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

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Aims: Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of death in people with epilepsy. For classification of definite SUDEP, a *post mortem* (PM), including anatomical and toxicological examination, is mandatory to exclude other causes of death. We audited PM practice as well as the value of brain examination in SUDEP. **Methods:** We reviewed 145 PM reports in SUDEP cases from four UK neuropathology centres. Data were extracted for clinical epilepsy details, circumstances of death and neuropathological findings. **Results:** Macroscopic brain abnormalities were identified in 52% of cases. Mild brain swelling was present in 28%, and microscopic pathologies relevant to cause or effect of seizures were seen in 89%. Examination based on whole fixed brains (76.6% of all PMs), and systematic regional sampling was associated with higher detection rates of underlying pathology ($P < 0.01$). Information was more frequently recorded regarding circumstances of death and body position/location than clinical epilepsy history and investigations. **Conclusion:** Our findings support the contribution of examination of the whole fixed brain in SUDEP, with high rates of detection of relevant pathology. Availability of full clinical epilepsy-related information at the time of PM could potentially further improve detection through targeted tissue sampling. Apart from confirmation of SUDEP, complete neuropathological examination contributes to evaluation of risk factors as well as helping to direct future research into underlying causes.

Keywords: audit, neuropathology, post mortem, Sudden unexpected death in epilepsy, SUDEP

Introduction

In 2002, the findings from a national UK audit highlighted sudden and unexpected deaths in epilepsy as 'deaths in the shadows', being systemically under-recognized, under-reported and poorly investigated by

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health professionals [1]. Sudden unexpected death in epilepsy (SUDEP) is now recognized as a leading cause of premature death in young adults with epilepsy with an estimated incidence of 1.16 cases per 1000 people with epilepsy per year [2] and is currently the focus of international initiatives aiming to address causes and identify preventative strategies [3]. In the UK, an estimated 500 annual epilepsy-related deaths are considered to be SUDEP (Joint Epilepsy Council UK, 2011). Many of these deaths are potentially preventable, thus promoting focused, multidisciplinary research initiatives to understand risk factors and mechanisms that underpin SUDEP [4]. Post mortem (PM) examination is requisite for the confirmation of SUDEP, through exclusion of other causes of death. Correct classification of the cause of death in people with epilepsy is evidently essential to any future research, and to epidemiological studies. Examination of the brain also offers a resource for further investigation and understanding of the different pathological mechanisms that lead to SUDEP.

The main alternative categories of epilepsy-related death that are considered at a suspected SUDEP autopsy are an accident during a seizure (including traumatic brain injury or drowning), death as a result of a prolonged seizure (status epilepticus) or aspiration during a seizure [5]. In the majority of such deaths in England, a Coroner's PM is mandated (outer membrane procedures in many other countries). The main objectives are to exclude other diseases which can both mimic seizures in life and be a cause of sudden death (e.g. cardiac disease), to identify a cause for epilepsy, and to provide accurate PM data on the mode of death for any inquiry and for deaths registers.

Acceptance of SUDEP was an important issue prior to the National Sentinel Audit in 2002 [1]. A UK national confidential enquiry (NCEPOD) in 2006 into Coroners' autopsies also highlighted examinations in epilepsy deaths, including brain examination, as an area of specific concern. Guidelines for autopsy practice in epilepsy deaths were devised in 2006 by the UK Royal College of Pathologists (www.rcpath.org). The key recommendations were that (i) the pathologist should have information regarding epilepsy, including seizure control, treatments and the circumstantial evidence surrounding the death; (ii) ideally, a neuropathologist should be involved in the interpretation of the brain pathology; (iii) a case should be made for whole brain fixation and examination; and (iv) specific protocols were recommended for tissue sampling and toxicology, including sampling of key or 'essential' brain regions known to be more vulnerable in epilepsy-related injury, of potential relevance to the mode of death, and to exclude other pathology. This document was formulated to provide guidance for overall good practice for general pathologists and neuropathologists, and to provide information for coroners and other personnel dealing with unexpected deaths in people with epilepsy.

The aim of this study was to review SUDEP PMs carried out in different neuropathology centres across England, including the methods practised and findings, to audit against current standards from the Royal College of Pathologists and to evaluate the contribution of brain examination to these PM investigations.

Methods

PM reports from unexpected deaths in people with epilepsy were audited from four participating neuropathology centres serving different regions of England (South-East, National Hospital for Neurology and Neurosurgery; South-West, Plymouth, Derriford Hospital; North-East, Newcastle-upon-Tyne, Royal Victoria Infirmary; and North-West, Preston, Lancashire Teaching Hospitals). The PM reports were ascertained from the period 1991–2014, with 65.5% of these deaths occurring after the 2002 UK National Sentinel audit into epilepsy-related deaths. In all cases, there was either consent from the next of kin for use of brain tissue and data in research or agreement from the Coroner (Table 1). Cases were included in which a diagnosis of SUDEP or likely SUDEP was included in the conclusion of the report, and other modes of epilepsy-related deaths (e.g. status epilepticus) or those confirmed as accidental deaths (e.g. head injury or drowning) were excluded.

All aspects of clinical information regarding the deceased's epilepsy history and investigations, the circumstances surrounding the death, the findings at PM examination, including general histology and toxicology as well as the pathological methods and findings from brain examination, were extracted from the reports. Where there was missing information for any component, for example regarding EEG findings, this was recorded as 'missing', and no additional attempt was made to retrieve data from clinical records, families or Coroner's Offices. Regarding the neuropathology, the findings were taken from those detailed in the reports. Re-review of brain material or slides was not undertaken. Statistical analysis of the data was carried out with SPSS (v20 IBM,

Table 1. The regional distribution of 145 SUDEP cases from four centres in the UK contributing to this study

*Region of England**	*Centre*	*Period from which PM reports taken*	*Cases after 2002 (%)*	*Number of cases*	*Coronial autopsies (%)*	*Neuropathology examination based on whole fixed brain (%)*
South East	London, National Hospital	1991–2013	52	79	81	92.4
South West	Plymouth, Derriford Hospital	2007–2012	100	10	100	100
North West	Preston, Lancashire Hospital	1999–2011	60	30	100	46.7
North East	Newcastle Royal Victoria Infirmary	2009–2013	100	26	100	53.8

The sample from the centres represent a proportion of epilepsy deaths from these periods indicated. These were taken from archives where consent for research purposes was available from the two centres in the South. In the two centres from the North of England, Coroner's permission was given for inclusion of data in cases included.*This denotes the approximate region of England served by this neuropathology service.PM, post mortem.

