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Sudden Death in Epilepsy: Insights from the last 25 years

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Highlights

- SUDEP is the leading cause of mortality in chronic refractory epilepsy
- Pathophysiology remains poorly understood but risk factors identified
- No proven intervention for its prevention
- Increasing awareness and research in the last 25 years
- Several promising future research avenues to minimise SUDEP impact

Sudden Death in Epilepsy: Insights from the last 25 years

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Abstract

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of mortality in patients with refractory epilepsy, and as such has been a major research focus over the last 25 years. The earliest SUDEP research papers were published in *Seizure*, as have scores of SUDEP papers since. In this review we discuss the efforts to try and describe the pathophysiological basis of SUDEP, the drive to discover the clinical risk factors that increase the likelihood of SUDEP, and the motivation to increase awareness of SUDEP. These three areas are the prime factors that, when answered, will allow us to better mitigate against SUDEP and help individuals monitor their personal risk. The field has benefited from strong definitions, multinational collaboration, the use of cutting edge genetic analysis, and ensuring that bereaved families are able to take part in research when this is appropriate. Clearly there is much that we do not know and yet, has any area of epilepsy research come so far in the last 25 years?

Key Words: Epilepsy, SUDEP, death

Abbreviations: Sudden Unexpected Death in Epilepsy (SUDEP); Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS); generalised tonic-clonic seizure (GTCS); postictal generalised EEG suppression (PGES); antiepileptic drug (AED); National Institute for Health and Care Excellence (NICE); long QT syndrome (LQTS); selective serotonin reuptake inhibitors (SSRI); implantable cardiac defibrillators (ICD).

Introduction

Epilepsy, unfortunately, is associated with a reduction in life-expectancy. Genetic and acquired epilepsies can be associated with life-limiting disorders, such as inborn-errors of metabolism syndromes, or primary brain tumours. People with epilepsy as part of a neurodevelopmental disorder, often comorbid with autism and physical impairment also have reduced longevity. It is now well recognised that the suicide rate in people with epilepsy is greatly elevated above the population means. The focus of this review however is of the peculiar apparently idiopathic deaths that occur in both sexes, people of all ages and with little or no precipitant. Cruelly it is most common in young adults and strikes when people are alone. We will discuss that some groups are at greater risk, but everyone with convulsive seizures appears to be at some risk.

For over a century, it has been recognised that patients with epilepsy are at risk of death from epilepsy itself.[1] Studies have consistently reported an increased mortality rate in epilepsy of two to four times that of the general population.[2] It has long been recognised that death may occur due to the underlying disease, as a result of a prolonged seizure or through injury. In the late twentieth century, it became apparent that there is an excess mortality in patients with chronic epilepsy that cannot be attributed to these mechanisms, with many deaths occurring unexpectedly and in benign circumstances.[1] Termed as Sudden Unexpected Death in Epilepsy (SUDEP), this was defined in 1997 by Nashef:[3]

“Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause for death.”

SUDEP is the leading cause of mortality in patients with chronic refractory epilepsy, estimated to cause 10-50% of deaths.[4-6] The topic has attracted increasing amounts of interest from both the scientific and epilepsy community since its definition. Given the sudden and devastating nature of SUDEP, most often affecting young people between the ages of 20-40, better knowledge of its pathophysiology and associated risk factors is crucial so that attempts at treatment and prevention can be made.[7] We will discuss the key developments in the field over the last 25 years before commenting on future clinical and research priorities.

Pathophysiology

Despite vigorous efforts, the pathophysiology of SUDEP today remains little better understood than when first described in the literature. The publication of several SUDEP epidemiological studies, case series of witnessed and monitored SUDEP and human and animal epilepsy research however, have provided data from which possible SUDEP mechanisms have been proposed.[8]

The 2013 MORTEMUS study was a milestone in SUDEP research; a multi-centre retrospective study examining SUDEP cases in epilepsy monitoring units. The 16 SUDEP cases and nine near SUDEP described offer a unique opportunity to better understand the mechanism underlying SUDEP as they occurred in monitored units. The study concluded that in the cases examined, a generalised tonic-clonic seizure (GTCS) led to early post-ictal, central-induced alteration of respiratory and cardiac function. This led either to immediate death or to a period of restored cardiorespiratory function before terminal apnoea causing cardiac arrest. The majority of patients remained in the prone position following seizure termination until death, with no attempt made to optimise their position. This may promote hypoxia, although it is noted that not all patients were in the prone position. As has been noted both anecdotally and in the literature, the majority of SUDEP cases occurred at night.[9] This may reflect decreased nocturnal supervision of epilepsy patients or may be suggestive that the circadian rhythm plays a role in SUDEP. The study reported that postictal generalised EEG suppression (PGES) was found to be more common at night, possibly promoting postictal central apnoea and asystole. [10] Two other studies published failed to replicate this finding.[11,12]

