Deaths in Epilepsy and Autopsy

Eleonora Aronica

Department of (Neuro)Pathology, AMC, University of Amsterdam
Outline

- Epilepsy, seizures (Classification and Terminology)
- Post Mortem pathologies (as cause of Epilepsy)
- Epilepsy-related mortality
- Sudden unexpected death in epilepsy (SUDEP)
- Post Mortem examinations in Epilepsy
  Deaths associated with epilepsy: the role of the autopsy
Epilepsy is one of the world's oldest recognized conditions (Hippocrates ~ 400 BC)

About 50 million people worldwide have active epilepsy with continuing seizures that need treatment

30% of patients are drug-refractory

High co-morbidity

High risk of premature death
An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
Epilepsy:
Epilepsy is considered to be a disease of the brain defined by any of the following conditions:

(1) At least two unprovoked seizures occurring >24 h apart

(2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

(3) diagnosis of an epilepsy syndrome.
How frequent is epilepsy?

**Incidence:** 45/100,000/yr

**Prevalence:** 0.8-1%
Classification of the epilepsies

ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

- Seizure types:
  - Focal
  - Generalized
  - Unknown

- Epilepsy types:
  - Focal
  - Generalized
  - Combined Generalized & Focal
  - Unknown

- Etiology:
  - Structural
  - Genetic
  - Infectious
  - Metabolic
  - Immune
  - Unknown

Co-morbidities

Epilepsia, 1–10, 2017 doi: 10.1111/epi.13709
Investigations for epilepsy

Epilepsy suspected → referral to neurologist → to epilepsy specialist

- Scalp EEG
- Video telemetry
- Depth electrodes/ intracranial monitoring
- Neuroimaging: structural MRI
  - MRI-EEG combined
- Functional Imaging

The WADA Test
Epilepsy

Can neuropathological examination determine epilepsy/seizures without a clinical history?

No: Epilepsy/seizures is a clinical diagnosis.

Specific alterations identified at post mortem could indicate the patients had epilepsy/seizures (highly epileptogenic pathology).
Structural causes of epilepsy

- Trauma
- Cerebrovascular disorders
- Inflammatory and infectious disorders
  (bacterial meningitis, viral encephalitis, parasitic infections; Rasmussen’s encephalitis; Multiple Sclerosis)
- Neurodegenerative and genetic disorders
  (Alzheimer’s disease; progressive myoclonic epilepsies)
- Metabolic disorders
- Tumors (astrocytomas, glioneuronal tumors)
- Hippocampal sclerosis
- Malformations of cortical development
Structural causes of epilepsy

- Congenital: 20%
- Tumor: 9%
- Vascular: 15%
- Trauma: 3%
- Infection: 10%
- Neurodegeneration: 3%

< 15 jaar

35-65 jaar
Epilepsy Mimics

Misdiagnosis of epilepsy in 2-30%

• **Syncope** (vasovagal, cardiogenic, orthostatic)
  – Myoclonic jerks in 15%
  – Tongue biting less common than with seizures

• **Drop attacks**
  – Intermittent obstructive hydrocephalus
    • **Colloid cyst**, Arnold-Chiari Malformation, etc

• **Pseudo-seizures**
  – Non-epileptic convulsions

• Other neurological conditions
Epilepsy Mimics

Misdiagnosis of epilepsy

40 year old female with a history of episodes of collapse and a clinical diagnosis of epilepsy under investigation. She was found death in bathroom.
Epilepsy: A benign condition?

The mortality of epilepsy

- Consistent evidence of premature mortality in people with epilepsy
  - In developed countries 2-3 fold increase over the general population

- Greatest in the young and those with chronic epilepsy
  - 20-40 years: standardized mortality ratios (SMR) 5-8
  - Chronic epilepsy: SMR 8-15

- Greater in Resource-poor settings
  - Young in rural China: SMR>20
  - Young in Georgia: SMR > 5

OCCASIONAL PAPER
The lifelong course of chronic epilepsy: the Chalfont experience

Jan Novy,1,2 Marco Belluzio,1,3 Luís Olávio Caboclo,1,3 Claudia B. Catarino,1
Mahinda Yogarajah,1 Lillian Martinian,1,3 Janet L. Peacock,4 Gall S. Bell,1 Matthias J. Koepp,1
Maria Thom,1,3 Josemir W. Sander1,5 and Sanjay M. Sisodiya1

