A time of change

Welcome to the first issue of Paediatric Epilepsy Current Awareness Service (PECAS) of 2018.

You may have noticed that PECAS had been absent from your inboxes and wondered whether the publication had ended. However, I’m delighted to say this is not the case.

The delay with PECAS has been down to a transfer period of the publication to its new publisher, Epilepsy Action. As you probably already know, Editor Brian Chappell is retiring, and has handed over the reins of this much-respected publication to Epilepsy Action. We certainly hope to maintain the high standards and educational value of PECAS that Brian has established over many years. We are extremely grateful for all his help and guidance during this period of transition and ‘hand-over’.

We are also grateful for the unwavering support from Co-Editor Professor Richard Appleton. He continues in his role, ensuring we bring you the most current, up-to-date and relevant information from the world of paediatric epilepsy.

During this period of transition, there have been significant developments within the field of epileptology. The developments focus predominantly on the underlying genetic basis of the epilepsies and the introduction of a medical cannabinoid in the treatment of two specific epilepsy syndromes.

In early 2017, GW Pharmaceuticals put in a New Drug Application for their cannabidiol (CBD) drug Epidiolex with the US Food and Drug Agency (FDA) and the European Medicines Agency (EMA). This followed a number of trials to assess its efficacy and safety profile in the treatment of Dravet syndrome and Lennox-Gastaut syndrome (LGS) [Devinsky et al 2017; 2018; Thiele et al, 2018]. Both of these epilepsy syndromes are rare, but severe, and the seizures are typically resistant to established anti-epileptic drugs (AEDs) and other treatments, including the ketogenic diet.

The literature has been punctuated with increasing interest in the use of cannabis-based medicines in epilepsy over many years [Cilio et al, 2014; Leo et al, 2016; Szaffarski and Bebin, 2014]. This has come alongside pleas and demands by the public to be allowed access to these medicines. Cannabinoids and epilepsy was a recent topic in PECAS published in 2017 [Henley and Gupta 2017].

Cannabis does seem to have inherent anticonvulsant properties, although the precise mechanism of action is unclear. Two phytocannabinoids (that is, cannabinoids that are naturally occurring in the cannabis plant), tetahydrocannabinol (THC) and cannabidiol (CBD) have attracted the most attention based on their abundance in the plant. Fortunately, the psychoactive compound (THC) is present in very small concentration in Epidiolex. The psychoactive part of cannabis can cause hallucinations, sedation and bizarre behaviours. In July, the FDA approved Epidiolex for use in Dravet syndrome and LGS. The medicine should become available in the US in the autumn. The EMA’s decision has not yet been announced, but it is expected to approve Epidiolex in early to mid-2019.

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However, in the meantime, the UK has been going through a cannabis-based medicine revolution of its own. News reports started to spread sharing the stories of UK children with rare forms of epilepsy who had seen success with cannabis-based medicines obtained from other countries. Parents were calling on the government to allow their children to continue to take their medicines, but with little success.

The most publicised stories were on Billy Caldwell, Alfie Dingley and Ava Barry (aged 12, six and eight years respectively). Each of these children has a rare and refractory form of epilepsy and had tried a combination of CBD oil and tetrahydrocannabinolic acid (THCA) oil for their epilepsy. However, THCA is illegal in the UK under the Misuse of Drugs Act, being linked to THC.

Last year, Billy Caldwell was prescribed cannabis oil on the NHS in what was hailed as the ‘first case of its kind’ in the UK. This was not the pharmaceutical grade oil produced by GW Pharmaceuticals. However, after the initial prescription, the family’s GP was told by the Department of Health he should not continue to do so as cannabis was not licensed in the UK as a medicine.

Subsequently, the government’s policy on cannabis-based medicines came under scrutiny with the story of Billy Caldwell. His mother, Charlotte Caldwell, had travelled to Canada for a supply of cannabis oil but on entry to the UK, it was confiscated at the airport. She spoke on ITV’s This Morning and warned of the risks to Billy if his medicine was stopped abruptly. He had his first seizure in 300 days at the start of the week, and by the end of the week was in hospital. This placed the government under a considerable amount of pressure and, after meeting with a number of consultants, Home Secretary Sajid Javid issued Billy with a 20-day licence for cannabis oil.

Subsequent to this high-profile media story, the government announced a review into the scheduling of cannabis. Speaking in the House of Commons, Mr Javid said: “It has become clear to me since becoming Home Secretary that the position we find ourselves in is not satisfactory. It is not satisfactory for the parents, it is not satisfactory for the doctors, and it is not satisfactory for me. I have now come to the conclusion that it is time to review the scheduling of cannabis.”

