Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors

Robert Kloster, Torstein Engelskjøn

Abstract

Objectives—To examine the risk factors and their relative importance and possible role in sudden unexpected death in epilepsy (SUDEP).

Methods—The study was conducted as a retrospective analysis of deaths in an outpatient population of a tertiary referral centre, based on clinical and pathological data.

Results—Of a total of 140 deaths, 61 (44%) had not been to postmortem and were excluded, 37 (26%) had a verified cause of death and formed the non-SUDEP group, and 42 (30%) were classified as SUDEP. In the SUDEP group there was pulmonary oedema in 62%, signs of preceding seizures in 67%, no visible seizures in three of six observed deaths. A high seizure frequency prevailed in SUDEP as well as non-SUDEP. Sixty percent of deaths were sleep related. Various other circumstances were temporally associated with death. The prone position at death was seen in 71% of the SUDEP patients; possible interpretations are discussed. Supposedly subtherapeutic serum concentrations of one or more antiepileptic drugs were found in 57% of those with reported serum concentrations. Alcohol was not a factor in the material, whereas hyponatraemia was seen in two cases.

Conclusions—Most cases of SUDEP are preceded by seizures; their presence, frequency, type, aetiology, tractability, and the use of antiepileptic drugs are factors in the demise. No common risk factor, present in all cases of SUDEP, could be found, suggesting the probability of multiple mechanisms behind SUDEP.

Keywords: sudden death in epilepsy; risk factors

SUDEP non-SUDEP p Value

<table>
<thead>
<tr>
<th>Variable</th>
<th>SUDEP</th>
<th>non-SUDEP</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>26 (62%)</td>
<td>19 (51%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Females</td>
<td>16 (38%)</td>
<td>18 (49%)</td>
<td></td>
</tr>
<tr>
<td>Age at epilepsy onset (y)</td>
<td>8.2 (8.6)</td>
<td>12.7 (11.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at death (y)</td>
<td>27.9 (15.7)</td>
<td>32.6 (19.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Duration of epilepsy (y)</td>
<td>19.8 (14.1)</td>
<td>19.8 (14.9)</td>
<td>0.94</td>
</tr>
</tbody>
</table>
in neuropathology, whereas the hearts and lungs were examined by general pathologists. Thirty seven patients with a defined cause of death constitute the non-SUDEP group. Forty two patients who fulfilled the criteria of our definition are included in the SUDEP group. No necropsy was performed in 61 patients and these were excluded from the study. Postmortem serum concentration analyses were carried out at the National Institute for Forensic Toxicology in Oslo, Norway. Statistical treatment of SUDEP versus non-SUDEP patients is based on Student’s t test or Pearson’s χ² test. Certain data—for example, measurement of postmortem serum concentrations—were incomplete, rendering comparisons inconclusive.

**Results**

On comparing the 42 patients with SUDEP with the 37 non-SUDEP patients (table 1), no significant differences were found for sex, age at death, or duration of epilepsy. Age at onset of epilepsy was significantly lower in the SUDEP group than in the non-SUDEP group (p=0.04).

**POSTMORTEM FINDINGS**

The pathological findings disclosed at postmortem did not explain death in any of the 42 SUDEP patients, whereas in the 37 non-SUDEP patients causes such as pneumonia, cardiac disease, status epilepticus, trauma, suicide, and drowning were found.

**Brain**

Pathological changes in the brain or brain stem were present in 30 of 42 SUDEP patients (71%). Two patients with cerebral oedema had minor tentorial impressions, but there was no structural damage to the brain stem, ventricular compression, or compression of gyri (table 2).

Among 37 non-SUDEP patients, only six had a structurally normal brain. The remaining 31 (84%) showed pathological changes, and two were considered fatal. Aetiologies of epilepsy (ICD-10), taking into account clinical, neuroimaging, and neuropathological findings, were assessed as 15 symptomatic and 27 idiopathic in the SUDEP group; 21 symptomatic and 16 idiopathic in the non-SUDEP group (p=0.008).

**Heart**

Pathological changes in the heart, which were all presumed to be non-fatal, were described in 33% of the SUDEP patients. In one patient a special investigation of the conduction system of the heart disclosed fibrosis and oedema of the conductive tissue. Thirty eight per cent of the non-SUDEP group showed pathological changes of the heart; fatal in at least seven patients.

