Epilepsy & Behavior 90 (2019) 99–106

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood☆,☆☆,★

Omar Abdel-Mannan [a,*], Henry Taylor [b], Elizabeth J. Donner [c], Alastair G. Sutcliffe [d]

[a] Department of Neurology, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom
[b] Department of Paediatrics, Northwick Park Hospital, London North West Healthcare NHS Trust, London, United Kingdom
[c] Department of Neurology, The Hospital for Sick Children, Toronto, Canada
[d] Population, Policy and Practice Unit, UCL Great Ormond Street Institute of Child Health, London, United Kingdom

ARTICLE INFO

Article history:
Received 17 October 2018
Revised 6 November 2018
Accepted 12 November 2018
Available online 3 December 2018

Keywords:
Sudden Unexpected Death in Epilepsy
Sudden Unexplained Death in Epilepsy
SUDEP
Epidemiology
Epilepsy mortality

ABSTRACT

Background: Sudden Unexpected Death in Epilepsy (SUDEP) is a significant cause of death in childhood epilepsy, and causes considerable concern to patients and their families. Despite this, the condition remains poorly understood. This systematic review investigates the risk factors, pathophysiology, and circumstances associated with childhood SUDEP. It aimed to explore the etiology of SUDEP and inform clinicians approaching SUDEP risk disclosure.

Methods: A structured electronic database search of MEDLINE, CENTRAL, EMBASE, and ISI web of science was conducted. Studies were included if they described clinical details of one or more patients, aged 18 years of age and below, who had SUDEP. Two reviewers independently reviewed each article for data extraction and quality assessment.

Results: Information on 108 cases of pediatric SUDEP was extracted from 22 included studies. These comprised five cohort studies, four retrospective case control studies, seven case series, and five case reports. Factors that appeared to be linked to pediatric SUDEP included those associated with severe epilepsy (early age of onset, high seizure frequency, intellectual impairment and developmental delay, multiple antiepileptic drug therapy, and structural abnormalities). The majority of included studies was noncomparative and had significant risk of bias.

Conclusions: There is currently insufficient evidence to determine the etiology of pediatric SUDEP. Current best practice to prevent pediatric SUDEP is to optimize the management of epilepsy. A national SUDEP registry would provide invaluable high-quality data and insights into modifiable risk factors, genetic predispositions, and novel prevention strategies.

1. Introduction

In addition to increased morbidity and rates of hospitalization, people with epilepsy are 2 to 3 times more likely to die early than the general population [1]. Both adults and children with epilepsy may die from a number of causes including; complication of a seizure such as aspiration of stomach contents, suffocation, injury, drowning; status epilepticus; a related underlying condition (e.g., brain tumor); suicide; or Sudden Unexpected Death in Epilepsy (SUDEP). The most widely used definition of SUDEP is "the sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause for death" [2]. In the most recently proposed system, SUDEP is subclassified into definite, probable, and possible SUDEP [3]. (Fig. 1).

1.1. What do we know about SUDEP incidence?

In adults, reported SUDEP rates vary greatly between studies depending on the studied cohort and range from as high as 6:1000 person years in intractable epilepsy surgery cohorts [4] to as low as 0.35/1000 person years in a population-based study [5]. This reported variation in adulthood SUDEP incidence is also mirrored in the pediatric population. Although the literature indicates the rate of SUDEP in children is lower than in adults, a recent systematic review as part of the American

☆ **Funding source**: No funding was secured for this study.
☆☆ **Financial disclosure**: All authors have no financial relationships relevant to this article to disclose.
★ **Conflict of interest**: All authors have no conflicts of interest to disclose.
* Corresponding author at: Department of Neurology, Great Ormond Street Hospital for Children, London, Great Ormond Street, London WC1N 3JH, United Kingdom.
E-mail address: o.abdel-mannan@ucl.ac.uk (O. Abdel-Mannan).

https://doi.org/10.1016/j.yebeh.2018.11.006
1525-5050/

Classification and definition of SUDEP subtypes

1. Definite SUDEP: Sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus in which **postmortem examination** does not reveal a cause of death.

2. Probable SUDEP: Same as Definite SUDEP but **without autopsy.** The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a known structural cause of death.

3. Possible SUDEP: SUDEP cannot be ruled out but a competing cause of death is present. If a death is witnessed, a cutoff of death within 1 hour from acute collapse is suggested.

Fig. 1. Subclassification of SUDEP (Modified from Nashef et al. 2012) [3].

Academy of Neurology (AAN) Practice Guideline on SUDEP found that the SUDEP risk in children with epilepsy is 0.22/1000 patient years (95% confidence interval [CI] 0.16–0.31) [6].