The government’s review is ongoing. Part 1 of the review evaluated the evidence of the medical benefit of cannabis-based products [Davies 2018]. It concluded that keeping them within Schedule 1 – ie labelled as having little or no therapeutic potential – would be difficult to defend. However, the evidence for cannabis-based products in epilepsy was found to be insufficient at the current time.

It is difficult to predict the future of cannabis-based medicines and the treatment of epilepsy in the UK. Research continues to assess the long-term efficacy and safety of CBD for different epilepsy syndromes. Research is also going into its use in potentially the largest (all-age) population with a medically-refractory epilepsy, namely those with a focal epilepsy.

In the interim, the British Paediatric Neurology Association (BPNA) has issued an important position statement. This describes the BPNA’s assessment of the use of many cannabis oils available, none of which have a licence to be prescribed: “The cannabis oils may have anti-epileptic effects and there are anecdotal reports of positive results in children with epilepsy. However, anecdotal reports should not determine treatment policy for the population as a whole and products with high concentrations of THC may cause significant damage to the developing brain. Consequently, the BPNA does not recommend their use.”

We are optimistic about the changes over the last few months and the future licensing of Epidiolex. We hope this will prove to be of benefit for many children with a complex and medically-refractory epilepsy, and their families.

Prof Richard Appleton
Kami Kountcheva

References


Forthcoming courses and conferences

The following are details of forthcoming conferences and courses in epilepsy and general paediatric neurology.

**September 2018**
20-22
19th International Symposium on Severe Infantile Epilepsies: Old and New Treatments (ISSET) 2018
Rome, Italy
bit.ly/2EZlmdi

26-28
ILAE British Chapter Annual Scientific Meeting
Birmingham, UK
ilaebritishconference.org.uk/

28
Irish Chapter of the ILAE 8th Annual Expert Day
Dublin, Ireland
bit.ly/2OEITkT

**October 2018**
7-11
46th Annual Meeting of the International Society for Pediatric Neurosurgery (ISPN 2018)
Tel Aviv, Israel
ispmeeeting.org/2018

**November 2018**
1-3
Video-EEG in Paediatric Epilepsies: From seizures to syndromes
Madrid, Spain
video-egg2018.com

**January 2019**
23-25
The 45th BPNA Annual Conference 2019
Liverpool, UK
statusepilepticus.eu

**April 2019**
7-9
7th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures
London, UK
statusepilepticus.eu

**June 2019**
22-26
33rd International Epilepsy Congress
Bangkok, Thailand
bpna.org.uk/conference/2019/
Childhood epilepsy and mortality
Richard Appleton, consultant and honorary professor in paediatric neurology
Alder Hey Children’s Health Park, Liverpool and Holton St Mary, Suffolk

This is an important, complex and emotionally-charged issue. This article provides a broad overview of the key components of why and when death may occur in a child with an epilepsy and the importance of communication before and following a death, should one occur.

At the outset, it is important to state two facts about childhood epilepsy and mortality:

1. Sudden unexpected death in epilepsy (SUDEP) is an important, but not the only, or the most common reason why a child with epilepsy may die prematurely
2. The vast majority of children with an epilepsy will enjoy a normal life-expectancy.

Introduction
An increased risk of early or premature death in people with an epilepsy has been recognised for over one hundred and fifty years. The standardised mortality rate (SMR) of people in ‘all-age’ populations with any type of epilepsy has been reported to range between two- and four-fold that of the general population.1,2 This increases to between seven and 13-fold in people, including children, with a severe and medically-refractory epilepsy.3-6

An early community-based study of mortality in children with epilepsy in Australia published 25 years ago determined that 12% of deaths were SUDEP deaths.3

The findings of two slightly more ‘recent’ paediatric population studies provide useful data of deaths in childhood epilepsy but reported different findings on SUDEP.

The Dutch study of epilepsy in childhood looked at 472 children that developed epilepsy between the ages of one month and 16 years who were followed up from diagnosis. Nine (1.9%) died during a five-year follow-up.5 No child with an idiopathic epilepsy died. This included children with childhood, juvenile-onset absence and juvenile myoclonic and childhood epilepsy with centro-temporal spikes (CECTS). The latter condition was previously known as ‘benign rolandic epilepsy’. The nine deaths occurred in children with an underlying static or progressive neurological disorder, most of whom had learning or physical impairments, or both. None died from drowning and no child was considered to have died as a result of SUDEP. Children with a symptomatic epilepsy (ie with an identified cause), had a 22-fold increased mortality risk compared to the general paediatric population. This gave a mortality of 11.5/1000 person-years compared to the general paediatric population (up to the age of 16 years) of approximately 0.5/1000 person-years.

