Risk Factors for Mortality in Epilepsy: Which Ones Are Correctible

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<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
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<tr>
<td>GSK</td>
<td>Travel grant</td>
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<td>UCB</td>
<td>Advisory board</td>
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Learning Objectives

• To understand the distribution of mortality in epilepsy

• To understand risk factors for different causes of death in epilepsy and which ones may be modifiable
The Diseases, and Casualties this year being 1632
Bills of Mortality, John Graunt, London, 1662

Number

Infants 2300
Consumption 1500
Fever 1000
Aged 500
Smallpox 400
Stillborn 300
Teeth 200
Bloody flux 100
Dropsie 50
Childbed 4
Convulsion 4

Annual Meeting
Overall mortality in epilepsy

- Mortality is 1.6 to 3.0 fold greater in people with epilepsy than expected in the general population
  - 10 years of life lost for epilepsy with known etiology
  - 2 years of life lost for epilepsy of unknown etiology

Forsgren et al, Epilepsia, 2005; Gaitatzis et al, Brain 2004
Mortality by age

SMR (95% CI)

0-24 years  25-44 years  45-54 years  55-64 years  60-69 years  >=70 years

Hauser et al, Epilepsia 1980
Mortality by number of years followed

SMR (95% CI)

0-1 years
2-4 years
5-9 years
10-14 years
15-19 years
20-24 years
24-29 years
30-34 years
35-41 years

Shackleton et al, J Neurol Neurosurg Psychiatry 1999
Long-term mortality by epilepsy etiology

UGPG: Unknown, genetic or presumed genetic

URC et al, Epilepsia 1980; Lhatoo et al Ann Neurol 2001
Causes of death in epilepsy

• Many causes of epilepsy are themselves associated with increased mortality, even in the absence of epilepsy
  – Stroke, central nervous system infection, traumatic brain injury, Alzheimer’s disease, neurological deficit present since birth

• This is reflected in mortality according to cause of epilepsy
Cause of death by years followed

SMR (95% CI)

Less than 2 years follow-up

at least 2 years follow-up

Neoplasms
Respiratory
Cardiovascular
CNS infection
Neoplasms
Respiratory
Cardiovascular
CNS infection

Shackleton et al, J Neurol Neurosurg Psychiatry 1999
Mortality in mental retardation and epilepsy

SMR (95% CI)

Forsgren et al, Epilepsia 1996
Cumulative risk of death by cause of epilepsy in childhood-onset epilepsy

Predictors of death in childhood-onset epilepsy

• Unadjusted analysis
  – Lack of 5 year terminal remission
  – Remote symptomatic etiology
  – History of status epilepticus
  – Onset < 2 years

• Adjusted analysis
  – Lack of 5 year terminal remission

Additional Factors Associated with Death in Epilepsy
Cardiovascular disease following epilepsy

- The risk for a first stroke is increased 2- to 7-fold following the onset of epilepsy of unknown cause.

- First strokes following onset of epilepsy may be explained by severe uncontrolled hypertension, which is associated with an increased risk for developing epilepsy in people without a history of stroke.

Additional causes of death in epilepsy

Nilsson et al, Epilepsia 1997
Hazard ratio for death in older people hospitalized with epilepsy in Western Australia

Referent

Einarsdottir et al, Medical Care 2010
Slide not available
Predictors of death in epilepsy

• Known cause of epilepsy

• Occurrence of a first stroke after epilepsy onset

• Few GP visits in the elderly with epilepsy

• Lack of 5 year terminal remission

• Continued seizures after epilepsy surgery
Status Epilepticus and Mortality
Long-term mortality after status epilepticus by etiology

UGPG: Unknown, genetic or presumed genetic

Logroscino et al Neurology 2002
Adjusted Relative Risk for death for first SE of unknown cause vs first unprovoked seizure of unknown cause

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<tr>
<th></th>
<th>N</th>
<th>Adjusted RR (95% CI)</th>
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<tr>
<td><strong>Epilepsy</strong></td>
<td></td>
<td></td>
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<tr>
<td>With SE</td>
<td>5</td>
<td>6.3 (1.5-26)</td>
</tr>
<tr>
<td>Without SE</td>
<td>118</td>
<td>Referent</td>
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<tr>
<td><strong>Over 65 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With SE</td>
<td>7</td>
<td>5.1 (1.6-15.7)</td>
</tr>
<tr>
<td>Without SE</td>
<td>38</td>
<td>Referent</td>
</tr>
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</table>

Adjusted for age and gender

Logroscino et al, Arch Neurol 2008
Epilepsy-related Causes of Death
Epilepsy-related causes of death

- Accidents
- SUDEP
- Suicide
Accidents
Accidents as a cause of death

Observed regardless of length of follow-up
MVA significant only in those with diagnosis age 20 and older
All accidents significant in all age groups, except MVA

Shackleton et al, J Neurol Neurosurg Psychiatry 1999
Deaths due to accidents and injuries in epilepsy

- 1% to 27% of all deaths in epilepsy

- Risk factors for accidents and injuries in epilepsy:
  - Longer duration of epilepsy
  - >3 adverse events due to AEDs
  - Increased seizure frequency

SUDEP
Cumulative Risk of All Epilepsy-Related Deaths and Sudden Unexplained Deaths in Epilepsy

SUDEP with adjunctive AEDs versus adjunctive placebo: A meta-analysis of phase III RCTs

Risk of SUDEP more than 5-fold greater on adjunctive placebo than on adjunctive AED at ‘efficacious’ doses

Overall risk of death on adjunctive placebo is not significantly increased

Ryvlin et al, Lancet Neurology 2011
Non-adherence to AEDs and mortality

Faught et al, Neurology 2008
Predictors of all deaths, epilepsy-related death and SUDEP

• Unadjusted analysis
  – Lack of 5 year terminal remission
  – Remote symptomatic etiology
  – History of status epilepticus
  – Onset < 2 years

• Adjusted analysis
  – Lack of 5 year terminal remission

Sillanpää and Shinnar, NEJM 2010
Conclusions
Mortality

• Mortality is *increased* in epilepsy
• Mortality is *increased* in the absence of AED compliance and the presence of continued seizures
• Status epilepticus *increases* the risk for mortality
• SUDEP is increased in the absence of AED polytherapy
Non-modifiable risk factors for death in epilepsy

- Age
- Gender
- Known etiology of epilepsy
Potentially modifiable risk factors for death in epilepsy

- Decreasing the risk for stroke following epilepsy
- Decreasing chronic alcohol and drug dependence
- Preventing status epilepticus
- Encouraging older people with epilepsy to visit a GP
- Decreasing seizure frequency
Impact on clinical care and practice - I

- Treating seizures lasting 5 minutes or more may prevent status and its consequences
- Identifying and reducing stroke risk factors in people at risk for a stroke after epilepsy onset
- Identifying alcohol dependence and drug dependence and offering treatment programs
- Stressing the importance of GP care
Impact on clinical care and practice -II

- Counseling about the importance of seizure control and AED compliance
References

- Sperling et al 2011 unpublished data
Partner Organizations

- American Epilepsy Society - ILAE
- Cure Epilepsy
- Epilepsy Foundation - Not another moment lost to seizures
- Epilepsy Therapy Project
- SUDEP Aware
- Faces
- Danny Did Foundation
- RTI International
- Epilepsy Alliance
- CDC
- National Institute of Neurological Disorders and Stroke
- LGS Foundation - Lennox-Gastaut Syndrome
- The Pittsburgh Foundation