



MINI-SYMPOSIUM: THE AUTOPSY IN SUDDEN UNEXPECTED ADULT DEATH

# The autopsy in sudden unexpected adult death: Epilepsy

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## KEYWORDS

Epilepsy;  
Autopsy;  
SUDEP;  
Neuropathology

**Summary** There are up to 500 epilepsy-related deaths annually in the UK, many of which are unwitnessed. Likely mechanisms for sudden and unexpected death in epilepsy (SUDEP) are cerebrogenic cardiac arrhythmias, or central respiratory depression occurring during the peri-ictal period. Pathologists should be informed of the circumstances of the death, severity of seizures, seizure control and the certainty of the clinical diagnosis of epilepsy; this allows accurate clinicopathological correlation. SUDEP autopsies include neuropathological assessment, histological examination of other organs and toxicology, and require the elimination of other causes of sudden death. Macroscopic (non-fatal) abnormalities described in SUDEP include evidence of previous cerebral injury, hippocampal sclerosis and cerebellar atrophy. Histological examination may reveal neuronal loss and gliosis consistent with seizure-related brain injury. Hippocampal sclerosis shows subfield-specific patterns of neuronal loss, granule cell dispersion and mossy fibre sprouting. Rarely, acute neuronal injury is seen as evidence of a more recent cerebral event. This article discusses the pathological findings and possible mechanisms in SUDEP, and future directions for pathology-based research.

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## Introduction

### Neuropathological causes of sudden death

An unexpected or unexplained death follows on so rapidly from the onset of symptoms (usually taken as less than 24h but often, in practice, less than 1h)<sup>1</sup> that the cause of death cannot be certified with confidence. Where the death was unwitnessed

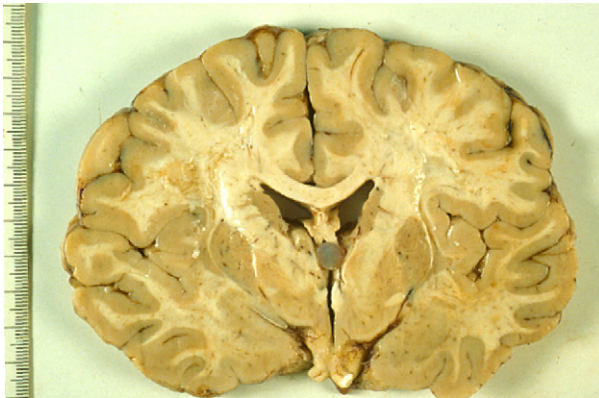
and the deceased was found dead unexpectedly, the duration of symptoms is unknown. Sudden deaths in England and Wales result in autopsies conducted under coronial authority to establish the cause of death. In a proportion of these cases, a neuropathological cause may be identified and the main categories are listed in Table 1. Subarachnoid haemorrhage (SAH), usually caused by spontaneous rupture of saccular aneurysm, results in sudden death within 1h of symptom onset in 8–10% of cases.<sup>1</sup> The major sites of intracerebral haemorrhage (ICH) leading to sudden death are the basal

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**Table 1** Neuropathological causes of sudden deaths identified at post-mortem.<sup>2,4</sup>

- Epilepsy
  - Sudden and unexpected death in epilepsy
  - Other epilepsy-related cause of death
- Stroke
  - Intracerebral haemorrhage
  - Subarachnoid haemorrhage
  - Cerebral infarction
- Space-occupying/cerebral mass lesions
  - Tumours
  - Colloid cysts
- Infectious disease
  - Cerebral abscess
  - Acute meningitis
- Inflammatory, metabolic disorders



**Figure 1** Colloid cyst causing sudden and unexpected death in young adult.

ganglia (40% of cases), pons (16%) and thalamus (15%).<sup>1</sup> The haemorrhage ruptures into the ventricle in 75% of cases and into the subarachnoid space in 15% of cases.<sup>1</sup>

Sudden death may occasionally be the initial presenting symptom of an intracranial tumour or an acute presentation of a previously diagnosed tumour. Sudden death has been reported with a variety of intracranial tumours, including glioblastoma, oligodendroglioma, medulloblastoma, lymphoma and pituitary adenomas as well as brainstem gliomas.<sup>2</sup> Colloid cysts of the third ventricle may also cause sudden death due to acute obstructive hydrocephalus (Fig. 1).<sup>3</sup>

A neuropathological cause of death may be macroscopically evident at the time of autopsy, but fixation of the whole brain and histological examination is advisable in many circumstances either to confirm the nature of the pathological process or to exclude another process. Brain fixation improves visualisation of primary brainstem pathologies, which can be difficult to delineate in the fresh state. Some pathologies, e.g. thin-walled colloid cysts, may be collapsed and missed in the unfixated state.

### Mechanisms of sudden death due to intracerebral lesions

Sudden deaths are attributed to the 'mass effect' of space-occupying lesions, or complications such as acute haemorrhage or obstructive hydrocephalus with associated rapid rise in intracranial pressure. At autopsy, the conventional patterns of internal brain herniation, midline shift and brainstem haemorrhage may be less well defined due to the rapidity of the death.<sup>1</sup>