A similar paediatric population-based study was undertaken in Nova Scotia, Canada, with a longer, 20-year follow up. This found a mortality rate of children with epilepsy without a severe neurological deficit of 0.7/1000 person-years and this was no different from the reference, non-epileptic population. However, the mortality rate was approximately 15/1000 person-years in those with a severe epilepsy and with a severe neurological deficit.6 These figures were very similar to those in the Dutch study. Four of the 26 deaths in the Canadian study were unexpected and occurred in young adults aged 18-30 years. Post-mortem analysis revealed two suicides and one homicide. The remaining person (a 21-year-old woman with tuberous sclerosis complex, refractory epilepsy and irregular compliance with antiepileptic medication) died of SUDEP. The Canadian authors concluded that children with epilepsy had a five-fold increased risk of dying than the general paediatric population in the first 15 to 20 years after the diagnosis. However, they found that most deaths were related to co-morbid neurological impairments and not epilepsy.

This is likely to be the experience of most paediatric neurologists and is certainly mine. In 26 years as a consultant with a specific interest in the epilepsies, I am aware of six SUDEP deaths in my patients. Two children had Dravet syndrome (both with refractory epilepsy and both aged <5 years) and two had severe, four-limb cerebral palsy (both aged <10 years). One death happened in a person with tuberous sclerosis complex aged 21 years. The last was in a young woman aged 24 years who lived on her own, with an idiopathic (presumed genetic) and un-classified generalised epilepsy.

Causes of death in epilepsy
Premature death in the childhood epilepsies may occur for many reasons. The most common, in probably the most likely descending order of frequency, include:

• Associated co-morbid condition (eg severe physical impairment; profound cognitive impairment)
• Underlying cause of the epilepsy (eg an acquired or inherited neurodegenerative disease)
• Accidental (including drowning)
• Convulsive status epilepticus (specifically established status epilepticus)
• Sudden unexpected death in epilepsy (SUDEP)
• Suicide (rare in children and young people; increases in adolescence and early adulthood and specifically in those with temporal lobe epilepsy and those that have failed epilepsy surgery)

Some of the above causes are modifiable although not necessarily preventable. The modifiable factors are those that will improve the diagnosis and management of an epilepsy. These factors include earlier consideration of surgery, the appropriate use of emergency or rescue care plans (for out-of-hospital use), and a more holistic approach. A holistic approach should include discussing a risk of major non-compliance with anti-epileptic medication and identifying and treating any psychiatric co-morbidities, in particular a depressive illness.
Associated co-morbid conditions
The co-morbid conditions most likely to be associated with mortality in children with epilepsy are:

- Severe, four-limb spastic tetraplegia (the most severe type of cerebral palsy, and irrespective of aetiology, whether perinatal or acquired)
- Severe or profound learning difficulties, with or without autism
- Severe psychiatric illness (depression, psychosis), with or without autism, and particularly in those aged 15-18 years

Precise causes of death in the first two groups are most often related to acute or acute-on-chronic respiratory difficulties. These are the cases that also have the highest risk of SUDEP deaths. Suicide is a much rarer cause, particularly in children and young people with an epilepsy.

Underlying cause of the epilepsy
Collectively, there are a number of neurodegenerative disorders that commonly feature a severe epilepsy and which are inherently life-shortening. Examples include:

- The infantile and late-infantile neuronal ceroid lipofuscinoses
- Mitochondrial cytopathies (particularly due to a mutation in the POLG1 gene)
- Many other metabolic disorders, most of which are genetically determined including Menke’s syndrome and the peroxisomal disorders (eg Zellweger’s syndrome and neonatal adrenoleucodystrophy)
- Rett syndrome (particularly in children with the early-onset seizure/infantile spasms variant due to a mutation in the CDKL5 gene)
- Mutations in a number of genes including FOXG1, GRIN1, GRIN2A and GRIN2B

Accidental
A number of studies have indicated or suggested that epilepsy is the medical disorder that is most likely to be associated with injuries, including drowning, that result in death.7 In the UK, drowning in the home is more likely than out of the home and is a well-recognised risk in any individual with epilepsy, irrespective of their age. A recent study examined unnatural mortality in people with epilepsy.8 This was undertaken in a cohort study of more than 50,000 people with epilepsy with one million matched individuals without epilepsy identified using two data-sets in the general populations of England and Wales. The study showed that adults with epilepsy had a three-fold increased risk of any unnatural mortality and a five-fold increased risk of unintentional medication poisoning. Psychotropic and opioid, but not antiepileptic, medications were most commonly linked to poisoning.8 Similar findings have been identified in different ethnic populations, including South Korea.9 Although these findings primarily relate to adults with an epilepsy, no one should ever be complacent about children and young people and particularly in those aged 12 to 16 years. This is a crucial period of their emotional and social development and self-empowerment.

Convulsive status epilepticus
Although convulsive status epilepticus is more common in children than in adults, the risk of dying is much less and has been estimated to be between 2-5%.10 The risk of death in established convulsive status epilepticus in children is approximately 2-5%. Established CSE is defined as the presenting tonic-clonic or clonic seizure has lasted >5 minutes and has not responded to the first-line antiepileptic, traditionally a benzodiazepine. Mortality rises significantly in refractory and super-refractory status epilepticus to approximately 25-30%. Refractory CSE is defined as failure of the seizure to stop after a benzodiazepine followed by another class of antiepileptic, in the UK phenytoin or phenobarbital. The most important factor that determines mortality in CSE is its underlying cause, but its duration and management are also important. The risk of death is lowest (0-1%) in children with prolonged febrile CSE and highest (up to 7 or 8%) in those with a neurological insult that is either acute (eg meningitis, encephalitis, trauma) or remote (eg as a sequelae of severe perinatal hypoxic injury, cerebral malformation).

Mismangement encompasses both under-treatment (anti-epileptic drugs (AEDs) given too late or in too low a dose), and overtreatment (AEDs given too rapidly or in too high a dose, or continuously, and this specifically relates to phenytoin).11

Sudden unexpected death in epilepsy (SUDEP)
The current and largely accepted definition of SUDEP is: “Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a toxicologic or anatomic cause for death”,12 SUDEP has also been further classified into:

- Definite: as defined above with a negative post-mortem
- Probable: as above but with no post-mortem information
- Possible: not fulfilling the criteria outlined in the above definition and with no post-mortem information

This has been further clarified by Dr Nasher13 as indicated below (with my comments in italics):

- That SUDEP be applied irrespective of whether there is evidence of a terminal seizure (ie although most SUDEP deaths have occurred following a tonic-clonic seizure, this is not invariably and of course, in people living alone a seizure may not have been witnessed or there may have been no convincing evidence of a seizure when the person was discovered)
- ‘Possible’ SUDEP should be used only for cases with competing causes of death, with cases left unclassified when there are insufficient data to reliably permit their classification
- Cases that would otherwise fulfil the definition of SUDEP should be designated as SUDEP ‘plus’ when evidence indicates that a pre-existing condition, known before or after autopsy, could have contributed to the death, which otherwise is classified as SUDEP (eg coronary insufficiency with no evidence of myocardial infarction or long-QT syndrome with no documented primary ventricular arrhythmia leading to death)
- To be considered SUDEP, the death should have occurred within one hour from the onset of a known terminal event
- For status epilepticus as an exclusion criterion for SUDEP, the death should have occurred within one hour from the onset of a known terminal event

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- To be considered SUDEP, the death should have occurred within one hour from the onset of a known terminal event
- For status epilepticus as an exclusion criterion for SUDEP, the duration of continuous seizure activity should be 30 minutes or more. SUDEP due to asphyxia should not be used, the distinction being largely impractical on circumstantial or autopsy evidence, with more than one mechanism likely to be
consider that:

- Death occurring in water but without circumstantial or autopsy evidence of submersion should be classified as ‘possible’ SUDEP. *Unequivocal* evidence of submersion precludes a SUDEP death
- A category of ‘near’ SUDEP should be agreed to include cases in which cardiorespiratory arrest was reversed by resuscitation efforts with subsequent survival for more than one hour.

However, very recently, this sub-classification of SUDEP has been challenged by a group in the USA. This challenge arose from “ambiguities that contributed to inconsistent classifications by experts in epilepsy, forensic pathology, cardiology and epidemiology”. This was found to be the case in the process of reviewing and adjudicating causes of death in the North American SUDEP Registry and from consecutive series in three Medical Examiners Offices (New York City, San Diego and Maryland).14 Specifically, the group consider that:

- ‘Near-SUDEP’ should be replaced by ‘Resuscitated SUDEP’
- ‘Definite SUDEP plus’ and ‘Probable SUDEP plus’ should be replaced by ‘Definite SUDEP plus co-morbidity’ and ‘Probable SUDEP plus co-morbidity’ respectively.

Although the authors make some interesting and valid points, they themselves recognise that the opinions of clinical epileptologists may differ from forensic pathologists in some cases of SUDEP.14 It is obviously important to identify SUDEP deaths as accurately as possible. However, there is a potential danger that repeated iterations of the classification of SUDEP and in a non-consensual way may confuse and not clarify SUDEP. This may ultimately prove detrimental to future epidemiological and research studies.

Sudden death is estimated to be nearly 24 times more likely in people with epilepsy than in the general population. It also disproportionately affects young adults, which may explain why epilepsy deaths are in the top 10 of all causes of premature deaths in the UK.

There are different ways of approaching the incidence of SUDEP:

- It is estimated to account for one death per 1,000 adults with epilepsy per year and one death in approximately 4,000 children with epilepsy. This means that rates of sudden death in children with epilepsy may be more than 10 times that of children in the general population
- In the general epilepsy population, it is reported to be 0.09-1.2/1000 person-years. In patients with medically refractory epilepsy, it is 1.1-5.9/1000 person-years and in patients who have failed resective epilepsy surgery, 6.3-9.3/1000 person-years. These figures apply to all ages, but predominantly adults.15
- From a different perspective, it accounts for approximately 2% of deaths in population-based cohorts of all epilepsies, and up to 25% of deaths in cohorts with more severe epilepsy. In adults and children with medically intractable epilepsy, rates may approach one in 100 people per year. However, these reported rates may be an underestimate because of poor case identification due to lack of awareness and inconsistencies in the investigation and recording of the deaths

### Research: past and future

Predictably, research into both the pathogenesis and the potential prevention of SUDEP has dramatically increased over the past decade. This reflects an increased awareness of the phenomenon by not only clinicians and families of patients that have experienced a SUDEP death, but also coroners when classifying a person’s cause of death.

There is no doubt that the results of the National Sentinel Clinical Audit on Epilepsy-related Deaths (NSCAED) published in 200216 were pivotal in alerting coroners throughout the UK about SUDEP. They showed that SUDEP could, and more importantly should, be recorded as the primary cause of death in a person with epilepsy in the absence of any other identified cause. However, it has taken many years for the Coronial Service throughout the UK to accept SUDEP as a classifiable cause of death,17 and it may not yet be ubiquitous. The work of SUDEP Action (previously, Epilepsy Bereaved), other charities and voluntary groups has been crucial in maintaining the public and professional momentum of the findings of the NSCAED. Their work has also been vital in supporting affected families and funding research. Early observational studies, supported by later epidemiological studies, identified specific factors that are associated with an increased risk of SUDEP. These include:

- Young, adult males (aged 18-40)
- Early onset of epilepsy (<16 years of age)
- Long duration of epilepsy
- A history of tonic-clonic seizures
- Poorly-controlled seizures
- Living alone18
- Sleep (the majority of SUDEP cases occur during sleep)
- Poor and particularly very irregular adherence to antiepileptic medication, including its sudden cessation

Many of the above factors may modify the risk of, although not necessarily prevent, any death in epilepsy, including a SUDEP death.

Relatively old data have not suggested any AED, whether old or new, is more, or less, associated with a risk of SUDEP.19 Predictably however, there may be so much ‘noise’ (contamination) from other factors that it may mask any obvious AED effect. Clearly, longer-term, prospective and international collaborative research is required to confirm, or refute, this current understanding.

Early data in adults suggested a reduced SMR and lower frequency of SUDEP in patients with a vagal nerve stimulator (VNS) *in situ*.20 More recently, a retrospective audit of 466 patients, 159 of whom were <16 years of age at VNS-implantation, demonstrated an SMR and SUDEP rate that were no different than other comparable cohorts with intractable epilepsies.21 The authors concluded that the use of VNS did not appear to reduce the risk of premature death overall.21 As with AEDs, there are likely to be many factors that might mask a direct effect of VNS.

There are, as yet, no specific reports that have evaluated the use of the ketogenic diet and the risk of SUDEP.

As mentioned, the risk of SUDEP is significantly lower in children with an epilepsy. However, it increases markedly in those children with...
an identified cause and significant learning difficulties, motor impairments (typically four-limb spastic cerebral palsy), or both. It is also higher in specific epilepsy syndromes (particularly Dravet and Lennox-Gastaut syndromes). Infants as young as 6-9 months have been reported to have died from SUDEP, including young children with the rare syndrome, epilepsy of infancy with migrating focal seizures.

Despite the increased knowledge and associated improved identification of a SUDEP death and its appropriate use in death certification, it is likely that some will still be missed. A recent study in the US evaluated 541 sudden cardiac deaths in individuals aged 18-90 years. Evaluation was undertaken by two groups. The first was a multi-disciplinary team (MDT) comprising pathologists, electrophysiologists and a vascular neurologist. The second was a panel of two epileptologists with expertise in seizure-related mortality. Of these patients, 525 (97%) underwent a post-mortem. Thirty-nine had seizures or an epilepsy, comprising 17% of 231 non-arrhythmic sudden deaths. The MDT identified 15 cases of epilepsy and six SUDEP deaths; in contrast, the epileptologists identified 25 cases of epilepsy and eight definite and 10 possible SUDEP deaths.

The pathogenesis of SUDEP remains unclear. Both cardiac (specifically a fatal arrhythmia leading to asystole) and respiratory (a prolonged and terminal apnoea) causes have been implicated. It is likely that both mechanisms may operate in different individuals. Evidence from epilepsy monitoring units indicates that hypopnoea or apnoea is a universal critical final stage before asystole. Evidence is also accumulating that there may also be an underlying genetic vulnerability or predisposition to SUDEP. This could be possibly through genes that predispose to a cardiac arrhythmia (through potassium or sodium channel dysfunction), often, but not exclusively, related to prolongation of the QT interval.

