

Review Article

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Sudden unexpected death in epilepsy

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People with epilepsy have increased risk of premature death, and their life expectancy may reduce by 2-10 yr. Population- and hospital-based studies have shown that the excess mortality in epilepsy is not entirely explained by deaths directly attributable to epilepsy such as accidents and drowning during a seizure. It is also significantly contributed by deaths from other causes such as cardiac deaths, deaths due to malignancies and other causes. It had recently been recognized that sudden unexpected deaths in epilepsy (SUDEP) contributed to a small yet important proportion of mortality in epilepsy. SUDEPs are deaths (witnessed or unwitnessed) unrelated to trauma, drowning or status epilepticus and not attributable to any specific medical conditions. Several factors related to epilepsy and drug therapy have been found to be associated with higher risk of SUDEP.

Key words Discussion with family members - epilepsy - premature death - risk assessment - sudden unexpected deaths - SUDEP

Introduction

Epilepsy is one of the most common neurological disorder that affect >50 million people across the world. It is now widely recognized that people with epilepsy are two to three times more likely to die early. It reduces life expectancy by 10 years for those with symptomatic epilepsy and by two years for those with idiopathic epilepsies¹. Accidents, sudden unexpected deaths, status epilepticus and suicides constitute a vast majority of cause of death in epilepsy². A population-based study in the UK showed that, during the period 1993-2005, the mortality from epilepsy increased by 31 per cent for males and 39 per cent for females, whereas the mortality from all causes declined by 16 per cent³. The standardized mortality ratio (SMR) for epilepsy in India varied from 2.58 to 7.6⁴⁻⁶. The prevalence of

epilepsy in low-income countries is comparable to that of high-income countries although the former has a higher incidence than the latter. This disparity between incidence and prevalence in low-income countries points towards higher mortality for epilepsy when compared to high-income countries^{7,8}.

The excess mortality in epilepsy cannot be entirely explained by deaths directly related to epilepsy such as accidents and drowning due to seizures or status epilepticus. The proportion of deaths from suicide, malignancies and cardiac causes are also increased in people with epilepsy. Sudden unexpected death in epilepsy (SUDEP) has recently emerged as an important cause of death in people with epilepsy. Although the phenomenon of SUDEP was known as early as latter part of 19th century, it was rarely

highlighted as important. Apparently, the stepdaughter of George Washington who was suffering from epilepsy had a sudden death⁹. SUDEP has considerable social significance as it is still not clear how and when the issue of SUDEP need to be presented to the patient or his or her caregivers^{10,11}.

Definition

The first detailed definition of SUDEP was put forward by Nashef¹² as sudden unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause for death. A post-mortem examination is mandatory for the diagnosis according to this definition. Food and Drug Administration and Borroughs Wellcome had set up a committee chaired by Leestma that had recommended a modified definition

that included definite, probable and possible SUDEP¹³. This definition was easy to use in epidemiological studies and for classification of deaths where autopsies were not performed. However, it does not provide any operational cut-off values for 'sudden death' or have provisions to handle alternate or other causes of death. A new unified set of criteria for the diagnosis of SUDEP was proposed in 2012 (Table I)¹⁴.

Incidence

Incidence of SUDEP varies according to the study population. The SMR in patients with epilepsy is 2.55 *i.e.* 2-3 times more than that of general population¹⁵. In the population-based studies, SUDEP incidence rates have been found to vary between 0.35 and 1.35/1000 person-years^{16,17}. The incidence reported was higher for people with chronic epilepsy (1.2-5.1/1000 patient years)¹⁸⁻²¹ and for those who had undergone surgery for refractory epilepsy

Table I. Unified criteria for diagnosis of sudden unexpected deaths in epilepsy (SUDEP)

Definite SUDEP: A sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding status epilepticus, in which post-mortem examination does not reveal a cause of death

Definite SUDEP plus: A satisfying definition of definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death

Probable SUDEP/probable SUDEP plus: Same as definite SUDEP but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death

Possible SUDEP: A competing cause of death is present

Near-SUDEP/near-SUDEP plus: A patient with epilepsy survives resuscitation for more than one hour after a cardiorespiratory arrest that has no structural cause identified after investigation

Not SUDEP: A clear cause of death is known

Unclassified: Incomplete information available; not possible to classify

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Table II. Sudden unexpected deaths in epilepsy (SUDEP) rates according to study characteristics