In sudden deaths, the autopsy may indicate brainstem compromise as the final event, either by compression and distortion or direct extension of, for example, an infiltrating glioma.<sup>2,4</sup> The medulla harbours centres vital to autonomic regulation of cardiorespiratory function [the dorsal and ventral nuclear groups of the reticular formation including the nucleus gigantocellularis (respiratory centre) and the nucleus ambiguus and nucleus of the solitary tract (cardiac centre)]. These medullary centres regulate sympathetic and parasympathetic output (via the vagus nerve). They are influenced by descending connections from the hypothalamus, periaqueductal grey nuclei, the amygdale and limbic system, the latter which regulate autonomic responses in situations of stress and anxiety. The insular cortex, orbito-frontal cortex and anterior cingulate also have significant roles in cardiac regulation.<sup>5,6</sup> Ventricular arrhythmias have long been recognised in patients with brain tumours in the absence of pre-existing cardiac pathology. Electrocardiogram changes (including QT prolongation, ectopic beats, inverted T-waves and prolonged QTc interval) have been observed following SAH, ICH, ischaemic stroke and head injury, as well as during neurosurgical procedures. The insular cortex has a key physiological role in the integration of 'brain-heart' autonomic interactions. In pathological situations, e.g. ischaemic strokes, arrhythmias and sudden death are more common where the insular cortex has been involved.<sup>7</sup> A fatal brain-induced or

'cerebro-corticogenic' cardiac arrhythmia may be a common mode of death from underlying acute or chronic intracerebral cortical pathology. The evidence for cerebral lateralisation of autonomic control is growing, with the left hemisphere implicated in parasympathetic effects and the right hemisphere (particularly the insula region) with sympathetic cardiac function. Examination of the heart in instances of fatal cerebrogenic arrhythmias may reveal focal myocytolysis, subendocardial congestion and haemorrhages that would support changes compatible with increased sympathetic activity.<sup>6</sup>

## Epilepsy and mortality

Epilepsy is the most common chronic disabling condition of the nervous system, affecting up to 400 000 people in the UK. Overall mortality in epilepsy is increased up to three-fold compared with the general population.<sup>8</sup> The underlying pathology causing epilepsy is often the cause of death, e.g. neurodegenerative disease, cerebrovascular disease, etc. In another group, death may result from seizure activity and there are approximately 1000 such epilepsy-related deaths (Table 2) in the UK annually. The category of sudden and unexpected death occurring in epilepsy (SUDEP) has gained increasing recognition over the last 10 years,<sup>9</sup> and represents the leading cause of death in young adults with drug-refractory epilepsy. A National Sentinel Audit conducted in the UK (2002) into epilepsy deaths highlighted that 87% of the autopsies performed to investigate these cases were inadequate, mainly due to incomplete investigations or inaccuracies in recording the cause of death. More recent reports continue to suggest that SUDEP is still underused as a final diagnosis.<sup>10</sup> A National Confidential Enquiry into Patient Outcome and Death audit into coronial autopsies (2006) noted incongruencies in the

**Table 2** Main categories of epilepsy-related deaths.

- Death due to status epilepticus
- Death due to injury (or drowning) occurring during seizure
- Death as a result of aspiration during seizure
- Death as a result of epilepsy treatment (surgical or medical)
- Sudden and unexpected death in epilepsy

recording of the cause of death, particularly in epilepsy patients.<sup>11</sup>

The actual incidence of SUDEP varies according to the epilepsy population under study. Community-based studies suggest an incidence of 0–2.5/1000 person-years, whereas the incidence in patients with drug-resistant epilepsy is 1.2–9/1000.<sup>12</sup> Risk factors for SUDEP include: young male patients with poorly controlled epilepsy; frequent generalised tonic-clonic seizures; and multiple anti-epileptic treatments.<sup>9,12,13</sup> These findings suggest that optimal seizure control may reduce the incidence of SUDEP. The beneficial effects of surgical treatment compared with medical treatment in the prevention of excess mortality in epilepsy remain controversial.<sup>12</sup>

## Sudden unexpected death and epilepsy

### Definition

SUDEP is defined as 'sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning deaths in patients with epilepsy, with or without evidence of seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicological or anatomical cause of death'.<sup>14</sup> For a definitive diagnosis of SUDEP, an autopsy is a requirement. SUDEP is essentially a diagnosis of exclusion of another cause of death. As the number of cases undergoing autopsies varies between countries,<sup>9</sup> alternative criteria have been proposed for the diagnosis of probable SUDEP (where autopsy findings are not available)<sup>9,15</sup> for epidemiological purposes (Table 3).

**Table 3** Criteria for probable sudden and unexpected death in epilepsy.

- The patient had epilepsy (recurrent unprovoked seizures as defined by the World Health Organization)
- The subject died unexpectedly while in a reasonable state of health
- Death occurred suddenly (usually in minutes, possibly over several hours)
- Death occurred during normal activities (e.g. at work or home or around bed) in benign circumstances
- An obvious medical cause of death was not found
- Death was not a result of status epilepticus or due to acute trauma in the setting of a seizure

## Mechanisms of SUDEP

Strong evidence favours SUDEP as an ictal or post-ictal event mediated by respiratory or cardiac dysfunction or both.<sup>12,16–18</sup> SUDEP may be multifactorial. Deaths may be due to respiratory suppression (i.e. a central ictal apnoea) or 'neurogenic' pulmonary oedema resulting from a transient flux in pulmonary intravascular pressure with altered pulmonary capillary permeability. Breathing difficulties during seizures may be exacerbated by positional asphyxia with collapse or obstruction of the upper airways, possibly due to a prone body position, particularly following generalised tonic-clonic seizures.<sup>12,18</sup> In many cases, deaths are not witnessed and occur in bed or at night.<sup>19</sup> Ictal respiratory suppression is a plausible explanation. Episodes of hypoventilation have been reported in animal models of status epilepticus. In SUDEP, respiratory depression could be mediated by endogenous opioid release or seizures mediating an inhibitory effect on brainstem respiratory centres.

