What Causes SUDEP
Thursday September 12, 2013

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Poll Question #1
Mortality in Epilepsy

• People with epilepsy have a 2 to 3 times increased risk of death

• Risk factors
  – underlying condition; symptomatic epilepsy
  – active epilepsy
  – AED adherence
  – medical intractability

Lhatoo, et al. 2001; Rakitin, et al. 2010; Sillanpaa and Shinnar 2010; Nickels and Wirrell 2010
• 245 children with a diagnosis of epilepsy in 1964; prospectively followed for 40 years
• 24% mortality: 3 X general population
  – Active epilepsy
  – Symptomatic epilepsy
What is SUDEP?

1. Deceased had epilepsy, defined as recurrent unprovoked seizures.
2. Death occurred unexpectedly, while the person was in a reasonable state of health.
3. Death occurred suddenly, with an understanding that following successful resuscitation, a death may occur at a later time as a consequence of the fatal event.
4. Death may have been witnessed or unwitnessed.
5. Evidence of a preceding seizure is not required.
6. Death occurred during normal activities in benign circumstances.
7. Death was not the consequence of documented status epilepticus, drowning, or trauma.
8. Postmortem examination did not demonstrate a cause of death.

See Nashef, et al, Epilepsia, 2011
Incidence of SUDEP

• 0.09 to 2.3 per 1000 patient-years in pop’n based studies
• Up to 9.3 per 1000 patient-years in refractory epilepsy and candidates for epilepsy surgery
• 7% risk of SUDEP over a 40 year follow-up period of childhood onset epilepsy

Tomson, et al. 2008; Dasheiff, et al. 1991; Sillanpaa and Shinnar 2010
Incidence in children

- Lower than in adults
- Up to 0.43 per 1000 patient-years of epilepsy
- > 10 times the rate of sudden death in children in general

Expecting the unexpected

- Highest risk:
  - adults
  - early onset epilepsy
  - refractory GTC seizures
- Seizure reduction, particularly GTC reduction, is most important treatment goal
Poll Question #2
What causes SUDEP??

• Definitive cause unknown
• More than one cause is certain
Theoretical considerations for mechanism of SUDEP

Intrinsic factors:
- Altered heart function/structure
- Altered brain function/structure
- Autonomic dysfunction
- Genetic factors
- Precipitating Seizure
- Prolonged postictal state

Extrinsic factors:
- AED management changes
- Poor AED adherence
- Sleep environment
- Lack of supervision

EPILEPSY

Respiratory arrest
Cardiac arrest
Electrocerebral shutdown

SUDEP
How can we study SUDEP?

• People living with epilepsy
  – During seizures
  – Between seizures
How can we study SUDEP?

• People living with epilepsy
  – During seizures
  – Between seizures

• People with epilepsy that have died
  – During intensive monitoring and hospitalizations
  – By interviewing families, reviewing records
  – By detailed post mortem studies/autopsy
How can we study SUDEP?

• People living with epilepsy
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• People with epilepsy that have died
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• Study people during life and after death
  – Prospective
  – Retrospective
Biomarkers for SUDEP

• Something measurable that identifies disease
  – Genetic
  – Cardiorespiratory
  – Neurophysiologic

• Aid in risk prediction and prevention
Current Theories and Research advances
Poll Question #4
Genetic Biomarkers

• Long QT syndrome (LQTS) is a well-recognized cause of sudden unexplained death in young people
• LQTS can be caused by mutations in 10 or more genes, including eight ion channels
• Ion channels also cause epilepsy
• Could a single ion channel mutation underlie epilepsy and cardiac arrhythmias and predispose to sudden death?
Arrhythmia in Heart and Brain: KCNQ1 Mutations Link Epilepsy and Sudden Unexplained Death

A. M. Goldman, E. Glasscock, J. Yoo, T. T. Chen, T. L. Klassen, J. L. Noebels*
(Published 14 October 2009; Volume 1 Issue 2 2ra6)

Neurobiology of Disease

Kv1.1 Potassium Channel Deficiency Reveals Brain-Driven Cardiac Dysfunction as a Candidate Mechanism for Sudden Unexplained Death in Epilepsy

The Journal of Neuroscience, April 14, 2010 • 30(15):5167–5175 • 5167

Edward Glasscock,1 Jong W. Yoo,1 Tim T. Chen,1 Tara L. Klassen,1 and Jeffrey L. Noebels1,2,3
Departments of 1Neurology, 2Neuroscience, and 3Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas 77030
SIDS brainstem hypothesis

• SUDEP has been compared to Sudden Infant Death Syndrome
• Both occur most often from sleep and no cause of death is found
• Some babies who die of SIDS have an abnormality of the brainstem... could this apply to SUDEP?
• Mouse seizure model
  – 75% stop breathing after a seizure
  – Prevent breathing problem with a drug that acts on a neurotransmitter implicated in SIDS

Tupal and Faingold, 2006
How Does SUDEP Occur?