235 subjects
Chalfont Centre for Epilepsy: 122 PM.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Chalfont patients N=122</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>35%</td>
</tr>
<tr>
<td>SUDEP</td>
<td>18%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>10%</td>
</tr>
<tr>
<td>Gl cause</td>
<td>7%</td>
</tr>
<tr>
<td>ICH</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombo-embolism</td>
<td>3%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3%</td>
</tr>
<tr>
<td>Cancer</td>
<td>3%</td>
</tr>
<tr>
<td>Other vascular</td>
<td>2%</td>
</tr>
</tbody>
</table>
Epilepsy: Co-morbidities

Epilepsy may cause premature death indirectly through co-morbid conditions

• High prevalence of physical and psychiatric co-morbidity

• Higher risk of
  – vascular disorders (hypertension, strokes, MI),
  – cancer
  – G-I disorders
  – dementia
  – sleep apnoea, migraine
  – tumours
  – injuries and fractures

Classification of epilepsy-related deaths

Deaths directly due to epilepsy

- Sudden unexpected death in epilepsy (SUDEP)
- Status epilepticus
- Drowning
- Motor vehicle accidents
- Falls, burns, and other seizure-related accidents
Classification of epilepsy-related deaths

Deaths due to acute symptomatic seizures

- With or without status epilepticus, occurring within 1 week of stroke, traumatic brain injury
- Anoxic encephalopathy, or intracranial surgery
- First identification of subdural hematoma or CNS infection
- Active phase of multiple sclerosis or other autoimmune disorders
Deaths indirectly due to epilepsy

- Aspiration pneumonia
- Suicide
- Cardiovascular disease that may be exacerbated or caused by antiseizure drugs
Classification of epilepsy-related deaths

Deaths due to underlying neurologic disease

- Brain tumor
- Stroke
- Metabolic/genetic and neurodegenerative diseases
- CNS infections
Epilepsy-related death is often underestimated

- Failure to identify sudden unexpected death in epilepsy
- Failure to ascertain a history of epilepsy
- Failure to recognize proximate role of seizure
- Failure to recognize the ultimate role of antiepileptic drugs

Underestimation of epilepsy-related mortality

Inconsistency between the stated and true cause of death

Epilepsy not mentioned in cause of death

Examination inadequate (no neuropathological examination)
Desirable information prior to post mortem examination

- Epilepsy syndrome / cause
- Type of seizures
- Frequency of seizures
- Age of onset
- Investigations - EEG, MRI
- Family history / genetics
- AED (anti-epileptic drug history)
- Co-morbidities
The role of Autopsy

- To establish that epilepsy has caused or contributed to:
  - death as a result of status epilepticus
  - death as a result of an accident during a seizure
  - death as a result of aspiration during a seizure
  - death as a result of epilepsy treatment
  - sudden and unexpected death associated with epilepsy (SUDEP – see definition below).

- To exclude other causes of death which might mimic SUDEP, e.g. sudden cardiac death.

- To identify the cause of the epilepsy if present, e.g. neuropathological lesion, acute intoxication.

- To provide accurate data for the inquiries into the incidence of and remedial factors around epilepsy-associated deaths.

Royal College of Pathologists UK, Guidelines on Autopsy Practice (Scenario 6: Deaths associated with epilepsy) 2006 / (www.rcpath.org)
Can identify:

**Cause:** Brain pathology likely causing the seizures

**Effect:** Brain pathology as a result of seizure(s)
Hippocampal Sclerosis

ILAE type 1 HS
(Blumcke et al., 2013)
(Classical pattern)
Focal malformations of cortical development

ILAE classification (Blumcke et al., 2011)
(FCD IIB)
Tuberous sclerosis complex (TSC)

Multisystem genetic disease

Boer et al, Neuropathology. 2008

Germline mutations of TSC1 (9q34) or TSC2 (16p13.3)
Long term epilepsy associated tumours (LEAT)

Dysembryoblastic neuroepithelial tumour
Brain tumors and epilepsy-related deaths

Audit of practice in sudden unexpected death in epilepsy (SUDEP) post mortems and neuropathological findings


145 PM reports in SUDEP

Tumours/lesions

DNT, oligodendrogloma, PA, meningioma, astrocytoma II, ganglioglioma
Evidence of old Traumatic Brain Injury

Vascular versus Traumatic Axonal Injury
Evidence of old cerebro-vascular accident
50-year old man
Age at epilepsy onset: 8 yrs
Dravet syndrome

49 m (epilepsy, mental retardation, autism)
Age at epilepsy onset: 4 months
Old CVA; cyst cerebellum (pilo. astrocytoma)
Cholangiocarcinoma