**Lungs**

There were marked differences between the groups, with pulmonary oedema in 62% of SUDEP patients and 27% of non-SUDEP patients, as well as various other pulmonary conditions in the second group (table 2).

**SEIZURES**

There was a significant difference in seizure types between the groups, with more primarily generalised seizures in the SUDEP group (p=0.03). All SUDEP patients had generalised motor seizures (19 primarily, 21 secondarily generalised, and two unclassified). Generalised motor seizures also prevailed in the non-SUDEP group, but 5% had only partial seizures (p=0.07).

In the SUDEP group, signs of seizures immediately before death in 67% (table 3 A) included observed seizures, fresh bites, blood on the pillow, and cyanosis, as well as reported sounds of ongoing seizures. Such signs are suggestive, if not conclusive, of generalised motor seizures. The great majority in both groups had a high seizure frequency with more than...
Due to interaction with erythromycin.

‡Two cases of lethal phenobarbital (440 resp. 800 µmol/l); one case of potentially lethal
†One without AEDs, one recently discontinued carbamazepine.

*Moderately raised phenytoin (150 µmol/l): not lethal
†Vigabatrin (two), ethosuximide (one).

### Table 5 Position at death (24 patients with a reported position)

<table>
<thead>
<tr>
<th>SUDEP %</th>
<th>Prone position</th>
<th>17</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine position</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Other position</td>
<td>6</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Preponderance of prone position in SUDEP; p=0.001

### Table 6 Choice of antiepileptic drugs (AEDs)

<table>
<thead>
<tr>
<th>SUDEP</th>
<th>non-SUDEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital, primidone</td>
<td>17</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>20</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>6</td>
</tr>
<tr>
<td>Valproate</td>
<td>9</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>5</td>
</tr>
<tr>
<td>Other AEDs</td>
<td>3*</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>Just discontinued AED</td>
<td>2</td>
</tr>
<tr>
<td>No AED treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

*Ethotoin (one), lamotrigine (one), vigabatrin (one).
†Vigabatrin (two), ethosuximide (one).

12/year (table 3 B), as could be expected in a cohort with chronic refractory epilepsy. A precise correlation between seizure type and seizure frequency was not possible. Of six observed deaths in the SUDEP group (table 4), three had generalised motor seizures and three had no clinical seizures.

### OTHER CIRCUMSTANCES

Twenty five of the SUDEP patients were found in bed, presumably dying before, during, or after sleep. Assuming 8 hours of sleep/24 hours, only 14 patients would be expected to have died in relation to sleep. Because many of the non-SUDEP cases died in hospital or in an accident, it is not meaningful to relate their deaths to the sleep-wake cycle. Various somatic conditions unrelated to epilepsy, and not life threatening, were reported among 47% of SUDEP patients. In the non-SUDEP group, 23 (62%) had a somatic disease with a fatal outcome.

There were 10 cases of mental retardation and two of dementia in the SUDEP group; in the non-SUDEP group there were 11 mentally retarded patients, three demented patients, and one patient with Wernicke’s encephalopathy (p=0.40).

### POSITION AT DEATH

We define the “prone position” as lying on the belly, chest, or face, with or without obstruction of the nose or mouth. The “supine position” is defined as lying on the back, with no obstruction of the nose or mouth.

Position at death was reported in 24 SUDEP patients (table 5). Seventeen cases (40% of all) were found in the prone position, and only one (2%) in the supine position, whereas six (14%) were found in other positions. Body position in the remaining 18 of 42 SUDEP patients was not recorded.

Considering only those with a verified position (table 5), 71% were lying prone, 4% supine, and 25% in other positions. Assuming an equal likelihood of either the prone or the supine positions, this difference was significant (p=0.001; two tailed test).

### TREATMENT WITH ANTIETEPILEPTIC DRUGS

A small excess of carbamazepine or oxcarbazepine treatment in the SUDEP group (table 6) is not amenable to statistical analysis, because of polytherapy and possible drug interactions. There were no significant differences between the groups for monotherapy or polytherapy (p=0.10).

