Sudden Unexpected Death in Epilepsy (SUDEP)

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Sudden Unexpected Death in Epilepsy (SUDEP)

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Learning Objectives

- Definitions and terminologies
- Epidemiology: incidence of SUDEP in various population of PWE
- Etiology and pathophysiology of SUDEP
- Modifiable and non-modifiable risk factors for SUDEP
- Means to minimize the risk or prevent SUDEP
- Practice guidelines
- Pediatric SUDEP registry
- Disclosure of SUDEP to patients and family
Disclosure Statement

• Dr. Mirsattari has received honorarium for speaking engagements for UCB Canada Inc., Eisai Co. Ltd (Canada), and Sunovion Pharmaceuticals Canada Inc.

• He has been member of the Epilepsy National Advisory Board for UCB Canada Inc., Eisai Co. Ltd (Canada) and Sunovion Pharmaceuticals Canada Inc.
Sudden unexpected death in epilepsy (SUDEP)

• SUDEP is a sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death of a PWE with or without evidence for a seizure and excluding documented SE.
SUDEP

- SUDEP is the leading cause of death in people with chronic refractory epilepsy.

Introduction

• SUDEP is a frequent cause of non-accidental, non-suicidal sudden death in young adults in general, and one of greatest concern for the epilepsy community.

• SUDEP most often affects patients with DRE, with an average incidence of 4 deaths per 1000 patient-yrs.

• 12% cumulative risk of SUDEP over 40 years for patients with uncontrolled childhood-onset epilepsy.

• Most cases of SUDEP are peri-ictal.

Definition criteria for SUDEP

1. The patient had epilepsy by reasonable criteria without reference to the criteria used for epilepsy

2. Deaths by drowning, trauma, or SE were excluded

3. Death could have occurred after a witnessed seizure

4. Other competing causes of death were excluded.

Types of SUDEP

- Definite SUDEP
- Probable SUDEP
- Near SUDEP
- Fatal near SUDEP

Definite SUDEP

• A SUDEP for which post-mortem examination failed to reveal a cause of death.

Probable SUDEP

• A SUDEP for which no post-mortem examination is available and the victim died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

Near SUDEP

- A sudden, unexpected, non-traumatic, and non-drowning CRA with no structural cause identified after investigation, occurring in benign circumstances in an individual with epilepsy, with or without evidence for a seizure excluding documented SE, where the patient survived resuscitation for more than 1 h after the CRA.

Fatal Near SUDEP

- A near SUDEP in which the CRA was responsible for irreversible major brain damage directly leading to death more than 1 h after the CRA.

Non-SUDEP

A sudden death in an individual with epilepsy with a clear cause of death other than SUDEP (e.g. MI, brain hemorrhage).

Annegers Criteria for SUDEP

- **Definite SUDEP**
  - All clinical criteria are met
  - An autopsy is performed that revealed no alternative cause of death

- **Probable SUDEP**
  - All clinical criteria are met
  - No autopsy is performed

- **Possible SUDEP**
  - SUDEP could not be ruled out
  - There is insufficient evidence regarding the circumstances of the death
  - No autopsy is performed

Unified Definition of SUDEP

• Definite SUDEP
• Probable SUDEP
• Possible SUDEP
• SUDEP Plus
  • There is a concomitant condition other than epilepsy
  • The death may have been due to the combined effect of both conditions
  • Definite or Probable
• Near SUDEP/near SUDEP Plus
  • A patient with epilepsy survives resuscitation for more than 1 hour after a CRA that has no structural cause identified after investigation
• Unclassified
  • Incomplete information is available
  • Not possible to classify the cause of death

Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:22733
SUDEP

- Incidence: 0.35 cases/1,000 person-years (Population-based studies)
- Chronic epilepsy: 1 - 2/1,000 person-years
- Severe, refractory seizures: 3 - 9 / 1,000
- The highest rates occur from 20 to 40 years
- Most cases are seizure-related
- Seizure frequency is the strongest risk factor for SUDEP
  - relative risk is 23 (95%, CI = 3.2-170) for persons with ≥ 1 seizure during the year of observation versus seizure-free patients
- Onset of epilepsy at an early age and long duration of the disorder are other risk factors

SUDEP in Epilepsy Monitoring Units (EMUs)

• Very rarely, SUDEP occurs in EMUs

• Provides highly informative data for pathophysiology of SUDEP.
Incidence and mechanisms of cardiorespiratory arrests (CRA) in epilepsy monitoring units (MORTEMUS): a retrospective study

- Comprehensive evaluation of CRAs in EMUs

MORTEMUS: MORTality in Epilepsy Monitoring Unit Study

- Study interval: Jan 1, 2008, and Dec 29, 2009
- A systematic retrospective survey of EMUs in Europe, Israel, Australia and New Zealand
- To retrieve data for all CRAs recorded in EMUs and estimate their incidence.
- An expert panel reviewed data, including video-EEG and EKG material at the time of CRAs whenever available.

