The Royal College of Pathologists
Pathology: the science behind the cure

Guidelines on autopsy practice

Deaths in patients with epilepsy including sudden deaths

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Contents

Foreword

The autopsy guidelines published by the Royal College of Pathologists (RCPath) are guidelines that enable pathologists to deal with non-forensic consent and Coroner's/Procurator Fiscal post-mortem examinations in a consistent manner and to a high standard. The guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. Given that much autopsy work is single observer and 1-time only in reality, it has to be recognised that there is no reviewable standard that is mandated beyond that of the FRCPath Part 2 exam or the Certificate of Higher Autopsy Training (CHAT). Nevertheless, much of this can be reviewed against ante-mortem imaging and other data. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological case type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report an autopsy in a way that that maximises benefit to the pathologist, Coroner/Procurator Fiscal and the deceased's family.

There is a general requirement from the General Medical Council (GMC) to have continuing professional development (CPD) in all practice areas and this will naturally encompass autopsy practice. Those wishing to develop expertise/specialise in pathology are encouraged to seek appropriate educational opportunities and participate in the relevant external quality assurance (EQA) scheme.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The following stakeholders were consulted for this document:

- SUDEP Action UK
- Epilepsy Society UK
- Coroners Society of England and Wales
- The Crown Office Procurator Fiscal Service
- The Coroners Service for Northern Ireland
- ILAE British Chapter.

The information used to develop this autopsy guideline was derived from current medical literature and a previous version of this guideline. PubMed was used to conduct a search

using the terms ‘SUDEP’ and ‘epilepsy + post mortem’ and dates searched were between March 2019 and July 2024. Publications on post-mortem approaches and findings including molecular data and risk factors for SUDEP were included with an aim to include large series, systematic cohorts (rather than case reports) or meta-analysis published in high impact journals. Guidelines published by the International League Against Epilepsy (ILAE) and guideline documents issued by NICE were also consulted for information and references. Much of the content of the document represents custom and practice and is based on the substantial clinical experience of the authors. All evidence included in this guideline has been graded using modified SIGN guidance (see Appendix A.) The sections of this autopsy guideline that indicate compliance with each of the AGREE II standards are indicated in Appendix B.

No major organisational changes or cost implications have been identified that would hinder the implementation of the guidelines.

A formal revision cycle for all guidelines takes place on a 5-yearly cycle. The full revised version (incorporating the changes) will replace the existing version on the College website.

The guideline has been reviewed by the Professional Guidelines team, Death Investigation Committee, Neuropathology Specialty Advisory Committee and Lay Advisory Group. It was placed on the College website for consultation with the membership from 16 January to 13 February 2025. All comments received from the membership were addressed by the author to the satisfaction of the Clinical Lead for Guideline Review.

This guideline was developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Professional Guidelines team and are available on request. The authors have declared no conflicts of interest.

1 Introduction

Epilepsy is a common neurological condition. It may arise from many types of underlying brain pathology, from neurodevelopmental disorders in the young, to stroke and neurodegenerative diseases in adults. Epilepsy can also be a manifestation of a genetic disorder (for example, a channelopathy) or may be idiopathic, for which no brain lesion may be found. A diagnosis of epilepsy during life is based on 2 unprovoked seizures, or a

high risk for recurrent seizures following a single event or associated with a defined epilepsy syndrome.[1]

Epilepsy may be unrelated to the cause of death but, in many cases, it is directly relevant – for example, an accident during a seizure or sudden unexpected death in epilepsy (SUDEP). The rate of SUDEP is around 1 in 1,000 people with epilepsy per year.[2] Risk factors for SUDEP include more difficult to treat epilepsy, frequent generalised tonic-clonic seizure (including focal to generalised seizures), nocturnal seizures, poor adherence to anti-seizure medications (ASMs) or treatment change/interruption and psychosocial factors, including neurodevelopmental abnormalities, substance/alcohol abuse and living alone or with lack of supervision at night.[2]

