National Association of Medical Examiners Position Paper:

Recommendations for the Investigation and Certification of Deaths in People with Epilepsy

Middleton OM, Atherton D, <u>Bundock E</u>, Donner E, Friedman D, Hesdorffer D, Jarrell H, McCrillis A, Mena OJ, Morey M, Thurman D, Tian N, Tomson T, Tseng Z, Warner M, White S, Wright C, Devinsky O

Acad Forensic Pathol 2018 8(1):119-135 Epilepsia 2018;1-14

Why a Position Paper?

- Investigation and certification of deaths related to epilepsy varies within and between jurisdictions.
- Terms and criteria to diagnose and classify seizures, seizure disorders and epilepsy vary.
- There were no guidelines for investigation and certification of epilepsy-related deaths.

The incidence of death due to epilepsy is likely underestimated by death certificate data.

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Goals of Panel

- Improve investigation and surveillance of epilepsy-related deaths by establishing recommendations for the practice and interpretation of:
 - Death investigation
 - Autopsy and ancillary test performance
 - Certification
- Better inform public health burden of seizure and epilepsy-related death.

Seizures, Seizure Disorder, or Epilepsy?

- Seizures ≠ epilepsy.
- A seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
- Epilepsy is a *disease* characterized by an enduring predisposition to generate *unprovoked* seizures.
 - The term can be used whether or not an underlying etiology is known
 - Epilepsy may be due to a genetic, developmental, tumor infarct) or unknown cause

A person is considered to have epilepsy if they meet any of the following conditions.

- Two or more unprovoked seizures occurring greater than 24 hours apart, or
- One unprovoked seizure and a probability of further seizures occurring over the next 10 years, or
- Diagnosis of an epilepsy syndrome (e.g. West Syndrome/Infantile spasms, Dravet Syndrome, Juvenile Myoclonic Epilepsy, Lennox-Gastaut Syndrome etc.)

Fisher RS et al. A practical clinical definition of epilepsy, Epilepsia 2014; 55:475-48:

What is an "unprovoked" seizure?

Provoked seizure are caused by an acute, transient process

- drug/alcohol withdrawl or intoxication
- transient metabolic derangements (e.g. hypoglycemia, hyponatremia), or • high fever

Unprovoked seizures are caused by

- genetic or developmental disorders
- chronic acquired conditions (e.g. trauma, tumor, infarct), or • unknown causes

Risk Factors for Sudden Death due to Epilepsy

- Generalized Convulsive Seizures>Complex Partial Seizures
- Uncontrolled seizures
- Escalating seizure frequency
- Anti-epileptic drug non-compliance or recent need to increase AEDs
- Presence of structural brain lesions, intellectual disability, alcohol abuse, and anxiolytic use

Mumber Orection 1 Within the bounds of state law, which deaths require assumption of jurisdiction and performance of an autopsy? 2 What constitutes appropriate and necessary scene investigation, epilepsy screening, and follow up? 3 When is it appropriate or necessary to perform toxicology and/or anticpileptic scizure medication testing? 4 What are the best analytes to office for laboratory testing and histologic analysis? 5 How are scene findings, autopsy findings, toxicology, and histologic anterpreted?

- 6 How are competing causes of sudden death assessed?
 - 7 What are the optimal methods for determining and certifying cause of death, manner of death, and how injury occurred?

Acad Forensic Pathol 2018 8(1):119-135

Within the bounds of state law, which deaths require assumption of jurisdiction, and performance of an autopsy?

- ME/C authority to assume jurisdiction or responsibility for these determinations is typically mandated by their respective state statutes.
- Beyond statute, the ME/C exercises their professional judgement on jurisdiction, taking into account the circumstances of the death and resources available in their jurisdiction.

What constitutes appropriate and necessary scene investigation, epilepsy screening, and follow-up?

- Ask sufficient questions to determine
 - If decedent had convulsive or non-convulsive seizures
- If an underlying etiology for epilepsy was known
- Characteristics of seizures (frequency, duration, last seizure, triggers, medication efficacy and compliance)
- Detailed description of terminal seizure
 - Activity prior to seizure
 - Verbalizations, behaviors, movements prior to and while becoming unresponsive
 - Duration
 - State of consciousness during and after

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When is it appropriate or necessary to perform toxicology and/or anti-epileptic seizure medication testing?

- When a specific anatomic cause of death is not identified at autopsy
- Toxicology testing should include quantification of anti-epileptic drugs

What are the *best* samples to collect for laboratory testing and histologic analysis?

- Blood, tissue, and other fluid samples should be retained as per the jurisdiction's usual protocol for routine toxicology testing.
- EDTA (purple top) tube of blood is preferred
- Blood spot card or frozen tissue (1 cubic centimeter of liver, spleen, or heart at -80°C) can also be used

What are the *best* samples to collect for laboratory testing and histologic analysis?