San Jose, Incorporation, CA, USA) using non-parametric tests (including Mann–Whitney).

Results

We included PM reports of 145 individuals (89 males) with a mean age of death of 40 years (range 2–82 years); 90% were Coroner's autopsies. Neuropathological examinations were based on the whole fixed brain in 111 cases (76.6%), with some variation of practice noted between centres (Table 1).

Clinical epilepsy history

The age of epilepsy onset was documented in 95/145 (66%) reports (mean age: 17.9 years, mean duration of epilepsy of 23.2 years; Table 2). Most (53%) had a duration of epilepsy of over 10 years; 12% had a recent onset/diagnosis (occurring in the 2 years prior to death). There were cases in this audit where death occurred within a year of onset of epilepsy in people who only had a few seizures.

The underlying cause of epilepsy was ascertained from 73/145 (50%) of the reports. This was either stated as such, or where highly epileptogenic pathologies such as malformations of cortical development (MCD) or tumours were identified, these were assumed to be the cause of seizures. Underlying structural/metabolic causes [6] (previously termed 'symptomatic', focal or lesion-related epilepsies) were the most frequent type, seen in 41% of the whole series. Temporal lobe epilepsy or post-traumatic epilepsy categories were based on clinical diagnosis alone and not the identification of hippocampal sclerosis or old traumatic injuries (Table 2). Idiopathic and genetic epilepsies each occurred in 5%; underlying genetic conditions were Down syndrome (three cases), Dravet syndrome (two cases) and Di George syndrome/velocardiofacial/22q11.2 deletion syndrome (two cases). In addition, there was one case each of neurofibromatosis type 1 (pilocytic astrocytoma) and Tuberous Sclerosis in individuals with lesion-related epilepsy. We found an association between structural epilepsies and a shorter duration of epilepsy prior to the sudden death (Figure 1).

Information regarding anti-epileptic drug treatments, including the number of drugs as well as the type, was documented in 121/145 of reports, with 54% maintained on two or three medications. In 64/145 (44%) of reports, the type(s) of seizures were not further detailed. Generalized tonic–clonic seizures were the most common reported seizure type, found in 76/145 (52%). Deaths often occurred during the night, but nocturnal seizures were only recorded in 8.3% of all cases (Table 2), and in only 10 cases were previous episodes of status epilepticus reported. General statements on seizure frequency/control, for example 'refractory epilepsy' or 'well-controlled epilepsy', were documented in 68% of reports; in 19%, a recent deterioration in seizure control was specifically suggested in the period prior to death. The time of the last seizure was documented in 28 reports, the majority occurring in the 24 h before death (Table 2). Information regarding relevant clinical investigations, specifically EEG or MRI/neuroimaging, was recorded in only around a third of all reports.

Circumstances of death and recent seizures Overall, there was more comprehensive documentation of the death scene in the PM reports (Table 3). In 126/145 (87%), there was information regarding whether the death was witnessed or not; the deaths were unwitnessed in 105 cases. In nine of the 21 witnessed cases, resuscitation attempts were

Table 2. Information available in PM reports regarding epilepsy histories and investigations

Clinical feature	*Number (*N *= number where specific information noted in report)*	*Percentage (of whole series of 145 cases unless indicated)*
Age of onset	17.9 years (range 0–82), *N* = 95	66
Duration of epilepsy	23.2 years (range 1–74), *N* = 96	66
Recent onset (1–2 years)	17	12
Intermediate duration (3–10 years)	13	9
Chronic epilepsy† (>10 years)	77	53
Epilepsy syndrome/cause specified	73	**51**
Idiopathic syndromes		**5**
Idiopathic (NOS)	3	2
Primary generalized epilepsy	2	1.4
Juvenile myoclonic epilepsy	2	1.4
Genetic syndromes		**5**
Dravet syndrome	2	1.4
DiGeorge syndrome	2	1.4
Down syndrome	3	2
Structural/metabolic		**41**
Post-traumatic epilepsy	9	6.3
Post-encephalitic	2	1.4
MCD	6	4
Tumours/operated lesions	10	7
TLE*	9	6.3
Based on clinical/EEG‡	12	8.3
Perinatal infarcts (ulegyria)	4	3
Old infarcts	1	0.7
Alcohol-related seizures	6	4
Epilepsy syndrome unknown/not specified	72	**49**
Seizure types		
'Seizures' NOS	64	44
Nocturnal seizures documented	12	8.3
Generalized seizures	76	52
Focal/partial seizures§	41	28
Myoclonic seizures	10	7
Episodes of Status epilepticus	10	6.9
Other seizure types¶	16	11
General information of seizure frequency/control	99	68
Recent deterioration in control	28	19
No change in seizure pattern	32	22
Time of last seizure recorded prior to death	19.1 h (range 0–240) *N* = 28 (*N* = 25 in last 24 h)	
History of previous CNS trauma	34 (*N* = 100)	34**
MRI/neuroimaging report available at time of PM	51	35
EEG report findings available at time of PM	46	32
Information on AED taken	121	83
No AED	6	5**
1 AED	36	30**
2–3 AEDs	65	54**
More than 3 AEDs	14	12**