SUDEP deaths are often unwitnessed and nocturnal; by definition, no cause of death can be ascertained at post mortem.[3] The mechanisms are unknown but a consensus, including evidence from witnessed SUDEP deaths on monitoring units,[4] favours a centrally mediated depression of respiratory and/or cardiac regulation. Mechanisms of SUDEP may vary according to the type of epilepsy. SUDEP can affect all age groups with emerging evidence that some sudden deaths in infancy and childhood may represent SUDEP.[5] Certain epilepsy syndromes, e.g. Dravet's syndrome, are associated with a higher SUDEP risk.[6]

Common challenges that can arise when conducting a post-mortem examination on a person with epilepsy or death associated with a seizure include:

- full clinical information may not be available at the time of autopsy regarding the epilepsy history and/or its underlying cause
- many deaths in epilepsy are unwitnessed and there may be a prolonged post-mortem interval, particularly if they lived alone
- brain retention protocols and coronial practice varies widely regarding epilepsy-related death
- death can be associated with a seizure without an epilepsy diagnosis (e.g. seizures provoked by alcohol, febrile seizures, etc.)
- death can be due to the disease causing epilepsy (e.g. malignant brain tumour, stroke)
- in SUDEP, the brain can show neuropathology and is not always normal, but this may not account for the sudden death (e.g. old contusion, low-grade tumour)

- in sudden deaths, attributing the relative contributions of other pathology identified (e.g. mild coronary artery disease) and epilepsy can be problematic
- SUDEP can go unrecognised with ‘unascertained’ or other terms used in their categorisation[7]
- a seizure does not have to occur (or be witnessed) for SUDEP categorisation in a patient with sudden death, epilepsy and a negative post mortem.

1.1 Target users and health benefits of this guideline

The target primary users of these guidelines are general pathologists, trainees and neuropathologists performing consented and coronial and Procurator Fiscal post mortems in persons with epilepsy. The recommendations will also be of value to the Coroner’s and Procurator Fiscal’s offices in dealing with epilepsy-related deaths and to epilepsy healthcare professionals and medical examiners.

2 The role of the autopsy

To establish whether epilepsy has caused or contributed to:

- death as a result of status epilepticus
- death as a result of trauma, including head injury, sustained during a seizure
- death as a result of drowning during a seizure
- death as a result of airway obstruction during a seizure
- death as a result of aspiration during a seizure
- death as a result of epilepsy treatment, e.g. anticonvulsant drug interaction, overdose or surgical treatments
- death as result of epilepsy-related suicide
- SUDEP (see definitions in section 14).

Other objectives:

- to exclude other causes of sudden or unexpected death, e.g. sudden cardiac death
- to exclude death from drugs, accidental poisoning or misdemeanor
- to identify or confirm an underlying cause of the epilepsy if present, as a focal brain lesion (tumour, cortical dysplasia, old contusion)

- to provide accurate data for inquests, families and audits into the incidence of SUDEP and epilepsy-associated deaths and identify remedial factors.

[Level of evidence – GPP.]

2 Pathology encountered at autopsy

Particular attention should be given to the presence or absence of the following in epilepsy-related deaths:

- external evidence of a seizure, e.g. incontinence, tongue biting
- evidence of traumatic injury sustained during a seizure, e.g. head injury, bruises, burns etc.
- brain swelling, focal brain abnormalities, e.g. tumours, cortical dysplasias, old stroke, hippocampal sclerosis etc.
- cardiac abnormalities that might be associated with sudden death (coronary artery disease, myocardial infarction, cardiomegaly, cardiomyopathy, myocarditis, etc.)
- pulmonary oedema, aspirated gastric contents
- pathology (brain and organ) related to an underlying epilepsy syndrome, e.g. tuberous sclerosis.

[Level of evidence – B.]

4 Specific health and safety aspects

No specific precautions beyond standard protocols are generally required in epilepsy post mortems. Local guidelines for the mortuary should be followed in each case to assess the risk based on available clinical information from the Coroner or Procurator Fiscal or hospital records. Personal protective equipment should be used as appropriate to minimise risks,[8] for example in epilepsy patients with coincidental HIV, hepatitis B and post mortems in suspected prion disease carried out according to local protocols. Some patients with epilepsy may have internal devices (e.g. vagal nerve stimulators) or pacemakers in situ (e.g. history of seizure-related arrhythmias/asystole).