- Brain examination after formalin fixation is recommended when possible.
 - Examination by a neuropathologist is preferred but at the discretion of the autopsy pathologist
 - autopsy pathologist.
 Recommended CNS histology, even in grossly normal brain:
 - Both hippocampi, Both amygdala, Watershed cortex, Basal ganglia, Hypothalamus, Midbrain, Pons, Medulla (Reichard and Vaubel, 2014)

 Heart – examined at autopsy/histology recommended
 Left ventricle x 3 and right ventricle x 1

 Left ventricle x 3 and right ventricle x 1 (Royal College of Pathologists)
 Lung – histology recommended

How are scene findings, autopsy findings,

The following topics are reviewed in position paper: • Livor pattern/Body position

- Tongue, Lip or Inner Cheek Trauma (supportive but not diagnostic)
- Incontinence of Urine
- Gastric Contents in Airway
- Pulmonary Edema
- Bronchopneumonia
- Neuropathologic Findings
- Alcohol and Drugs of Abuse
- Antiepileptic Drugs

- Comorbid Coronary Artery Disease
 Factors that support cardiac disease rather than epilepsy as the cause of death
 - Severe coronary stenosis,

 - Coronary thrombus,
 Coronary thrombus,
 Acute myocardial infarction in territories served by stenotic arteries, and/or Cardiomegaly / large ventricular chambers
 - When circumstances or findings suggest seizure (e.g., witnessed sz or tongue bite) but acute cardiac changes are present:
 - the elevated stress and sympathetic response to the seizure may have triggered the cardiac event
 - Can consider possibility of epilepsy as cause and acute cardiac even as mechanism.

- · Factors that support arrhythmogenic disorder rather than epilepsy as the cause of death
- Personal or family history of arrhythmogenic disorder
- Report of seizure activity following peak exercise
 Ventricular tachycardia or fibrillation documented by EMS favors cardiac etiology

and recording (certifying) cause of death, manner of death, and how injury occurred (including wording on the death certificate)?

- Sudden death in person diagnosed with epilepsy and no other cause identified, any of the following can be used for COD, but sudden nature should be emphasized:
 - "Sudden unexpected death in epilepsy" (SUDEP)
 - "Epilepsy"
- "Seizure disorder" may be substituted for "epilepsy" when clinical diagnosis is not provided or history is inconsistent.

Cause of Death Certification continued.

- When there is a known underlying etiology for the epilepsy, it should be indicated:
 - Sudden death due to epilepsy due to blunt trauma of head
 - Sudden death due to epilepsy due to cerebral infarct due to cerebrovascular disease.
- Cardiac or pulmonary disease considered insufficient to cause death may be included in contributory causes (Part II).

Cause of Death Certification continued.

In unwitnessed, apparently 'sudden' death with competing causes that may be mechanistically related, inclusion of both possibilities is recommended. Possible wordings may be:

- Person with epilepsy dead in bed with 90% atherosclerotic stenosis
- of coronary artery: Part I: Atherosclerotic Coronary Artery Disease Part II: Epilepsy
- Person with epilepsy and alcohol intoxication
 - Part I: Sudden death due to epilepsy Part II: Alcohol intoxication
 - (or vice versa depending on alcohol concentration)

- Person with epilepsy submerged in bathtub:
 Part I: Drowning, Part II: Epilepsy
 MOD: Accident
- Person with epilepsy due to prior brain injury:
 Part I: Sudden death due to epilepsy due to blunt trauma of head
 MOD: Accident, Homicide or Suicide depending on circumstances of head trauma

Table 3. Case Vignettes with Recommended Death Certificate Wording						
History	Cause of Death (Part I)	Other Signifi- eant Conditions (Part II)	How Injury Occurred	Manner		
Decedent with epilepsy found dead in bed; no other cause of death discovered	Sudden death due to epilepsy		N/A	N		
Decedent with epilepsy found dead in bed; competing cause of death such as severe coronary artery disease discovered	Atheroselerotic coronary artery disease	Epilepsy	N/A	N		
Decedent with epilepsy found dead in bed; contributing factor such as moderate coronary artery disease discovered	Sudden death due to epilepsy	Atherosclerotic coronary artery disease	N/A	N		
Decedent with epilepsy found dead in bed; ethanol concentration reported as 0.41 g/dL	Acute ethanol intoxication	Epilepsy	Decedent with epilepsy ingested an excess of ethanol	А		
Decedent with epilepsy due to blunt head trauma occurring from an accidental fall 10 years prior	Epilepsy due to blunt head trauma due to fall		Decedent with epilepsy found dead; suffered head injury in fall 10 years prior	А		
Decedent with epilepsy due to blunt head trauma occurring from an assault 10 years prior	Epilepsy due to blunt head trauma due to assault		Decedent with epilepsy found dead; suffered head injury in assault 10 years prior	Н		
Decedent with epilepsy found dead, submerged in bathtub; no other cause of death discovered	Drowning	Epilepsy	Decedent with epilepsy found submerged in bathtub	А		
Driver with epilepsy had witnessed seizure in motor vehicle accident; examination revealed no competing cause of death	Sudden death due to epilepsy		N/A	N		
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