The percentage of cases in the main epilepsy categories are shown in bold. *TLE cases were classified as such based on the clinical diagnosis only and not by the identification of hippocampal sclerosis at PM. Similarly, cases were only classified as post-traumatic epilepsy when this was documented in the reports and not based on the finding of old brain injury at PM. In cases with pathological identification of known epileptogenic tumours and malformations, such as dysembryoplastic neuroepithelial tumours and focal cortical dysplasia IIB, these were assumed as the underlying cause of epilepsy.†Duration of epilepsy: In some cases, the report stated 'onset of seizures in childhood' without specifying exact age of onset; where the death was in adulthood, a duration of >10 years was assumed.‡Cases of focal epilepsy based on clinical/EEG diagnosis included cases with frontal lobe epilepsy; in some of these cases, no underlying pathology was confirmed at PM.§Focal/partial seizures included documented complex partial seizures in TLE.¶Other seizure types noted in the PM reports included febrile seizures, atonic seizures and absence seizures. AEDs: This refers to information available of AEDs prescribed at the time of death, and in all these cases, the named drugs were recorded in the PM reports.**In these cases, the percentage is in relation to the number of cases where information was available rather than the entire series of 145 cases.MCD, malformation of cortical development; NOS, not otherwise specified; AED, anti-epileptic drugs; TLE, temporal lobe epilepsy; PM, post mortem.

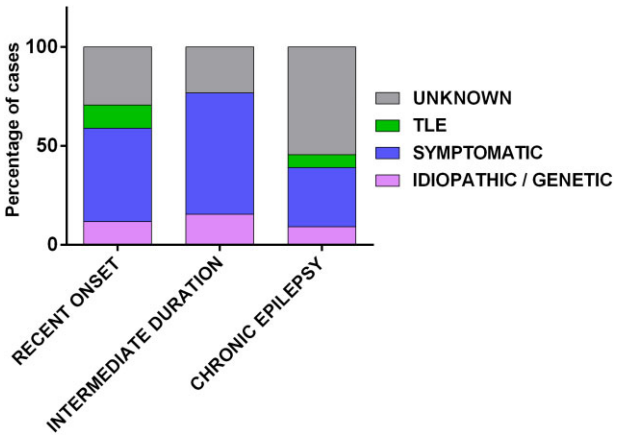

Figure 1. Bar chart of epilepsy syndrome in relation to chronicity of epilepsy in SUDEP cases. Recent onset epilepsy cases = onset in the 2 years prior to death, intermediate duration = 3–10 years of epilepsy prior to death, and chronic = more than 10 years of epilepsy prior to death. There was a significant difference in the epilepsy syndromes between the three groups with more structural/lesion-related and temporal lobe epilepsies in recent and intermediate cases compared with chronic epilepsy ($P = 0.05$).

followed by variable short survivals without regain of consciousness; such cases are termed 'near miss' SUDEP in the new classification system [7]. Convulsive seizures were not reported in all witnessed deaths, but terms such as 'collapse/cardio-respiratory arrest/apnoea' were used. Information regarding the location of the body was recorded in 114/145 (79%) of cases, mostly occurring in the domestic environment. In 60% of all cases, the death occurred in the bedroom setting (Table 3). In nine cases, the body was found on the floor just adjacent to the bed. Circumstantial evidence or witness statements from the PM report suggested that the death had probably occurred nocturnally or during sleep in 49%. In seven cases, the body was found in a bath, but evidence of drowning was not confirmed at PM. Detail was recorded regarding the position of the body in 61/145 (42%) reports, with potential external airway compromise or prone position (typically face down on bed) noted in 39% (Table 3).

Neuropathology findings There was positive documentation of findings on external examination of the body of potential relevance to a recent seizure in only 46/145 (32%) of cases, with tongue or lip biting reported in 21 cases (Table 4). Regarding the internal examination, evidence of lung congestion or variable degrees of pulmonary oedema was a frequent macroscopic finding, reported in 99/145 (68%).

Macroscopic brain abnormalities were recorded in 76/145 (52%) (Table 4, Figure 2). These included potentially epileptogenic lesions such as MCD, perinatal infarcts and low-grade tumours. Specific macroscopic abnormalities of the hippocampi were documented in 28% of cases, including asymmetries, volume loss and mal-rotational abnormalities. Mild degrees of brain swelling were reported in 28% of cases; this was based on report descriptions of swelling, excessive 'fullness' of the brain with flattening of the gyri over the convexities (Figure 2**A**), an exaggerated impression of the tentorium on the unci or by assessment by the level of the Greenhall line. No significant swelling or tonsillar herniation was reported in any case. Brain weights were recorded in 136/145 (94%) cases, and in 55, both the fresh and post-fixed fixed weights were recorded. There was no significant difference in brain weights, stratified according to age and sex, between all SUDEP cases and reference control values [8] (Figure S1). There was a significant increase in brain weights in SUDEP cases with reported swelling compared with those without swelling ($P < 0.005$). Mild increases in brain weight were noted for females with macroscopically normal or mildly swollen brains compared with age-matched reference control values [8,9], but these were not significant (Figure S1).

Microscopic neuropathology was reported in 89% of cases overall. The most common potentially epileptogenic pathologies either diagnosed or confirmed microscopically included malformations (MCD and vascular) (15%), tumours or mass lesions (7%) and hippocampal sclerosis (21%; Table 4, Figure 2). Unilateral hippocampal sclerosis was more common on the left side in this series. Malrotational abnormalities of the hippocampus were noted in 14 cases. Secondary neuropathologies, probably a consequence of seizures, included cerebellar atrophy of varying degrees (41%); mild atrophy was noted histologically as evidenced by Purkinje cells loss in 12% and severe atrophy, detectable macroscopically, in 29% (Table 4). Old traumatic brain injuries were identified in 17%, which included cases without a clinical diagnosis of post-traumatic epilepsy. The commonest reported histological finding was acute eosinophilic neuronal (AEN) change, observed in 80/145 (55%) (Table 4, Figure 2**C**). In the majority of cases, AEN was limited to the hippocampus, typically the CA1/subiculum territory, but in 16%, more widespread AEN was seen involving more than one brain region, such as cortex, basal ganglia, thalamus and cerebellum. In 6/7 'near-miss' SUDEP cases, AEN was

