HIGH LIGHT

Case-control study of SUDEP

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Abstract—*Objective:* To examine the influence of various factors on the risk of sudden unexpected death in epilepsy (SUDEP). *Methods:* The authors investigated 154 cases in which a postmortem examination was performed. Each case had four controls with epilepsy from the community, matched for age and geographic location. Backward stepwise conditional logistic regression analysis was performed and odds ratios for risk and protection were determined. *Results:* The risk of SUDEP was increased with a history of generalized tonic-clonic seizures in the previous 3 months (odds ratio [OR]: 13.8, 95% CI: 6.6 to 29.1). The presence of supervision at night was found to be protective (OR: 0.4, 95% CI: 0.2 to 0.8) when a supervising individual shared the same bedroom or when special precautions such as a listening device were employed (OR: 0.1, 95% CI: 0.0 to 0.3). *Conclusion:* This work lends support to the view that SUDEP is a seizure-related phenomenon and that control of tonic-clonic seizures is important in its prevention. Nocturnal supervision seems to protect against SUDEP.

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Cohort studies have reported risk factors for SUDEP including youth, male sex, remote symptomatic epilepsy, structural findings on neuropathology, severe epilepsy, alcohol abuse, abnormal EEGs with epileptiform changes, mental handicap, use of psychotropic medication, nonadherence to treatment, abrupt medication changes, low antiepileptic drug (AED) levels, and unwitnessed nocturnal seizures.[1]

Case-control studies have identified a number of risk factors for sudden unexpected death in epilepsy (SUDEP).[2-5] A study from Stockholm[3] found that a higher risk of SUDEP was observed in those with more frequent seizures, polytherapy, frequent medication changes, longer disease duration, and idiopathic epilepsy. Another study from the United States[4] reported increased risk of SUDEP by tonic-clonic seizures, polytherapy, and the presence of a learning disability. Another US study of mortality in AED development programs found that disease severity was significantly related to the risk of SUDEP.[5] Limitations of these studies include small numbers,[4] low postmortem rates,[4] and the exclusion of patients off AED therapy.[3] Some risk factors identified by cohort studies were not found to be significant in case-control studies.

We undertook a large case-control study to confirm previous results and to look at factors not previously examined.

Methods. People with epilepsy who died suddenly between the ages of 16 and 50 years were identified by coroners and neurologists and by interviews with bereaved families. Deaths occurred between 1989 and 1998.

Coroners in England and Wales were invited to notify neurologists of cases considered to be SUDEP. Neurologists were contacted via the British Neurologic Surveillance Unit,[6] an organization that coordinates and improves the ascertainment of rare neurologic disorders in the United Kingdom. Cases were also identified through interviews with self-referred parents and partners of the deceased through Epilepsy Bereaved?, a UK support charity.

Interviews involved a semistructured questionnaire that examined aspects of the patients' epilepsy, medical and social background, and the circumstances of death. Written informed consent was obtained before the interview.

Subjects were individuals with a history of active epilepsy (at least one seizure in the past 5 years or taking an AED if in remission) whose death fulfilled the following definition: sudden, unexpected, witnessed, or unwitnessed, nontraumatic, and nondrowning death in an individual with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus in which the postmortem examination does not reveal a cause for death.[7]

Background information was obtained from general practitioners, hospital consultants and, where appropriate, coroners. Where necessary, information was traced through the Office for National Statistics.

Each case had four controls matched for age (±5 years) and geographic location. Practices in the appropriate geographic areas were identified from the MRC General Practice Research Framework, a network of approximately 900 groups of family practitioners (general practitioners) throughout the United Kingdom and includes practices in urban and rural areas. The groups allow access to 11% of the UK population.

Individuals with epilepsy suitable to act as controls were identified using a diagnostic index or prescription database. Controls were randomly chosen from this eligible population, and, once a diagnosis of epilepsy was confirmed, data were extracted from the patients' medical records. The factors under examination included duration of epilepsy, seizure type and control including changes in seizure severity, treatment history and compliance, recent AED withdrawal, concomitant use of psychotropic medication, family history of sudden death, learning disability, EEG changes, history of drug or alcohol abuse, presence of other medical conditions, level of attendance at doctor or hospital appointments, and supervision at night. Supervision at night was defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device.

For both cases and controls, 10% of entries were randomly chosen and the accuracy of data retrieval from notes and data entry into the database checked. The error rate was less than 5%.

Backward stepwise conditional logistic regression analysis[8]

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Table 1 *Evidence of a recent seizure*

Witnessed seizure	21
Bitten tongue	41
Incontinence	3
Posturing	22
Usual seizure time	4
Secretions/blood	7

was performed and odds ratios with the CI were determined. An unknown category was inserted for each of the above variables to optimize data use. Variables with information missing in more than 35% of cases were excluded from the analysis. The excluded variables were the presence of hippocampal sclerosis, corrected QT interval, and AED and alcohol levels. The analysis controlled for frequency of convulsive seizures so that the effect of other variables could be assessed independently of their relationship to seizure frequency. For each variable found to be significant, the model was retested after removing cases with information missing for that variable. Only variables that remained significant in this situation were included in the final model.

The study was ethically approved centrally and also by the individual local research ethics committee for each general practice involved in the ascertainment of controls.

Results. One hundred fifty-four cases (97 men, 57 women) were identified, 27 through Epilepsy Bereaved? Mean age was 32 years. Most were found dead in bed, and there was evidence to support a recent seizure in most (table 1).