5 Clinical information relevant to the autopsy

Before commencing the examination, information from the Coroner's officer, Procurator Fiscal or from the hospital records should be obtained as listed below, where available. Additional information may be obtained from GP records and the family, through the Coroner's office or Procurator Fiscal, and are often a key source of information. The autopsy report should contain a summation of all clinical information available to the pathologists at the time of issue of the final report. A separate neuropathology report from a specialist centre, cardiac pathology, genetic and toxicology reports can be integrated into the main report.

5.1 Circumstances of death

5.1.1 Deaths in the community

Witnessed deaths

Ascertain if death occurred during seizure or the recovery (post-ictal) phase, or if no seizure/convulsive movements were noted, only loss of consciousness. Gather any information on the duration of seizure and if prolonged (>5 to 30 mins), representing status epilepticus,[9] any resuscitation attempts made and survival time.

Unwitnessed deaths

Ask if any photographs were taken or information was available at scene, evidence of incontinence/vomiting, position of body (supine versus prone), evidence for suffocation/airways obstruction or compromise (e.g. pillow covering face or abnormal position of neck), circumstances that might have caused injury, deaths in bath/water (e.g. if head was submerged), or if death occurred during night/sleep including any information from seizure monitors/detection devices.[10] Information on the number of tablets in bottles and dates of prescribing/doses, eye-witness accounts. In addition, when the person was last seen alive and their state of health, recent seizures and any deterioration in control.

5.1.2 Deaths in hospital/care

- Details of recent seizure control, witness reports, any monitoring around the time or during death (electroencephalogram [EEG], cardiac, video, etc.), changes in medications or recent procedures (surgical interventions etc.), resuscitation and treatments and survival times.

5.2 Epilepsy history

- Details of age of onset, type and frequency of seizures.
- Details of any recent change in seizure frequency or severity.
- Details of ASMs, compliance and any recent changes to treatment (drug, dose, etc.), a history of non-drug treatments (e.g. vagal nerve stimulation, epilepsy surgery, previous ASM treatments) and a full drug history for other comorbidities should be taken.
- Cause of epilepsy (if known) and any information from hospital investigations (e.g. magnetic resonance imaging [MRI] and EEG findings), genetic conditions, family history.
- Any history of previous episodes of collapse (e.g. seizure-related asystole, near-miss SUDEP), status epilepticus or traumatic events associated with seizures.

  At the time of the post-mortem examination limited clinical information may be available regarding the epilepsy. Information should be gathered from the Coroner's office, family, GP/clinicians/care home workers etc. to obtain a full as history as possible, prior to the finalisation of the report.

5.3 Other relevant history

Key past medical history to ascertain, if available, that may help in the examination.

- Cardiac disease, abnormal electrocardiograms, syncopal attacks, family history of sudden cardiac death. Patients with epilepsy are at increased risk of cardiac disease.[11]
- History of previous traumatic brain injury or neurosurgery. In cases of post-traumatic epilepsy due to a previous criminal act, full discussion of the case with the Coroner or Procurator Fiscal and any legal implications is advisable prior to the autopsy.
- Alcoholism, psychiatric illness, learning difficulties, autism and clinical conditions associated with epilepsy.

[Level of evidence – B.]

6 The autopsy procedure

6.1 External examination

Attention should be paid to the following on external examination of the body.

- Body identification and preservation: identification of body and any decomposition (if unwitnessed death in the community).
- Hypostasis: distribution in relation to information of position of body when found.
- Medical intervention: signs of resuscitation (e.g. cannulas).
- Injury: documentation of external injuries/burns (old or recent) that may have been sustained during seizures and/or any surgical scars (including cranium).
- Mouth: evidence of tongue biting (tip or lateral sides of tongue, fresh or old scars) or any blood-tinged foam around mouth.
- Clinical stigmata: external evidence of syndromes/disorders such as neurofibromatosis, Sturge-Weber syndrome or tuberous sclerosis often associated with epilepsy.

[Level of evidence – GPP.]

7 Specific organ systems to be considered

In suspected epilepsy-related deaths, a full post-mortem examination, including neuropathology, organ histology and toxicology, is required. In some hospital deaths, organ donation may have taken place prior to post-mortem examination, dependent on suitability of organs and agreement with the Coroner/Procurator Fiscal. All organs that have not been previously harvested should be weighed and examined. In the post mortem, particular attention should be given to the following systems.