Table 3. Circumstances of death

Category	*Number (N = number where specific information noted in report)*	*Percentage (of whole series of 145)*
Death witnessed		
Not witnessed	105	72
Witnessed	21	15
No information	19	13
Evidence of seizure around time of death		
Seizure confirmed	18	12
Suspicious†	36	25
No evidence	49	34
No information	42	29
Nocturnal death*		
Yes	71	49
No	41	28
No information	33	23
Location of body		
In bed	62	43
Bedroom/floor next to bed	25	17
Bathroom	5	3.5
In bath	7	5
Other room/place	15	10
No detail of location	31	21.5
Position of body		
Face down	43	30
Potential airways compromise‡	13	9.0
No airways compromise	5	3.4
No detail on body position	84	58

†Suspicious signs for seizure include micturition, tongue biting noted at scene or based on body position and disrupted environment. *Nocturnal deaths included deaths during sleep/rest or where the person was found in bed even if the body was found during the day. The position of the body in the majority of reports was specifically stated in the Coroner's report and only in a minority of cases by the distribution of post mortem hypostasis on the body.‡Potential external airways compromise was defined as being present when an object was found over the mouth/face (e.g. duvet, pillow) or the position of the neck suggested possible compromise to upper airways.

extensive. Clinical-pathological correlations showed significantly more AEN in SUDEP cases where there was a prone body position, external airways obstruction or brain swelling, than without these features ($P < 0.01$) (Figure 3). AEN was present in 68% of cases where a seizure was reported in the 24 h prior to death. Further minor histological changes noted included single foci of axonal injury (one case), foci of inflammatory cell infiltrates (11 cases), mineralization of basal ganglia and vessels (six cases), gliosis of the amygdala (two cases), and granule cell dispersion in the hippocampus in the absence of hippocampal sclerosis (six cases).

We evaluated the identification of neuropathology in relation to the method of brain examination. In 111/145 (76.6%), the neuropathological examination had been carried out on the whole fixed brain. In 17% (24/145), neuropathology examination was based on slicing of the fresh brain at time of the autopsy by a neuropathologist with sampling of selected regions for histology. In the remaining 10/145 cases, the whole brain was not examined by a neuropathologist before histological analysis. The number of tissue samples or blocks taken for histology was recorded in 123 cases with a mean number of 12.5 blocks per case. The reports were also reviewed to investigate whether six essential brain regions (amygdala, hippocampus, watershed cortical region, cerebellum, basal ganglia and brainstem) had been examined histologically or if sampling was more limited. In 143 of the reports, these data were retrievable, and in 58%, all regions were examined, with one essential region absent in 30% and more than one region not examined in 12%. The most common region not submitted for histology was the amygdala. Examination of the whole fixed brain compared with other methods ($P < 0.01$) and examination of all essential regions microscopically compared with more limited sampling ($P < 0.05$) were associated with

Table 4. Neuropathological and PM findings

Pathology finding	*Number*	*Percentage*
External findings/general PM examination		
Relevant to SUDEP* (cases with recent tongue /lip biting)	46 (21)	32 (14.5)
No relevant findings	62	43
Missing data	37	25
Pulmonary oedema/congestion	99	68
Macroscopic brain examination		
Macroscopic abnormality (specific hippocampal abnormality†)	76 (41)	52 (28)
Mild brain swelling	41	28
Cases with microscopically confirmed localized lesion(s)‡	66	46
Categories of potential 'epileptogenic' lesions		
Malformation types (MCD and VM)	22§	15
FCD type IIB	4	
Tuberous sclerosis	1	
Hemimegalencephaly	1	
Grey matter heterotopia	3	
Polymicrogyria	2	
Ulegyria/perinatal cortical infarct (+ associated FCDIIId)	4	
Other FCD types (FCD I and mild MCD)	3	
Aicardi syndrome	1	
Vascular malformations	7	
Tumours/lesions	10	6.8
DNT, oligodendroglioma, PA, meningioma, astrocytoma II, ganglioglioma	6	
Old surgical scars	4	
Hippocampal sclerosis (confirmed on histology)	31$	21
Left side	15	
Right side	6	
Bilateral	9	
HIPMAL (macroscopic/microscopic)	14	9.7
Categories of secondary neuropathology (sequel of seizures)		
Old traumatic brain injuries/contusions#	24	17
Old CVA	10	6.9
Mild cerebellar atrophy (microscopic)	17	12
Severe cerebellar atrophy (macroscopic)	42	29
Evidence of acute neuronal injury (AEN)	80¶	55
CA1/subiculum	36	
Other location (cortex, basal ganglia)	16	
Extensive changes	25	

*Relevant external PM findings include recent injuries or skin abrasions, evidence of incontinence prior to death, petechial haemorrhages, and tongue or lip biting.†Specific hippocampal macroscopic abnormalities include evidence of volume reduction, asymmetry or rotational abnormality.‡Localized pathological lesions included structural abnormalities that could be a cause or effect of seizures but excluded diffuse microscopic changes as AEN, cerebellar atrophy as well as lesions of uncertain significance (e.g. HIPMAL). # Old traumatic brain injuries were mainly cortical contusions.§A proportion had more than one MCD, for example complex malformations as polymicrogyria and heterotopia or vascular malformations and cortical malformations were reported in four cases. Hippocampal sclerosis included all patterns of sclerosis but not the finding of end folium gliosis or dentate granule cell dispersion alone ($In one case the side of sclerosis was not stated). HIPMAL was evident macroscopically or only microscopically and either bilateral or unilateral.¶In three cases, the distribution of acute eosinophilic neurones (AEN) was not further detailed.FCD, focal cortical dysplasia; MCD, malformations of cortical development; VM, vascular malformations (AVM and telangiectasia); DNT, dysembryoplastic neuroepithelial tumour; PA, Pilocytic astrocytoma; CVA, cerebro-vascular accident; HIPMAL, hippocampal malrotational abnormality.

