independently to the pathogenesis of SUDEP.

Neurological status

A higher incidence of SUDEP has been found for patients with neurological deficits and learning difficulties.[26] This may be attributed to the severity of epilepsy that is usually present in these patients and the higher all-cause mortality generally found in such patients.

Other factors

Alcohol abuse has been implicated for some patients,[7] although this has not been confirmed by other researchers.[17] Psychotropic drugs have been found to be associated with an increased risk of SUDEP [9] and this appeared to be true in a case-control study where there was a similar distribution of patients with psychiatric disorders and control subjects.[17] Recent head injuries have also been mentioned as a possible risk factor.

Autopsy findings

Autopsy findings, by definition, should not indicate an anatomical or a toxicological cause of death, although this does not necessarily imply that no abnormalities are found on postmortem examination. Pulmonary oedema is often found, although this is usually of insufficient severity to be an attributable cause of death.[7,21,40,41] Similarly, increased liver, cardiac, and brain weights are also found. Some studies have found brain lesions at autopsy that could have caused seizures in those patients.[7,21,41] A recent study noted the presence of interstitial cardiac fibrosis in patients who had epilepsy-related sudden deaths.[42]

Pathogenetic mechanisms

Seizure activity remains central to 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 observations in seizures in patients in hospital, 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 causes of death.[43-45] Significant ST segment changes[46] and corrected QT interval prolongations have been observed with epileptiform electroencephalography discharges in patients with chronic epilepsy, although the investigators also found that this prolongation remained within normal limits for almost all patients.[47] Intrinsic cardiac disease has been implicated and, in one recent study, a significant number of patients were found to have interstitial cardiac fibrosis, although whether this is directly related to a mechanism of death is debatable.[42] The influence of cardioactive antiepileptic drugs also remains speculative.[48]

In an interesting study where seizures were chemically induced in sheep, central hypoventilation was found to be a mechanism of death.[49] 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.[50] In another study of 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, although why this should happen is unclear.[51]

In one study, transient bradyarrhythmias were found to occur in association with apnoea and/or a change in respiratory pattern in patients experiencing seizures, suggesting that both cardiovascular and central mechanisms are important and cardiorespiratory brainstem reflexes may play a role in SUDEP.[52] In summary, while there are several postulates, the true mechanism of sudden death remains unclear.

Conclusion

Seizure control is an important issue in sudden death in epilepsy and evidence from many studies strongly suggests an important role played by uncontrolled epilepsy in SUDEP. Infrequently, SUDEP may occur in a first or second known seizure, and is known to occur in patients with relatively infrequent seizures. 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 may be low, its occurrence is often devastating to relatives, carers, and physicians. For patients with chronic epilepsy, where the incidence is considerably higher, the role of adequate supervision is equally important, especially among children and institutionalised people. As newer antiepileptics 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 decrease. The role of further studies examining the risk factors involved in SUDEP cannot be emphasised enough and further studies should be encouraged.

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