- CEarly onset fever- or temperature-sensitive seizures → evolve into generalised and other Sz
- Many die prematurely and high risk of SUDEP (60% of cases)
- 80% have loss-of-function mutations in SCN1A (NaV1.1) - in interneurones
- SCN1A expressed in both heart and brain
Infections of the CNS
- Viral Infections
- Bacterial Infections
- Fungal Infections
- Protozoal Infections
- Helminthic Infestations

Rasmussen’s encephalitis
- Unknown aetiology childhood onset of seizures
- Seizures and progressive deterioration of motor and cognitive function
- Presumed T-cell mediated
- Cortical inflammation restricted to one brain hemisphere
- Regions of inflammation (active) and scarring (burnt-out)

Antibody mediated / autoimmune encephalitis
- Paraneoplastic / non-paraneoplastic
- Amnesia, confusion and often prominent seizures.
- VGKA, NMDA, GAD AMPA receptor antibodies
- Respond to immunotherapy rather than AEDs
- Limbic pattern or (mild) generalised encephalitis

Inflammation in Epilepsy
- Secondary to seizures
- Increased in specific pathologies
  - Tumours
  - FCD
  - Hippocampal sclerosis
Effects of Status epilepticus.

Cortical lamina necrosis/gliosis
Hippocampal gliosis/atrophy and other regions

Vulnerable regions to seizures:
Neocortex
Cerebellum
**Hippocampus**, Amygdala
Thalamus and networks
Loss of recent memory

**Epilepsy/SE/hippocampus**

45-year old woman

- Memory complaints, depression/mania
- Pharmacoresistant epileptic seizures: CPS/status epilepticus (7 x yrs; 4 years)
- MRI: multiple white matter lesions

**Progressive atypical MS**

Memory deficits (no new memory)
Sudden death (after 10 yrs)
Bilateral hippocampal sclerosis
Acute encephalopathy and status Epilepticus

3-year old girl

One week before to be admitted to the hospital she had fever for 2 days (also the sister)

Onset of seizures, the seizures rapidly exacerbated into uncontrolled SE (3x) diazepam, fenytoine en midazolam; topiramaat, Keppra, sabril, vigabatrine en ketamine; barbiturate (phenobarbital) coma.

Intensive care (27 days)

DD

Infectious disease, Metabolic disorders, intoxication, Autoimmune neurologic disease: excluded
Acute encephalopathy with inflammation-mediated status Epilepticus

Fever-induced refractory epileptic encephalopathy in school-aged children (FIRES)
Deaths directly due to epilepsy

- **Sudden unexpected death in epilepsy (SUDEP)**
- Status epilepticus
- Drowning
- Motor vehicle accidents
- Falls, burns, and other seizure-related accidents

Post mortem in SUDEP

Royal College of Pathologists UK, Guidelines on Autopsy Practice (Scenario 6: Deaths associated with epilepsy) 2006/(www.rcpath.org)
SUDEP

Sudden, unexpected, un-witnessed or witnessed, non-traumatic and non-drowning death in a patient with epilepsy, with or without evidence for a seizure and excluding status epilepticus, where post-mortem examination does not reveal a cause for death.

- Victim suffers from epilepsy (recurrent, unprovoked seizures)
- Victim died suddenly while in a reasonable state of health
- The death occurred suddenly (in minutes) when known
- The death occurred during normal activities and benign circumstances (i.e. no trauma/drowning)
- An obvious cause of death was not found
Patients at risk for SUDEP

SUDEP is the leading cause of death in patients with intractable epilepsies and accounts for 40–50% of mortality

- Frequent generalised tonic-clonic seizures
- Multiple anti-epileptic drug treatments
- Male
- Age group 20-40 years

Incidence:

Patients with drug resistant epilepsy: 1.2 to 9 / 1000 person years
Mean annual SUDEP incidence: 3.7 / 1000 person years
Cause of SUDEP

Precise mechanism unknown
Heterogenous / multifactorial
Peri-ictal event

Cardiac Autonomic Dysregulation
Ictal bradycardia
Asystole or ‘cardiac pause’
Heart rate variability reduced (nocturnal)
Ictal tachycardia
Peri-ictal hypotension
Catecholamine surges during GTCS

Respiratory dysregulation
Apnoea
Hypoventilation
Hypoxaemia & hypercapnia

Post ictal generalised EEG suppression (PGES)
Serotoninergic mechanisms ?
SUDEP categories