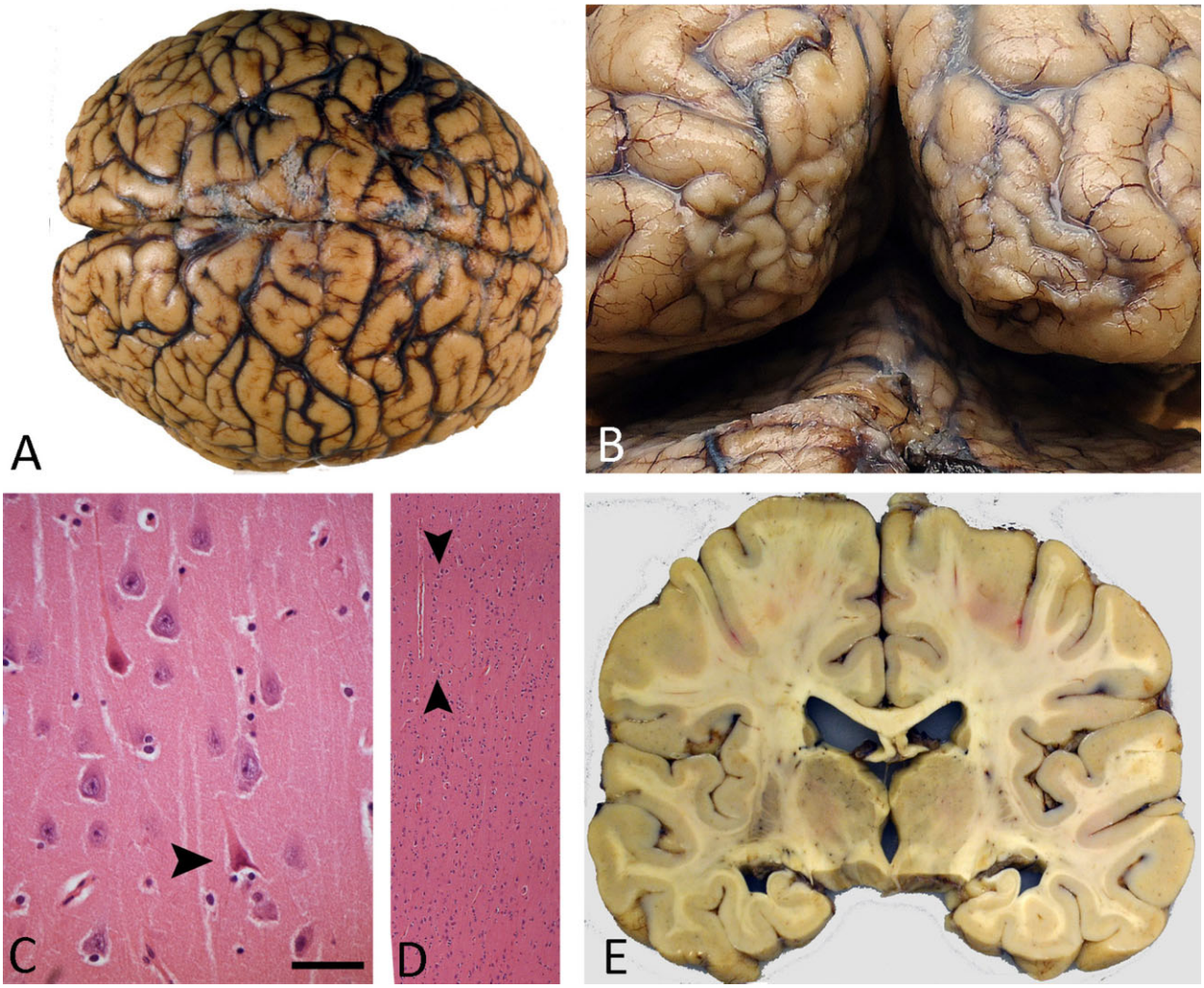

Figure 2. Examples of some of the neuropathological abnormalities in SUDEP. (**A**) Evidence of brain swelling in SUDEP with gyral flattening over convexities in a 39-year-old female. (**B**) Bilateral occipital ulegyric malformation following a focal perinatal ischaemic event, simulating polymicrogyria, in a 52-year-old male with SUDEP. (**C**) Acute eosinophilic neuronal change in the CA1 sector with scattered pyramidal neurones showing this alteration in SUDEP (arrow) (**D**). An individual with a clinical diagnosis of DiGeorge syndrome showing an impression of exaggerated micro-columnar cytoarchitecture (arrows showing columns of >10 neurones and loss of horizontal lamination) in the middle temporal lobe gyrus; also in this case, bilateral hippocampal atrophy was due to hippocampal sclerosis (**E**) with an impression of incomplete hippocampal inversion with an upward pointing hilus. Bar is equivalent to 40 microns approximately in (**C**) and 250 microns in (**D**).

significantly higher rates of detecting relevant pathology (Figure 4).

Categories of SUDEP Based on the data available from each PM report, the cases were re-classified as definite, probable, possible or 'near-miss' SUDEP according to the latest classification [7] (Table 5). Definite and probable SUDEP represented approximately three-quarters of cases. The categories were compared between SUDEP PMs carried out before and after 2002 (the time of publication of the UK Sentinel audit); there were more definite SUDEP cases reported after 2002 (46% *vs.* 20%), and overall classifications were significantly different between these eras ($P < 0.005$).