It is more likely that a seizure-induced or cerebrogenic cardiac arrhythmia occurs. Arrhythmias may occur during seizures and have been reported in 42% of temporal lobe epilepsy patients.<sup>20</sup> Sinus tachycardia is the most common arrhythmia and accompanies 90% of seizures.<sup>21</sup> Bradycardias are less common (0.5%).<sup>21</sup> Potential arrhythmogenic side effects of anti-epileptic medication must be considered as potential contributing factors to SUDEP.<sup>22</sup>

Inter-ictal variability in heart rate patterns has been noted in patients considered at risk for SUDEP.<sup>12,21</sup> Electrocardiogram abnormalities reported during seizures include QT prolongation, R on T phenomenon, bundle branch block, bradycardia and asystole.<sup>23,24</sup> The most plausible explanation for these cardiac phenomena is the spread of the seizure discharges to involve cortical regions harbouring autonomic-regulatory functions, or possibly the synchronisation of vagal- and sympathetic-mediated discharges during a seizure. Temporal lobe seizure discharges may extend to the perisylvian and insular region known to have cardioregulatory functions. During surgery for epilepsy, stimulation of the anterior cingulate, uncus, orbito-frontal cortex, insular and temporal cortex have demonstrated brady- and tachyarrhythmias in association with epileptiform discharges.<sup>17</sup> The presence of cortical pathology may shift the normal networks involved in cardiac control.<sup>17</sup> There has been much focus on the 'ictal-bradycardia or asystole' syndrome that has been reported with both temporal and frontal lobe focal epilepsies as a potential risk factor for SUDEP.<sup>17</sup>

In 20 patients with refractory focal seizures, monitoring over 18 months revealed three asystolic events in association with seizures.<sup>21</sup> Important clinical questions arise regarding screening to identify patients at risk for asystole and SUDEP and when to treat with pacemakers.

## Post-mortem examination in epilepsy deaths, particularly SUDEP

### Clinical information

In potential SUDEP cases, initial information should include the certainty of the clinical diagnosis of epilepsy during life. The clinical distinction of epilepsy from other disorders, including syncopal attacks, is not always easy, with cardiac disorders being misdiagnosed as epilepsy and vice versa. Definitive diagnosis of epilepsy and classification of particular syndromes may require the opinion of an expert epilepsy neurologist and appropriate necessary investigations, e.g. electrocardiogram/electroencephalogram, magnetic resonance imaging (MRI) and telemetry to distinguish it from other conditions that may mimic seizures. Myoclonus, abnormal eye movements and visceral sensations mimicking epileptic aura can occur in syncope.<sup>24</sup> Other information that should be sought prior to autopsy is listed in [Table 4](#).

### Neuropathology findings at SUDEP autopsy

The brain may show mild swelling or 'fullness' of the convexities reflected in high average brain weights.<sup>25</sup> By definition, significant swelling, shift

**Table 4** Information required before the autopsy begins.

- Type, duration and frequency of seizures
- Any recent deterioration in seizure control
- Anti-epileptic drug regimens and compliance
- Underlying cause of epilepsy (if known)
- Circumstances of death
  - Scene photographs
  - Evidence of incontinence, vomiting or injury
- Eye-witness accounts
- Other known medical conditions
  - Heart disease
  - Alcoholism
  - Learning difficulties
  - Vaso-vagal attacks

or herniation is absent.<sup>25</sup> A common misconception is that the brain is normal in the vast majority of SUDEP cases. Analyses from the larger SUDEP series report macroscopic abnormalities in up to two-thirds of cases.<sup>1,26</sup> More frequently reported macroscopic abnormalities include old cerebral traumatic lesions (contusions, gliosis, previous craniotomy sites), hippocampal or cortical atrophy, cerebellar atrophy, haemangiomas, low-grade tumours and cortical malformations.<sup>26</sup> There is no accurate data regarding the relative risk or association of any of these specific pathological lesions for SUDEP. Some lesions, including old injuries and cortical neuronal damage, may indirectly indicate the clinical severity of the epilepsy.

Histopathological examination is required to confirm the type of macroscopic lesion identified and to exclude significant pathology when the brain appears normal. Focal Purkinje cell loss and hippocampal neuronal loss may support that seizures had occurred in life. The aims of the neuropathologist examining a brain from any patient with a history of epilepsy are: identifying any potentially epileptogenic pathology (see below); seeking evidence that previous seizures have resulted directly or indirectly in cerebral injury; and determining how or if epilepsy has contributed to the death.

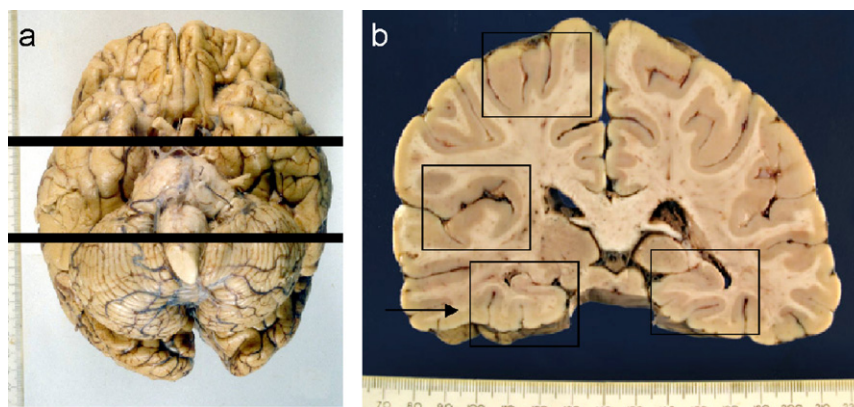
It is neither possible nor necessary for neuropathologists to perform all the autopsies on patients with epilepsy, although a specialist neuropathologist should be involved in the interpretation of the histological findings. The Royal College of Pathologists' (RCPATH) guidelines on autopsy practice in epilepsy recommend that a case should be made to the Coroner and relatives for retention of the whole brain for fixation. This allows optimal examination