Study	Sample population-based/special groups	City, country	Period	SUDEP/1000 patient yr
Ficker <i>et al</i> ¹⁶	Population	Rochester	1935-1996	0.35
Tennis <i>et al</i> ¹⁷	Population	Saskatchewan, Canada	1976-1987	0.54
Langan <i>et al</i> ²⁸	Population	Ireland	1992-1994	1.6
Walczak <i>et al</i> ²⁹	Epilepsy	US	1991-1996	1.21
Nilsson <i>et al</i> ³⁰	Epilepsy surgery	Sweden	1990-1998	6.3
Weber <i>et al</i> ²⁵	Children with epilepsy (<18 yr)	Switzerland	1984-2001	0.43
Mohanraj <i>et al</i> ²⁰	Newly diagnosed epilepsy	Glasgow, UK	1981-2001	1.08
Mohanraj <i>et al</i> ²⁰	Chronic epilepsy	Glasgow, UK	1981-2001	2.46
Edey <i>et al</i> ²⁷	Women with epilepsy	UK	2006-2008	1
Pack ¹⁹	Epilepsy monitoring unit	Multicentre (international)	2008-2009	5.1 (2.6-9.2)

(6.3-9.3/1000 person-years)^{22,23}. The risk of SUDEP in children was lower (0.36-0.43/1000 person-years)²⁴⁻²⁶. Study on women in their reproductive age with epilepsy in the United Kingdom revealed a SUDEP rate of 11 per cent (1/1000 maternities) (Table II)²⁷.

Predictors of sudden unexpected deaths in epilepsy (SUDEP)

Several studies have identified important predictors for SUDEP. The rate is marginally higher for males, particularly for those with generalized tonic-clonic seizures (GTCS)²³. Studies have shown that onset of epilepsy before 16 yr of age carries higher risk of SUDEP^{31,32}.

It is important to recognize that the presence of certain comorbidities increases the risk of SUDEP. Mental retardation, dementia, psychiatric illness, alcohol and other substance abuse are associated with increased risk of SUDEP, though none has been conclusively proven^{29,33}. Jick *et al*³⁴ have pointed towards the relationship between certain aspects of pharmacotherapy and SUDEP. There are conflicting reports on the association between polypharmacy and SUDEP. It has been shown that the addition of a second antiepileptic drug (AED) to the first one increases the risk of SUDEP and the presence of three AEDs increases risk 10 fold³⁰. In contrast, Opeskin *et al*³³ have failed to establish any association between SUDEP and polypharmacy.

A population-based study in Norway showed that of the 26 patients with SUDEP, 10 were on lamotrigine (9 females). There was a significant association between the use of lamotrigine and SUDEP in women. This observation is particularly significant as lamotrigine is increasingly recommended for the treatment of generalized epilepsy in women³¹. A secondary analysis of data from randomized controlled clinical trials involving lamotrigine showed that there was no significant difference in the rate of SUDEP between lamotrigine and comparator groups. The confidence intervals were wide and clinically significant effect could not be ruled out³⁵. The possible association between lamotrigine and SUDEP may be mediated through cardiac autonomic dysfunction as in kainate model of epilepsy, lamotrigine was found to increase the cardiac autonomic instability³⁶. Kloster and Engelskjøn³⁷ found that seizures were more common amongst patient taking carbamazepine and oxcarbazepine, but this was not proved in other studies. In SUDEP cases that had undergone autopsy studies, the blood level of AEDs were found to be in subtherapeutic range³⁸.

The duration and severity of epilepsy seem to have an association with risk of SUDEP. People who suffered SUDEP had a longer duration of epilepsy than others in case-control studies³⁹. The risk of SUDEP was 15-fold higher for people with >50 GTCS per year³⁹. Nocturnal seizures were more common amongst the SUDEP group. Patients suffering from GTCS have been found to have increased risk of SUDEP³⁹ when compared to patients with complex partial seizures and absences. Prolonged tonic phase of the seizure has been found to correlate with postictal immobility and has a role in mechanism of SUDEP⁴⁰. Postictal generalized electroencephalogram (EEG) suppression following seizure has a predictive role in SUDEP but has not been proved in subsequent studies⁴¹.

Idiopathic/cryptogenic epilepsy was at a lower risk to SUDEP compared to symptomatic epilepsy and females with idiopathic generalized epilepsy were lesser prone for SUDEP compared to males with idiopathic generalized epilepsy. Patients with Dravet syndrome were at higher risk of sudden death and so were children younger than six years of age^{42,43}.

Pathophysiology

SUDEP is a descriptive term that conveys little about the pathophysiology that leads to the sudden death. Various hypotheses involving respiratory, cardiac, cerebral and autonomic dysfunctions have been put forward to explain the phenomenon.