Discussion

The main findings in this audit of SUDEP PMs were the frequent finding of macroscopic brain abnormalities of relevance to the cause or effects of epilepsy in over half the

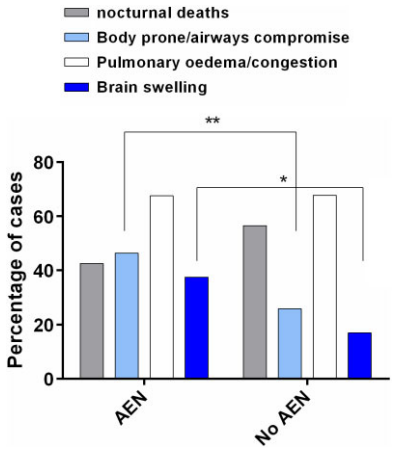

Figure 3. Acute eosinophilic neuronal (AEN) change in SUDEP cases and clinical-pathological correlations. The presence or absence of AEN change was correlated with four features identified at post mortem: whether the death was presumed nocturnal/during sleep; whether the body was found prone or there was a suspicion from the position of the body of an element of external airways compromise; the presence of pulmonary oedema/congestion; whether or not there was brain swelling. Significant differences are shown as $^{**}P = 0.001$ and $^{*}P = 0.008$.

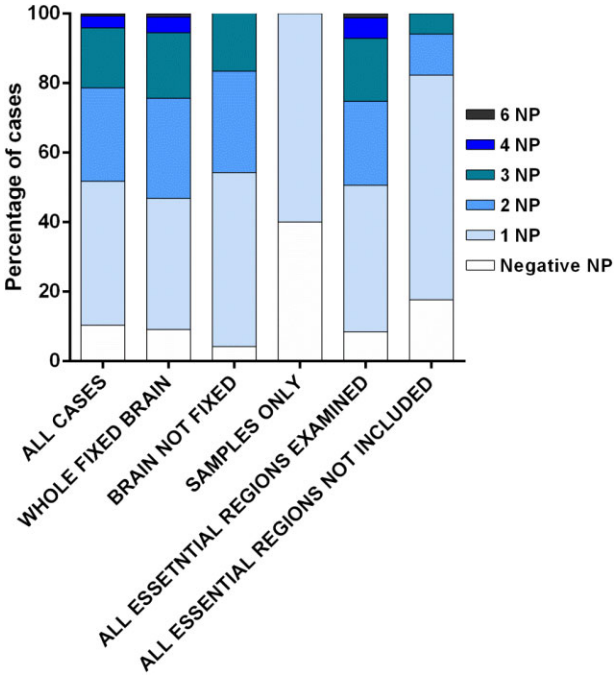

Figure 4. Identification of relevant neuropathology in relation to brain examination methods and sampling protocols. The number of different neuropathologies identified either macroscopically and/or microscopically per case was evaluated. These included the following nine categories: old traumatic brain injury, tumours, malformations, old infarcts, hippocampal sclerosis, hippocampal malrotation, cerebellar atrophy and acute neuronal injury. This was evaluated in all SUDEP cases, and only 11% had normal neuropathology with the maximal number of neuropathologies identified in a single case as six. This was further evaluated according to the different protocols of (i) whole brain fixation, (ii) no fixation of the brain/fresh sampling, and (iii) histological samples only were evaluated by neuropathologist/general pathologist (i.e. whole brain not available for neuropathologist to review). There was a significant difference in the identification of neuropathology between these methods ($P < 0.01$). In addition, cases where all the essential brain regions were included (as outlined in the Royal College of Pathologist's document, Scenario 6 deaths in epilepsy, 2006), and cases where essential regions were not included were compared; there was also a significant difference in the number of pathologies identified between these different methods ($P < 0.05$).

cases and microscopic abnormalities in 89%. Incomplete documentation of clinical epilepsy history was noted, with more complete recording of the immediate circumstances surrounding the death. Furthermore, brain abnormalities were more frequently detected following the recommended practice of whole brain fixation and adherence to a systematic regional brain sampling protocol. This audit also demonstrates that PM examinations have become more thorough following the National Sentinel Audit, with more cases being categorized as 'definite' SUDEP.

In SUDEP, by definition, no cause of death is identified. This has perhaps led to a misconception that brain examination is non-contributory and a rigorous, systematic neuropathological examination not always necessary. Previous national enquiries and audits have highlighted that neuropathological examinations in epilepsy deaths are often omitted (https://www.sudep.org/national-audit-epilepsy-deaths-0 and http://www.ncepod.org.uk/2006Report/index.html). In three previously reported series of SUDEP which detailed brain PM findings, neuropathology-negative cases represented between 34% and 91% of cases [10–12] compared with only 11% in the present series (Table 6). The range of pathologies reported in all series were similar, but the frequency of all pathology types, with the exception of old traumatic brain injuries, was higher in the current series (Table 6). The age and sex demographics are similar across the four series, and we attribute the higher detection rates of pathology in our series to the fact that examinations were based mainly on fixed whole brains, subjected to systematic histological sampling and conducted primarily by neuropathologists. Indeed, it was previously noted that higher detection rates for intracerebral pathology followed whole brain fixation [10]. Within our four-centre cohort, there was some regional variation in the method of brain examination, which mainly reflected restrictions imposed by local

Table 5. Categories of SUDEP

Category SUDEP	*Number (%)*	*Definition**	*Mean age (years)*	*Number (%) of cases pre-2002 (N = 50)*	*Number (%) of cases post-2002 (N = 95)*
Definite SUDEP	54 (37)	All criteria met for SUDEP All results of PM examination available	16.8	10 (20)	44 (46.3)
Probable SUDEP	57 (39)	Criteria met for SUDEP apart from: Missing toxicology report or Missing organ histology report	15	25 (50)	32 (33.7)
Possible SUDEP	14 (10)	A competing potential cause of death identified at PM*	34.8	4 (8)	10 (10.5)
Near Miss SUDEP	7 (5)	Resuscitation following a seizure event with no recovery but variable short survival of hours to few days	41.0	4 (8)	3 (3.2)
Combined SUDEP	13 (9)	Possible + probable (10) Probable + near miss (2) Possible + near miss (1)	11.3	7 (14)	6 (6.3)

In addition to the SUDEP categories [7], we included a 'combined SUDEP' group where criteria for two of the following were met in the same case: 'possible', 'probable' or 'near-miss' SUDEP. The age of death was older, but not significantly, in the possible SUDEP compared with the definite and probable SUDEP groups. The categories were compared between SUDEP PMs carried out before and after 2002 (the time of publication of the UK Sentinel audit); there were more definite SUDEP cases in the post-2002 group and overall significant differences in the categorization of the SUDEPs between these two eras ($P = 0.003$).*Competing causes of death in this series included evidence of coronary artery disease (10), cardiac hypertrophy (2), suspected early bronchopneumonia but not confirmed by histology (2), evidence of aspiration at PM not confirmed by histology (3) and cases where the deceased was found in the bath but drowning not confirmed at post mortem (7): All these cases, on balance of the available information, favoured SUDEP as the cause of death.

