SUDDEN UNEXPECTED DEATH IN EPILEPSY

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SUDEP: Introduction

Epilepsy is a disease that, “destroys life suddenly and without warning through a single, brief attack... and does so in from 3-4% of all who suffer from it”.

Spratling W.P., 1904

Mortality in Epilepsy

- Mortality rate in epilepsy is raised to 2 to 3 times that of the general population
- Mortality rates are increased at all ages, but disproportionately so in persons under the age of 50 years.
Mortality in Epilepsy:
Epilepsy-related deaths
- Directly related
  - SUDEP
  - Status epilepticus
- Indirectly related
  - Accidents as a consequence of seizures
  - Aspiration pneumonia after seizures
  - Iatrogenic: drug toxicity and idiosyncratic reactions
  - Suicide

Sudden Unexpected Death in Epilepsy: SUDEP
- Sudden
- Unexpected, unexplained
- Death
- Epilepsy

SUDEP: Definition
The sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of patients with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, and in whom post-mortem examination does not reveal a structural or toxicological cause of death.

SUDEP: Epidemiological classification
- Definite SUDEP (with autopsy)
- Probable SUDEP (without autopsy)
- Possible SUDEP

SUDEP
- The most important epilepsy-related cause of death
- Leading cause of death in people with chronic uncontrolled epilepsy

INCIDENCE
Person-Years

\[ n \text{ patients } + n \text{ years of active epilepsy} = \text{patient-years} \]

5 years
10 years
15 years
30 patient-years

Incidence of SUDEP: Community studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases (n)</th>
<th>Total person-years</th>
<th>SUDEP incidence (per 1000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ficker et al</td>
<td>9</td>
<td>25,940</td>
<td>0.35</td>
</tr>
<tr>
<td>Lhatoo et al</td>
<td>1</td>
<td>11,400</td>
<td>0.09</td>
</tr>
<tr>
<td>Jick et al</td>
<td>11</td>
<td>8,460</td>
<td>1.3</td>
</tr>
<tr>
<td>Tennis et al</td>
<td>18</td>
<td>33,299</td>
<td>0.54</td>
</tr>
</tbody>
</table>

1. Retrospective review of deaths in all epilepsy patients in Rochester, MN
2. Prospective follow-up of newly-diagnosed epilepsy cohort
3. Retrospective review of deaths
4. Retrospective review of deaths

SUDEP: Incidence

Type of Study

- Community-based: analysis of unselected cohorts of incident cases of epilepsy
- Community-based: review of post-mortem records
- Community-based: review of databases of AED prescriptions
- Epilepsy Populations
- Epilepsy surgery candidates

SUDEP incidence (per 1000 person-years)

- 0.09 – 0.35
- 0.9 – 2.3
- 0.54 – 1.3
- 1.1 – 5.9
- 6.3 – 9.3

SUDEP: Incidence in Children

SUDEP is less frequent in children than in adults

Study

- Victoria, Australia
- Ontario, Canada
- Switzerland
- Nova Scotia, Canada

SUDEP incidence (per 1000 person-years)

- 0.36
- 0.2
- 0.43
- 0.11

RISK FACTORS

- High frequency of seizures
- Generalized tonic-clonic seizures
- Absence of therapy with AEDs
- Onset of epilepsy at a young age
- Long duration of epilepsy
SUDEP: Other less clear risk factors
- Polytherapy
- Carbamazepine use
- Mental retardation
- Death in bed/floor
- Prone position

SUDEP: Proposed Mechanisms
- Cardiac arrhythmia
- Apnea, central or obstructive
- Primary cerebral shutdown

SUDEP: Electrocerebral Shutdown
SUDEP recorded in an ambulatory EEG

SUDEP: Mechanisms

SUDEP: Experimental Data
- Animal models
  - Mice model of audiogenic seizures associated with respiratory arrest
  - Status epilepticus in sheep associated with hypoventilation and respiratory arrest
**SUDEP during EEG monitoring**

- Six cases, 4 SUDEP and 2 near SUDEP, have been reported.
- All cases occurred during or immediately after a partial or secondarily generalized seizure.
- In 3 SUDEP cases, terminal flattening of the EEG seemed to occur before any cardiac or respiratory arrest.

**SUDEP during EEG monitoring**

- The fourth SUDEP case seemed to be related to a seizure-triggered ventricular fibrillation followed by terminal asystole, in a patient with history of myocardial infarction and angina.
- In the 2 near SUDEP cases, apnea was thought to be the primary dysfunction that led to cardiac arrest.

**SUDEP during EEG monitoring**

- Three potential seizure-induced mechanisms identified:
  - Primary cerebral shutdown
  - Cardiac arrhythmia
  - Apnea, central or obstructive

**Witnessed SUDEP**

- The proportion of SUDEPs that were witnessed varies from 7-38%.
- A seizure, most commonly a GTC, was reported to occur immediately before death in 90% of cases.
- One study specifically searched for a history of post-ictal breathing difficulties and found confirmative evidence in most cases.


**Seizure-induced cardiac and respiratory dysfunction**

- Central apnea found in 59% of patients, and in 20 of 47 seizures, during video-EEG with systematic monitoring of cardiorespiratory variables.
- Ictal bradycardia and sinus arrest during video-EEG monitoring was found in 0.3 to 0.4% of patients.

**SUDEP and Channelopathies**

- Increased incidence of SUDEP in a family with GEFS+ and a mutation in the sodium channel gene SCN1A.
- Increased incidence of sudden death in Dravet syndrome, also caused by a mutation in the SCN1A gene.
- SCN1A has also been found to play a role in the pacemaker function of the sino-atrial node in the heart.
Prevention of SUDEP

- Adherence to AEDs and avoidance of seizure triggers
- Epilepsy surgery (?)
- Cardiac intervention (?)
- Supervision

SUDEP Prevention: Supervision

- A significant proportion of SUDEP cases occur in bed and most are unwitnessed
- More SUDEP cases were found prone (71%) than supine (4%)
- Langan et al found a protective effect of:
  - Sharing the room with someone capable of giving assistance
  - Using a special monitoring device


SUDEP: Informing Patients and Relatives

- Whom?
- How?
- When?
- Who?