

A step to modify and prevent SUDEP- The validity of risk factors in the SUDEP and Seizure Safety Checklist: a case control study

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Abstract:

Aim:

Our objectives were to compare people with epilepsy (PWE) who died of Sudden Unexpected Death in Epilepsy (SUDEP) with live controls using the risk factor items of the SUDEP and Seizure Safety Checklist.

Method:

All 48 SUDEPs of 93 epilepsy deaths which occurred in Cornwall UK 2004-2012 were compared to 220 live controls using the SUDEP and Seizure Safety Checklist, an evidenced based tool used to communicate person centred risk of SUDEP to PWE. The odds ratio for having a specific factor in those who died was compared to controls and ranked according to P value using a sequential Bonferroni correction for multiple comparisons.

Result:

Of the 17 modifiable and non- modifiable risk factors analysed 9 were statistically significant of which 7 are potentially modifiable. Well known modifiable factors such as nocturnal monitoring, compliance and sleeping position featured prominently in the risk association.

Conclusion:

This is the 1st case control study exploring the risk factors for SUDEP since 2009. The findings are compared to the current considered risk factors as identified in a major recent review. The study further validates certain SUDEP risk factors. It highlights that the majority of risk factors strongly associated with SUDEP are potentially modifiable. There is an emerging profile to rank the risk factors. It furthers the evidence to use structured risk assessment and communication tools such as the SUDEP and Seizure Safety Checklist in daily clinical practice. It highlights key areas for a person centred discussion to empower PWE to mitigate risk.

Introduction

Sudden unexpected death in epilepsy (SUDEP) is the most important direct cause of deaths in epilepsy¹. People with epilepsy (PWE) are 20 times more likely to die suddenly compared to the general population². SUDEP is the most common cause of death in PWE. In the UK in 2013, 1187 people died from epilepsy (includes SUDEP, Status etc.) , roughly the same amount of that died from asthma (1255) despite there being a population of over 5.3 Million people with asthma while PWE number around 600,000. The 2013 Office of National Statistics UK data suggest that up to 60.5% of these epilepsy deaths were seen as avoidable whereas 25.5% of asthma deaths were. This suggests that there may be improvement in the way we identify risk and manage PWE in the community.

In a recent literature review on risk factors for SUDEP³, twenty factors were identified that increased the risk of SUDEP. These 20 factors were subsequently applied to a previously unexposed set of all SUDEPs (n=48) extracted by going through all epilepsy deaths (n=93) in the county of Cornwall UK (population 550,000) between 2004 -2012 to see if they remained consistent with the literature review findings⁴. It was found that 17 factors remained well associated with SUDEP and are directly relevant for people living with epilepsy. These 17 factors forms the background of the Seizure and SUDEP safety checklist, a 10 minute risk assessment tool used in epilepsy clinics across UK and the self-monitoring of epilepsy risk mobile app EpSMon^{5,6,7}. We compared these 17 factors between the 48 subjects who died from SUDEP in Cornwall with 220 of 231 continuous patients living with epilepsy who attended local outpatient epilepsy clinics to determine how strongly these factors are associated with SUDEP risk in a well defined population.

Method

We compared data collected over 9 continuous years of SUDEPs at the Cornwall Coroner's office using the SUDEP and Seizure Safety Checklist^{3,4} with data from medical records of clinical discussion with a full year of most PWE attending local epilepsy outpatient clinics on the potential risk factors identified for SUDEP using the same checklist.

