Sudden Unexpected Death in Epilepsy

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Understanding SUDEP: Risk Factors, Mechanism, and Preventive Strategies

- Epilepsy-Related Mortality & Definition of SUDEP
- Epidemiology of SUDEP
- Risk factors
- Case examples: who is at low v. high risk?
- What causes SUDEP: defining mechanisms
- Strategies to reduce SUDEP
- Talk about it: Need for patient education
Disease-related mortality in epilepsy

- Status epilepticus
- Accidents and drowning (~16% of deaths)
- Suicide (~11% of deaths, Jones et al, 2003)
- Drug reactions
- Aspiration pneumonia
- Psychiatric illness is a significant risk factor (Fazel et al, Lancet, 2013)
- Sudden unexpected death in epilepsy
  - Most common cause in treatment-resistant cases
  - Relevant for TSC patients
SUDEP

- Sudden, unexpected, non-traumatic death in a person with epilepsy, w/o post-mortem exam evidence of structural or toxicological cause of death
  - Definite – with autopsy, no other cause
  - Probable – no autopsy, no other cause
  - Possible – alternative cause of death, clinical data are lacking
Figure 1. Incidence of Sudden, Unexpected Death in Epilepsy According to Population Type.
Lifetime Risk Model – SUDEP in Treatment-Resistant Epilepsy

- **Assumptions:**
  - Childhood onset, no life-limiting comorbidities
  - Overall annual incidence **6.2/1000**
  - Peak incidence age 30

- **Cumulative Incidence:** **35%** to age 80

- **Patients with Autism & Epilepsy:** 55% have T-R Epilepsy (Sansa et al, 2011)


David Thurman, with permission
Public Health Burden of SUDEP—Annual Years of Potential Life Lost (YPLL)

YPLL (Thousands)

- Stroke: 180
- SUDEP: 80
- ALS/MND: 60
- MS: 40
- Alz: 20
- Men/Enc: 10
- PD: 5

Courtesy of David Thurman
SUDEP by AGE

Terrence et al, Neurology 1975;25:594
## Risk factors: Case Control Studies

<table>
<thead>
<tr>
<th>Factors associated with increased SUDEP risk</th>
<th>Factors associated with decreased SUDEP risk</th>
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<tbody>
<tr>
<td>Frequent seizures, especially <strong>GTCs</strong>, nocturnal seizures</td>
<td>Seizure freedom</td>
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<tr>
<td>Symptomatic etiology</td>
<td>Sharing bedroom/supervision</td>
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<tr>
<td>Subtherapeutic AED levels</td>
<td>Recent addition of AED</td>
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<tr>
<td>AED polytherapy**</td>
<td></td>
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<tr>
<td>Early age of epilepsy onset/long duration of epilepsy**</td>
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<tr>
<td>Male sex</td>
<td></td>
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<td>Mental retardation, learning disability</td>
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</tbody>
</table>

Cause of death after epilepsy surgery

- SUDEP 10
- CANCER 3
- SUICIDE 2
- MVA 1
- PNEUMONIA 1
- MYOCARDITIS 1
- PERIOPERATIVE 1

Sperling et al Annals of Neurology 1999
courtesy of DC Hesdorffer
Mortality in post-surgical patients

Resective Surgery:  
- Without seizure recurrence: 0.85 Rate per 1000 person yrs
- With seizure recurrence: 9.14

Callosotomy:  
- Without seizure recurrence: 0 in 4.5
- With seizure recurrence: 22.6

Excluding perioperative mortality: 18.9

Sperling et al Annals of Neurology 1999
courtesy of DC Hesdorffer
Treatment Resistant Absence Epilepsy: High or Low Risk?

7 year old boy, absence seizures since age 5 yo

Treated with ethosuximide, valproic acid and lamotrigine in 1-2 drug combos

1-4 absence seizures per day when tired or with certain visual stimuli

No tonic-clonic or myoclonic seizures
Treatment Resistant Absence Epilepsy: High or Low Risk?

- 38 year old single woman with temporal lobe epilepsy on lamotrigine and levetiracetam
- 1 complex partial seizure/month; 1 nocturnal tonic-clonic seizure/year related to sleep deprivation or missed medication.
- Depression treated with sertraline
15 year old boy with cerebral palsy and Lennox-Gastaut Syndrome

Meds: valproate, lamotrigine, clobazam

1-3 atonic and tonic seizures per day, most often around arousal in am.

1-2 tonic-clonic seizures per month

Relatively high functioning with good verbal and social skills
Mechanisms

- A terminal seizure usually occurs and is ultimate cause of death in most cases
- Clinical observations of witnessed SUDEP or near-SUDEP
  - Seizures precede 90% of witnessed cases (Langan et al 2000; Tomson et al 2005)
    - Difficulty breathing observed in most
  - Autopsy cases have histopathological evidence of recent seizure (Thom et al 2003)
# SUDEP in the EMU

- **7 SUDEPs and 5 near-SUDEPs reported in the literature**
- **All followed seizures, 11 after GTC and 1 after CPS; in 7, there were >2 GTCs prior to terminal seizure**
- **8 primary respiratory**
- **2 cerebral shutdown**
- **2 cardiac**