Table 6. Comparison of neuropathological findings in previous reported SUDEP series compared with present series [9–11]

Series	*Shields* et al. *[11]*	*Black and Graham [10]*	*Zhuo* et al. *[12]*	*Current study*
Number of cases	70	131	74	145
Nature of cohort	Forensic autopsy series: State of Kentucky, USA	Forensic autopsy series; Glasgow, UK	Forensic autopsy series; State of Maryland, USA	Neuropathology centres, UK
Age range (years)	16–71	3–74	14–63	2–82
Male (%)	54%	64%	58.1%	61.1%
Cases with whole brain fixed	No information	31.3%	No information	76.6%
Cases with brain histology	73%	31.3%	32%	100%
Brain swelling	No information	–	Not mentioned	28.3%
Traumatic lesions	27.1%	% Not stated	13.5%	16.6%
Cortical malformations	0%	–	6.8%	14.5%
Vascular malformations	2.8%	–	4.1%	
Hippocampal sclerosis	12.8% (cortical and hippocampal atrophy)	7.3%	2.7% ('gliosis')	21.4%
Old infarcts	–	–	2.7%	6.9%
CNS tumours	3%	–	2.8%	13%
Cerebellar atrophy	14.2%	–	5.4%	40.7%
Acute hypoxic–ischaemic change/AEN	No information	% Not stated	1.4% (hippocampus)	55.2%
No pathology findings	54.2%	34% (Fixed brains) 91% (Fresh brains)	41.9%	11%

AEN, acute eosinophilic neurones.

coronial practice in individual cases. In 2006, the Royal College of Pathologists issued guidelines on autopsy practice in epilepsy deaths, recommending that a neuropathologist should be involved in the interpretation of the brain pathology and that a case should be made for whole brain retention as best practice. This current study was not designed to assess what proportion of sudden epilepsy deaths is currently being referred to neuropathologists in the UK. It does show, however, that when such 'best practice' guidelines are implemented, underlying pathology relevant to the cause of epilepsy and death is significantly more likely to be detected.

In parallel with the frequent detection of focal, potentially epileptogenic, neuropathology, symptomatic/structural epilepsies were the most common epilepsy syndrome, estimated at 41% in this current series and more frequent in SUDEP cases with shorter epilepsy histories than those with longer histories. In epidemiological studies, the percentage of epilepsies considered to be structural/localization-related varies from 9% to 62%, largely dependent on age and the population studied [13]. In the UK, around a third of epilepsies are considered idiopathic/genetic [14]. High rates of symptomatic/structural epilepsy in SUDEP have been previously noted [12,15,16], implying that a structural brain anomaly may be a risk factor. The mechanism for any increased risk is unknown, and no specific lesions have been singled out. Hippocampal sclerosis was observed, unilaterally or bilaterally, in 21% in this series, which is less than reported in surgical (33.6–66% [17,18]) and PM epilepsy series (30.5–45% [19,20]). We did note more frequent involvement of the left than the right hippocampus, which in view of different anatomical connectivity with other brain regions [21,22] may be of potential significance to the mechanism of death. Hippocampal malrotational abnormalities were noted in 9.7% of SUDEP cases; the degree of abnormality varied, with some apparent macroscopically and others only visible microscopically, with hyperconvolutional folds of CA1/subiculum in the hippocampal body [23]. MRI studies have shown hippocampal malrotation in people with epilepsy [24], but a frequency of 19% has been reported in series of healthy volunteers [3]. The significance of hippocampal malrotation in epilepsy, or as a pathological risk factor for SUDEP, is therefore uncertain. One limitation of this study is potential ascertainment bias as it reflects current referral practice to only four neuropathology centres; certain types of epilepsy may be under-represented.

Detailed clinical information at the time of PM provides security regarding the epilepsy diagnosis as well as directing tissue sampling to identify any underlying subtle cortical abnormalities; this was not always available to pathologists based on recorded information in the report. Circumstantial details of the death scene were more consistently reported. The observation of SUDEP primarily occurring in the domestic setting, many being nocturnal and the majority in the bedroom and unwitnessed, is consistent with previous reports [25]. Information regarding body position can provide further information on potential contributing factors to the mode of death, such as upper airways obstruction following a seizure. Prone position of the body has been strongly associated with risk for SUDEP, and has already been established in SIDS [24]. Information on body position was not always detailed, and there is potentially a bias for including 'positive' findings in PM reports, such as 'body found face down' and 'tongue biting present', whereas negative/absent findings, which are equally important, are not always stated. Only 30% of the series were reported to be found in the prone position, but this represents 70% of cases in which positional information was reported. There were also several cases in this series where the body was found on the floor adjacent to the bed, suggesting a traumatic component to a final unwitnessed seizure. There are likely to be several causes of SUDEP, not only in terms of the underlying epilepsy substrate but also in the combination of pathophysiological conditions that determine the final sequence of events, as has been shown in SIDS [26]. Therefore, precise documentation of potential contributing agonal factors is important in classifying each case for future research purposes.