following 2–3 weeks of fixation. If this is not permissible, the next best process is to fix coronal slices of the brain (taken 1.5-cm thick just in front of the midbrain and just behind the midbrain) (Fig. 2) for a short period (48–72 h), followed by photography and histopathology sampling. If even this is not permissible, small tissue samples must be selected and trimmed for histopathological analysis. It has been shown in SUDEP series that if the brain is cut and examined in a fresh rather than a fixed state, there is less likelihood of identifying any relevant pathology.<sup>1</sup> The Coroner and family should be made aware of this limitation when retention of the brain is denied. A suggested block sampling protocol is listed in Table 5. It is important to sample tissue from both hemispheres, as unlike most neurodegenerative diseases, pathological processes associated with epilepsy may be lateralised rather than symmetrical or generalised. Where possible, tissue should be frozen and banked (ideally from the frontal cortex and hippocampus), e.g. in cases where a metabolic or genetic disease underlying the epilepsy is suspected or where the family express interest in research into SUDEP and epilepsy.

## Specific neuropathological lesions in SUDEP

### Epileptogenic pathologies—cortical malformations

A variety of generalised and focal cortical malformations are strongly associated with clinical seizures. A detailed description of these lesions is



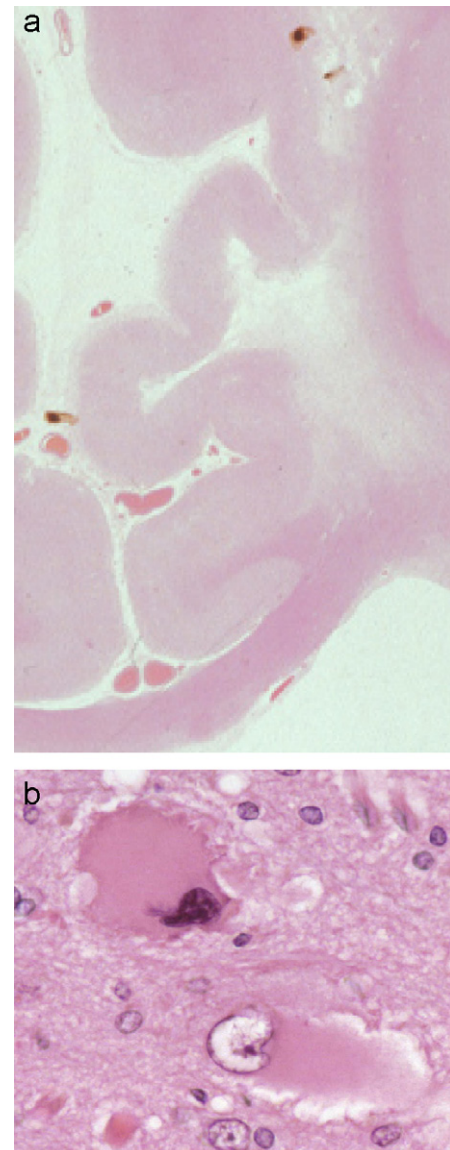
**Figure 2** Whole fixed brain in sudden and unexpected death in epilepsy (SUDEP) cases. Coronal sections taken at the approximate levels as shown in (a), in front of and behind the midbrain (after removal of the hindbrain) will allow adequate sampling of the mesial temporal lobe and cortical structures. (b) A coronal slice from a young male with SUDEP with known hippocampal sclerosis and refractory epilepsy and awaiting temporal lobectomy. The left hippocampus is visibly atrophic (arrowed) with volume loss and atrophy. The blocks that should be sampled at this level are superimposed to include the temporal neocortex/insula and vascular watershed region.

**Table 5** Suggested block-sampling protocol in sudden and unexpected death in epilepsy cases (more essential blocks in *italics*).

Blocks to be taken (sample left and right hemisphere)	Rationale
<i>Identified macroscopic abnormality</i>	To categorize the nature of the pathological process, e.g. tumour, malformation
Blocks from the presumed epileptogenic brain region (based on data from MRI/EEG if available)	To evaluate the potential of the lesion as the cause of seizures (e.g. some pathologies—focal cortical dysplasia, dysembryoplastic neuroepithelial tumours—are virtually always associated with focal epilepsy)
Mesial temporal lobe structures (hippocampus and amygdale)	Regions susceptible to epilepsy-related damage (neuronal loss and gliosis)
Cerebellum	Acute neuronal injury may be identified that could support recent seizure(s)
Cortex, e.g. superior temporal gyrus	In cases with severe cortical neuronal loss, episode(s) of status epilepticus should be considered
Thalamus	
Watershed vascular territories	To exclude hypoxia–ischaemia as a result of cerebral hypoperfusion To exclude occult pathology, e.g. acute meningitis
Cortex	Regions involved in cardiorespiratory control
Brainstem and hypothalamus	To exclude specific pathology in these regions, e.g. brainstem encephalitis
Amygdala and insular cortex	

MRI, magnetic resonance imaging; EEG, electroencephalogram.