We systemically inspected all epilepsy and epilepsy associated deaths which occurred in Cornwall between 2004 and 2012 all made available to us by the HM Cornwall coroner. These are the deaths where epilepsy was a primary or a secondary cause. The Cornwall coroner's office has a computerized system with a search engine to explore all registered death certificates. The data were collected from the coroner's records using the terms 'ep', 'epilepsy', 'Seizures', 'fits', 'Sudden death' and 'SUDEP' in either part 1 or 2 of the death certificate. Ninety three deaths were thus identified by the coroner's office. Each death's case file which included all comprehensive medical records up to the point of death was reviewed to ascertain those deaths which met the SUDEP criteria and classification using the operational definition of SUDEP provided by Nashef and Anneger^{4,8}. Of the 93 cases of epilepsy related deaths which occurred in Cornwall between 2004 and 2012. Forty eight cases met the criteria for SUDEP. We cross-referenced the

epilepsy deaths of these years (2004-2012) with public health data on epilepsy deaths held by the Public Health Department of Cornwall and the Isles of Scilly Primary Care Trust. The public health data showed 73 epilepsy deaths (43 male and 30 females) for the period of 2006 -2012. This is in keeping with our estimates for that period. The public health data only had the year, number of deaths and sex recorded. We then applied the clinical risk factors of the SUDEP and Seizure safety Checklist to all the SUDEP deaths. The detailed definitions used for the risk factors are described in previous papers^{3,4,6} and table 1.

The control population attended two specialist epilepsy outpatient clinics in Cornwall and for whom the Seizure safety and SUDEP checklist^{3,5,6,7} was administered as part of routine clinical practice over one year. The population was a continuous sample. Of 231 attendees in the one year (05/2013- 05/2014) to the two clinics 220 consented to the use of the Checklist. One year was chosen in order to sample the whole clinic population (maximum follow up time is one year).

We calculated the odds ratio for having a specific factor in those who died from SUDEP compared to controls. We ranked the factors according to P value and used a sequential Bonferroni to correct for multiple comparisons. Low numbers and missing data prevented a logistic regression analysis.

Results

The United Kingdom (UK) has a population of about 60 million. Cornwall is a county in UK with a population of 600,000 (about 1% of the UK population). It is largely a rural county and not subject to major immigration/emigration (except for large number of tourists during summer). The incidence of SUDEP has been estimated as 0.1% of all people diagnosed with epilepsy per year though it can raise to 1 in 150 PWE in refractory cases. An estimated 600 deaths occur in a year due to SUDEP in the UK and thus Cornwall would be expected to have approximately 6 SUDEP deaths a year. Our study is consistent with these numbers as 48 deaths over 9 years represent a rate of 5.33 SUDEP deaths/ year.

Our case sample was 48 people, 33 male and 15 female who died from SUDEP in Cornwall UK over the 9 year period⁴. Among the 48 deaths, the mean age was 42.5 years and median 42 years with a range of 2-82 years. Our control sample was 220 outpatients attending epilepsy clinics within Cornwall of whom 115 were male and 105 female. Among the 220 people, the mean age was 42.76 years and median 47.5 years with a range of 9-86 years. The majority of the SUDEP cases had been known to the local specialist epilepsy services sometime in their lifetime. However 80% of the SUDEP cases did not see a specialist in the year prior to death.

The comparison between the groups is given in Table 1 and illustrated in Figure 1. Of the 17 risk factors, 9 showed a significant difference between the two groups. Two significant risk factors - duration of epilepsy and diagnosis of generalised tonic clonic epilepsy – are not modifiable. However, there were seven potentially modifiable risk factors: unclear treatment history, poor adherence to medication, sub-therapeutic medication levels, alcohol misuse, no night surveillance, sleeping in the prone position and increasing seizure frequency, which could be ranked.

Conclusion

This is the first case control study exploring the risk factors for SUDEP since 2009. There were four major case control studies looking at SUDEP risk factors^{9, 10,11,12,13} whose data was pooled and a combined analysis of the identified risk factors conducted in 2011⁹. Our study supports many of the pooled findings from those studies that certain factors have a considerable impact upon the risk of SUDEP, and importantly, a large proportion of these factors can be modified. Some factors considered are new or are bearing different results to the pooled analysis. This study finding has been compared to the current evidence of a recent major review on SUDEP risk factors (table 2).