Results from MORTEMUS Study

- 147/160 (92%) of the surveyed EMUs
- 29 CRAs were reported by 27 EMUs from 11 countries:
  - 16 SUDEP (8 definite, 8 probable; 14 at night)
  - 9 near SUDEP (2 eventually fatal)
  - 4 deaths from other causes (2 SAH, 1 MI and 1 brain edema complicating subdural grids).
- 28/29 (97%) of the patients with CRA
- All were adults.
- 6/29 (21%) had a documented history of postictal apnea, postictal CRA or ictal asystole.


<table>
<thead>
<tr>
<th>Sex/age (years)</th>
<th>Age of onset of epilepsy (years)</th>
<th>Epilepsy</th>
<th>GTCS during past 3 months</th>
<th>Characteristics of triggering seizure and CRA</th>
<th>Delay from end of seizure to CPR (min)</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>Brain area</td>
<td>Side</td>
<td>AED tapering</td>
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</tr>
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</table>

Corresponding reference numbers for published case reports are shown alongside patient numbers. SUDEP= sudden unexpected death in epilepsy. GTCS= generalised tonic-clonic seizure. CRA= cardiorespiratory arrest. CPR= cardiopulmonary resuscitation. AEDs= antiepileptic drugs. VEEG= video electroencephalogram. M= male. EPINVB= early postictal neurovegetative breakdown. F= female. CPS= complex partial seizure. NA= not applicable. “> between 2200 h and 0600 h. Fatal near SUDEP.

Table 1: Patient characteristics and observations at the time of SUDEP or near SUDEP, by patient number.
<table>
<thead>
<tr>
<th>Relevant History</th>
<th>Epilepsy Cause</th>
<th>GTCS</th>
<th>Pre-surgical VEEG</th>
<th>Days of VEEG</th>
<th>Awake or Sleep Stage</th>
<th>Number of GTCS in past 12 h</th>
<th>Available Respiratory Data</th>
<th>Available Cardiac Data</th>
<th>Observations at Time of Event</th>
<th>Autopsy Findings</th>
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<td>ECG</td>
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<td>ECG</td>
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<td>ECG</td>
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<td>ECG</td>
<td>普</td>
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</table>

Table 2: Additional patient characteristics, by patient number.

Results from MORTEMUS Study

- The epileptic focus in 25 cases of SUDEP or near SUDEP:
  - Temporal lobe 16 (64%)
  - Insula 2 (8%)
  - R-sided 13 (52%)
  - L-sided 6 (24%)
  - Bilateral or generalized 5 (20%).
- GTCS within the preceding 3 months 14 (56%)
- 6/29 (21%) had a documented history of postictal apnea, postictal cardiorespiratory arrest, or ictal asystole.

Results from MORTEMUS Study

- Cardiorespiratory data were available for 10 SUDEP cases:
  - Rapid breathing (18-50 BPM) developed after sGTCS, followed within 3 min by transient or terminal cardiorespiratory dysfunction.
  - Where transient, this dysfunction later recurred with terminal apnea within 11 min of the end of the seizure, followed by cardiac arrest.

Results from MORTEMUS Study

• All non-monitored SUDEP and fatal near SUDEP occurred at night in a unit where nocturnal staff resources and level of supervision were similar to that of a standard neurological ward, precluding nocturnal VEEG recording.

• Monitored SUDEP occurred between 19:30 h and 06:00 h in all but 1 patient.

• CPR was undertaken in 11/16 cases of SUDEP and all fatal near SUDEP with a delay always exceeding 10 min after initial apnea.

• CPR was started within 3 min in all 7 non-fatal near SUDEP, 6 of which occurred during the daytime, with one needing defibrillation.

Patterns of postictal cardiorespiratory functions, starting from the end of seizure, in 9 patients with monitored SUDEP.

Patterns of respiratory rate and cardiac rate during the first 3 min postictally in patients who had a monitored SUDEP

A. RR in 10 patients with monitored SUDEP. All had a RR ≥18 BPM at the end of GTCS, which rapidly deteriorated until transient or terminal apnea.

B. HR in 9 patients with monitored SUDEP. HR varied between 55-145 BPM at the end of GTCS, and deteriorated in parallel with respiration until asystole or major bradycardia in 1 patient (5).

Results from MORTEMUS Study

- SUDEP incidence in adult EMUs was 5·1 (95% CI 2·6-9·2) per 1000 patient-yrs
- SUDEP risk was 1·2 (0·6-2·1) per 10,000 VEEG monitorings
- SUDEP risk was probably aggravated by:
  - Suboptimum supervision
  - AED withdrawal

MORTEMUS Study: Conclusions

- SUDEP in EMUs primarily follows an early postictal, centrally mediated, severe alteration of respiratory and cardiac function induced by GTCS, leading to immediate death or a short period of partly restored cardiorespiratory function followed by terminal apnea then cardiac arrest.

- Improved supervision is warranted in EMUs, in particular during night time.

Postictal Generalized EEG Suppression

- Defined as the generalized absence of EEG activity greater than 10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts.