Cardiac hypothesis: One of the postulated mechanisms of SUDEP involves sudden cardiac arrest. Dysfunction of sodium channel has an important role in the electrophysiological basis of epilepsy and cardiac arrhythmias and altered cardiac electrical function may contribute to susceptibility for arrhythmogenesis and SUDEP. Ion channel abnormalities may be a potential mechanism for both epilepsy and cardiac dysfunction. The most common ion channel implicated is *SCN* gene mutation^{44,45} as in Dravet syndrome that is associated with higher risk of SUDEP. Channelopathies have been linked to long QT interval syndrome and familial epilepsies. There have been multiple case studies^{44,45} and animal experiments⁴⁶ that have noted susceptibility of this gene in this condition. There is a possible pathogenic link between SUDEP, mutations in ion channel genes and familial Long QT syndrome (LQTS). Familial LQTS has been implicated in the sudden cardiac death. Ion channels such as *KCNQ1*, *SCN1A*, *LQTS*, *KCNH2* and *SCN5A* regulating the QT interval are

likely to play an important role in the predisposition of epilepsy patients to sudden death⁴⁷.

Autonomic dysfunction: Autonomic involvement in the form of excessive sympathetic and parasympathetic drive has been found to play a role in SUDEP. It is widely recognized that heart rate increases during seizures⁴⁸. Two or more autonomic function tests have been found to be impaired in patients with refractory epilepsy^{49,50}. Extensive derangement of autonomic functions such as higher sympathetic tone, higher vasomotor tone, lower parasympathetic reactivity, lower parasympathetic tone and severe dysautonomia has been demonstrated in patients with intractable epilepsy^{49,50}. People with intractable epilepsy on treatment with antiepileptics have been shown to have decreased heart rate variability⁵¹. Decreased heart rate variability is an important risk factor of sudden cardiac death in patients with type II diabetes and myocardial infarction. The role of reduced heart rate variability in causation of SUDEP needs further validation. It is unclear whether the reduced variability in heart rate is a result of antiepileptic usage or a part of refractory epilepsy^{52,53}.

Mortality in epilepsy monitoring unit study (MORTEMUS⁵⁴) was an international initiative using in-hospital, presurgical data to assess SUDEP mechanisms and risk factors. Video EEG (VEEG) and electrocardiogram data at the time of cardiac arrest during epilepsy monitoring were retrospectively analyzed between January 2008 and December 2009. Of the 160 units enrolled in the study, 147 responded to the survey. A total of 16 SUDEP and nine near SUDEP were reported. The incidence of SUDEP was 5.1/1000 patient-years (95% confidence interval 2.6-9.2) and risk of 1.2/1000 was documented. This study proposed a centrally mediated alteration of respiration and cardiac function following GTCS. They found that following a GTCS, profound bradycardia and apnoea ensue after an initial variation in the cardiac and respiratory rates. This suppression of the cardiac and respiratory rhythm is associated with a postictal generalized suppression of the EEG. This study in epilepsy monitoring units showed altered cardiorespiratory function leading to terminal apnoea and cardiac arrest.

Peri-ictal hypoxaemia occurs in at least 25 per cent of patients with SUDEP⁵⁵. The ictal phase of generalized seizures is more often associated with tachycardia than bradycardia. Both ictal hypoxaemia and ictal tachycardia were associated with risk factors implicated in SUDEP-refractory epilepsy, generalized seizures and normal neuroimaging⁵⁵.

SUDEP often happens during sleep and nocturnal seizures were more frequent in patients who had SUDEP than survivors⁵⁶. Almost all SUDEP deaths have occurred in prone position and during sleep. Excessive autonomic activity (ictal tachycardia), autonomic imbalance during seizure (switch from parasympathetic tone to sympathetic tone) and sympathetic overstimulation on AED withdrawal might be the probable precipitating factor for SUDEP.

Postictal generalized suppression of EEG (PGES) has been observed in some patients after GTCS. It has rarely been reported after other types of seizures. Lhatoo *et al*⁵⁷ found that PGES of 50 sec or more in refractory epilepsy patients was associated with increased risk of SUDEP. However, this was not reconfirmed in later studies^{41,58}. PGES is representative of the cortical electrical activity. It is unclear at present whether it is secondary to postictal depression of cortical activity or postictal hypoxia or due to derangement of the ascending arousal system.