The 4 case control studies^{10,11,12,13} while all trying to enumerate risk factors were diverse in their design, examination of population of risk and controls (table 3). Risk factor examination was more explorative in nature. The pooled analysis⁹ was a function of the results of these studies. Our study unlike other SUDEP case control studies had a pre-designed questionnaire which had the advantage of having extracted the risk factors of all the other studies in particular the pooled analysis⁹ and re-testing it in a new population thus looking to see if the factors identified by the pooled analysis were generally applicable. The pooled analysis got its data from studies of different geographic regions and demographics. The current study observed if such a pooled result could be representative in a new region with a well-defined population.

There are other advantages to our study too. Three of the four past studies^{10, 12, 13} were hospital centric with the deaths being traced from hospital records and not community based. One of the four studies¹¹ collected referrals from diverse streams but was not structured to identify the full population at risk and thus not systematic. Our study has the advantage that controls and SUDEP were drawn from the same population. Moreover, it is also the only study where a pre-developed checklist has been used in both the people who died and controls..

Poor accessibility of services or poor engagement with services as indicated by an unclear treatment history, poor adherence, increasing seizure frequency and sub-therapeutic medication levels increased the risk of being in the SUDEP group. As previously found if patients misuse alcohol they add to their risk of SUDEP. If patients have night surveillance through someone sleeping with them or using a monitor, risk is reduced, as is sleeping in the non-prone position. While the association of the 'prone position' is strong and theoretically a modifiable risk factor the actual and

practical modifiability of this factor is contested. People don't typically stay just prone in bed while sleeping they toss and turn. Patients with epilepsy typically roll over when having seizures to turn their face into the pillow. There might be a role for anti-asphyxia pillows¹⁴. Night surveillance, while a practically achievable issue, should take into account privacy issues and the choice to live alone. A practical person-centred approach to such social situations might pay dividends. All of these factors can be addressed but require the patient to be informed about SUDEP risks (an aim of the SUDEP checklist).

As with the combined analysis⁹ carbamazepine as a risk factor was not significant thus further consolidating its safety profile with regard to SUDEP. Interestingly being male and taking antidepressants were not significant; this may have been the result of an underpowered study but it does indicate that these factors are probably not so critical.

The negative finding on intellectual disability (ID) is difficult to interpret. Other studies have shown this to be a risk factor of SUDEP^{9, 10, 15, 16}. However Cornwall has a dedicated ID epilepsy service as approximately 25% of PWE have ID and our data suggest only 6.3% of people dying from SUDEP have an ID⁴ compared to 23.4% in other studies¹⁵. It is possible that ID as a risk factor is dependent on the quality of services rather than the ID itself.

There are clear limitations to this study. The cases of people dying from SUDEP were taken over 9 years between 2004 and 2012. The controls were patients attending specialist clinics between 2012 and 2014. However the management of epilepsy has not changed radically over this period as reflected in the similar NICE guidelines for the management of epilepsy published in 2004 and 2012. The 1st line drugs and many other strategies for managing seizures remain pretty much the same. In spite of being proposed as a NICE guidance since 2004 the communication of the risk of SUDEP has been significantly low in fact 4% in 2013¹⁷. Both the 2001 and 2011 national census confirms Cornwall is one of the poorest parts of the United Kingdom in terms of per capita GDP and average household incomes. They also reveal social deprivation, ethnicity and migration rates (very low) have not changed substantially. In fact the same epilepsy teams and personnel have been in place managing this same population of PWE which has a low turnover. While all the controls were from specialist clinics it is worth noting that the highest risk patients were being compared. It can be thus argued that the impact of the potential bias of the various limitations emerging from the control group selection is minimal.

Given that sub-therapeutic drug levels may be a reflection of medication nonadherence, the two are by no means independent of each other. The same is true for early onset of epilepsy¹⁸ and prolonged (>15 years) duration of epilepsy

not necessarily mutually exclusive. Unfortunately, given low numbers and missing data a logistic regression analysis could not be performed.