beyond the scope of this article. Focal cortical dysplasias (FCD) are occasionally encountered at autopsy and in SUDEP cases (Fig. 3). FCD is a common cause of focal refractory epilepsy in children and young adults, is usually diagnosed by MRI scan, and may be amenable to surgical resection. At autopsy, FCD lesions are recognised macroscopically as a region of cortical thickening with poor definition from the underlying white matter. Common sites include the frontal lobe and around the pre-central gyrus. Lesions may be 1 cm or more across. On haematoxylin and eosin (H&E) sections, subcortical hypomyelination or pallor may



**Figure 3** Cortical malformation in sudden and unexpected death in epilepsy. (a) Focal cortical dysplasia (FCD) was identified in the cingulate gyrus with marked associated pallor of the subcortical white matter on haematoxylin and eosin stain. (b) Balloon cells were noted in histological sections; the hallmark of FCD type IIB lesion.

be seen in FCD (Fig. 3a). The overlying cortex shows ill-defined cortical laminae and the presence of abnormal cell types, including hypertrophic or dysmorphic neurones. In more severe forms of FCD, balloon cells are characteristic (Fig. 3b), have abundant glassy cytoplasm and may label for GFAP, nestin and CD34. The presence of balloon cells in the cortex is equivalent to the 'Taylor-type' of FCD, now termed 'FCD type IIb' in the updated classification system.<sup>27</sup> Milder or microscopic cortical malformations (formerly termed

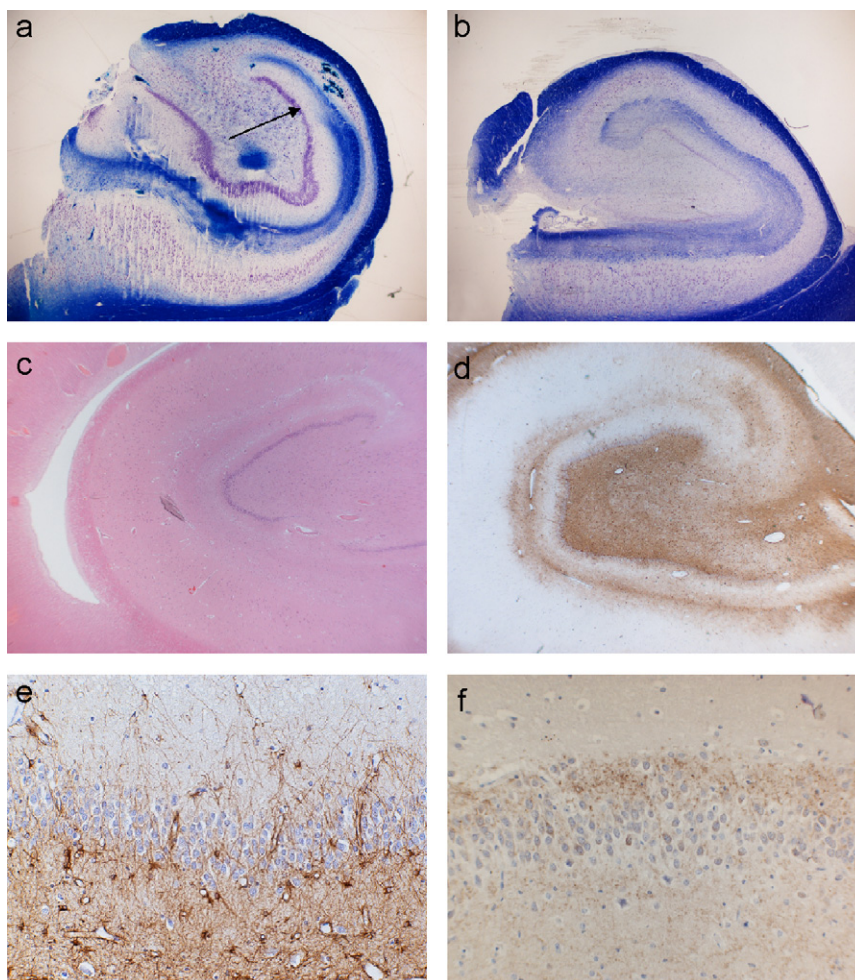
'microdysgenesis'<sup>28</sup>) have also been described in SUDEP cases.<sup>26</sup> These include an excess of morphologically normal neurones in heterotopic locations including cortical layer I and the white matter. Precise criteria for the definition of milder malformations are lacking; the diagnosis is more open to subjective interpretation and, compared with FCD, a clear association of these lesions with epilepsy is less well documented.<sup>27,29</sup>

### Hippocampal sclerosis

Hippocampal sclerosis (HS; Ammon's horn sclerosis) is the most common lesional pathology identified in patients with temporal lobe epilepsy<sup>30</sup> and has been reported in patients with SUDEP<sup>1,26</sup> (Fig. 2a). The exact aetiology is unknown and it is possible that an early cerebral event, such as a prolonged

febrile seizure, superimposed on an abnormally developed hippocampus results in a cascade of cellular events, including cell death, synaptic re-organisation and altered neurogenesis, resulting in a hyperexcitable but sclerotic hippocampus. Hippocampal structural re-organisation can also be induced in patients with cortical epileptogenic pathologies, such as a low-grade tumour or cortical malformations. These cases are sometimes referred to as 'secondary HS' or 'dual epileptogenic' pathologies.

