Unraveling SUDEP
Recent Developments
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Elson L. So, MD
Professor of Neurology
EEG and Epilepsy

Mayo Clinic
Rochester, MN
Disclosures

• Speakers Bureau – none
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• Intellectual Property – Epilepsy Treatment Planning Software, no financial proceeds
• Editorial Boards
  • Epilepsia
  • Epilepsy Research
  • Journal of Clinical Neurophysiology
Acknowledgment

SUDEP Benchmark Stewards

• Alicia M. Goldman, MD, PhD, Baylor College of Medicine, Texas
  • Identify the mechanisms responsible for SUDEP

• Samden Lhatoo MD, Case Western Medical Center, Ohio
  • Develop and validate at least one prevention strategy
SUDEP Recent Developments
News Headlines

“Arrhythmias in the Brain & the Heart – A Genetic Basis for SUDEP?”

“Peri-ctal Hypoxia – More Common & Severe Than You Think”

“Heart Rate Variability – A Potential Marker For SUDEP”

“Brain “Shut Down” After A Seizure Increases Risk For SUDEP”
Arrhythmia in Heart and Brain: KCNQ1 Mutations Link Epilepsy and Sudden Unexplained Death

Goldman A et al, 2009
American Epilepsy Society | Annual Meeting
Seizure-Associated Sudden Death Event in a \textit{Kcna1}-Null Mouse

Glasscock E et al: 2010
Post-Mortem Review and Genetic Analysis of Sudden Unexpected Death in Epilepsy (SUDEP) Cases

- Retrospective blood test in 48 SUDEP cases

- 6 (13%) with Familial Long QT syndrome genes
  - Two with $KCNH2$
  - Four with $SCN5A$

Tu A et al., 2010
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Ictal Hypoxemia in Children

- More likely with generalized sz (44% vs 19%)
- More likely with AED taper (75% vs 35%)
- More likely with prolonged complex partial seizures
- No association with location or side of seizure onset
- Ictal bradycardia only with extratemporal CPS

Moseley B et al, 2010

<table>
<thead>
<tr>
<th>Desaturation (%)</th>
<th>Latency to desaturation from seizure onset(s) (range)</th>
<th>Duration of desaturation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80-89.9</td>
<td>65.91±55.47 (1-305)</td>
<td>65.8±110.39 (2-599)</td>
</tr>
<tr>
<td>70-79.9</td>
<td>77.01±77.61 (1-434)</td>
<td>52.82±67.6 (5-343)</td>
</tr>
<tr>
<td>60-69.9</td>
<td>95.52±115.23 (1-585)</td>
<td>48.67±55.7 (4-243)</td>
</tr>
<tr>
<td>&lt;60</td>
<td>112.83±140.87 (1-600)</td>
<td>42.94±59.82 (1-219)</td>
</tr>
</tbody>
</table>
Peri-ictal Hypercapnia

- Baseline ETCO$_2$ = 35 mm Hg
- 37% ≥50 mm Hg
- 16% ≥60 mm Hg
- 5% ≥70 mm Hg

ETCO$_2$ change above peri-ictal baseline (mm Hg)

Seconds following peak ETCO$_2$

Seyal M: 2010

American Epilepsy Society  |  Annual Meeting
Effect of Fluoxetine on Susceptible DBA/2 Mice

Respiratory arrest (%) vs. Dose (mg/kg)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Control</th>
<th>Drug</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

No. | 5 | 10 | 12 | 15

*P<0.001; **P<0.005

Tubap & Faingold: Epilepsia 47:21, 2006

American Epilepsy Society | Annual Meeting
Abnormal Serotonin Receptor Expression in DBA/2 Mice Associated with Susceptibility to Sudden Death Due to Respiratory Arrest

Uteshev W et al, 2010

C57BL/6J

DBA/2

Expression level (%)

C57BL/6J

DBA/2

Expression level (%)

C57BL/6J

DBA/2

American Epilepsy Society  |  Annual Meeting
# Ictal-Related Oxygen Desaturation Findings with Nongeneralized and Secondary Generalized Seizures

Seizures with Oxygen Desaturation <85%

<table>
<thead>
<tr>
<th></th>
<th>Seizures (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nongeneralized seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI+</td>
<td>6</td>
<td>0.007</td>
</tr>
<tr>
<td>SSRI−</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary generalized convulsions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI+</td>
<td>71</td>
<td>0.806</td>
</tr>
<tr>
<td>SSRI−</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

Bateman L et al, 2010
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“Brain “Shut Down” After A Seizure Increases Risk For SUDEP”
What is Heart Rate Variability (HRV)?

