

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

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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 out-patient 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 per cent 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.

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Sudden unexpected death in epilepsy (SUDEP) is a major diagnostic category in studies of mortality in epilepsy, accounting for an incidence of 1/1000 to 1/100, depending on the cohort studied.¹ Among risk factors identified are presence of seizures, poor seizure control, chronic refractory epilepsy, male sex, subtherapeutic concentrations of antiepileptic drugs, and the influence of sleep as well as alcohol. No risk factor common to all cases of SUDEP has been found.

The mechanism of SUDEP is not fully understood. Seizures usually start the final event. White *et al*² have described the effect of seizures in human volunteers with epilepsy, and

found marked changes in cerebral dynamics with an increase in CSF pressure to more than 1000 mm H₂O. Pressure rise is tolerated until it approaches diastolic pressure, impairing normal cerebral circulation.³ Most seizures are accompanied by apnoea and a fall in oxygen tension in humans and animal models alike.^{4,5} Johnston *et al* studied an animal model and concluded that hypoventilation is an important cause of death during seizures.⁵

The present study is a retrospective investigation of deaths in a population with chronic refractory epilepsy, with an emphasis on risk factors and their relative importance in SUDEP.

Methods

We adopted the definition of SUDEP proposed by Nashef: "Sudden unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death".⁶

"Sudden" means in a matter of minutes or hours after the onset of the final ictus or event. Unexpected means that the subjects were in a reasonable state of health before the final event.⁶

We examined 140 patients with epilepsy who died between 1965 and 1996. Most had been outpatients of a tertiary referral centre in the past or at the time of death. Most had chronic refractory epilepsy. They came from different parts of Norway, but do not constitute a complete list of deaths in a circumscribed population, and are not conducive to studies of incidence. Information was collected from medical histories in our hospital as well as from local hospitals, local doctors, family members, police, and postmortem reports. All data in this report are based on statements from one or more of these sources.

All patients included in the present study were necropsied, most of them in university departments of pathology. Each brain was examined by pathologists with a special interest

Table 1 Demography and time relations (mean values)

	SUDEP	non-SUDEP	p Value
Males	26 (62%)	19 (51%)	0.34
Females	16 (38%)	18 (49%)	
Age at epilepsy onset (y) (SD)	8.2 (8.6)	12.7 (11.3)	0.04
Age at death (y) (SD)	27.9 (15.7)	32.6 (19.0)	0.31
Duration of epilepsy (y) (SD)	19.8 (14.1)	19.8 (14.9)	0.94

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Table 2 Main postmortem findings: brain, heart, and lungs

	Brain		Heart		Lungs	
	SUDEP	non-SUDEP	SUDEP	non-SUDEP	SUDEP	non-SUDEP
Normal	12	6	28	23	11	3
Oedema or congestion	8	3	3	0	26	10
Old change, non-fatal	20*	20†	11§	6¶	4††	5‡‡
Recent change, fatal	0	2‡	0	7**	0	17 ^{§§}
Terminal changes or no data	2	6	0	1	1	2
Sum	42	37	42	37	42	37

Brain: *malformation four; traumatic or surgical six, hypoxic 10; †malformation four, traumatic or surgical five; hypoxic 11; ‡traumatic one, mitochondrial encephalopathy one.

Heart: § atherosclerosis three; fibrosis three, various five; ¶atherosclerosis three, various three; **infarction two, myocarditis two, various three.

Lungs: ††emphysema one, various three; ‡‡aspiration two, various three; §§pneumonia 12, aspiration two, drowning two, carcinoma one.

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 χ^2 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),⁷ 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 (table 2).

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

Table 3 Presence of seizures

(A) Signs of seizure preceding death		
	SUDEP	Non-SUDEP
Positive signs	28	13
No sign	11	10
No data	3	14
Significant difference between SUDEP and non-SUDEP ($p=0.002$)		
(B) Seizure frequency		
(high: >12 seizures/y, intermediate: 2–12/y, low: ≤1/y)		
	SUDEP	Non-SUDEP
High	32	26
Intermediate	3	1
Low	4	6
No data	3	4

No significant difference between SUDEP and non-SUDEP ($p=0.56$)

Table 4 Six witnessed cases of sudden, unexpected death in epilepsy

Patient No	Preceding event	Time span	Seizure	Time span before death	Relevant pathology
A 18	Exercise	1 hour	GTC	Failed resuscitation	None
24	None	Immediate	GTC	Failed resuscitation	Pulmonary oedema
257	Exercise	Immediate	GTC	Failed resuscitation	Terminal changes
B 25	Minor surgery*	12 hours	None	Immediate	Pulmonary oedema
26	None	—	None	Immediate	Cerebello-olivary degeneration
40	None	—	None	Immediate	None

*Uneventful removal of mandibular exostosis.

A: with seizures (three cases). B: without seizures (three cases).
GTC: generalised tonic-clonic seizure.