HS may be unilateral but evidence of bilateral or asymmetrical damage may be found.<sup>31</sup> The macroscopic features include hippocampal volume loss or atrophy (Fig. 2a) which may be harder or gliotic on sectioning. There is corresponding dilatation of the temporal horn of the lateral ventricle. The adjacent temporal neocortex and ipsilateral amygdala, thala-



**Figure 4** Patterns of hippocampal sclerosis in sudden and unexpected death in epilepsy: (a) neuronal loss may be primarily from the CA1 subfield (note the broadening of the granule cell layer, arrowed) on Nissl-stained sections or may affect most subfields, (b) in more severely sclerosed cases. Predominant neuronal loss and gliosis on GFAP staining in the hilar region is not an uncommon pattern seen at autopsy (c–e). Demonstration of mossy fibre sprouting even in these cases with mild hippocampal neuronal loss using dynorphin immunohistochemistry, (f) may be an indicator of seizures in life and resulting synaptic re-organisation.

mus and mamillary bodies may also show anterograde atrophic changes. The microscopic changes of HS can be confirmed on standard H&E sections, but additional Nissl staining and immunohistochemistry for neuronal markers and GFAP are helpful to confirm the characteristic patterns of neuronal loss and gliosis (Fig. 4). The classical pattern shows neuronal loss and gliosis predominantly in the hilar (which includes CA4 neurones) and CA1 subfields. The neurones of CA2 are typically better preserved. In approximately half of classical cases, there is dispersion of the granule cells (Fig. 4a), appearing as a broadening of this cell layer at low magnification. Granule cell layer dispersion is virtually exclusive to patients with epilepsy and HS, although the exact factors that induce this phenomena have not been characterised.<sup>32</sup> In a smaller percentage of patients with epilepsy, the neuronal loss is more restricted to the CA1 subfield or the hilar region (so-called 'end folium pattern of sclerosis'). The subiculum subfield (the distal continuation of CA1 pyramidal cell layer towards the parahippocampal gyrus) is strikingly spared in HS,<sup>31</sup> and this may aid in the distinction of epilepsy-induced hippocampal neuronal injury from other causes, including ischaemia, which often show less subfield-specific damage. Synaptic re-organisation is another exclusive pathological hallmark of HS, and sprouting of mossy fibres in the dentate gyrus can be readily shown with dynorphin immunohistochemistry.<sup>33</sup> Demonstration of this process provides strong evidence that the patient had seizures. This finding may be seen even when there are milder degrees of HS, including end folium sclerosis (Fig. 4f).

## Epilepsy-related cerebral changes

### Do seizures inevitably damage the brain?

Experimental models and human studies have established that prolonged seizures, including status epilepticus, may cause neuronal injury. The vulnerable regions of the brain include the hippocampus, cortex, thalamus and cerebellum.

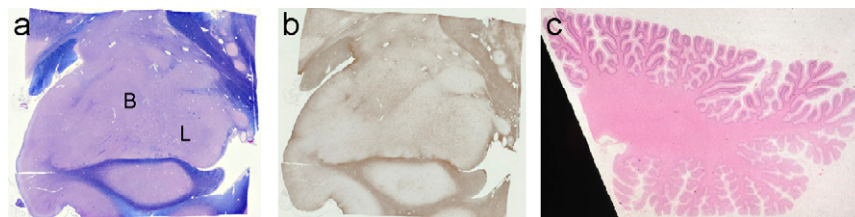
Whether single, brief seizures occurring repetitively over years result in accumulative neuronal injury is less clear. Serial MRI volumetry in epilepsy patients has been used to address this question, with some studies suggesting that there is progressive volume loss over time.<sup>34</sup> Autopsy stereological quantitative studies have shown that hippocampal injury (measured as neuronal loss) is not an inevitable consequence, even after thousands of lifetime seizures including episodes of status epilepticus. The absence of neuronal injury or loss in a patient with a history of chronic seizures does not contradict the clinical diagnosis of epilepsy.

## Amygdala sclerosis

Neuronal loss and gliosis of the amygdala has been noted in association with HS<sup>35</sup> or in isolation,<sup>36</sup> particularly affecting the lateral nuclei and the basal nuclei (Fig. 5). The exact incidence of amygdala sclerosis (AS), the functional consequences, and its relationship to temporal lobe epilepsy are unknown. The amygdala has a role in autonomic regulation, for example, with efferent connections via the central nuclei to cardiorespiratory centres in the dorsal medulla and hypothalamus. An appealing hypothesis is that specific patterns of neuronal loss and AS in epilepsy may have functional implications through a susceptibility to cardiac arrhythmias and act as a risk factor for SUDEP. Quantitative analyses do not suggest that specific patterns of amygdala neuronal loss are observed in SUDEP patients.<sup>37</sup>

## Traumatic lesions, cortical atrophy and cerebellar atrophy

Cerebral trauma may result from injury during a seizure, and conversely, a patient may develop epilepsy following a severe head injury. Traumatic brain injury accounts for 20% of symptomatic epilepsy and 5% of all epilepsy.<sup>38</sup> High-risk factors for developing late seizures include alcoholism, age, penetrating dural injury, intracranial haemorrhage



**Figure 5** There may be regional neuronal loss and gliosis of the amygdala (a) in epilepsy patients involving the lateral (L) and basal nuclei (B) as seen on GFAP stain (b). Sections from the cerebellum may reveal atrophy of the folia from the posterior lobe (c).

or contusion, depressed skull fracture, and focal neurological deficit. The overall risk of epilepsy following a cerebral contusion is estimated at around 10%, being highest in the first year.