7.1 Cardiovascular system

- Structural cause for a sudden cardiac death including:
  - ischaemic heart disease/coronary artery disease
  - myocardial hypertrophy, cardiomyopathy, cardiomegaly
  - valve disease (refer also to *Guidelines on autopsy practice: Sudden death with likely cardiac pathology*).[12]

- Patients with epilepsy have a higher incidence of cardiac disease.[11]
- Although an increase of mild cardiac hypertrophy and fibrosis has been reported in SUDEP series, there is conflicting evidence.[12] Careful consideration is required for attributing minor cardiac pathologies as the underlying cause of death (see section 14).
- Channelopathies and genes causing long QT syndrome may be relevant to both sudden arrhythmic death syndrome with no gross cardiac pathology and epilepsy aetiology. Advice should be sought on referral of heart for specialist examination and genetic testing in suspected hereditary cardiac disease/sudden cardiac death, which has potential implications for family members[14] (see section 11).

7.2 Respiratory system

- Check airways and larynx for any obstruction or foreign bodies (exclude choking during seizure).
- Evidence of aspiration: gastric contents may be displaced in main airways – trachea and bronchi – in SUDEP; presence in distal airways may represent true aspiration.
- Pulmonary oedema and congestion have been consistently reported in SUDEP series to varying degrees, are regarded as a non-specific finding and are also identified in non-SUDEP deaths.[15]
- For bodies found in water (bath, swimming pool), with any evidence of drowning, including over-distended lungs and emphysema aquosum, refer also to *Guidelines on autopsy practice: Autopsy for bodies recovered from water*.[16]

7.3 Central nervous system

7.3.1 Assessments prior to brain slicing

- The scalp should be examined for any bruises or other injury.
- The skull should be examined for any fractures, previous surgery or healed trauma.
- The meninges and dura should be examined for any evidence of acute or old haemorrhage.
- The dural venous sinuses should be opened.

- Meninges should be assessed for evidence of meningeal infiltration (thickening, increased opacity).
- The circle of Willis should be examined for vascular disease.
- Brain swelling and any herniation (uncal, tonsillar, subfalcine or through a bone defect) should be evaluated. Mild degrees of brain swelling (effacement of gyri but without herniation) can occur in SUDEP, but brain weight is usually within normal range.[15,17]
- The surface of the brain should be examined for evidence of old contusions, previous surgery, arteriovenous malformation, tumours or other lesions.

7.3.2 Brain slicing (fixed or unfixed)

The aims of macroscopic brain examination are to:

- identify a potential structural cause of epilepsy:
  - common lesions identified in SUDEP and epilepsy autopsy series include hippocampal sclerosis, cortical malformations, vascular malformations /cavernomas, primary brain tumours, old scars/contusions, etc.
  - there is no clear evidence that any specific neuropathology lesion confers a greater risk of SUDEP.[18,19]
- identify the effects of previous/recent seizures
  - acute neuronal injury/eosinophilic neurones (can be absent, limited to hippocampus or extensive if the patient is resuscitated or survives for short time after the event)
  - cerebellar atrophy, thalamic atrophy
  - cortical atrophy/scarring from seizures (status epilepticus, mitochondrial disease, epileptic encephalopathies, autoimmune encephalitides)
  - evidence of neurosurgery
- identify any unsuspected (unrelated) cause of death
  - colloid cysts in third ventricle/hydrocephalus
  - acute stroke/haemorrhage/brain swelling
  - acute (infective) meningo-encephalitis.

The brainstem and cerebellum should be removed by an axial slice through the midbrain. The cerebellum should be removed from the brainstem by cutting through the 3

pairs of cerebellar peduncles. The brainstem is then sliced in the axial plane at 5-mm-thick blocks to inspect the medulla and pons structures. The cerebellum is sectioned through the sagittal midline to inspect the vermis and the hemispheres to expose the dentate nucleus/superior peduncle.

The cerebral hemispheres should be sliced in the coronal plane at approximately 0.5–1 cm intervals (see Figure 1).