Twenty-three deaths were witnessed (15%), the majority occurring in association with a convulsive seizure. As previously reported, there was often breathing difficulty before death.[9]

The variables included in the model and their odds ratios are illustrated in table 2. There were eight individuals in the "don't know" category for carbamazepine, which resulted in a failure of the model to converge; therefore, these individuals were omitted from the analysis. A history of generalized seizures and a high frequency of them in the recent past was associated with a significant increased risk of SUDEP. Use of more than three AEDs also appears to increase the risk, as does the use of carbamazepine. Supervision at night and a history of asthma appear to be protective.

Table 2 *Variables included in the model*

	No. of cases	Controls	OR	95% CI
History of generalized tonic-clonic seizures				
No	31	426	1	
Yes	120	108	13.8	6.6–29.1
No. of tonic-clonic seizures in previous 3 mo				
0–5	87	496	1	
6–10	17	13	0.7	0.2–2.5
11–20	13	2	19.4	1.7–226
21–50	7	3	14.6	1.3–165
>50	7	3	11.7	0.3–419
Total no. of AEDs ever				
1–2	42	400	1	
3–4	30	128	1.3	0.6–2.8
>4	47	50	3.1	1.4–7.0
0	14	12	21.7	4.4–106
Not known	21	26	8	2.7–25.6
Carbamazepine (current use)				
No	72	381	1	
Yes	74	235	2	1.1–3.8
Supervision				
None	109	169	1	
Same room	34	156	0.4	0.2–0.8
Special precautions	11	42	0.1	0.0–0.3
Asthma				
No	142	522	1	
Yes	6	67	0.2	0.1–0.9

AED = antiepileptic drug.

Discussion. This case-control study is large, with postmortem examinations having been performed for all cases. We accept that using different sources of information for cases and controls may have introduced bias, but we have made efforts to minimize this by having a case:control ratio of 1:4 and making allowances for unknown information in the analysis.

In the United Kingdom, 90% of such deaths will be referred to the coroner and undergo postmortem examination. The recent National Clinical Sentinel Audit of Epilepsy-Related Death suggests, however, that postmortem examinations may be inadequate and that investigations such as toxicology are often underused.[10]

There was an excess of males among the 154 cases identified; however, gender was not found to be an independent risk factor for SUDEP. Other authors[11,12] have also reported an excess of males in series of SUDEP cases, but this has not been a universal finding.[4,13]

The fact that SUDEP risk is increased by convulsive seizures is in keeping with the findings of previous research.[2-5,9,12,14] Death has also been linked to convulsive seizures in an animal model of SUDEP.[15,16]

Greater frequency of generalized tonic-clonic seizures also adversely influenced the risk of SUDEP in our study, and this finding has been reported by others.[3-5] This relationship did not hold for those with more than 50 convulsive seizures in 3 months, but numbers were small. The control of such seizures may be important in SUDEP prevention. The risk of

SUDEP should be considered whenever decisions are made about changes to AED therapy.

To date, no AED has been clearly associated with an altered risk of SUDEP.[3,17] Some authors have suggested that carbamazepine may adversely affect such a risk,[18] particularly at high doses.[19] Our findings also suggest an association with current use of this AED; the arrhythmogenic potential of carbamazepine is recognized, as is its influence on heart rate variability.[20-23] Nevertheless, there may be confounding factors that have not been examined and causality should not be assumed.

We did not find current polytherapy, which may reflect both seizure frequency and severity, to be an independent risk factor. Other authors[3,4,24] have commented on polytherapy as a risk factor for SUDEP.

We found that the greater the number of AEDs ever taken, the higher the risk was of SUDEP. A case-control study from Sweden[3] found that frequent drug changes increase the risk of SUDEP. In this study, risk was also increased in those who have never been on AEDs or whose treatment history is unclear, which may reflect the risk associated with the lack of treatment and uncontrolled seizures.

In some studies, poor adherence with the medication has been associated with an increased risk of SUDEP,[4,25] but there is also evidence to the contrary.[17] In this study, adherence was not found to be a significant independent risk factor for SUDEP, although this was not assessed objectively.

Asthma appears to be protective, although it should be noted that the data reflect a diagnosis of asthma noted in the medical record but not verified. Such individuals may be protected through increased supervision or medical input. Alternatively, because of our rigid definition of SUDEP, cases with other medical conditions including respiratory disease may have been excluded, increasing the relative incidence of asthma among controls. Antiasthma medications may antagonize mechanisms responsible for SUDEP or the asthma itself may prevent pulmonary complications of seizures. Nonepileptic attacks, which may have a high event frequency, may be overrepresented in the control group and indeed there has been a report suggesting that asthma is a risk factor for nonepileptic events.[26]

We have previously suggested that because most deaths are unwitnessed, supervision and attention to recovery after a seizure may be important in SUDEP prevention,[9] and our findings here support this view. Supervision has emerged as a protective factor independent of seizure control, suggesting that it is not just a surrogate marker for epilepsy control. A study of SUDEP in a residential school for children with epilepsy who were closely supervised at night and carefully monitored after a seizure found a lower SUDEP incidence and no witnessed deaths during term time.[13] Alterations of lifestyle may reduce the risk of SUDEP, and caregivers need to be advised of the action that they should take on witnessing a seizure, such as placing the individual in the recovery position, checking on respiration, and maintaining a vigil in the postictal phase.

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