Mortality in Childhood-Onset Epilepsy

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Disclosures

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- NINDS
- Pediatric Epilepsy Research Foundation

Speaker Honoraria
- AES
- UCLA
- BIAL
- NINDS
- Case Western Reserve
- MUSC
Learning Objectives

• Recognize the primary causes of mortality in young people with epilepsy

• Relate risk of death and of SUDEP specifically to mortality risks in the population
  – overall
  – common causes of death
Pediatric Epilepsy Mortality Collaborators

- **Nova Scotia:**
  - Peter and Carol Camfield
- **Netherlands:**
  - Petra Trinka, Ada Geerts, Willem Arts
- **Rochester-Mayo Clinic:**
  - Katherine Nickels, Elaine Wirrell
- **Connecticut:**
  - Christina Rios, Anne Berg

**Funding Sources:**
NIH-NINDS NS-R37-31146
Mayo Foundation CR20 grant
The National Epilepsy Fund, Houten, The Netherlands (A72 and A85)
Mortality

• Inevitable
  – Frequency
  – Reasons
    Intervention?

• Force of mortality and reasons for death vary
  – By region of the world
  – By country within region
  – By subgroups within a country or population
    • Gender
    • Socio-economic group
    • Access to care
    • AGE!

death rate / 100,000 per year
Map of the world – Surface area

Worldmapper.com
Landmass versus population

Worldmapper.com
WHO statistics
English speakers

Worldmapper.com
Deaths to women in childbirth

Vaccine preventable deaths

Infant mortality

Childhood mortality 1-4 years

Worldmapper.com
WHO statistics
Incidence of epilepsy by age
Iceland

rate / 100,000 per year

Olafsson et al. Lancet Neurology, 2005
Epilepsy Deaths

population
Standardized mortality ratios (SMR) for people with epilepsy

**General Population**

**Children**

<table>
<thead>
<tr>
<th>Country</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>2.3</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2.0</td>
</tr>
<tr>
<td>Iceland</td>
<td>2.1</td>
</tr>
<tr>
<td>US (MN)</td>
<td>2.4</td>
</tr>
<tr>
<td>UK</td>
<td>4.1</td>
</tr>
<tr>
<td>France</td>
<td>5.1</td>
</tr>
<tr>
<td>Canada</td>
<td>6.7</td>
</tr>
<tr>
<td>Netherlands</td>
<td>7.4</td>
</tr>
<tr>
<td>US (CT)</td>
<td>9.2</td>
</tr>
<tr>
<td>US (MN)</td>
<td>6.6</td>
</tr>
<tr>
<td>US (GA)</td>
<td>5.8</td>
</tr>
</tbody>
</table>
## Four Pediatric Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Nova Scotia Camfield &amp; Camfield</th>
<th>Netherlands Callenbach, Geerts, &amp; Arts</th>
<th>Connecticut Berg &amp; Rios</th>
<th>Rochester Nickels &amp; Wirrell</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Prospective, population-based</td>
<td>Prospective-regional</td>
<td>Prospective, community based</td>
<td>Retrospective, population-based</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Newly diagnosed epilepsy ≥2 unprovoked seizures</td>
<td>Newly diagnosed epilepsy ≥2 unprovoked seizures</td>
<td>Newly diagnosed epilepsy ≥2 unprovoked seizures</td>
<td>Newly-diagnosed epilepsy ≥2 unprovoked seizures +</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1m – 16 years</td>
<td>1m-16 years</td>
<td>1m-16 years</td>
<td>1m – 17 years</td>
</tr>
</tbody>
</table>
Ascertainment of Deaths

• Systematic efforts
• Sources of information:
  – Parent report to study interviewer
  – Physician report to the study team
  – Review of National Death Indices or other administrative and health records
  – Rochester Epidemiology Project Surveillance
Mortality in young people with epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Person-years</th>
<th>Avg Follow-up</th>
<th>Deaths</th>
<th>Rate/100,000/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nova Scotia</td>
<td>686</td>
<td>8918</td>
<td>13y</td>
<td>26</td>
<td>292 (179, 404)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>494</td>
<td>6867</td>
<td>13.9y</td>
<td>18</td>
<td>262 (141, 382)</td>
</tr>
<tr>
<td>Connecticut</td>
<td>613</td>
<td>10,066</td>
<td>16.4y</td>
<td>19</td>
<td>189 (104, 274)</td>
</tr>
<tr>
<td>Rochester</td>
<td>467</td>
<td>4561</td>
<td>9.8y</td>
<td>16</td>
<td>350 (179, 522)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2260</strong></td>
<td><strong>30412</strong></td>
<td><strong>13.5y</strong></td>
<td><strong>79</strong></td>
<td><strong>260 (202, 317)</strong></td>
</tr>
</tbody>
</table>

![rate/100,000/year](image-url)
Cumulative % of deaths since initial diagnosis of epilepsy