The following key elements are assessed on coronal slices:

- Greenhall line to assess for diencephalic descent/brain swelling
- ventricles for symmetry, dilatation or compression
- cortical ribbon (any lesions and acute/chronic infarct with attention to watershed regions)
- symmetry of hemispheres and hippocampus/amygdala
- regions of relative atrophy, e.g. cerebellum or thalamus (hindbrain weight should represent 12–15% of total).

[Level of evidence – C.]

8 Organ retention

It is not possible or necessary for specialist neuropathologists to perform all the autopsies on patients with epilepsy, but it is best practice for a specialist to be involved in the interpretation of the neuropathology/histology. Organ retention must abide within the limits of the consent from the relatives or following discussion with the Coroner or Procurator Fiscal. The Coroner or Procurator Fiscal can provide families with details of the support organisations, SUDEP Action or the Epilepsy Society.

8.1 Brain retention protocol scenarios

1. Recommended practice: a case should be made for whole brain retention with fixation for around 2 weeks and referral to a neuropathologist (particularly in cases where there is consent for research donation). This would be regarded as best practice to limit missing any relevant neuropathology.
2. The next best practice is to fix the brain for a short interval, slice (either locally or at regional neuropathology referral centre), document the gross appearances of the brain

(ideally with photography), sample for histopathology and reunite the organ with the body.

3. A further option is to fix a single coronal slice 1–2 cm thick at the hippocampus level (see Figure 1) and a section of brainstem and cerebellum (amounting to ~5–10% of brain weight), returning the rest of the brain to the body. The fixed tissue samples can be examined by a neuropathologist. A study reported that this method did not impact on frequency of neuropathology findings.[15]
4. Histological sampling of brain is done at the time of autopsy with no organ retention.

In making the case for whole brain retention to the Coroner or Procurator Fiscal, the importance of optimal examination in epilepsy-related deaths must be emphasised.

8.2 Heart retention

If a sudden cardiac death is suspected, such as a sudden arrhythmic death syndrome or conduction defect, retention of the heart and referral to specialist centre is advisable.

[Level of evidence – GPP.]

9 Histological examination

Tissue sampling must be taken within the limits of consent from the next of kin or agreement with the Coroner or Procurator Fiscal. Recommend sampling protocols include any grossly abnormal areas and:

- vascular watershed region/frontal watershed regions (F1/2): acute hypoxic/ischaemic damage, meningitis, encephalitis, chronic neuronal loss (from previous seizures or episodes of status epilepticus, e.g. laminar atrophy)
- insular cortex/basal ganglia: acute neuronal injury, hypoxic/ischaemic
- damage, meningitis, encephalitis
- amygdala: acute neuronal injury, hypoxic/ischaemic damage, limbic encephalitis, chronic astrocytosis; amygdala dysfunction is implicated in SUDEP
- hippocampus: acute neuronal injury (CA1), hypoxic changes, limbic encephalitis, hippocampal gliosis, sclerosis, malrotational abnormality, neurodegenerative disease
- thalamus: acute neuronal injury, chronic regional gliosis

- temporal cortex (T1/2): meningitis, encephalitis, gliosis, global hypoxic changes, chronic atrophy, traumatic brain injury, malformation, neurodegenerative pathology
- cerebellum: acute or chronic atrophy, inflammation. Watershed region +/- sampling of the cortex with dentate nucleus
- medulla: inflammatory disease.