Multiple neurotransmitters are released during a seizure, and their role in the pathogenesis of SUDEP needs further evaluation. The important neurotransmitter implicated in this is serotonin. Serotonin has been found low in patients with epilepsy and low serotonin levels have been found to be associated with SUDEP^{59,60}. Serotonin levels are also found to be lower in sleep. Serotonin is a central neurotransmitter which stimulates thalamocortical circuits. Serotonin has been found to modulate respiratory activity in brainstem⁶¹. In an animal model (DBA/2 mouse model) treatment with serotonin antagonist fluoxetine reduced respiratory depression⁵⁹. SUDEP may be related to sudden infant death syndrome where low medullary serotonin levels have been found^{62,63}. Other substances released during seizures such as opioids and adenosine have also been found to have a role in SUDEP^{64,65}. In a systematic review a significant association was found between prone position and SUDEP⁶⁶, suggesting that prone position was a major risk factor.

Autopsy changes in SUDEP

In a study on SUDEP³⁷ though pathological findings were found, there were no definitive changes noted in post-mortem findings of SUDEP and non-SUDEP patients. Most common findings in lung were pulmonary oedema, and this as a cause resulting in SUDEP was considered unlikely. Most common pathology in cardiac system was fibrosis of the conduction system. In brain, SUDEP patients had predominantly cerebral

oedema, but there was no associated mass effect or hydrocephalus. Structural brain lesions were common amongst the SUDEP group, but this was a clue for aetiology rather than cause of death. Neuropathology showed evidence of acute neocortical and brainstem hypoxic neuronal changes^{67,68}.

Prevention

Various mechanisms have been postulated for SUDEP. Understanding those mechanisms will help in prevention of SUDEP. SUDEP patients are mainly found in prone position, hence immediately post-seizure preventing the patient from compromised position may help in prevention of SUDEP. Prone position has been found to result in hypopnoea, leading to respiratory failure. Use of lattice pillows prevents suffocation and appears to reduce asphyxia risks⁶⁹. The patients require nocturnal supervision. Post-seizure attention to recovery of patients after seizure and positioning after seizure or stimulating if necessary may be required to prevent SUDEP. MORTEMUS study⁵⁴ suggested the routine use of pulse oximetry, EEG or pulse alarm system will help in improvement of nocturnal monitoring and supervision.

A reduction in frequency of GTCS can reduce the risk of SUDEP. Similarly, change adoption of monotherapy may also reduce the risk of SUDEP as polypharmacy has been found to have increased risk of seizures³⁹. However, polytherapy and frequent GTCS may be indirect evidence of refractory epilepsy.

There have been reports of lamotrigine implicated in SUDEP; however, its role has not been conclusively proved. Lamotrigine and carbamazepine combination was found to have increased risk. A study by Hesdorffer *et al*³⁹ suggested that prevention of SUDEP should include reduction of GTCS than AEDs alone. Some new detection devices are under study such as 'wearable apnoea detection devices that could help prevent SUDEP'⁷⁰.

Selective serotonin reuptake inhibitors on chronic administration have been found to prevent seizure-induced sudden cardiac death in chronic SUDEP model⁷¹. Furthermore, adenosine and opiod antagonists have also been under study for the prevention⁷².

Risk assessment

Studies have shown that neurophysicians fail to tell the risk of SUDEP amongst patients with epilepsy⁷³. This may be due to non-availability of biomarkers or inventories. New SUDEP-7 inventory has been

developed to help in risk assessment⁷⁴. They correlated the risk of SUDEP with heart rate variability. Root mean square differences of successive R-R intervals (RMSSD), a measure of low-frequency heart rate variability (HRV), was significantly associated with SUDEP Risk Inventory (SUDEP-7) scores⁷⁴. RMSSD is independent of respiratory effects and measure of vagal function. HRV is a measure of autonomic function, which can be assessed as a biomarker in SUDEP patients^{49,50}. Low heart rate variability has been found in patients with SUDEP; however, these findings need further validation⁵¹. PGES duration has also been suggested to be useful as biomarkers⁷⁵; however, its role in SUDEP is not proved.

Conclusion

SUDEP is an important yet under recognized aspect of epilepsy care. Several risk factors and possible predictors of SUDEP have been identified through epidemiological, clinical and experimental studies. Nevertheless, the precise mechanisms and possible preventive measures are yet to be found out. Health care professionals need to be aware of this condition and need to discuss regarding SUDEP with patients and their relatives for the better treatment and prevention of the same. Wider discussion and long term research programs are necessary in this direction.

Conflicts of Interest: None.

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