The cases and controls were not matched samples. The review of medical notes was not blind to the reviewers which may be a source of bias, and the controls were determined from an outpatient clinic. However this is the first study where a structured application of a predesigned risk checklist to both the demised PWE and controls has been done. Both sets were also drawn from the same at risk epidemiological population i.e. county of Cornwall (population 550,000) UK. This has provided an opportunity to rank the risk factors thus highlighting that SUDEP is not only modifiable and multi-dimensional but likely to be associated with different intensity and degrees of risk. It again highlights that SUDEP could be a cumulative effect of few or many of these risk factors, many modifiable and possibly coming together in a 'perfect storm' to cause an adverse outcome. There were 2 children under 15 in the study. Some factors would not apply to children and others might be less modifiable. Given the small numbers we do not believe it would have influenced the outcome of our study.

Overall, our study supports the use of an evidenced based checklist in order to discuss potentially modifiable factors with patients, especially those people at a high risk of SUDEP. Cornwall Public Health and coroner annual data show SUDEP deaths have reduced considerably in the last 2 years compared to previous years, though given the small numbers involved and the multiple variables these at best are early trends. It sits well with the fact that of PWE and/or their carers administered the Checklist in the last 3 years in epilepsy clinics (n=400+) in Cornwall UK, 98% of patients approved, felt empowered and felt safer knowing person-centred risk^{5,6}. There is anecdotal evidence to suggest it contributed to improved compliance and adherence of medication and more importantly contact with health services if problems existed with the medication as opposed to generally stopping it without advice. A structured approach may pay dividends in focusing individuals on items in their locus of control and may mitigate risk.

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Table 1 Univariate analysis

Rank	Factor and its description	Odds ratio	95% CI	P value
1	<p>Sleeping in prone position</p> <p>Independent risk factor evidenced by several studies including a systematic review.</p> <p>The prone position is defined as lying on the belly, chest, or face, with or without obstruction of the nose or mouth. Sleeping in the prone position or remaining in a prone position post seizure is considered a risk.</p>	0.034	0.012, 0.094	<0.001*
2	<p>Treatment History – unclear</p> <p>This is defined as where the rationale for treatment in the last 6 months is not supported by current clinical evidence base such as NICE. For example not modifying AED treatment if someone has refractory epilepsy or not considering referring to a comprehensive epilepsy center for a surgical evaluation.</p>	0.03	0.01, 0.1	<0.001*
3	<p>Generalised tonic clonic epilepsy</p> <p>Combined data from the previous four case-control studies found this is the most important risk factor</p>	0.03	0.01, 0.09	<0.001*
4	<p>Increasing seizure frequency</p> <p>Active Seizures which in the last 6</p>	0.05	0.02, 0.14	<0.001*

	months were noted to worsen in frequency of > 25%			
5	<p>Compliance issues</p> <p>This factor is defined by finding of variable AED hair strand levels in SUDEP group. Compliance issues were also assessed via patient reporting as evidenced by medical records in both groups. Adherence issues (including not picking up prescriptions) found as a factor across all epilepsy-related deaths as increasing risk by 50%</p>	0.09	0.03, 0.23	<0.001*
6	<p>Alcohol problem</p> <p>Is defined as where there is a clinically definable alcohol disorder as identified by the WHO ICD 10 diagnostic Manuel. A systematic analysis of epilepsy deaths confirmed this risk factor.</p>	0.10	0.04, 0.28	<0.001*
7	<p>Sub therapeutic AED levels</p> <p>Is a finding linked closely to compliance</p>	0.08	0.025, 0.24	<0.001*
8	<p>Night surveillance</p> <p>Nocturnal Seizures were shown to have a 4 fold increased risk. 60% of all SUDEPs in large control study.</p> <p>Nocturnal surveillance thus where present is considered to be a protective</p>	13.0	3.7, 45.26	<0.001*