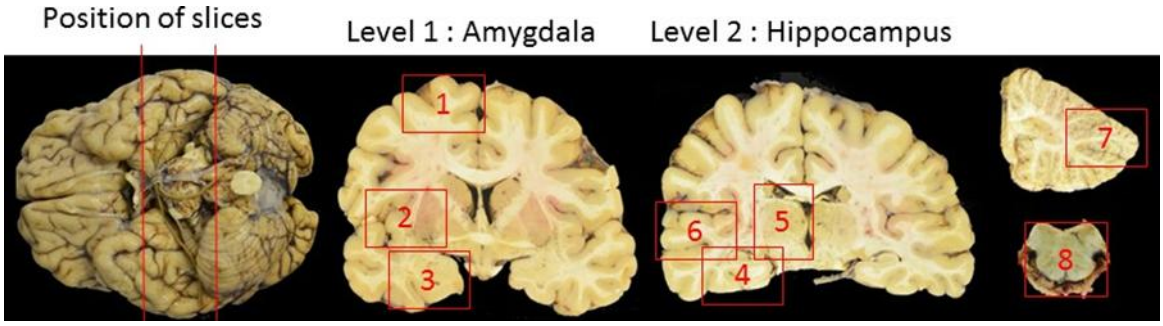

Figure 1: Lines indicate approximate coronal levels for block sampling, following hindbrain removal. (This is also the level for 'slice fixation' protocol (iii), section 8.) The samples 1–6 are shown on 1 hemisphere to illustrate anatomy, but paired samples from the left and right hemispheres for blocks 3–5 are recommended as good practice.

Tissue sampling may also be guided by clinical information of seizure localisation from EEG or MRI investigations during life. Samples from both left and right hemispheres should be taken, where possible, as epilepsy can lateralise (particularly in the hippocampus where sclerosis can be unilateral). Selection of the cerebellar block may depend on pattern of atrophy visible. All blocks should be stained with haematoxylin and eosin stain. Myelin stains are useful for neuroanatomical assessment. Gliosis can be demonstrated with glial fibrillary acidic protein and neuronal loss with Cresyl violet or neuronal markers. Seizure-specific patterns of reorganisation (e.g. hippocampal mossy fibre pathway) or assessment for cortical malformations can be carried out in specialist centres.

9.1 Organ blocks for histology

- Heart: if there is no identified lesion, multiple blocks should be taken across the right ventricle and left ventricle/septum with histological examination for fibrosis, myocarditis, etc. (refer to *Guidelines on autopsy practice: Sudden death with likely cardiac pathology*).[12]

- Lung: to confirm any suspected pneumonia or aspiration. The presence of acute inflammatory response does not necessarily indicate aspiration prior to death.
- Other samples from organs based on post-mortem findings determined by the pathologist as relevant to the investigation and cause of death.

[Level of evidence – C.]

10 Toxicology

This is carried out to evaluate:

- blood levels of ASMs and compliance:[20]
  - to confirm prescribed ASMs were being taken at the correct dosage
  - to establish whether the patient had stopped taking the prescribed ASMs (this is common in pregnancy-associated fatal epilepsy, e.g. for fear of damaging the fetus)
  - to establish whether there was an accidental or intentional overdose
- other medications or non-prescribed drugs, including illicit drugs
- alcohol levels.

The occurrence of acute symptomatic seizures with alcohol and drugs of abuse, particularly in withdrawal, is recognised. Alcohol intoxication can also trigger seizures in patients with an epilepsy diagnosis, chronic abuse is also associated with increased risk of epilepsy and it is also associated with an increased risk of SUDEP.[21] Death due to seizure in acute intoxication (without an epilepsy diagnosis) is not categorised as a SUDEP but does not preclude the seizure as a contributor to death.

The following samples are recommended:

- 10 ml peripheral blood preserved/unpreserved samples (femoral or iliac) and 20 ml urine
- gastric contents, which should be inspected for any undigested tablets, but are not needed for analysis if blood sample taken
- hair for ASM analysis to assess long-term compliance may be indicated,[22] e.g. allegations of medical negligence or possible inappropriate drug administration.

For other samples (e.g. vitreous), refer to *Guidelines on autopsy practice: Autopsy when drugs or poisoning may be involved*.[23]

[Level of evidence – C.]

11 Other relevant samples

11.1 Microbiology

If encephalitis is suspected, a cerebrospinal fluid sample and fresh brain cortical tissue should be retained for microbiological, viral or metagenomics studies (guided by local departments).

11.2 Molecular genetics

If a potentially inheritable/genetic cause of epilepsy (e.g. a channelopathy causing both arrhythmia and seizures) is suspected and genetic analysis may be required, a sample should be reserved according to local genetics laboratory requirements. Genetic testing may also be considered to identify epilepsy conditions and mutations associated with SUDEP although, at present, compared to genetic screening and counselling in inherited sudden cardiac death[13] there is less data on 'SUDEP-risk' genes.[24,25] Any genetic analysis is usually arranged through a local clinical geneticist and cardiologist or neurologist in the setting of a clinic with appropriate family counselling services and typically with the consent of the family.