A full autopsy with histology, neuropathology examination and toxicology is required for the diagnosis SUDEP

<table>
<thead>
<tr>
<th>Definite SUDEP</th>
<th>Negative post mortem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable SUDEP</td>
<td>No or incomplete post mortem examination</td>
</tr>
<tr>
<td>Possible SUDEP</td>
<td>A competing cause of death is identified</td>
</tr>
<tr>
<td>Near SUDEP</td>
<td>Survives for &gt; 1 hour following CPR during seizure</td>
</tr>
<tr>
<td>Unclassified</td>
<td>Incomplete information e.g seizure history</td>
</tr>
</tbody>
</table>

Desirable information prior to post mortem examination

How certain the diagnosis of epilepsy
- Investigations done - EEG, MRI, telemetry
- Type of seizures / cause of epilepsy
- Recent change in frequency of seizures
- Medications

• Other medical conditions
  • Alcoholism, heart disease etc.

• Circumstances of death
  • Witnessed, position of body, evidence of seizure?
Autopsy Findings in SUDEP

• **External Findings**
  – Tongue biting, injuries, bruises, burns
    • Lateral tongue bites (epilepsy)
    • Tip of tongue bites (syncope)
  – Petechial haemorrhages in the skin and conjunctiva (asphyxial signs)

• **Cardiovascular system**
  – Increased heart weight
  – Focal myocardial fibrosis (in some studies)

• **Respiratory system**
  • Pulmonary oedema and / or congestion
Examination of the brain in Epilepsy-related deaths

Temporal (T1, pole)
Frontal (cingulate, watershed, pole, basal)
Any lesion
Hippocampus (both sides, two levels) with parahippocampal gyrus
Amygdala,
Thalamus (Level AV nucleus)
Basal ganglia
Cerebellum (anterior and posterior lobe)
Brainstem (midbrain pons and medulla)

Rationale for selection
1. To exclude unsuspected pathology e.g. Meningitis/encephalitis
2. Seizure-related pathology
3. Causative lesion
4. Acute neuronal injury
5. Examine autonomic centres

Fix whole brain by suspension in 10% formalin prior to slicing for ~2 weeks

Royal College of Pathologists UK, Guidelines on Autopsy Practice (Scenario 6: Deaths associated with epilepsy) 2006 (www.rcpath.org)
Other samples required in Suspected SUDEP PM

• Screening for anti-epileptic drugs (blood samples, gastric contents, urine)
  – To determine drug levels, compliance or potential over-dosage
  – Interpretation may be complicated by PM redistribution
  – Hair sample analysis → reflect drug taking variability over longer periods

• Screen for alcohol and illicit drugs

• Vitreous for biochemistry – if diabetes or metabolic disorder
**SUDEP and Postmortem examination**

*Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy*  
Neurology 76  May 31, 2011

<table>
<thead>
<tr>
<th>Postmortem, including case identification</th>
<th>Education of, and collaboration with, medical examiners to increase recognition and documentation of SUDEP, and referral to central study sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Development of a standardized SUDEP protocol for autopsy and clinical data collection at time of death</td>
</tr>
<tr>
<td></td>
<td>Role of establishing SUDEP as a reportable condition with requirements for autopsy and tissue banking</td>
</tr>
<tr>
<td></td>
<td>Investigation of brainstem respiratory centers, including serotonergic system as in SIDS</td>
</tr>
<tr>
<td></td>
<td>Investigation and banking of DNA and tissues for genetic studies</td>
</tr>
<tr>
<td></td>
<td>Detailed cardiac studies, including thin slices for subtle fibrosis or other injury</td>
</tr>
<tr>
<td></td>
<td>Postmortem examinations with specific protocol, including investigation of brain, heart, lungs, and autonomic system, preferably at centralized site or sites</td>
</tr>
</tbody>
</table>
Should I retain the brain in epilepsy death?

- Neuropathological examination can reveal pathology relevant to seizure history
- May be helpful to family to identify cause of epilepsy
- Further genetic tests e.g. for channelopathies
- Tissue banks for use in research programmes
Conclusions and Future Directions

- The neuropathologist should be involved in the interpretation of the brain pathology.

- Implementation and harmonization (at the national and international level) of specific guidelines is essential:
  - to improve detection of underlying pathology relevant to the cause of epilepsy and death
  - for classification of definite SUDEP
  - for research on prevention of epilepsy-related mortality.
Roland D. Thijs

Post-mortem collection of material of SUDEP cases for a national genetic SUDEP database.