1.2. What have we learnt from the adult literature?

There have been few controlled studies to date looking at childhood SUDEP risk factors; the majority of larger studies have included mostly adults. The studies are not without limitations, including: small numbers of SUDEP cases, inappropriate choice of controls, retrospective design, misclassification of SUDEP cases, lack of uniformity in definitions, and use of antiepileptic drug (AED) prescriptions to ascertain cases [7–9]. The Task Force on Epidemiology of the International League Against Epilepsy (ILAE) pooled data from four major case–control studies of SUDEP [10–13] and showed that the risk of SUDEP was 1.4 times higher in male patients than in female patients. However, the recent AAN practice guideline systematic review determined that the male sex was not a significant risk factor and that the presence and frequency of generalized tonic–clonic seizures (GTCS) was the major risk factor associated with SUDEP [6].

1.3. What are the pathophysiological mechanisms underlying SUDEP?

There has been intense on-going study into possible mechanisms for SUDEP, and it remains unknown whether pediatric and adulthood SUDEP share a common mechanism. In general, the proposed mechanisms of SUDEP are cardiac, respiratory, or central/autonomic dysregulation, all of which may occur independently or in combination [14]. A proposed SUDEP mechanism, based on a retrospective review of 16 definite or probable SUDEP cases from 147 epilepsy-monitoring units of cardiorespiratory arrests during video-electroencephalography recordings suggests an early, centrally mediated alteration of both respiratory and cardiac functions occurs after GTCS [15].

A better understanding of the risk factors, pathophysiology, and circumstances associated with childhood SUDEP deaths would aid clinicians in several ways. First, any modifiable risk factors could be targeted to reduce the incidence of SUDEP further. Second, clinicians will be more able to approach SUDEP risk disclosure in an evidence-based manner with families when deemed appropriate [16]. Relatives of both adult and child patients who had SUDEP consistently indicate that they wish they had been informed that epilepsy can be fatal [17]. Finally clues to the mechanism and etiology of SUDEP could be derived from the risk factors, prompting further research. Therefore, the aim of this paper was to systematically review the limited literature on childhood SUDEP, focusing on knowledge of risk factors of this important clinical entity.

2. Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Supplementary Information) guidelines.

2.1. Search strategy and selection of studies

A structured electronic database search of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (1966 to February 2018), EMBASE, and ISI Web of Science (1945 to February 2018) was conducted with no language restriction (Supplementary Table 1). The reference list and ISI citations of all included studies were hand searched, as were the conference abstract issues of selected neurology journals for the year preceding our electronic search.

Studies were included if they described clinical details of one or more patients, aged 18 years and below, who had SUDEP. Studies that described adult and pediatric cases were included if information on only the pediatric cases was available (either published or provided in correspondence with study authors). Studies were excluded if only combined adult and pediatric data were available.

Two authors [OA, HT] independently screened titles and abstracts of all studies identified in the literature search. Independent full-text review of all potentially eligible studies was also conducted by two authors [OA, HT]. Any disagreements were resolved through discussion, or through consultation with a senior author [AS].

Duplicates were removed using EndNote software. Multiple reports of the same study were collated. Authors were contacted via email if further data were required, or if there was no published subgroup analysis of pediatric cases.

2.2. Data extraction and analysis

Two authors [OA, HT] extracted study characteristics and outcome data from included studies using a standardized data collection form. Disagreements were resolved through discussion or consultation with the senior author [AS]. The following details were extracted: patient population, number of patients, age of patients, study design, duration and follow-up, outcome measures, study findings, and author conclusions based on findings, strengths, and limitations of the study.

Where studies included individual pediatric cases of SUDEP, we extracted the following information for each case: age at death, age at onset of epilepsy, epilepsy syndrome/diagnosis/etiology of epilepsy, types of seizures, frequency of seizures, circumstances at death, medication status prior to death, AED levels at autopsy, comorbidities, autopsy findings, cause of death (definite, probable, possible SUDEP), and any other relevant information.

Risk of bias assessment was conducted independently by two authors [HT, OA] using an assessment tool adapted from the effective public health practice project (Supplementary Information). Disagreements of a single point were resolved through discussion where possible; all others were reviewed by a senior author [AS].

3. Results

3.1. Search findings

A total of 590 possible titles were identified in the electronic database search and ten were identified through hand-searching citation lists (Fig. 2). Following title and abstract review, 497 papers were excluded on the basis that they did not include data on cases of SUDEP in children. Forty-five duplicate papers were identified and excluded, as were 12 papers for which the full text could not be obtained. During full-text review, eight papers were excluded as they did not meet inclusion criteria, and 17 were excluded as individual case information was not available and could not be provided by the study authors (Supplemental Table 3).

From the 22 included studies (Table 1), we were able to obtain individual information for 108 children who had SUDEP (Fig. 3) [18–39]. Five of the 22 included studies were cohort studies; four were retrospective case control studies; eight were case series, and five were case reports.

3.2. Risk of bias

Risk of bias was assessed for all included studies (Supplemental Table 2). There was good agreement between the two authors (complete agreement for 94% of measures, minor difference resolved by discussion for 6% of measures).

3.3. Case demographics

There was a male predominance of SUDEP cases (51%) over females (38%). The mean age at seizure onset was 3.1 years (standard deviation [SD] 4.3 years, range 1 month–17 years). The average age at death was 10.2 years (SD 5.4 years, range 7 months to 18 years).