The most common proposed mechanism reported in other studies is that of seizure-induced respiratory dysfunction.[13] Although the majority of patients are found in the prone position, the face is usually tilted to one side and the airway is not completely obstructed. A case series of witnessed deaths reported that most patients experienced breathing difficulties before death.[11] This may be due to a combination of obstructive and central apnoea ultimately leading to asystole. The persistence of hypoxia and hypercapnia after respiratory effort has been restored or increased has suggested the possibility of intrinsic pulmonary

dysfunction. The evidence remains circumstantial with post-mortem examination showing pulmonary oedema in many SUDEP cases but not significant enough to cause death.[10]

Another proposed mechanism is that of seizure related cardiac arrhythmia. There are many case reports of patients receiving cardiac pacemakers as a result of postictal bradycardia and asystole. Genetic mutations in ion channels have also been studied as a potential cause for SUDEP, particularly long QT syndrome (LQTS).[8] A study of 61 people with SUDEP (the majority with definite SUDEP) were studied with exome sequencing and four had mutations in genes known to contribute to LQTS; two with *KCNH2*, one *KCNQ1* and a fourth with *SCN5A*. A further nine had variants in candidate genes for cardiac arrhythmia; that is to say genes coding for ion channels that may contribute to LQTS, Brugada syndrome or catecholaminergic polymorphic ventricular tachycardia. [14] An ultra-rare variant in *SCN5A* has previously been identified in a young woman with SUDEP.[15] It remains unclear whether patients with LQTS and epilepsy are at increased risk of SUDEP, and this mechanism is unlikely to be the primary cause of SUDEP in the majority of patients

Other proposed mechanisms include that prolonged PGES leads to electrocerebral shutdown, leading to cardiorespiratory dysfunction. This was proposed in the MORTEMUS study, but studies have been inconsistent in determining the role played by PGES in SUDEP.[8] A study by Shen et al. explored the possibility that adenosine may play a role in centrally-induced cardiorespiratory dysfunction, suggesting that adenosine receptor antagonists such as caffeine may have a protective effect against SUDEP when given at seizure onset.[16]

Risk factors

Since its definition, there have been numerous studies to attempt to define and assess the impact of individual patient risk factors that may increase the likelihood of SUDEP. There are several fixed, non-modifiable risk factors but of more interest are those significant but modifiable risk factors that patients and healthcare professionals can together attempt to address in order to reduce the risk of SUDEP.

The significant but non-modifiable risk factors for SUDEP appear to be male sex,[17-18] history of GTCS,[17,19-22] younger age of onset,[17-19,22-23] longer duration of

epilepsy,[19,21,23-25] symptomatic aetiology,[18,26] and associated learning disability.[25-27] Although fixed, the knowledge of these risk factors are useful for clinicians when counselling patients for SUDEP. More importantly for the drive to minimise the risk of SUDEP, several modifiable risk factors have also been identified. Consistently reported are higher frequency of GTCS,[7,19-20,22,24,29] and antiepileptic drug (AED) polytherapy,[17,19-21,24-25,29] although it is recognised that AED polytherapy may be a surrogate for seizure frequency. Identification that the seizure frequency may increase in the months prior to a SUDEP has implications for SUDEP surveillance and healthcare system delivery.[30] The majority of SUDEP cases occur at night and several studies have reported that a lack of night-time surveillance as a risk factor for SUDEP.[2] Inconsistently reported is the use of lamotrigine and carbamazepine; further research is required to establish their roles as potential SUDEP risk factors.[2,26,31]

SUDEP awareness

Despite sudden deaths in people with epilepsy being reported for over a century, the concept of SUDEP only gained recognition just over two decades ago. Until the 1990s, there was almost no public awareness of its potential impact on people with epilepsy and very little in the medical literature. In the early 1995, the charity Epilepsy Bereaved was founded by families who had been affected by SUDEP in order to raise awareness amongst the public and medical community.[32] The first international conference was held in 1996 which led to the first international publication on SUDEP.[33] Following the landmark paper by Nashef in the same year which standardised the definition of SUDEP, research into SUDEP gained huge momentum. This is shown by the frequency of research using the word 'SUDEP' since the first instance in 1993 (figure), note the peak in 1997. It is worth noting that these first two papers were published in *Seizure*. [34-35]

Increased awareness of SUDEP amongst the medical community has been vital in ensuring that cases of possible SUDEP are referred to the coroner for investigation. All cases should

receive a tailored SUDEP autopsy in order to exclude other causes of death. There have been many reports of likely SUDEP cases being issued another cause of death, such as status epilepticus, or accidental death, by medical professionals and coroners despite there being no evidence for this. SUDEP may therefore be under-reported and the inaccurate classification of these deaths may skew epidemiological studies aiming to identify relevant risk factors.