Serum concentrations of antiepileptic drugs were analysed in 23 of the SUDEP patients (table 7). Of these, 39% had drug concentrations in the recommended range and 57% had supposedly subtherapeutic concentrations of one or more antiepileptic drugs.

### BLOOD ALCOHOL

In 28 SUDEP cases examined for blood alcohol postmortem, there was a low ethanol concentration in only one, and none in the non-SUDEP group.

### HYponatraEMIA

Two cases of hyponatraemia were found in the SUDEP group. One was based on serum sodium measured at necropsy and associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), the other on serum sodium measurement 1 month before death. Both were associated with the use...
of oxtcarbazepine; one had recently changed from carbamazepine. Serum sodium values before death or at necropsy were missing for the remaining cases presented here.

**Discussion**

Our material comes from a selected group with chronic refractory epilepsy. It contained a high percentage of SUDEP cases (30% of the total). Other studies report up to 50%; highest in cohorts with intractable epilepsy. There were no significant demographic differences between SUDEP and non-SUDEP groups, except for a slightly lower age at epilepsy debut in SUDEP and a non-significant excess of males. A male dominance in SUDEP has been found in other studies.

By definition, no adequate explanation of death was found at necropsy, but pathological changes were found in various organs. The most consistent finding was oedema of the lungs, often haemorrhagic. In an experiment on sheep, Johnston et al found evidence that central hypoventilation had a role in the aetiology of sudden unexpected death and confirmed the association with pulmonary oedema, but they did not think that the development of hypoventilation could be due to pulmonary oedema.

Cardiac pathology was found in 14 patients in both groups. Three SUDEP patients showed fibrosis localised in the conducting system, around the atrioventricular bundle, or diffusely in the myocardium. Seizure related ischaemia or hypoxic changes have been suggested as a possible explanation, rendering the heart vulnerable to subsequent epileptic seizures.

In both groups, a large proportion had pathological changes in the brain. No predilection could be found with respect to type and location of pathology. Oedema was seen more often in the SUDEP group, but there was no evidence of mass effect or cerebral herniation. Thirty SUDEP patients had structural brain lesions versus 31 in the non-SUDEP group. Some of these changes provide an aetiology for the epilepsy—for example, cortical dysgenesis or tuberous sclerosis. Most of the changes imply neurological deficit of a static nature, and provide no obvious explanation for the final event.

There were signs of seizures starting the final event in 67% of SUDEP patients, all suggestive of generalised motor seizures. This is a minimal figure, as not all seizures can be detected. In our material of six observed deaths three were associated with clinical seizures and in three patients no seizures were seen. Among a total of 12 witnessed SUDEP patients three were not associated with visible seizures. Leestma et al and Nashef et al found evidence of seizures in 50% and 64%, respectively, of SUDEPs. Subclinical epileptic activity may be an explanation, as pointed out by Lathers et al.

Most of our patients had relatively high seizure frequency, with more than 12/year, mainly generalised motor seizures. Consistent with epidemiological studies, there is a high percentage of SUDEP in our material, which shows that cohorts with high seizure frequency have a relatively high risk of sudden death, whereas the opposite is the case for those with few seizures. In our study, however, there was no difference in seizure frequency between the SUDEP and non-SUDEP groups to support this finding. The expected low seizure frequency in the non-SUDEP group was not found because our patients were selected on the basis of poor seizure control, and patients with low seizure frequency are few in both groups.

Clearly, seizures play an important part in SUDEP, but some patients die without visible seizures. We must consider the possibility that some of these deaths are unrelated or only indirectly related to epilepsy. The incidence of sudden cardiac death due to ischaemic heart disease is increased in people with epilepsy. Examples of seizure related changes in the heart have been given by White et al, Natelson et al, and Mosier et al. Acute symptoms may not be registered if the patients die alone, and ischaemic changes in the heart may not be visible at necropsy unless they survive for more than 2 hours. Such cases may be difficult to diagnose. We have included the case of a 40 year old woman with epilepsy who had moderate chest pain, normal ECG, and was found dead in the daytime, having urinated, without coronary obstruction at necropsy. We cannot establish the cause of death with any degree of certainty and have included her in the SUDEP group.