Possible Mechanisms of SUDEP

Long QT Syndrome Pathogenic Variants in SUDEP

KCNQ1, KCNH2, and SCN5A proteins with positively charged transmembrane segments (green)

Previously reported pathogenic mutations (blue circles)

*De novo* missense mutation (red circle)

Candidate pathogenic variants (green circles)

## Genes associated with SUDEP

<table>
<thead>
<tr>
<th>Gene</th>
<th>OMIM disease</th>
<th>Evidence for association with SUDEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KCNA1</strong></td>
<td>Episodic ataxia/myokymia syndrome</td>
<td>Animal model; variant found in SUDEP case</td>
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<tr>
<td><strong>SCN1A</strong></td>
<td>Dravet syndrome</td>
<td>Animal model; <em>de novo</em> variants found in SUDEP cases</td>
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<tr>
<td><strong>SCN2A</strong></td>
<td>Early-infantile epileptic encephalopathy 11</td>
<td><em>De novo</em> variants found in SUDEP cases</td>
</tr>
<tr>
<td><strong>SCN8A</strong></td>
<td>Early-infantile epileptic encephalopathy 13</td>
<td>Animal model; <em>de novo</em> variants found in SUDEP cases</td>
</tr>
<tr>
<td><strong>DEPDC5</strong></td>
<td>Familial focal epilepsy with variable foci</td>
<td><em>De novo</em> variants found in SUDEP cases</td>
</tr>
<tr>
<td><strong>KCNQ1</strong></td>
<td>Long QT syndrome type 1</td>
<td>Variants found in SUDEP cases</td>
</tr>
<tr>
<td><strong>KCNH2</strong></td>
<td>Long QT syndrome type 2</td>
<td>Variants found in SUDEP cases</td>
</tr>
<tr>
<td><strong>SCN5A</strong></td>
<td>Long QT syndrome type 3</td>
<td><em>De novo</em> variant found in SUDEP case</td>
</tr>
</tbody>
</table>

Neuropathology of SUDEP: Role of inflammation, BBB impairment and hypoxia

- Immunohistochemistry for specific markers of inflammation, gliosis, acute neuronal injury due to hypoxia and BBB disruption in SUDEP.
- Markers (CD163, human leukocyte antigen-antigen D related, GFAP, HIF-1a, immunoglobulin G, and albumin)
- Hippocampus, amygdala, and medulla
- N= 58: 28 SUDEP (definite and probable), 12 epilepsy controls, 18 nonepileptic sudden death.
- Immunoreactivity for inflammatory reaction, BBB leakage, and HIF-1a in SUDEP cases was not different from that seen in control groups.

Pulmonary and cardiac pathology in SUDEP (Review)

- **Pulmonary pathology (14 studies; 2 on lung weights):**
  - Pulmonary changes (72%)
    - Pulmonary edema/congestion (most common)
    - Intra-alveolar hemorrhage (less frequent)

- **Cardiac pathology (11 studies):**
  - Cardiac abnormalities (25%)
    - Myocyte hypertrophy (. The most common)
    - Focal interstitial myocardial fibrosis

- **Living PWE:**
  - Postictal pulmonary abnormalities
  - Postictal transient LV dysfunction
    - Takotsubo or neurogenic stunned myocardium

Comparison of durations in seizure phases, postictal generalized EEG suppression (PGES) and the recovery phase in children and adults.

- VEEG data from EMU
- 105 GTCS in 61 consecutive patients
- 12 children (23 seizures)
- 49 adults (82 seizures)
- Total seizure duration, tonic phase, PGES and recovery phases were significantly shorter in children (p<0.01).
- PGES durations were on average 28s shorter in children.

Autonomic dysfunction and SUDEP

- Assessed cardiovascular fitness as a measure of autonomic function
- Maximal treadmill test (the Bruce protocol) in 30 consecutive PWE with no known cardiovascular diseases and matched healthy controls.
- Peak heart rate, Duke Score and MET, were significantly lower in PWE.
- Chronotropic incompetence, a known risk marker for death was more prevalent in PWE.
- Age of epilepsy onset, seizures and polytherapy were related to lower fitness.
- Risk for SUDEP may be related to autonomic dysfunction linked to lower fitness.
• Maximal Predicted-Karnoven: Predicted maximal heart rate= (220 − age)
• Maximal Predicted-Tanaka: Predicted maximal heart rate= {208 − (0.7 × age)}
• Chronotropic index-Karnoven: {[(Peak heart rate− rest heart rate)/(220 −age −rest heart rate)]}
• Chronotropic index-Tanaka: {[(Peak heart rate− rest heart rate)/(208 − (0.7 × age) −rest heart rate)]}.
• *Statistically significant (p < 0.05).

HR Variability (HRV) and the risk of SUDEP in patients with DRE

- N= 47 patients with DRE and 45 healthy control subjects
- 24-hour Holter recordings
- Potential SUDEP risk was estimated using SUDEP-7 inventory

Patients with DRE present with significantly lower HRV measures, which may increase the risk for sudden cardiac death.

Increased HR and diminished HRV measures may constitute one of the possible mechanisms underlying SUDEP.