The discussion of SUDEP with patients and their caregivers has always been a controversial topic. The National Institute for Health and Care Excellence (NICE) updated their guidelines on epilepsy management in 2004 to include SUDEP.[36] They advise that giving patients tailored information about their risk of SUDEP should be done as part of a counselling checklist for children, young people and adults with epilepsy and their families.

Several papers have been published that suggest that this is not routinely done in epilepsy clinics, with rates of clinicians routinely discussing SUDEP ranging from 4-6.8%.[37-39] The most common reasons given for not discussing SUDEP is that neurologists feel that their patients are at low risk and the fear of a negative reaction.[39] The commonest reasons given for discussing SUDEP was the patient enquiring about it and the neurologist counselling someone with known SUDEP risk factors.[40] Beran et al. reported in 2004 that to disclose the risk of SUDEP when not sought by the patient may in fact be unethical and transgress the basic principle to "do no harm", as there is no proven intervention to minimise SUDEP and that knowledge of the condition may negatively impact quality of life.[41] It was also reported that doctors are unlikely to be found negligent for not discussing SUDEP as, unlike the 'back to sleep' campaign for lessening sudden infant death, there is no proven treatment or intervention.[41-42] However, there is mounting evidence that patients and their families do wish to be informed of the risk of SUDEP, both within the paediatric and adult population.[43-45] Despite not routinely being informed of the risk, this does not mean that patients are ignorant of SUDEP and they may resort to inaccurate and unreliable information sources that do not take into account their personal risk of SUDEP.[40] Given that the majority of reported patient reactions by physicians are negative following these conversations, further research is required to determine the best way of delivering the information to patients and their families.[39]

Treatment and prevention

There remains no effective evidence-based treatment or prevention against SUDEP. The mainstay of management has been in addressing the modifiable risk factors to reduce SUDEP risk. This includes promoting AED compliance to reduce the incidence of GTCS and making patients and families aware of the potential consequences of uncontrolled nocturnal seizures.[36] The use of a safety checklist has gained interest since it was first proposed and has subsequently been developed in to a smart-phone app.[2] Patient education is important in promoting adherence to AEDs, avoiding factors that may trigger seizures, appropriately reacting to clusters of seizures and being aware of the interaction of other drugs with AEDs.[46] Lattice pillows have been proposed as an intervention to reduce the risk of airway obstruction,[46-48] but there have been no studies to evaluate their use in epilepsy. Nocturnal supervision has been found to be protective against SUDEP in one study,[29] possibly suggesting that nocturnal seizure alarms may have a role in improving night-time supervision.[46,48] The use of selective serotonin reuptake inhibitors (SSRI), opiate receptor inhibitors, adenosine receptor inhibitors, cardiac pacemakers and implantable cardiac defibrillators (ICD) have also been proposed as future targets for SUDEP prevention but there have been no trials examining the benefits of these in the prevention of SUDEP.[46]

Within the hospital setting, several interventions are recommended to reduce the duration of seizures, respiratory dysfunction and EEG suppression. These include repositioning of the patient, oral suctioning and oxygen administration as well as prompt administration of AED if indicated.[48] The MORTEMUS study also showed that in near-SUDEP cases, resuscitation was prompt whereas in the SUDEP cases it was delayed suggesting that close monitoring of patients in hospital with the use of direct supervision, ECG, EEG and oxygen saturations may reduce the risk of SUDEP.[10,48]

Ultimately there remains no consistently proven preventative strategy or treatment for SUDEP,[49] although several of those described show promise and deserve further research to determine their effectiveness.

The next 25 years

There are several key challenges that we face over the next 25 years in improving epilepsy care provided to patients and minimising the devastating impact of SUDEP. More research is required into the pathophysiology of SUDEP which may ultimately lead to the development of preventative strategies. It is quite plausible that just as we consider 'epilepsy' to be a collection of disparate epilepsies, we may need to identify the pathophysiologies of SUDEP. The reliance of EEG as a key biomarker for determining PGES currently limits all studies of SUDEP in the community. The identification of biomarkers for SUDEP that go beyond electrophysiological measures may help this.

As discussed, many significant risk factors have been identified that place patients with epilepsy at increased risk of SUDEP. Whilst some of these are not modifiable, those that are must be addressed with each patient. In particular, seizure control must be optimised and nocturnal seizures minimised. Clinicians can focus on communicating the benefits of medication adherence and tailoring the medication regimen to the person with the use of longer-acting agents where indicated. Sleep-related convulsions may not always be recognised by the patient and when they do occur, they may be perversely considered to be benign as they may not necessarily affect driving status[50] and they occur in a place of perceived safety.