Specific populations that have been subject to SUDEP research, albeit retrospective, have been those with chronic and medically-refractory epilepsy. A study published in 2011 evaluated deaths in patients (predominantly adults) that had participated in randomised clinical trials (RCTs) of new AEDs. They were compared against either very low or ‘non-efficacious’ doses (the latter being a more popular approach than using placebo in the USA), or placebos. This study showed that treatment with a new and ‘add-on’ or adjunctive AED in efficacious doses may have reduced the incidence of definite or probable SUDEP. The reduction was more than seven-fold compared with placebo in previously medically-refractory seizures. The authors suggested this provided evidence to avoid placebos and use active treatments in future RCTs of new AEDs.

Patients undergoing very close, in-hospital observations may also die a SUDEP death. In 2013, a somewhat chilling study demonstrated that, in 147 adult epilepsy-monitoring units (including those evaluating patients for possible epilepsy surgery) over one year, there were 29 cardiorespiratory arrests. They included 16 SUDEP (14 at night), nine near-SUDEP, and four deaths from other causes.

Cardiorespiratory data, available for 10 cases of SUDEP, showed a consistent and previously unrecognised pattern in which rapid breathing developed after a secondary generalised tonic-clonic seizure. This was followed, within three minutes, by transient or terminal cardiorespiratory dysfunction. In those cases where this was transient, it later recurred with terminal apnoea occurring within 11 minutes of the end of the seizure, followed by a terminal cardiac arrest. Overall, this represented a risk of SUDEP of 1.2 per 10,000 video-EEG telemetry investigations.

This study also showed that resuscitation instigated within three minutes of cardio-respiratory arrest was successful, but not if instigated after 10 minutes. One could argue this would be similar in other medical arrests in people that did not have epilepsy. The authors appropriately concluded that suboptimal supervision and sudden withdrawal of antiepileptic medication (to ‘capture’ seizures) contributed to many of the deaths.

SUDEP research is challenging, both methodologically and analytically for many reasons. These include a global lack of correct identification, its relative rare occurrence (when considering all epilepsies together and not by individual type or syndrome), disagreements over terminology and classification, and the many potential confounding variables. This clearly dictates a need for robust and international studies to narrow confidence intervals and identify the clinical relevance of any potential causative factors. Further reading can be found in a supplement dedicated to this topic published in 2016 that evaluates the importance of research to better understand and, wherever possible, reduce the incidence of SUDEP.

Communication: ‘why, how and when’

Much has been written and debated repeatedly, about the ‘why’, ‘when’ and ‘how’ to discuss death in the epilepsies.

The ‘why’ should no longer be a question as it is now accepted that premature death in the epilepsies is a fact. It is understood that it may arise from a number of causes (as outlined earlier) and although improved and even optimal management and care will not eliminate it, it will certainly reduce this risk. Predictably, it would be anticipated parents would want to be informed about SUDEP. This was identified in a small questionnaire-based survey reported in 2010 among parents and paediatric neurologists. Unfortunately, this survey excluded parents of children with absence seizures or whose children were in remission or had discontinued anti-epileptic medication treatment; this will have inevitably biased the results. Most parents stated they would want to know about SUDEP. Of these, 67% stated they would want to be told about SUDEP at the same time they were informed about the diagnosis of epilepsy in their child. These responses almost certainly reflect the retrospective nature of the survey.

Another survey identified that parents were “emphatic” they should not be expected to hear about SUDEP purely from a leaflet or website. This is an opinion that is both predictable and entirely appropriate. Surveys such as these have a role in helping to inform clinicians about important communication issues, but only if they are appropriately designed and undertaken in un-selected and therefore un-biased populations.

The ‘when’ and the ‘how’ are not as straightforward. It may be useful to begin this section with some old, but still relevant information. A study looked at 50 parents of 36 consecutive children admitted to hospital with their first febrile convulsion. The majority said they
thought their child was dying (or would die) when interviewed up to a few hours after the event. However, they only gave this information when specifically asked, and not voluntarily. The authors suggested this common fear be kept in mind when discussing febrile seizures with parents; it would equally apply to afebrile seizures (ie epilepsy). Such a discussion may also serve as a useful entry point into a wider discussion about death and dying in the epilepsies. From the author’s experience, many parents still experience this fear, almost 40 years after publication of this report.

Some strongly advocate that all patients with an epilepsy (and their carers) should be proactively informed about the fact that it may be associated with premature death. This is irrespective of epilepsy type, syndrome, age or other accompanying medical conditions. This group also believe that this information should always be given at the time of diagnosis disclosure. A very small minority would recommend the opposite view, arguing that because the risk of premature death is so low it should never be discussed proactively, but only in response to a specific question from the patient or carers. These clearly represent two extreme views and consequently, both could be considered as inappropriate, for a number of reasons.