	factor.			
9	<p>Duration (>15 years)</p> <p>This has been suggested by several studies, but not after multiple logistical regression analysis for seizure frequency</p>	0.22	0.10, 0.49	<0.001*
10	<p>Early onset epilepsy</p> <p>Where the onset of epilepsy is before the age of 15 years</p>	0.40	0.18, 0.90	0.025
11	<p>Frequent AED changes</p> <p>This is defined as where the changes of dose or medication were not following British National Formulary (BNF) guidance on titration in the last 6 months.</p>	0.3	0.10, 0.92	0.035
12	<p>Presence of anxiolytic medication</p> <p>This is defined as having ‘anxiolytic medication’ as defined by BNF 4.1.2</p> <p>Currently it is unclear how relevant a risk factor this is as it has not been clearly defined.</p>	0.41	0.16, 1.05	0.06
13	<p>Intellectual Disability (ID)</p> <p>2 case-control studies found ID to be a risk factor whereas 2 others did not. In the combined analysis ID was not a significant risk factor</p> <p>The incidence of SUDEP was higher among children with “complicated” epilepsy</p>	2.5	0.66, 9.34	0.18

	(with known structural brain lesion, intellectual disability) than those without. Concerns exist on the way ID is described and cases collected.			
14	<p>Male Gender</p> <p>Was found a risk factor commonly in descriptive studies but has not been replicated in controlled studies.</p>	0.62	0.29, 1.31	0.21
15	<p>Depression treatment</p> <p>This is defined as having clinical depression as per ICD 10 /DSMV and/or being on antidepressant medication' as defined by BNF 4.3 and/or having therapy/counseling for depression.</p> <p>Currently it is unclear how relevant a risk or a safety factor depression or its treatment particularly SSRIs are. This is has not been clearly defined.</p>	0.74	0.31, 1.80	0.50
16	<p>Carbamazepine</p> <p>there is no significant association between use of carbamazepine and SUDEP risk as per current evidence</p>	1.10	0.51,2.32	0.83
17	<p>Increasing seizure severity</p> <p>This is evidenced by an increase in the last 6 months of the administration of rescue medication such as Midazolam, paramedic call outs or ED visits as recorded in clinical notes</p>	0.94	0.26, 3.40	0.92

Factors are ranked by P value. * indicates significant using a sequential Bonferroni correction for multiple comparisons with alpha = 0.05