AEN was the most frequently reported microscopic finding, more often observed in the hippocampus. This cytopathological change is considered to represent acute ante mortem neuronal injury, as supported by studies showing HSP-70 and HIF-1α hippocampal neuronal expression in SUDEP [27,28]. AEN is commonly stated as being histologically detectable after 4–6 h following the injurious cerebral 'event' [29], which could include either cerebral hypoxia or a seizure, implicating a prolonged agonal period in the majority of SUDEP cases. In the MORTEMUS study, witnessed seizure-related deaths in an epilepsy monitoring unit occurred within 3–8 min of the terminal seizure [30]. In this current series, AEN was noted in witnessed sudden deaths with short survival times ('near miss' cases) but was also frequent in cases with a seizure reported in the 24 h prior to death. In terms of its cause, we showed a correlation of AEN with prone body position as well as evidence of brain swelling, and both these features could suggest impaired brain perfusion/oxygenation. Aside from these issues regarding timing and cause of AEN in SUDEP, its distribution could reflect cellular/network dysfunction of relevance to understanding the physiological mechanisms leading to, or resulting from, the fatal seizure.

The reporting of brain swelling itself may also be relevant to the final mechanism of death. Brain swelling

has been quoted as a 'common' finding in SUDEP; cases with tonsillar herniation have been described [31]. In our series, brain swelling was noted in 28% to a mild or 'non-significant' degree with flattening of the gyri, and/or prominent uncal grooving, but no cases with significant swelling and tonsillar herniation were reported. Objective measures of swelling, such as the Greenhall line measurement, were rarely recorded, possibly due to the lack of any caudal mesencephalic shift. Brain weights, however, were consistently recorded, and although dependent on gender, age, BMI, accuracy and calibration of equipment, completeness and fixation state of the specimen, we noted significantly higher brain weights in SUDEP cases with swelling than without. We did not, however, find any overall significant difference between all SUDEP cases and age–gender-matched control values. As seizure-related brain atrophy, as well as lesions such as hemimegalencephaly, may alter brain weight in either direction, we also analysed only SUDEP cases without macroscopic brain pathology, but there was only a trend for higher brain weights in females with SUDEP than in controls. One possible cause of the brain swelling is seizure-mediated vasogenic oedema as sometimes noted on post-ictal MRI and following status epilepticus [32,33]. As even mild degrees of brain swelling could potentially affect brainstem function through compression, improved recording of brain swelling in SUDEP PMs would be valuable.

Underlying genetic causes of epilepsies are increasingly recognized [34] with some syndromes, such as Dravet syndrome, associated with an increased risk of SUDEP [35]. There is considerable interest in the identification of candidate genes linked to SUDEP as those involving ion channels [36,37]. It is unlikely that all SUDEP cases have an underlying genetic cause, but identification of genetic associations and mechanisms [38] affords an important opportunity for understanding critical processes that could be more widely implicated. It is possible that some genetic epilepsies, for example mild forms of Dravet Syndrome, were under-recognized, but in this series, only a minority had known underlying genetic disease. These included two individuals with DiGeorge syndrome (velocardiofacial syndrome/22q11.2 deletion syndrome), which has high phenotypic variability affecting multiple organs including the heart [39]. Although epilepsy is not a prominent feature [40], brain malformations including heterotopia [41], subtle FCD-like microcolumnar cortical architecture [42] as well as hippocampal malrotational abnormalities [43] have been previously reported in Di George syndrome, as noted in one of our cases (Figure 2). Attention to subtle malformations in this condition may provide insight into causes of epilepsy and SUDEP. Furthermore, microscopic malformations of the brainstem and the dentate gyrus have been reported as relevant in SIDS [44], and in this study, granule cell dispersion was recorded in six SUDEP cases in the absence of sclerosis. These observations suggest that a systematic analysis for microscopic malformations in SUDEP is also warranted.

We were able to re-categorize the SUDEP cases according to revised definitions [7], with more than three-quarters of cases classified as definite or probable. In the majority of probable cases, one or more pieces of information were lacking from the records: Either the organ histology or the laboratory toxicology report was not available at the time of the neuropathology report or a test was missing. We were able to demonstrate improved practice since the 2002 audit, with more cases assigned to the definite category. Definite SUDEP cases also need to be separately recorded from 'possible SUDEP' where competing pathologies or circumstances (including deaths in the bath with no pathology evidence of drowning) imply an element of uncertainty regarding the final mode of death.

This study identifies high rates of neuropathology in SUDEP and justifies the current PM guidelines of the Royal College of Pathologists for a thorough neuropathological examination as recommended best practice. It highlights improvements in PM practice since 2002 but also points out areas that could be further improved to enable the most accurate ascertainment of SUDEP in line with our current knowledge of this condition. This will provide more robust epidemiological data for national and epilepsy deaths registers (e.g. sudep.org.uk) and for research centres undertaking tissue-based SUDEP research (http://csr.case.edu/index.php/Main_Page).

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Author contributions

M Thom: data collection, analysis and writing manuscript. Z Michalak and G Wright: case and data collection and analysis. T Dawson, D Hilton and A Joshi PM: post mortem data collection and critique of manuscript, and T Dawson: design of audit. B Diehl, M Koepp, S Lahtoo, L Sander and S Sisodiya: design of study, interpretation and presentation of audit data, and findings and critique of manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Bar graph of mean brain weights in males (**A**) and females (**B**) with SUDEP. These are shown for all SUDEP cases for each gender, for cases with no macroscopic brain abnormality and cases with evidence of mild brain swelling. Although increases in brain weight were noted, particularly for females from 35 to 54 years with macroscopically normal brains or mildly swollen brains, these were not significantly different from control values. There was a significant difference between SUDEP cases with and without evidence of brain swelling ($P < 0.005$; not shown on graph).The control values for brain weights were taken from Dekaban [9]. For the SUDEP brain weight, fresh brain weights were used; where the fixed brain weight only was available, this was used and 22 g was subtracted from this measurement (22 g was the mean difference in weight increase following fixation from the 55 cases in this series where both fresh to fixed weights were recorded; standard deviation 56.99, range –122–166 g).

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