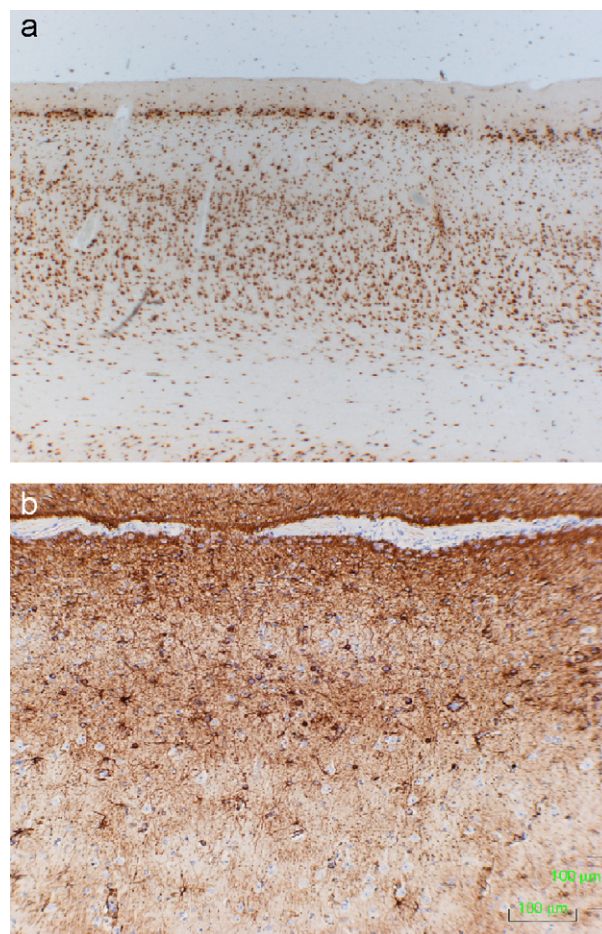
Patients with established epilepsy have a higher incidence of minor and severe cerebral injuries, including cerebral haemorrhage and contusions, and risk is related to seizure frequency, type and control.<sup>39,40</sup> Head injuries have been reported in 24% of epilepsy patients<sup>41</sup> and not infrequently in SUDEP, although precise data are lacking.<sup>26</sup> Commonly identified sequelae of head injuries include old cystic cortical contusions, particularly in the fronto-temporal regions.

In patients with documented episodes of status epilepticus, neuronal loss may be seen in the neocortex (mid-cortical layers), entorhinal cortex, Purkinje cell layer of the cerebellum,<sup>42</sup> dorsal medial nuclei of the thalamus,<sup>43</sup> basal ganglia<sup>44</sup> and the hippocampus. With a history of hemiconvulsions, cerebral hemiatrophy can be observed with striking unilateral laminar cortical necrosis.<sup>45</sup> Neuronal loss from the cortical mid layers can occur with repetitive seizures in the absence of episodes of status (Fig. 6).

Cerebellar atrophy is not an uncommon autopsy finding in patients with epilepsy, and may involve the anterior or posterior lobes, and may preferentially affect one hemisphere (the latter often associated with contralateral cortical hemispheric atrophy) (Fig. 5), or be more generalised. Cerebellar atrophy can be estimated from the weight of the hindbrain, which should normally be 12–15% of the total brain weight. The probable causes included phenytoin toxicity or seizure-induced neuronal excitotoxic injury, and the microscopic correlates are Purkinje cell loss and progressive gliosis of the molecular layer. The functional consequences are unknown as are any effects on seizure control or any links with SUDEP.

### Identification of acute neuronal injury in SUDEP

The identification of chronic neuronal loss and scarring of the brain in the specific patterns described above may support that the patient suffered severe chronic epilepsy. Confirmation that a recent seizure has taken place, which may be related to the cause of death, is more difficult. Occasionally in SUDEP brains, acutely damaged or eosinophilic neurones expressing cell stress proteins are identified in vulnerable regions of the brain, including the hippocampus, which could support a ante-mortem cerebral injury including a



**Figure 6** Cortical neuronal loss from the mid layers in a patient with epilepsy may be more easily visible with neuronal staining (NeuN) (a) and mirrored by a gliosis in the affected laminae on GFAP staining (b).

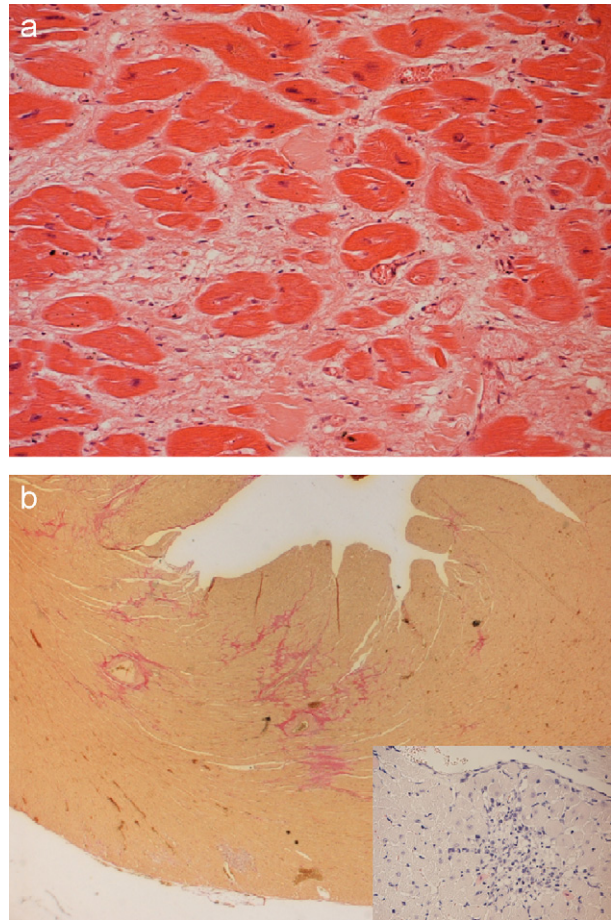
seizure in the previous few hours.<sup>46</sup> In many cases, presumably death occurs too rapidly to activate the cell cascades that result in irreversible neuronal injury.