Cardiac arrhythmias may be primary or they can be triggered by epileptogenic activity, and sometimes, although rarely, by carbamazepine. Withdrawal of antiepileptic drugs (carbamazepine or phenytoin) may also influence the cardiac activity and, possibly, cause sudden death. Prolonged QT time is probably related to cardiac activity and, possibly, cause sudden death. Accordingly, we cannot distinguish reliably between sudden deaths related to epilepsy and other causes, sudden cardiac death being the predominant category. Most SUDEP material is likely to include deaths unrelated to epilepsy.

Seventy one per cent of patients were found dead in the prone position, 4% in the supine position, and 25% in other positions. Assuming an equal chance of either the prone or the supine position, a simple probability test shows that the difference is significant (p=0.001). Earnest et al found 81% of SUDEP cases in the prone position. Coyle et al report 58% prone of those with a reported position. Nashef et al report 11 of 26 in which the position of the head was such that breathing could have been compromised. Position may influence ventilation in several ways. The supine position may affect ventilation in an unconscious patient because of the gravitational pull on the tongue and other mechanisms, as has been demonstrated in obstructive sleep apnoea.

The prone position may cause obstruction of the nose and mouth due to pressure against the bed clothing. Changing the sleeping position from prone to supine has brought about a marked reduction in the incidence of the
Sudden unexpected death in epilepsy (SUDEP)

Sudden infant death syndrome. Several explanations have been suggested, some of them possibly relevant also for the discussion of SUDEP—for example, influence of flexion or extension of the cervical spine on the patency of the upper airways. Closing the mouth, the term central sleep apnoea as a general description for sleep induced failure of the neural elements that control breathing. Epileptic seizures are also associated with central apnoea and sometimes death, often occurring during sleep.

During sleep, respiration is dependent on the inherent rhythmicity of the metabolic and automatic respiratory control system located in the medulla oblongata. Central sleep apnoea syndromes are characterised by cessation of rhythmical breathing during sleep, sometimes with a cardiac arrhythmia. The diagnosis is supported by the finding of an increased heart rate and a change in the respiratory pattern during sleep.34–36

Central sleep apnoea syndromes are characterised by cessation of rhythmical breathing during sleep, sometimes with a final outcome.35–37 Sullivan et al use the term central sleep apnoea as a general description for sleep induced failure of the neural elements that control breathing.38 Epileptic seizures are also associated with central apnoea and sometimes death, often occurring during sleep.

Death occurred in direct relation to physical exertion in four patients, two of them in the SUDEP group, all apparently from precipitating seizures. This relation has been pointed out by Hirsch and Martin.39

We found more use of carbamazepine and oxcarbazepine in the SUDEP group than in the non-SUDEP group, but the difference in antiepileptic drug use was not amenable to statistical analysis. Timmings found SUDEP patients significantly more likely to be taking carbamazepine.40 Others have found no specific pattern of antiepileptic drug use in SUDEP.41–43 Monotherapy versus polytherapy does not seem to be a factor in our study. Leestma et al44 and Timmings35 found similar findings, whereas Derby et al45 found that subjects taking two or more antiepileptic drugs may be at a somewhat increased risk of SUDEP.

Supposedly subtherapeutic concentrations of one or more antiepileptic drugs have been found in 57% of SUDEP patients; 77% had concentrations in the recommended range of one or more antiepileptic drugs. Other studies report similar findings.46–48 Other drugs could play a part in sudden death due to toxicity, interactions, and lowering of the seizure threshold, but comedication did not differ appreciably between our groups. Tennis et al found that the incidence of SUDEP increased with prescription of psychotropic drugs.49–51 Suicidal use of drugs is a relatively frequent cause of sudden death, and should be diagnosed by a complete toxicological investigation.

Three cases of hyponatraemia have been recorded among SUDEP patients known to us, two of them in the SUDEP group presented here; all on oxcarbazepine medication. Two of these cases were associated with SIADDH.52–54 and are presented separately. Hyponatraemia and SIADDH have been associated with other drugs and pathological conditions.

Conclusions

Most cases of SUDEP are preceded by seizures. Their presence, frequency, type, triggering factors, and individual tractability with antiepileptic drugs are factors in the demise. No risk factor common to all cases of SUDEP could be found, suggesting the probability of multiple mechanisms behind SUDEP.

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