11.3 Metabolic

If the possibility of metabolic brain disorders/mitochondrial disease is considered, appropriate samples (guided by clinicians and chemical pathologists) should be reserved.

[Level of evidence – GPP.]

12 Imaging

Imaging-based post-mortem examination should never be undertaken without an expert external examination of the body having first been performed by an appropriately trained and experienced individual. Post-mortem imaging has been used in cases of sudden paediatric deaths and epilepsy-deaths.[26] However, evidence for primary role in epilepsy death investigation is not available.[27] Post-mortem imaging may, however, provide useful

information in circumstances where no standard autopsy service is available. Structural lesions identified in the brain pertaining to epilepsy on post-mortem imaging should be correlated with any neuroimaging during life. If cause of death is not ascertained on imaging, standard post-mortem examination and toxicology is advised.

[Level of evidence – GPP.]

13 Clinicopathological summary

- Documentation of all morbid anatomical, histological and toxicological findings.
- Description of if and how epilepsy has caused or contributed to death.
- The aetiology of the epilepsy, if ascertained.

14 Examples of cause of death opinions/statements

14.1 Definitions and notes

- **SUDEP (or 'definite' SUDEP[25])**: 'Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non- drowning deaths in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, where necropsy examination does not reveal a toxicological or anatomical cause of death.'
  - Neuropathological abnormalities may be identified but do not account for the sudden death.
  - SUDEP also includes cases with short survival following resuscitation but with no recovery following a seizure- related cardio-respiratory arrest
  - A seizure does not have to occur/be witnessed for a SUDEP categorisation in a patient with an epilepsy diagnosis with unexplained sudden death.
- **Possible SUDEP**: Where a potential competing cause of death is identified at post mortem (e.g. non-significant coronary atheroma [50–75% occlusion], mild cardiac hypertrophy, found dead in bath but no definitive drowning), the term 'possible SUDEP' can be used. The term 'SUDEP-plus' has also been used for scenarios where 'a concomitant condition other than epilepsy is identified before or after death, if the death may have been due to the combined effect of both conditions, and if autopsy or direct observations/recordings of terminal event did not prove the concomitant condition to be the cause of death'.[28]

- For neuropathologists examining the brain only in epilepsy deaths (and not conducting the full post mortem) where no neuropathological cause of death is identified, an example of wording that can be used on their report is 'neuropathology findings in keeping with SUDEP in the context of a negative full post mortem with toxicology'.
- **Status epilepticus** requires witnessed evidence of unremitting seizure activity for >5–30 minutes or electro-clinical (EEG) evidence of prolonged seizure activity in the absence of convulsive seizures (see reference for definitions of status epilepticus).[9]

14.2 The following scenarios fulfil criteria for SUDEP

- Epilepsy patient; no other relevant pre-existing conditions; found dead; negative post-mortem examination.
- Epilepsy patient; witnessed sudden death in sleep or during activity including exercise, no seizure; negative post-mortem examination.
- Epilepsy patient; no other relevant pre-existing conditions; witnessed seizure, post-ictal coma, no evidence or history of terminal status epilepticus; negative post-mortem examination.
- Epilepsy patient found dead face down in bed or on floor, mild coronary artery disease only finding.
- Sudden death in conjunction with first seizure; post mortem shows brain tumour without significant mass effect, otherwise negative post mortem. (The enduring predisposition for seizures when a tumour is identified meets criteria for epilepsy despite death coinciding with first seizure.)

The above and similar scenarios should be recorded as:

1a) SUDEP

1b) Epilepsy

1c) Cause of epilepsy if known, e.g. oligodendroglioma

In cases where 'seizure-like' events had been reported, but the patient had not yet received an epilepsy diagnosis/clinical investigation as EEG and no cause of death established, SUDEP should be potentially considered and discussed with Coroner/Procurator Fiscal.