### Cardiac pathology and SUDEP

Several studies have addressed the presence of associated or significant cardiac pathology in SUDEP, which may relate to the cause of death. Initial reports suggested cardiomegaly and co-existing cardiac hypertrophy in some patients with SUDEP.<sup>47</sup> In more recent studies, no difference in heart mass compared with non-SUDEP controls was noted when corrected for body mass.<sup>19,48</sup> Extensive sampling of the myocardium in SUDEP frequently reveals foci of reversible pathology (myocyte vacuolisation and interstitial oedema) in addition to irreversible pathological changes

(contraction band necrosis, haemorrhage, fibrosis and hyper-eosinophilia of myocardial fibres) compared with control groups.<sup>19</sup> Regions of myocardial fibrosis have been described around vessels or interdigitating between bundles of fibres.<sup>19</sup> In a further study, 13 blocks of myocardium were sampled from each of 23 SUDEP cases, and a significant increase in deep and subendocardial fibrosis was shown in 40% of the SUDEP patients compared with the controls.<sup>49</sup> Cardiac fibrosis, however, has not been reported in all SUDEP series.<sup>47</sup>

One possible explanation for the finding of cardiac fibrosis in SUDEP is that seizures themselves damage the heart. In patients with long histories of frequent, recurrent seizures, hypoxia due to apnoea, possible coronary artery spasm occurring during a seizure,<sup>19</sup> or a catecholamine surge could theoretically induce an interstitial fibrosis. Excessive sympathetic drive is known to induce focal cardiac myocytolysis, myofibrillar degeneration, subendocardial congestion and haemorrhages, lipofuscin deposition in myofibrils and histiocytic infiltrates in the absence of acute infarction or coronary artery disease.<sup>6</sup> Focal cardiac fibrosis in SUDEP could represent a noteworthy finding and may lead to impaired cardiac conduction and re-entrant rhythms that are a risk for sudden death (Fig. 7). Detailed specific examination of the main cardiac conduction system has shown no abnormalities in SUDEP.<sup>47,49</sup> Abnormal sympathetic cardiac innervation and neural remodelling within the myocardium as a result of cardiac sympathetic activation during seizures have been suggested as plausible mechanisms of facilitating ventricular arrhythmias,<sup>5</sup> but have not been investigated thoroughly in SUDEP or experimental models. Future human research studies in SUDEP are needed involving extensive sampling of the heart following standard protocols in order to establish any relationship between cardiac pathology and SUDEP. RCPATH guidelines for autopsy practice in epilepsy deaths recommend that three blocks of left ventricle and one block of right ventricle are sampled to exclude vascular ischaemic damage or other causes of cardiac death, e.g. myocarditis. This limited sampling may mean that smaller foci of cardiac fibrosis are missed, and more generous sampling protocols of up to 10 blocks per case, as in the investigation of other sudden adult death cases,<sup>50</sup> may be a more cautious approach. In practice, the identification of cardiac interstitial fibrosis in the absence of coronary vascular disease should not preclude the diagnosis of SUDEP. Where there is an absence of a structural cardiac pathology and there is doubt



**Figure 7** (a) Regions of interstitial cardiac fibrosis in a patient with sudden and unexpected death in epilepsy. (b) EVG staining in a rat model of status epilepticus with small foci of myocardial fibrosis and inset regions of inflammatory cell infiltrates.

regarding the patient's epilepsy history, molecular genetic analysis to look for mutations associated with sudden cardiac death should be considered, particularly where there is a relevant family history.<sup>50,51</sup>

### Additional pathology

Several relevant non-central nervous system, non-cardiac changes may be identified. External examination may reveal evidence of previous trauma or burns in a patient with epilepsy. There may be evidence of recent tongue biting or lip contusion following a recent seizure. Cutaneous and visceral petichiae have also been reported.<sup>1,26</sup> Pulmonary oedema has been reported in 50–90% of SUDEP cases.<sup>25,26,47</sup> Lung weights in SUDEP cases do not differ from non-SUDEP cases.<sup>48</sup>

## Ancillary tests and final reports

Toxicology screening is important in the investigation of SUDEP to exclude a toxic cause of death and for the monitoring of anti-epileptic drug levels to assess compliance. Blood, urine and gastric contents should be analysed for anti-epileptic drugs, drugs of abuse and alcohol-level estimations. Vitreous humour should be taken for biochemistry if diabetes or another metabolic disorder is considered. Hair may also prove useful to test for long-term drug compliance.<sup>52</sup>

The autopsy report summary should document all morbid anatomical, histological and toxicological findings, describe how the epilepsy caused or contributed to the death, and state the aetiology of the epilepsy if ascertained. With increasing age, it is more likely that an 'alternative' cause of death that competes with the diagnosis of SUDEP will be found.<sup>48</sup> There may be cases where both epilepsy and a cardiorespiratory co-morbidity are considered to have contributed to death, and both should be recorded in order that epilepsy deaths are not under-recorded and these deaths do not remain 'in the shadows'.

### Practice points

- In patients with suspected SUDEP, autopsies are necessary to exclude other (including neuropathological) causes of death
- Where possible, the brain should be retained for neuropathological analysis in SUDEP
- Focal macroscopic cerebral abnormalities may be present in around half of SUDEP cases
- Examination of the heart may reveal areas of cardiac fibrosis in the absence of coronary artery disease
- The most likely mechanisms of sudden death include respiratory depression during a seizure or a cerebrogenic arrhythmia
- Research into SUDEP and epilepsy will include tissue-based studies, and if appropriate consent is available, tissue should be archived (fixed and frozen samples) for future studies

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