Sudden Unexpected Death in Epilepsy in pregnant Women

risks * mechanisms * prevention

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Nottingham University Hospital
Sudden unexpected death in epilepsy

- Who is affected?
- What are the mechanisms?
- What are the implications for women?
- How can we prevent it?
- What do we say?
Sudden death: The Chalfont colony
SUDEP: the definition

• A sudden, unexpected, witnessed or unwitnessed, death in a patient with epilepsy
• With or without evidence for a seizure
• Non-traumatic and non-drowning
• Exclusion of status epilepticus
• Post-mortem examination does not reveal a structural or toxicological cause
SUDEP: the epidemiology

SUDEP is the leading cause of premature death in chronic epilepsy

Population cohort of 245 children in Turku with epilepsy followed for 40 years

½ had epilepsy due to CNS damage

SUDEP: the epidemiology

7 - 9% died of SUDEP

Accounted for 38% of deaths

Active seizures the key risk

Median age of SUDEP 25y

Figure 2. Cumulative Risk of All Epilepsy-Related Deaths and Sudden, Unexplained Deaths in Subjects with Epilepsy.
Data shown are for patients at risk (i.e., receiving medication, with or without 5-year terminal remission).
Danish nationwide study of SUDEP

Determined all sudden deaths 2000-2006 in people aged 1-35

National epilepsy registry

National death registries

33,000+ : with epilepsy

3 million without epilepsy

Holst Epilepsia, 54(9):1613–1620, 2013
Sudden expected death incidence rates

With epilepsy

41 per 100,000 person-years (32-55)

Definite SUDEP

72 per 100,000 person-years (59-89)

+ Probable
+ Possible

Without epilepsy

0.8 per 100,000 person-years (0.68-0.95)
Sudden expected death incidence rates

Age 1- 18 17 per 100,000 (10-33)
Age 24-35 72 per 100,000 (53-104)

Holst Epilepsia, 54(9):1613–1620, 2013
Danish study: age matters

Supervision?

Nature of adult seizures?
Risk varies depends on type of epilepsy

Shorvon Tomson Lancet 2011
Risk factors

- Young adults > children and elderly
- Tonic-clonic seizures
- High seizure frequency
- Nocturnal seizures
- Prone position
- Complex epilepsy with intellectual disability
- Drug changes or withdrawal
### Re-analysis combining GTC and Drugs
Hersdorfer D. Epilepsia 2013

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GTC per year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>5</td>
<td>2.9 - 8.7</td>
</tr>
<tr>
<td>&gt;3</td>
<td>15</td>
<td>10 - 24</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mono</td>
<td>0.5</td>
<td>0.3 - 1</td>
</tr>
<tr>
<td>2 drugs</td>
<td>0.9</td>
<td>0.4 – 1.8</td>
</tr>
<tr>
<td>3 drugs</td>
<td>2.0</td>
<td>0.9 - 4</td>
</tr>
</tbody>
</table>
## Re-analysis combining GTC and Drugs

Hersdorfer D. Epilepsia 2013

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AED</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other AED</td>
<td>0.7</td>
<td>0.4 – 1.4</td>
</tr>
<tr>
<td>Lamotrigine mono-therapy</td>
<td>0.9</td>
<td>0.1 – 3.6</td>
</tr>
<tr>
<td>Lamotrigine poly-therapy</td>
<td>2.0</td>
<td>0.4 -2.2</td>
</tr>
</tbody>
</table>
Summary so far

• SUDEP is mainly found in young adults

• Tonic-clonic seizures a key risk

• AED Treatment is not a risk factor
Mechanisms

135 SUDEP cases

80 found dead in bed
35 found dead elsewhere in home
5 found dead outside home
15 witnessed

Langan Y. J Neurol Neurosurg Psychiatry 2000;68:211–213
Witnessed SUDEP

15 deaths witnessed:

12/15 after tonic-clonic seizure

2/15 early post-ictal collapse

13/15 resuscitation attempted

12/15 “difficulty breathing”
The role of supervision

310 students 1970-1993
4000+ person-years follow-up
28 deaths
20 epilepsy related
14 SUDEP

All when not monitored by school

Potential cardio-respiratory mechanisms

Respiratory
- Central apnoea
- Obstructive apnoea
- Neurogenic pulmonary oedema

Cardiac
- Asystole
- Tachy-dysrhythmias (Long QT, VT)
What happens to pO2 in seizures?

Bateman 2008

304 seizures

- P0² < 90: 33%
- P0² < 80: 10%
- P0² < 70: 4%

Partial and generalized seizures

Usually central apnoea
What happens to heart rate in seizures?

Rugg Gunn 2004

20 patients implanted with loop recorders for 24 months

377 seizures

Tachycardia the usual response

2% of seizures significant bradycardia (<40bpm)

4 patients had a significant pause
Mortemus study

Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study


• Retrospective survey of EEG, ECG and Respiratory data on all deaths on epilepsy monitoring units
• 1968 – 2007
• Many patients undergoing drug reduction to trigger seizures
### Mortemus study

#### Definitions

<table>
<thead>
<tr>
<th>SUDEP</th>
<th>Definite: PM</th>
<th>Probable PM-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Near SUDEP</td>
<td>SUDEP like-event but lived &gt;1 Hr. with CPR</td>
<td></td>
</tr>
<tr>
<td>Fatal Near SUDEP</td>
<td>near SUDEP evolving to death</td>
<td></td>
</tr>
</tbody>
</table>
Mortemus study: Deaths

29 cardio-respiratory arrests
  16 SUDEP
  9 near SUDEP (2 died)
  4 other causes

Risk of 2 in 10,000 V-EEG recordings

Equivalent to 7 per 1000 patient-years
Deaths: key characteristics

A GTC preceded all SUDEPs

All SUDEPs were on drug reduction. Many 100%

All SUDEPs at night. Most prone.