14.3 The following scenarios do not fulfil SUDEP or definite SUDEP

- Death during documented status epilepticus (defined as unremitting seizure activity for >5–30 minutes, depending on seizure type).[9]

  Cause of death formulation example:

  1a) Status epilepticus

  1b) Antecedent cause if appropriate (e.g. new-onset refractory status epilepticus (NORSE), encephalitis, ischaemic infarct etc.).

- Evidence of significant aspiration during fatal seizure (minor degrees of aspiration allowed in SUDEP)

  Cause of death formulation example:

  1a) Aspiration

  1b Epilepsy

- Evidence of fatal traumatic injury sustained during seizure.

  Cause of death formulation example:

  1a) Acute subdural haemorrhage with mass effect

  1b) Traumatic head injury

  1c) Generalised epileptic seizure

- Evidence of drowning during seizure.

  Cause of death formulation example:

  1a) Drowning

  1b) Idiopathic generalised epilepsy

- Death during or following a provoked seizure (where there is not an epilepsy diagnosis), e.g. alcohol-withdrawal seizure, febrile seizure.

  Cause of death formulation example:

  1a) Sudden death in seizure associated with alcohol withdrawal

  2) Alcoholic liver disease

- A clear alternative cause of death is found at post mortem e.g. acute cerebral haemorrhage.

  Cause of death formulation example:

  1a) Acute intracerebral haemorrhage

  1b) Saccular aneurysm

  2) Epilepsy

- A sudden unexplained death where the clinical criteria for epilepsy diagnosis is lacking and no cause of death identified.

  Cause of death formulation example:

  1a) Unascertained

- Sudden and witnessed cardio-respiratory collapse following a convulsive seizure in a patient with known generalised epilepsy syndrome. Post mortem identifies an enlarged and dilated heart (no previous history or family history of cardiac disease)

  Cause of death formulation example:

  1a) Possible SUDEP

  (Cardiac gene analysis advised)

There is an epilepsy deaths register in the UK for SUDEP and other epilepsy-related deaths at www.epilepsydeathsregister.org.

[Level of evidence – GPP.]

15 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure a post-mortem report for coronial autopsies conducted at an institution comply with the national recommendations provided by the 2006 NCEPOD study.

- Supporting documentations for clinical history:
  - standards: 95% of supporting documentation was available at the time of the autopsy
  - standards: 95% of autopsy reports documented are satisfactory, good or excellent.

- Reporting internal examination:
  - standards: 100% of the autopsy report must explain the description of internal appearance
  - standards: 100% of autopsy reports documented are satisfactory, good or excellent.
- Reporting external examination:
  - standards: 100% of the autopsy report must explain the description of external appearance
  - standards:100% of autopsy reports documented are satisfactory, good or excellent.
- Inclusion of toxicology, microbiology, neuropathology, cardiac pathology, genetic reports where conducted
  - standards: 100% final reports should contain reports/documentation of results where applicable
- Include details of organ retention and any consents obtained in the report.

A template for coronial autopsy audit can be found on The Royal College of Pathologists' website.[29]

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Appendix A Summary table – Explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008; 337:1832)

Grade (level) of evidence	**Nature of evidence**
Grade A	At least 1 high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix B AGREE II guideline monitoring sheet

The guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this guideline that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard		Section of guideline
Scope and purpose		
1	The overall objective(s) of the guideline is (are) specifically described	Introduction
2	The health question(s) covered by the guideline is (are) specifically described	Introduction
3	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement		
4	The guideline development group includes individuals from all the relevant professional groups	Foreword
5	The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6	The target users of the guideline are clearly defined	Introduction
Rigour of development		
7	Systematic methods were used to search for evidence	Foreword
8	The criteria for selecting the evidence are clearly described	Foreword
9	The strengths and limitations of the body of evidence are clearly described	Foreword
10	The methods for formulating the recommendations are clearly described	Foreword
11	The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12	There is an explicit link between the recommendations and the supporting evidence	2–14
13	The guideline has been externally reviewed by experts prior to its publication	Foreword
14	A procedure for updating the guideline is provided	Foreword
Clarity of presentation		
15	The recommendations are specific and unambiguous	2–14
16	The different options for management of the condition or health issue are clearly presented	2–14
17	Key recommendations are easily identifiable	2–14

Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Main text
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	15
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword