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

M. Thom*,†,‡, Z. Michalak*,†, G. Wright*, T. Dawson§, D. Hilton¶, A. Joshi**, B. Diehl*,††, M. Koepp*,††,++, S. Lhatoo†, J. W. Sander*,††,§§, and S. M. Sisodiya*,††,‡‡

*Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Departments of †Neuropathology and ††Neurology, National Hospital for Neurology and Neurosurgery, NIHR University College London Hospitals Biomedical Research Centre, London, §Department of Neuropathology, Lancashire Teaching Hospitals, Preston, ¶Department of Cellular Pathology, Derriford Hospital, Plymouth, **Department of Neuropathology, Royal Victoria Infirmary, Newcastle upon Tyne, ‡‡Epilepsy Society, Buckinghamshire, UK, §§NINDS Center for SUDEP Research and University Hospitals Case Medical Center, Department of Neurology Cleveland, OH, and §§Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

M. Thom, Z. Michalak, G. Wright, T. Dawson, D. Hilton, A. Joshi, B. Diehl, M. Koepp, S. Lhatoo, J. W. Sander and S. M. Sisodiya (2016) Neuropathology and Applied Neurobiology 42, 463–476
Audit of practice in sudden unexpected death in epilepsy (SUDEP) post mortems and neuropathological findings

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
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,
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. 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

© 2015 The Authors. Neuropathology and Applied Neurobiology published by John Wiley & Sons Ltd on behalf of British Neuropathological Society

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.
### 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 (1–10 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-encephalactic                                    | 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 dysgenetic neuroepithelial and focal cortical dysplasia IIB, these were assumed to be 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, atomic 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.
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 2A), 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 2C). 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
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), giosis 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

| 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.
| 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**                                                 |        |            |
| Macropscopic 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. §Localised 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.

© 2015 The Authors. Neuropathology and Applied Neurobiology published by John Wiley & Sons Ltd on behalf of British Neuropathological Society
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
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
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.

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) Possible + 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% | 9.8% |
| 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) | 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.

© 2015 The Authors. Neuropathology and Applied Neurobiology published by John Wiley & Sons Ltd on behalf of British Neuropathological Society

NAN 2016; 42: 463–476
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 microcolumbar 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).

Acknowledgements

This work was undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. SUDEP studies at UCLH/UCL are supported by the Center for SUDEP Research through the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Numbers U01 NS090415 and U01 NS090407; the work and ZM was supported by a grant from CURE (Citizens United for Research in Epi-
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.

References

1. Hanna NJ. National Sentinel Clinical Audit of Epilepsy-Related Death: Report 2002. Norwich: Stationery Office, 2002
2. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. EPILEPSIA 2014; 55: 1479–85
3. Smithson WH, Colwell B, Hanna J. Sudden unexpected death in epilepsy: addressing the challenges. Curr Neurol Neurosci Rep 2014; 14: 502
4. So EL, Bainbridge J, Buchhalter JR, Donalty J, Donner EJ, Finucane A, Graves NM, Hirsch LJ, Montouris GD, Temkin NR, Wiebe S, Sierzant TL. Report of the American Epilepsy Society and the Epilepsy Foundation joint task force on sudden unexplained death in epilepsy. Epilepsia 2009; 50: 917–22
5. Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997; 38: S6–8
6. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshe SL, Nordli D, Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010; 51: 676–85
7. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012; 53: 227–33
8. Dawson TP. Neuropathology Techniques. London: Arnold, 2003
9. Dekaban AS. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Ann Neurol 1978; 4: 345–56
10. Black M, Graham DI. Sudden unexplained death in adults caused by intracranial pathology. J Clin Pathol 2002; 55: 44–50
11. Shields LB, Hunsaker DM, Hunsaker JC 3rd, Parker JC Jr. Sudden unexpected death in epilepsy: neuropathologic findings. Am J Forensic Med Pathol 2002; 23: 307–14
12. Zhuo L, Zhang Y, Zielke HR, Levine B, Zhang X, Chang L, Fowler D, Li L. Sudden unexpected death in epilepsy: evaluation of forensic autopsies cases. Forensic Sci Int 2012; 223: 171–5
13. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy—a review. Epilepsy Res 2009; 85: 31–45
14. Neligan A, Hauser WA, Sander JW. The epidemiology of the epilepsies. Handb Clin Neurol 2012; 107: 113–33
15. Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy. Potential role of antiepileptic drugs. CNS Drugs 2013; 27: 113–19
16. Surges R, Sander JW. Sudden unexpected death in epilepsy: mechanisms, prevalence, and prevention. Curr Opin Neurol 2012; 25: 201–7
17. Blumcke I, Coras R, Miyata H, Ozkara C. Defining cliniconeuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. Brain Pathol 2012; 22: 402–11
18. de Tisi J, Bell GS, Peacock JL, McEvoy AW, Harkness WF, Sander JW, Duncan JS. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. Lancet 2011; 378: 1388–95
19. Meencke HJ, Veith G, Lund S. Bilateral hippocampal sclerosis and secondary epileptogenesis. Epilepsy Res Suppl 1996; 12: 335–42
20. Novy J, Belluzzo M, Caboclo LO, Catarino CB, Yogarajah M, Martinian L, Peacock JL, Bell GS, Koepp MJ, Thom M, Sander JW, Sisodiya SM. The lifelong course of chronic epilepsy: the Chalfont experience. Brain 2013; 136: 3187–99
21. Fang P, An J, Zeng LL, Shen H, Chen F, Wang W, Qiu S, Hu D. Multivariate pattern analysis reveals anatomical connectivity differences between the left and right mesial temporal lobe epilepsy. Neuroimage Clin 2015; 7: 555–61
22. Jin SH, Jeong W, Chung CK. Mesial temporal lobe epilepsy with hippocampal sclerosis is a network disorder with altered cortical hubs. Epilepsia 2015; 56: 772–9
23. Sloviter RS, Kudrimoti HS, Laxer KD, Barbaro NM, Chan S, Hirsch LJ, Goodman RR, Pedley TA. 'Tectonic' hippocampal malformations in patients with temporal lobe epilepsy. Epilepsy Res 2004; 59: 123–53
24. Liebenthal JA, Wu S, Rose S, Ebersole JS, Tao JX. Association of prone position with sudden unexpected death in epilepsy. Neurology 2015; 84: 703–9
25. Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langen Y, Walczak TS, Beghi E, Brodie MJ, Hauser A. Combined analysis of risk factors for SUDEP. Epilepsia 2011; 52: 1150–9

© 2015 The Authors. Neuropathology and Applied Neurobiology published by John Wiley & Sons Ltd on behalf of British Neuropathological Society.
Bar graph of mean brain weights in males (3rd edn. Boca Forensic Neuropathology 2014; 40.005; not shown 2014; 40.005). The control values for brain weights were taken without evidence of brain swelling (MORTEMUS): a retrospective study. Lancet Neurol 2013: 12: 966–77

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 macroscopic brain abnormality. The mean difference in weight was 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).