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

	SUDEP	%
Prone position	17	71
Supine position	1	4
Other position	6	25

Preponderance of prone position in SUDEP, $p=0.001$

Table 6 Choice of antiepileptic drugs (AEDs)

	SUDEP	non-SUDEP
Phenobarbital, primidone	17	18
Phenytoin	10	13
Carbamazepine	20	15
Oxcarbazepine	6	3
Valproate	9	11
Benzodiazepines	5	8
Other AEDs	3*	3†
Unknown	0	1
Just discontinued AED	2	2
No AED treatment	0	1

*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 ANTIEPILEPTIC 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.

Five of the SUDEP patients used neuroleptic or antidepressant drugs and two used cardiopulmonary drugs. Corresponding figures for the non-SUDEP group were five and three. No cases of street drugs were discovered.

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),⁸ the other on serum sodium measurement 1 month before death. Both were associated with the use

Table 7 Postmortem serum concentrations of antiepileptic drugs (AEDs)

	SUDEP	non-SUDEP
No AEDs detected	0	2†
All in recommended range	9	4
One in recommended range, one supposedly subtherapeutic	9	0
All subtherapeutic	4	0
Toxic	1*	3‡

*Moderately raised phenytoin (150 $\mu\text{mol/l}$): not lethal

†One without AEDs, one recently discontinued carbamazepine.

‡Two cases of lethal phenobarbital (440 resp. 800 $\mu\text{mol/l}$); one case of potentially lethal carbamazepine (275 $\mu\text{mol/l}$): due to interaction with erythromycin.

of oxcarbazepine; 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%¹; 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.⁹

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.⁵

Cardiac pathology was found in 14 patients in both groups. Three SUDEP patients showed fibrosis localised in the conduction system, around the atrioventricular bundle, or diffusely in the myocardium. Seizure related ischaemia or hypoxic changes have been suggested as a possible explanation,^{10–12} 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.^{13–14} Leestma *et al* and Nashef *et al* found evidence of seizures in 50% and 64%, respectively, of SUDEPs.^{15–16} Subclinical epileptic activity may be an explanation, as pointed out by Lathers *et al*.¹⁷

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.¹⁸ 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.¹⁹ Examples of seizure related changes in the heart have been given by White *et al*,² Natelson *et al*,¹² and Mosier *et al*.²⁰ 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,¹⁷ and sometimes, although rarely, by carbamazepine.²¹ Withdrawal of antiepileptic drugs (carbamazepine or phenytoin) may also influence the cardiac activity and, possibly, cause sudden death.²² Prolonged QT time is probably related to sudden death and life threatening arrhythmias.²³ Accordingly, we cannot distinguish reliably between sudden deaths related to epilepsy and some 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.¹⁴ Coyle *et al* report 58% prone of those with a reported position.²⁴ Nashef *et al* report 11 of 26 in which the position of the head was such that breathing could have been compromised.²⁵ 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.^{26–28} 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 infant death syndrome. Several explanations have been suggested, some of them possibly relevant also for the discussion of SUDEP—for example, the influence of flexion or extension of the cervical spine on the patency of the upper airways.²⁹ Clearly, both the reporting of position and the interpretation of findings are inadequate in the current literature.

In the SUDEP group, 58% were found dead in bed, presumably dying in relation to sleep. This may be related to the horizontal position as described, or it may be due to sleep itself. Control of sleep is closely related anatomically and functionally to respiratory control.^{30–32} During sleep, respiration is dependent on the inherent rhythmicity of the metabolic and automatic respiratory control system located in the medulla oblongata.^{31–32} Central sleep apnoea syndromes are characterised by cessation of rhythmical breathing during sleep, sometimes with a fatal outcome.^{30–33} Sullivan *et al* use the term central sleep apnoea as a general description for sleep induced failure of the neural elements that control breathing.³² 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.¹³

We found more use of carbamazepine and oxcarbazepine in the SUDEP group than in the non-SUDEP group, but the difference in anti-epileptic drug use was not amenable to statistical analysis. Timmings found SUDEP patients significantly more likely to be taking carbamazepine.^{34–35} Others have found no specific pattern of anti-epileptic drug use in SUDEP.^{9–36} Monotherapy versus polytherapy does not seem to be a factor in our study. Leestma *et al*¹⁵ and Timmings³⁵ made similar findings, whereas Derby *et al*²⁷ found that subjects taking two or more anti-epileptic drugs may be at a somewhat increased risk of SUDEP.

Supposedly subtherapeutic concentrations of one or more anti-epileptic drugs have been found in 57% of SUDEP patients; 77% had concentrations in the recommended range of one or more anti-epileptic drugs. Other studies report similar findings.^{15–38–40}

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.⁴¹ 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 SIADH,^{42–44} and are presented separately.⁸ Hyponatraemia

and SIADH have been associated with other drugs and pathological conditions.⁴⁴

Conclusions

Most cases of SUDEP are preceded by seizures. Their presence, frequency, type, triggering factors, and individual tractability with anti-epileptic 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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