There needs to be increased awareness of SUDEP both by healthcare professionals and by patients as it is only by doing this that patient risk factors for SUDEP can be addressed. Whilst there are many studies reporting the lack of discussion of SUDEP with patients and the fact that patients and their caregivers wish to receive such information, there is further work required to identify the best way in which to divulge this information whilst minimising patient anxiety and distress. Increased awareness of SUDEP within the wider medical community beyond the specialty of neurology is also required, to encourage the reporting of sudden epilepsy deaths to the coroner and for adequate SUDEP post mortem examinations to be undertaken. This may lead to better appreciation of the pathophysiology of SUDEP and the identification of more modifiable risk factors.

Through the above, a better understanding of SUDEP may lead to effective prevention strategies. It is chilling to recognise that most people with epilepsy who die a SUDEP death,

die alone. More research is required particularly for the role of nocturnal supervision of epilepsy patients, as though it is currently suggested in the literature that supervision is protective, to routinely advise this could have a deleterious effect on the quality of life of epilepsy patients and should not be undertaken lightly without substantive evidence for its recommendation. Nocturnal seizure alarms appear to be a promising alternative and these warrant further research to determine whether offer any protection against SUDEP. Further research is also required to determine the effectiveness of SSRIs, opiate and adenosine receptor inhibitors, cardiac pacemakers and ICDs in the prevention of SUDEP. We hope that reducing the treatment gap and ensuring the highest quality epilepsy care for everyone may reduce SUDEP rates; already there is evidence that successful epilepsy surgery reduces mortality, in part, by lowering SUDEP rates.[51]

The aim in 25 years is to reduce the incidence of SUDEP and the anxiety that the threat of SUDEP has on patients and their families. The ultimate goal is to find a treatment or prevention so effective that it is abolished. Hopefully through continued high quality research as has been the case over the last two decades, this is an attainable goal.

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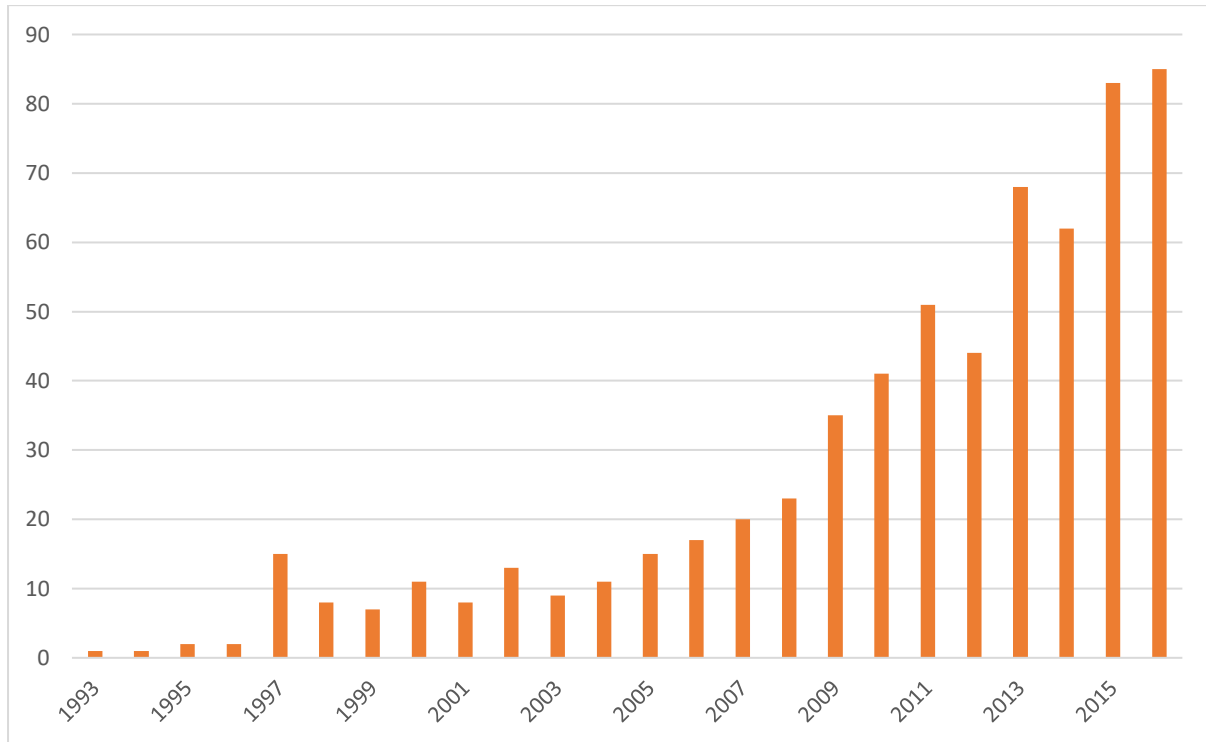


Figure: The exponential growth in SUDEP research as measured by the use of the word 'SUDEP' in PubMed. The first instance is in 1993. The 2016 figures are for the year up to and including August.