Cardio-respiratory arrests detected <3 minutes survived

SUDEPs all persisted more than 10 minutes before CPR
Physiological pattern

1. Profound Post-ictal EEG suppression
Physiological pattern

1. Profound Post-ictal EEG suppression
2. Early brief tachypnoea (? 2° to ictal hypoxia)
3. Drop in respiratory rate
4. Bradycardia / asystoles
5. Terminal apnoea
6. Terminal asystole
The cardio-respiratory pattern of SUDEP

Type 1 sequence
Brief Tachypnoea ➔ apnoea ➔ bradycardia then asystole
The Cardio-respiratory pattern of SUDEP

Type 2 sequence
Tachypnoea ➔ Apnoea ➔ recovery ➔ relapse then asystole
Hypothetical sequence

Preictal  Seizure  Postictal
Focal seizure  Bilateral seizure  PGES

EEG1
EEG2
ECG
bpm

TV

PO₂  PCO₂

Partial pressure (torr)

Massey CA 2014
Mechanistics insights from the Lab

1. In sheep model of status epilepticus some die of apnoea

2. DBA/2 Sound – induced mouse seizure model
   5HT2c knockout mouse
   Both have seizures and die of apnoea
   Some protective effect of SSRIs

3. 5HT Brainstem neurons involved in respiratory burst firing and chemo-sensation

Sowers LP. Respiratory Physiology & Neurobiology 189 (2013) 315–323
1. Tonic-clonic seizures can induce profound cardio-respiratory depression

2. Inhibition of brain-stem cardio-respiratory centers is a possible mechanism

3. Young adults, nocturnal seizures and absence of medication are risk factors
So what about pregnant women?
Saving mothers’ lives 2011

2006-2008 Deaths

154 Indirect    14 due to epilepsy

9 on Lamotrigine

No levels. Dose increase made in 3

Sub-therapeutic levels at PM

Lack of specialist input and social deprivation
14 deaths: 12 SUDEP
3/14 controlled epilepsy
2/14 pre-conception counselling
7/14 epilepsy review in pregnancy
10/14 care could have been improved
Lamotrigine 4/14
Socio-economic factors
Recommendations

• Joint obstetric and neurological care (epilepsy specialist nurses)
• Guidelines are urgently required
• Do not accommodate pregnant women in single rooms
• Pre-conception counseling for women with epilepsy is not always provided effectively and should be robustly delivered in all care settings on an opportunistic basis.
Prevention in pregnancy: reducing seizures

Optimize seizure control

Prevent risky drug withdrawal at onset of pregnancy

Improve compliance

Stratify risk

Avoid break-through seizures due to falling Lamotrigine levels

Anticipate early fall of Lamotrigine and increase dose from week 10.

Aim 100% dose increase. 4 weekly levels
Prevention – responding to seizures

First aid

Turn from prone to recovery position

Stimulation if apnoea is present

? Supplemental oxygen

Lattice pillows
SUDEP: Prevention – devices work

Seizures alarms

EMFIT

11/13 Nocturnal GTC detected

Van Poppel E. Prospective study of EMFIT monitor
Journal of Child Neurology 2013
Talking about SUDEP

How well do we do?

What to people with epilepsy want to know?
What do UK neurologists say?

<table>
<thead>
<tr>
<th>How often is SUDEP discussed?</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always</td>
<td>5</td>
</tr>
<tr>
<td>Majority</td>
<td>25</td>
</tr>
<tr>
<td>Very Few</td>
<td>61</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
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N=385  Morton JNNP. 2006;77:199-202
# Surveys of SUDEP disclosure

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Disclosure</th>
<th>%</th>
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<tbody>
<tr>
<td>Dundee 2009</td>
<td>13/345</td>
<td>4%</td>
</tr>
<tr>
<td>Dundee 2012</td>
<td>81/240</td>
<td>34%</td>
</tr>
<tr>
<td>Paediatric sample</td>
<td>Some</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>All children</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Parents opinion</td>
<td>91% Yes</td>
</tr>
</tbody>
</table>

Gatatri, N. Epilepsia 2010
‘If you’re gonna die, you’re gonna die’: Young adults’ perceptions of sudden unexpected death in epilepsy.
Harden J. 2015

- Survey of 27 young people who had been told about SUDEP
- All agreed they should be informed at diagnosis
- Most coped with the knowledge
- Few sought other information
- Several had misunderstandings

“I think, everyone should have access to information and not be, like, have things withheld from them cos I think it kind of causes a bit of mistrust . . . being told what you should and should not know isn’t good”.
Fatalism and “it happens to others”

There’s not a lot you can do. If you’re gonna die, you’re gonna die (Max, 21).

I’m kinda, a believer in fate type of thing, so if something’s gonna happen, it’s gonna happen anyway, but . . . you can’t really live your life in fear of what might happen (Liam, 19)

‘Folk that are taking one [seizure] like every week, twice a week, they would be at risk’.

Harden J. Chronic illness 2015
Tonberg A. Epilepsy and behavior 2015
Talking about SUDEP

Proactively discuss SUDEP in most if not all cases especially in any in which there seems an increased risk (poor compliance, ceased treatment, GTC)

- average well controlled case 1:1000 annual risk
- compares with 1:10,000 risk of pregnancy

Discuss balance of risk at pre-conception counselling

Teach first aid measures
Conclusions

1. SUDEP is a rare but tragic complication of epilepsy
2. The key risk factors are now clear
3. Better seizure control and supervision after GTC are the main interventions
4. We should be informing women better; they wish to know
5. The challenge is making it happen

Review References