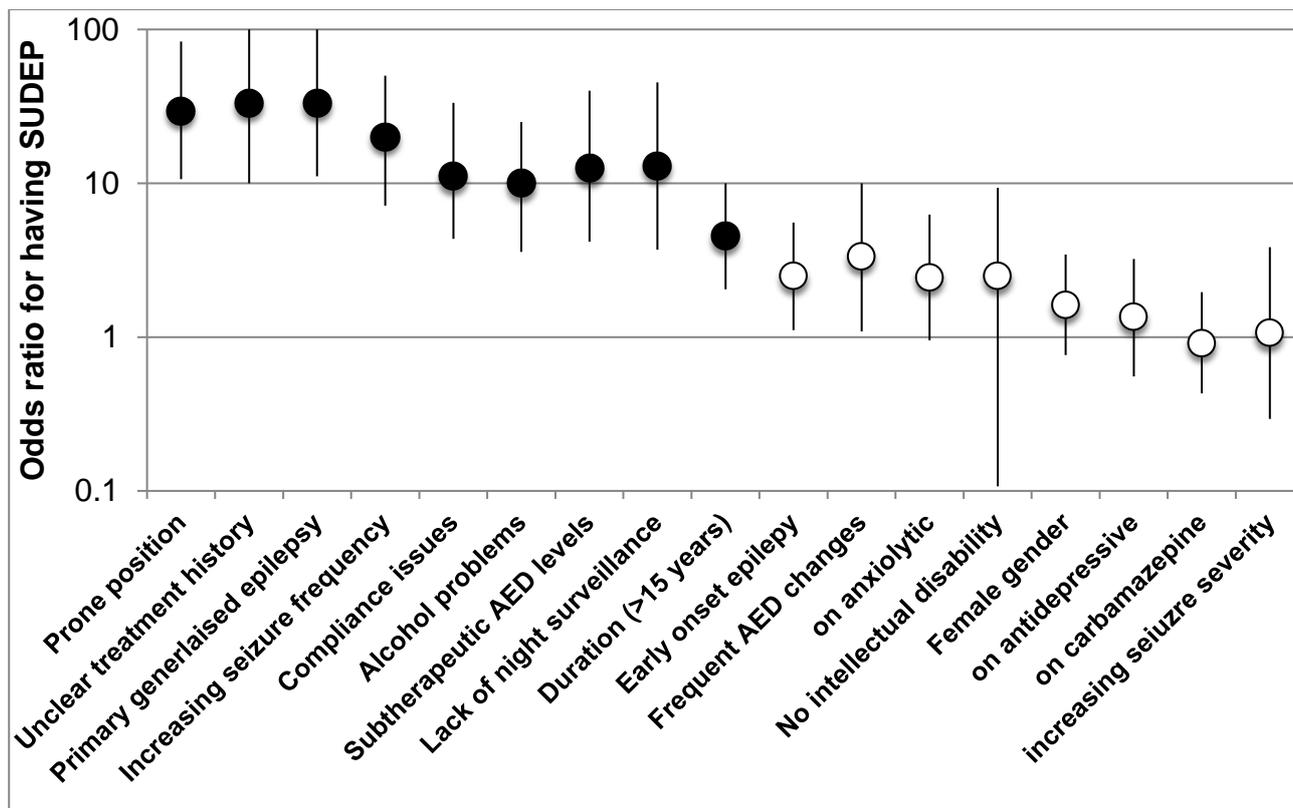


Figure 1: Odds ratios for having SUDEP given risk factor. Bars represent 95% CI. Solid circles are significant factors after sequential Bonferroni correction.

Table 2:

Comparison between identified risk factors in the study and recently published review of risk factors for SUDEP

Risk Factor	Shankar et al findings	Tomson et al 2016 ¹⁷ review of risk factors
Sleeping in prone position	Significant	A risk factor requires more confirmation
Treatment History – unclear	Significant	Not considered in review
Generalised tonic clonic epilepsy	Significant	Strong risk factor
Increasing seizure frequency	Significant	A risk factor
Compliance issues	Significant	Possible risk factor
Alcohol problem	Significant	Possible risk factor
Sub therapeutic AED levels	Significant	Unreliable as a risk factor
Night surveillance	Significant	A risk factor but requires more confirmation
Duration (>15 years)	Significant	A risk factor
Early onset epilepsy	Close to significant – power might play a role	A risk factor
Frequent AED changes	Close to significant – power may play a role	Not considered in review
Presence of anxiolytic medication	Close to significant –power may play a role	Not considered in review
Intellectual Disability (ID)	Not significant – confounder recognized	Conflicting evidence on risk factor. Require more studies.
Male Gender	Not significant	A risk factor
Depression treatment	Not significant	Not considered in review
Carbamazepine	Not Significant	Not a risk factor
Increasing seizure severity	Not Significant	Not considered in review

Table 3:

	U.S. Study¹⁰	Swedish Study¹³	Scottish Study¹²	English Study ¹¹	Our Study
Rough Time period of Study	1991 -1996	1980-1989	From 1982 all deaths till near the study (2007)	1989-1998	2004 -2012
Case to controls mix	20 cases and 80 controls	56 cases and 157 controls	64 cases and 119 controls	149 cases and 602 controls	48 cases and 220 controls
Case description	SUDEP in specialist epilepsy centres	Discharged from hospitals diagnosis of epilepsy on death certificates	Those registered with the epilepsy unit	SUDEP were identified by coroners, neurologists, self-referred by family members, and by the charity Epilepsy Bereaved	SUDEP in community and being representative of all deaths in Cornwall UK (pop: 600,000)
Case specifics		Identified deaths between 15-70 years		16-50 years	No age limit
Control description	Controls randomly selected	For each case of SUDEP 3 living controls were randomly drawn from the study population and matched on year of birth, sex, and assessment period.	2 living controls were randomly selected from the Epilepsy Unit population and matched on year of birth, gender, and syndrome classification	4 controls with epilepsy were randomly selected from a diagnostic index and a prescription database and matched to each SUDEP case according to age and geographic location.	The control population attended two specialist epilepsy outpatient clinics in Cornwall. The population was a continuous sample.