<table>
<thead>
<tr>
<th>Author</th>
<th>TYPE</th>
<th>A/S</th>
<th>Putative Mechanism</th>
<th>Preceding Sz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bird</td>
<td>SUDEP</td>
<td>47M</td>
<td>Cerebral shutdown, pulmonary edema</td>
<td>5 2nd GTC</td>
</tr>
<tr>
<td>Lee</td>
<td>SUDEP</td>
<td>41F</td>
<td>Cerebral shutdown</td>
<td>4 GTC</td>
</tr>
<tr>
<td>Purves</td>
<td>SUDEP</td>
<td>27F</td>
<td>Respiratory, suffocation</td>
<td>5 GTC</td>
</tr>
<tr>
<td>Bateman 1</td>
<td>SUDEP</td>
<td>42F</td>
<td>Central apnea</td>
<td>2 GTC</td>
</tr>
<tr>
<td>Bateman 2</td>
<td>SUDEP</td>
<td>62M</td>
<td>Central apnea</td>
<td>2 GTC</td>
</tr>
<tr>
<td>Tao</td>
<td>SUDEP</td>
<td>35F</td>
<td>Respiratory, suffocation</td>
<td>GTC</td>
</tr>
<tr>
<td>Dashief</td>
<td>SUDEP</td>
<td>48M</td>
<td>Cardiac ischemia, Vfib</td>
<td>2 GTCs</td>
</tr>
<tr>
<td>Espinosa</td>
<td>NM</td>
<td>51F</td>
<td>Vfib (resp effort not reported)</td>
<td>GTC 4.5 mins</td>
</tr>
<tr>
<td>Pezzella</td>
<td>NM</td>
<td>14M</td>
<td>Respiratory; pulmonary edema</td>
<td>GTC</td>
</tr>
<tr>
<td>Tavee</td>
<td>NM</td>
<td>42</td>
<td>Laryngospasm</td>
<td>3 GTC</td>
</tr>
<tr>
<td>So</td>
<td>NM</td>
<td>20F</td>
<td>Central apnea</td>
<td>4 GTC</td>
</tr>
<tr>
<td>Thomas</td>
<td>NM</td>
<td>18M</td>
<td>Laryngospasm &amp; obstructive apnea</td>
<td>CPS</td>
</tr>
<tr>
<td>Pezzella</td>
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Summary of Observations

- Witnessed, EMU-recorded, and post-mortem studies all support a seizure, typically GTC, as the terminal event.

- 3 main mechanisms emerge from EMU cases:
  - Primary respiratory causes: central or obstructive apnea
  - Cerebral shutdown: diffuse post-ictal suppression of EEG preceding EKG or respiratory changes
  - Cardiac arrhythmias

Friedman et al. JCI 2013
Pathophysiology of SUDEP – Human & Animal Data

- Primary Respiratory Mechanisms
- Cerebral Shutdown
- Cardiac Abnormalities
- Autonomic Dysfunction
Cerebral Shutdown

- After GTC: EEG flat, coma
- Difficult to show on exam; respiratory monitoring is rare

- Pts who died of SUDEP had greater degree of postictal suppression on VEEG (Lhatoo et al, 2010)
  - 30x risk of SUDEP if postictal suppression >60s
  - Finding not replicated (Surges et al, 2011)
Cardiac Mechanisms

- Seizure-related tachycardia
  - 40% have ictal/postictal ST segment changes
  - In case-control study, pts with subsequent SUDEP had higher ictal HRΔ than controls (Nei et al 2003)
- Seizure-related bradycardia/asystole (Schuele 2009)
  - 0.4% of patients have asystole >60 s
  - After pacemaker for ictal asystole, none went off
- Cardiac channelopathies
  - Mutant mice (KCNQ1 & KCNA1) with epilepsy suffer seizure-induced cardiac death (Goldman et al 2009; Glasscock et al 2010)
**Challenges**

- Seizure-related changes in cardiopulmonary function are common, but SUDEP is rare
  - Common seizures rarely cause SUDEP. Why?
  - A due to failure of recovery mechanisms?
  - Perfect storm?
- Why are adults and treatment-resistant patients at higher risk?
- 20% of SUDEPs occur in patients with rare or no GTCs
  - Low risk patients may have different mechanisms
  - Neuro-cardiac channelopathies may contribute to death in patients with recent onset epilepsy
  - Increased risk for epilepsy & sudden death
Strategies to Reduce SUDEP

- Seizure freedom
  - Medication adherence
  - Lifestyle factors – restorative sleep, limit alcohol, optimize seizure meds, consider surgery, dietary, or neurostimulation
  - TSC - ? mTOR inhibition (eg, Everolimus)
- Prolonged seizures and seizure clusters
  - Rescue medications
Strategies to Reduce SUDEP

- Fluctuating medication levels
  - Education about drug interactions (e.g., OCP/lamotrigine), effects of GI preps/vomiting/diarrhea on absorption

- Identify nocturnal seizures
  - Ask about confusion, headaches, soreness, incontinence on awakening
  - Consider increased meds at bedtime
  - Consider seizure monitor
Strategies to Reduce SUDEP

- Sleeping alone, history of nocturnal convulsions
  - Ensure adherence of meds, esp night-time
  - Consider seizure monitor, esp if others nearby
- Family members should know seizure first aid
  - Resposition patient from prone position
  - Mild stimulation may help (Bateman et al, 2013)
Why Do We Need to Talk About SUDEP?

- More than 95% of patients and caregivers want to learn about SUDEP.
- Understanding that seizures, especially TC seizures, can injure the brain & lead to cognitive and psychiatric disorders, & SUDEP.
- Patients can reduce their risk TC seizures:
  - medication adherence,
  - lifestyle factors (eg, adequate sleep, avoiding excess alcohol).