First, it is well-recognised that extremes of opinion, often dogmatically-expressed, may be dangerous and should always be regarded with caution, if not suspicion.

Second, epilepsy is not a single disease but a heterogeneous group of diseases with different syndromes, types, causes, associated comorbid conditions, treatments and outcomes, including the risk of premature death. Importantly, premature deaths, including SUDEP, have never been reported in a number of epilepsy syndromes. These are specifically benign myoclonic epilepsy in infancy and childhood-and juvenile-onset absence epilepsy (CAE). Only very recently have children (thus far only three boys), with childhood epilepsy with centro-temporal spikes (CECTS), been reported to have died from SUDEP. Respectfully, and perhaps with a healthy curiosity, one should consider whether these children were diagnosed with the correct epilepsy syndrome. This is because, despite being considered to represent between 15 and 20% of all epilepsies in children, CECTS and CAE have never previously been linked with SUDEP, including in two well-conducted, non-selected and population-based studies.

Third, it may at best be confusing, but at worst extremely alarming to discuss the risk of death (premature or otherwise) at the same time as disclosing a diagnosis of epilepsy. The latter is the far more common emotion in my experience. An epilepsy diagnosis and its attendant management and lifestyle implications are, in themselves, enough of a challenge for the family and child. Consequently, many paediatric neurologists and paediatricians would argue that the discussion about premature death, including SUDEP, should take place at the first follow-up consultation following disclosure of diagnosis, or even later, depending on the clinical and family situation. This could be with an epilepsy specialist nurse or the consultant, and within the context of a broad overview of the lifestyle, risks and safety issues associated with epilepsy, that subsequently addresses the risk of death, including SUDEP.

Recently, the legal profession has strayed into the minefield of SUDEP-advice. In 2011, the Sheriff presiding over a Fatal Accident Inquiry of two adolescent women who suffered SUDEP deaths in Scotland gave the following statement:

“The vast majority of patients with epilepsy, or their parents or carers ... should be advised of the risk of SUDEP at first diagnosis or if, in the particular circumstances of that patient, there are exceptional circumstances for delaying immediate provision of the information, then within a very short time thereafter. Advice about the risk of SUDEP should only be withheld if there is assessed to be, in the case of a particular patient, a risk of serious harm to the patient in proving the information or the patient has learning difficulties.”

Medicine has never been and will never be an exact science; there has been, and one can only hope there will always be an art to the practice of medicine and this includes good communication. Consequently, it is my opinion that there is no single and ideal (in both occasion and content) way to communicate the risk of death in epilepsy, and specifically, SUDEP. There is a time and a place for this important and emotionally-traumatic discussion and in part this will depend on the child’s type of epilepsy, family situation and with sensitive discernment by the clinical team.

The aftermath of a premature death in epilepsy, and particularly a SUDEP death, will be extremely traumatic and demands early, clear and compassionate counselling and communication skills. Unfortunately, practice does not always correlate with principle as was highlighted in the NSCAED and this is particularly true for adult deaths. Although the management of, and immediately following, a child’s death was better, it was certainly not perfect. The situation has clearly improved over the ensuing decade. This was identified in the findings of a nation-wide audit of deaths in children with an epilepsy undertaken by the Royal College of Paediatrics and Child Health (RCPCH). However, the audit also showed that often families were not being offered support and counselling from relevant healthcare professionals. In only 56% of the 33 families in whom a child had died (and this was not limited to SUDEP deaths), was this offered. The communication issues involved in discussions and counselling both before and after a SUDEP death are clearly and comprehensively addressed in the supplement in Epilepsia published in 2016.

Conclusion

It is a well-recognised fact that a child with an epilepsy is at an increased risk of dying prematurely, and from a range of causes. Conversely, the vast majority of children will survive and enjoy a normal life-expectancy. It is crucial to communicate the risk and context of premature death correctly and also to check the family’s or carer’s understanding of what has been discussed. The risk of premature death is closely linked with the epilepsy syndrome, type of seizure(s), seizure control, underlying cause and associated co-morbidities; the earlier the age of onset and the more complex and medically-refractory, the greater the risk. Optimal management will reduce, but never completely eliminate, the risk of a premature death, including from SUDEP. The approach to the emotionally-charged and potentially alarming issue of death in epilepsy is very important. It must be addressed appropriately and with a clear understanding of why, and in what situations it might occur. There should be clear and sensitive communication, both before and, should it occur, following
a death. The pattern of this discussion must always be tailored to the individual child and their family. Finally, it is good clinical practice, as well as a reflection of our litigation-trigger society, that these discussions are always documented. This should be done both in the medical notes (by hand or electronically) and correspondence.