• Beat-to-beat variation in heart rate is normal

• Reduction in variability is associated with higher mortality following heart attacks, and other cardiac and non-cardiac disorders
HEART Rate Variability (HRV) in Complex Partial Seizures (CPS) vs Secondary GTCS

Adapted from Surges R et al: 2010

American Epilepsy Society | Annual Meeting
### SUDEP Risk Factors from Combined Analysis of 4 Case-Controlled Studies

<table>
<thead>
<tr>
<th>Significant risk factors</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male vs female</td>
<td>1.42</td>
</tr>
<tr>
<td>Epilepsy onset at &lt;16-year old vs 16-60</td>
<td>1.72</td>
</tr>
<tr>
<td>Epilepsy duration of &gt;15 years vs ≤15 yr</td>
<td>1.95</td>
</tr>
<tr>
<td>AED polytherapy vs no AED</td>
<td>1.95</td>
</tr>
<tr>
<td>Symptomatic generalized epilepsy vs idiopathic</td>
<td>1.4</td>
</tr>
<tr>
<td>GTCS frequency (per year) 1-2 vs 0</td>
<td>5.07</td>
</tr>
<tr>
<td>GTCS frequency (per year) &gt;3 vs 0</td>
<td>15.4</td>
</tr>
<tr>
<td>Lamotrigine therapy vs none</td>
<td>1.96</td>
</tr>
</tbody>
</table>

Hesdorffer D et al., 2011
Inverse Correlation Between HRV and SUDEP-7 Score

Degiorgio C et al: 2010

Heart rate variability RMSDD (msec)

SUDEP-7 score

American Epilepsy Society | Annual Meeting
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Postictal Generalized EEG Suppression and SUDEP

Lhatoo S et al: 2010
Postictal Generalized EEG Suppression (PGES) and SUDEP

• Compared 30 recorded seizures in 10 SUDEP cases with controls
• Percentage of seizures with PGES
  • 50% in SUDEP cases vs 38% in controls
• Duration of PGES
  • Mean of 90 s in SUDEP vs 15 s in controls (P=<0.01)

Lhatoo S et al: 2010
Odds Ratio of SUDEP by Duration of PGES in Generalized Motor Seizures

<table>
<thead>
<tr>
<th>Duration</th>
<th>Odds ratio</th>
<th>Adjusted&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>11.42</td>
<td>0.98-132.4</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>12.99</td>
<td>1.24-135.78</td>
<td>&lt;0.05</td>
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<tr>
<td>&gt;30</td>
<td>7.61</td>
<td>1.23-47.03</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>8.1</td>
<td>1.56-41.98</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>8.9</td>
<td>1.47-53.76</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>15.18</td>
<td>2.42-95.41</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>15.18</td>
<td>2.42-95.41</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>30.06</td>
<td>4.45-203.07</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>30.06</td>
<td>4.45-203.07</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<sup>b</sup>Adjusted for age, gender, and age of epilepsy onset
Lhatoo S et al: 2010
Seizure

↓ heart rate/arrest

Brainstem suppression, ↓ lung stretch receptors

Hypoxia and ↑ carotid chemoreceptor sensitivity

So E, 2008
Strategies to Reduce SUDEP Risk

- Optimize seizure control
  - Reduce GTCS frequency
  - Reduce number of AED used
  - Avoid frequent AED changes
  - Consider epilepsy surgery
- Prevent serious consequences of seizures (eg, injuries, asystole, severe apnea, hypoxia, or hypotension)
- Subscribe to favorable lifestyle
  - Adhere to medication regimen
  - Avoid aggravating factors (eg, recreational drugs, sleep deprivation)
- Seizure detection and intervention unproven (eg, supervision and alarm devices)
Mortality in Epilepsy

SUDEP: Where are we now?

Research Methodology – Clinical Studies

Research Methodology – Bench Research

Talking About SUDEP

Physiologic Mechanisms

Molecular & Genetic Mechanisms

SUDEP Prevention

Role of Lay Community in Facilitating Research

Where Do We Go From Here?
References


• Glasscock E, Yoo J, Chen T, Klassen T, Noebels J. Kv1.1 Potassium Channel Deficiency Reveals Brain-Driven Cardiac Dysfunction as a Candidate Mechanism for Sudden Unexplained Death in Epilepsy. The Journal of Neuroscience 2010;30:5167-75.
References (cont)

References (cont)

• So E. What is known about the mechanisms underlying SUDEP? Epilepsia. 2008; 49(Suppl 9):93-8.