OVERALL

50% of observed deaths within 5 years of diagnosis

Average follow-up 13.5y
Years since diagnosis

0-1 2-4 5-9 10-14 15-19 20-24 25-29

US
Hauser, Epilepsia 1980

Netherlands
Shackleton, JNNP, 1999

Years since index seizure

0-1 1-2 2-3 3-4 4-9 9-14

UK
Lhatoo, Ann Neurol 2001

Sweden
Lindsten, Epilepsia 2000

Time since diagnosis

0-1 2-4 5-9 10-14 15-19 20-24 25-29

US
Hauser, Epilepsia 1980

Netherlands
Shackleton, JNNP, 1999

Years since diagnosis

0-1 2-4 5-9 10-14 15-19 20-24 25-29

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Years since index seizure

0-1 1-2 2-3 3-4 4-9 9-14

UK
Lhatoo, Ann Neurol 2001

Sweden
Lindsten, Epilepsia 2000

Years since diagnosis

1 2 3 4 5 6 7 8 9 10

SMR

0 5 10 15 20

Years since diagnosis

0-1 2-4 5-9 10-14 15-19 20-24 25-29

SMR

0 5 10 15 20

Years since diagnosis

1 2 3 4 5 6 7 8 9 10

SMR

0 5 10 15 20

Years since index seizure

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Years since index seizure

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SMR

0 5 10 15 20

Years since diagnosis

1 2 3 4 5 6 7 8 9 10

SMR

0 5 10 15 20

Years since diagnosis

1 2 3 4 5 6 7 8 9 10

SMR

0 5 10 15 20
Complicated vs. Uncomplicated Presentation of Epilepsy

- **Complicated:**
  - associated with
    - structural brain lesion,
    - neuro-metabolic condition,
    - neurologic impairment,
    - intellectual disability

- **Uncomplicated:**
  - normal exam (and imaging)
  - no intellectual disability,
  - no identified underlying cause of epilepsy
# Death Rates by Presentation of Epilepsy

<table>
<thead>
<tr>
<th></th>
<th>Complicated</th>
<th>Uncomplicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>640 (28%)</td>
<td>1620 (72%)</td>
</tr>
<tr>
<td>Person-years</td>
<td>8286 (27%)</td>
<td>22,126 (73%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>71 (90%)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Death rate/100,000/year</td>
<td><strong>857 (657, 1056)</strong></td>
<td><strong>36 (11, 61)</strong></td>
</tr>
</tbody>
</table>

**Bar chart**

- Complicated: 857
- Uncomplicated: 36
Overall mortality / 100,000 / year

Assigning Cause of Death

• Sources of information
  – Death certificates
  – Eye-witness reports
  – Hospital records from terminal visit
  – Autopsy reports
## Causes of Death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Complicated</th>
<th>Uncomplicated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUDEP*</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Other seizure-related**</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other-natural***</td>
<td>56</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>Non-natural+</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Unknown++</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*Based on Nashef et al. Epilepsia 2012
  ( includes definite (N=6), probable (N=2), possible (N=2) )
** Includes status epilepticus, aspiration with seizure, iatrogenic
***Infections, chronic illnesses
+  Homicide (1), suicide (2), accidental deaths (2)
++No information
Other Natural Causes of Death (N=58)

- Respiratory (43)
  - Primary infectious pneumonia
  - Aspiration Pneumonia
  - Unclear aspiration versus primary
  - Other respiratory
- Sepsis (N=3)
- Shunt malfunction (N=3)
- Not fully clear, but… (3)
  - All with lethal neurometabolic diseases
- Other (6, cancer, cardiomyopathy, stroke)

Moderate to Severe Cognitive impairment

52/58 (90%)
52/54 (96%) of those with unrelated causes of death (e.g. cancer)
## Descriptive factors

<table>
<thead>
<tr>
<th></th>
<th>SUDEP (N=10)</th>
<th>Respiratory/Sepsis (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>5.7y (1m – 12y)</td>
<td>2.3y (0 -12y)</td>
</tr>
<tr>
<td>Age at death</td>
<td>13.9y (2-28y)</td>
<td>9.8y (0.5 – 22y)</td>
</tr>
<tr>
<td>Time to death</td>
<td>8 (3m – 16y)</td>
<td>6.2y (1 – 20y)</td>
</tr>
<tr>
<td>Male</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Complicated</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Cognitive level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td>Mildly impaired</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Moderately-severely impaired</td>
<td>40%</td>
<td>98%</td>
</tr>
<tr>
<td>Drug-resistance</td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td>convulsions</td>
<td>90%</td>
<td>61%</td>
</tr>
<tr>
<td>Seizure in last year</td>
<td>90%</td>
<td>78%</td>
</tr>
<tr>
<td>status epilepticus</td>
<td>50%</td>
<td>50%</td>
</tr>
</tbody>
</table>
SUDEP mortality / 100,000 / year

Overall population mortality

SUDEP mortality

Figures for US, Canadian, Dutch populations by age. Epilepsy based on combined 4 studies.
Figures for US (NCHS, CDC). Epilepsy based on combined 4 studies.
Summary

✖ Good news:
- We benefit from generally low death rates in young people…
- No evidence of increased risk from many preventable, accidental causes.

✖ Sobering news:
- Against the backdrop of low childhood and young adult mortality, death rates are high.

✖ Majority of deaths are secondary to infections and complications of neurological impairment.
- Long-term and palliative care issues, not seizures per se.
Summary

- **SUDEP**
  - SUDEP alone doubles the overall risk of death
  - Uncomplicated epilepsy: SUDEP rates are comparable to death rates from leading causes of early death.
  - *If* everyone in the population had epilepsy, SUDEP could be one of the leading causes of early death.
Take Home Message

- Provide a rational perspective for discussing mortality risks, especially with new patients.
Types of epilepsies

No CAE, JAE, JME, BECTS

%
SMR by age at onset

Age at onset
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70+

SMR
0 2 4 6 8 10 12 14

Shackelton JNNP 1999