References
30. Fatal Accident Inquiries. www.scotland-judiciary.org.uk/10/0Fatal-Accident-Inquiries
Recently published papers

This section highlights recently published papers. Hopefully this will be very useful to all, helping to keep everyone up to date with the latest developments. It will certainly save you research and reading time, not having to search so many journals.

There are many (often over 300) epilepsy papers published every three months, so what follows has been edited. All animal papers have been excluded and as many review papers as possible have been included. We hope you find the papers of interest in your pursuit to keep abreast of the very latest knowledge.


Sleep architecture and epileptic characteristics of drug naive patients in childhood absence epilepsy spectrum. A prospective study


Chiang LM, Huang GS, Sun CC, Hsiao YL, Hui CK, Hu MH.

Association of developing childhood epilepsy subsequent to febrile seizure: A population-based cohort study


Wong-Kisiel LC, Blauwblomme T, Ho ML, Boddart N, Parisi J, Wirrell E, Nabbout R.

Challenges in managing epilepsy associated with focal cortical dysplasia in children


Healy L, Moran M, Singhal S, O'Donoghue MF, Alzoubidi R, Whitehouse WP.

Relapse after treatment withdrawal of antiepileptic drugs for Juvenile Absence Epilepsy and Juvenile Myoclonic Epilepsy


Reilly C, Atkinson P, Memon A, Jones C, Dabydeen L, Das KB, Gillberg C, Neville BGR, Mahoney JM, Scott RC.

Global development and adaptive behaviour in children with early-onset epilepsy: a population-based case-control study


Ryvin P, Ciumas I, Wisniewski I, Beniczky S.

Wearable devices for sudden unexpected death in epilepsy prevention


Myers KA, Bello-Espinosa LE, Symonds JD, Zuberi SM, Clegg R, Sadleir LG, Buchhalter J, Scheffer IE.

Heart rate variability in epilepsy: A potential biomarker of sudden unexpected death in epilepsy risk


Allahkaram A, Alshibani F, Tabarki B.

Extending the use of stiripentol to SLC13A5-related epileptic encephalopathy


Effect of valproic acid on perampanel pharmacokinetics in patients with epilepsy


Fernandez-Baca Vaca G, Mayor CL, Losarcos NG, Park JT, Lüders HO.

Epileptic seizure semiology in different age groups


Hur YJ.

Comparison of lamotrigine and oxcarbazepine monotherapy for pediatric focal epilepsy: An observational study


Vasquez A, Farias-Moeller R, Tatum W.

Pediatric refractory and super-refractory status epilepticus


Holtkamp M, Theodore WH.

Generic antiepileptic drugs – Safe or harmful in patients with epilepsy?


Kanner AM, Ashman E, Gloss D, Harden C,
Psychological treatments for adults and children with epilepsy: Evidence-based recommendations by the International League Against Epilepsy Psychology Task Force


A UK survey of the experience of service provision for children and young people with epilepsy


Fohlen M, Taussig D, Ferrand-Sorbets S, Chipaux M, Dorison N, Delalande O, Dormfiumler G.

Refractory epilepsy in preschool children with tuberous sclerosis complex: Early surgical treatment and outcome


Bain E, Keller AE, Jordan H, Robyn W, Pollanen MS, Williams AS, Donner EJ.

Drowning in epilepsy: A population-based case series


Gha-Hyun L, Dae SJ.

Brand name to generic substitution of levetiracetam in patients with epilepsy


Sarkis RA, Goksens Y, Mu Y, Rosner B, Lee JW.

Cognitive and fatigue side effects of antiepileptic drugs: An analysis of phase III add-on trials


Goldstein LH, Reuber M, LaFrance WC Jr, Lundgren T, Modi AC, Wagner JL.

Psychological treatments for adults and children with epilepsy: Evidence-based recommendations by the International League Against Epilepsy Psychology Task Force


Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results


Attilakos A, Dinopoulos A, Paschalidou M, Tsiourda M, Karalexi M, Prasouli A, Garoufi A.

Long-term effect of levetiracetam monotherapy on haematological parameters in children with epilepsy: A prospective study


Kavlíc A, Rener-Primec Z.

Predictive Value of Epileptiform Discharges for Subsequent Epilepsy After Febrile Seizures


Jain P, Subendran J, Smith ML, Widjaja EPEPSQOL Study Team.

Care-related quality of life in caregivers of children with drug-resistant epilepsy


Kirkpatrick M.

Incidence of sudden unexpected death in epilepsy in children is similar to adults


Keller AE, Whitney R, Li SA, Pollanen MS, Donner EJ.

Incidence of sudden unexpected death in epilepsy in children is similar to adults