• The causes of SUDEP may be different in different individuals

• Studies focus on three main mechanisms:
  • Electrical shutdown of the brain
  • Problems with the heart
  • Problems with breathing
Cerebral Electrical Shutdown (CES)

- In some patients who died of SUDEP while having EEG recordings, the EEG became flat after the terminal seizure, though the patient continued to breathe and the patient’s heart continued to beat for a period of time.

- This suggested that electrical shutdown of the brain might lead to failure of the heart and breathing resulting in death.
The Heart and SUDEP

- Heart rate often increases (tachycardia) with a seizure
  - The severity of this may be associated with SUDEP risk
- Less commonly, heart rate slows (bradycardia) or stops beating (asystole) with a seizure
- Other abnormal heart rhythms can occur during or after a seizure
- Some individuals have specific genetic mutations that predispose them to irregular heart rhythms and seizures
- Some patients with abnormal heart rhythms during or after seizures have had pacemakers implanted

Before a Seizure

After a Seizure
Takotsubo Syndrome

• Acute cardiomyopathy in response to stressful conditions
  • Reported with GTCS & status epilepticus
• Fatal in 8% - embolism, shock, heart failure, arrhythmia, sudden death

*Dupuis, et al. Seizure 2012. TKS: A possible mechanism of SUDEP.*
Breathing and SUDEP

• Breathing problems are commonly reported in witnessed SUDEP and near-SUDEP cases
  • Apnea (breathing stops)
    • Central (problem in the brain)
    • Obstructive (problem in the airways)
  • Hypoxia (low oxygen), hypercapnia (high carbon dioxide)
  • Increased secretions
  • Pulmonary edema
  • Laryngospasm
  • Suffocation
Hypoxemia and Hypercapnia

Seyal, et al., 2010. Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns.
Breathing and SUDEP

• Potential effects of hypoxia:
  • Somnolence
  • Initially increased heart rate and blood pressure
  • Later decreased heart rate and blood pressure
  • Seizures, coma, death

• Potential effects of hypercapnia:
  • Acidosis and hypoxia
  • Abnormal heart rhythms
  • Decreased blood pressure
  • Increased intracranial pressure
  • Confusion, headache, coma, seizures, death
The heart is more likely to slow down or stop beating if breathing is depressed. Abnormal heart rhythms are more likely to occur with hypoxia and hypercapnia.

Abnormal heart rhythms impair blood flow to the brain. The brain exerts control over both heart rhythms and breathing patterns. Hypoxia and hypercapnia depress brain function (and make the EEG flatter).

The heart is more likely to slow down or stop beating if breathing is depressed. Abnormal heart rhythms are more likely to occur with hypoxia and hypercapnia.
Lessons from the EMU: MORTEMUS

• Survey of epilepsy monitoring units in Europe, Israel, Australia, and New Zealand to identify and review deaths and near-deaths occurring in these units

• Review of previously reported SUDEP cases from other EMUs

# MORTEMUS
MORTality in Epilepsy Monitoring Unit Study

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Lessons from MORTEMUS

- 29 cardiorespiratory arrests
  - 18 SUDEP (14 at night)
  - 7 near-SUDEP
  - 4 not SUDEP (2 SAH, MI, brain oedema)

- Seizure (most often GTCS) followed by:
  - A period of rapid breathing, then
  - Transient or terminal cardiorespiratory dysfunction within 3 minutes
  - Where transient, apnoea recurred within 11 min of the end of the seizure, followed by cardiac arrest

What causes SUDEP—Are we there yet??

• The search is on…
  – Genetic
  – Cardiorespiratory
  – Neurophysiologic

• More than one cause is likely
Poll Question #4
Prevention

• Seizure reduction, particularly GTC reduction, is most important treatment goal
• Taking prescribed anticonvulsant medications regularly and reliably
• Identifying and avoiding triggers for seizures
• Keeping regular appointments with healthcare team
• Considering other epilepsy treatments when medications are not sufficient to control seizures