SUDEP cases were classified as definite (66 cases, 61%), probable (26 cases, 24%), and possible (16 cases, 15%), as classified by the study authors according to definition criteria used by Nashef and Annegers [3]. An autopsy +/− histological examination of the brain was performed in 74 cases.

3.4. Seizure characteristics

Types of seizure were reported for 60 patients. Fifty-three had generalized tonic–clonic seizures (88%), and 20 had either simple or partial complex seizures (33%). Seizure frequency was reported in only 12 patients, with an average of 16.3 seizures per month (SD 14.6, range 0.5 to 45).

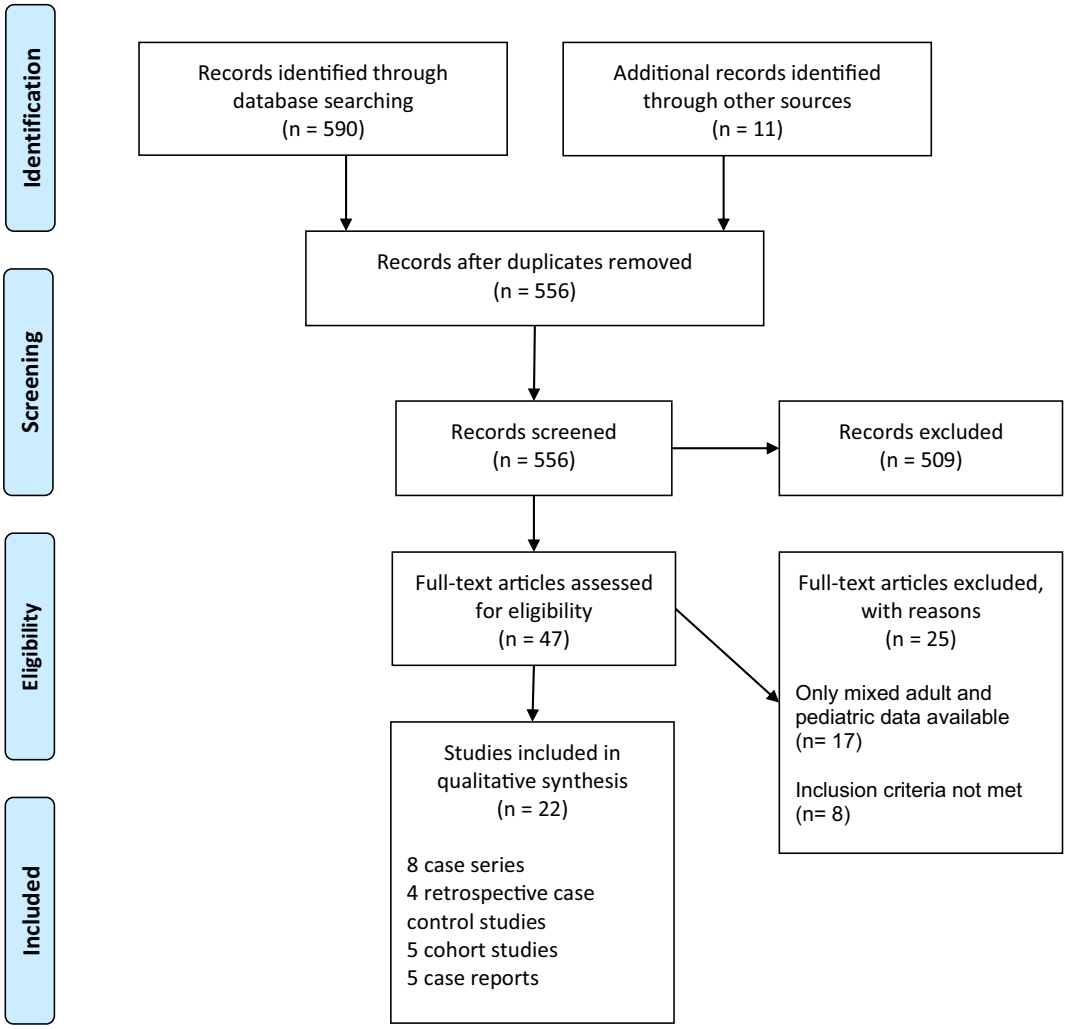

Fig. 2. Systematic review PRISMA flow diagram.

Table 1
Description of 21 studies included in systematic review.

Study	Country	Study design	Population	Number of childhood SUDEP cases (total n = 108)
Ackers et al. 2011	United Kingdom	Retrospective cohort study	Children aged 0–18 years prescribed AEDs between 1993 and 2005	3
Aurelian et al. 2012	Norway	Retrospective case–control study	Adults and children (over 10 year period)	1
Bagnall et al. 2014	Australia	Retrospective case series from epilepsy cohort and postmortems	Adults and children	5
Berg et al. 2011	USA and The Netherlands	4 separate prospective cohort studies in two countries	Adults and children	5
Donner et al. 2011	Canada	Retrospective case series of deaths from coroner's office, forensic unit and tertiary center	Children (0–18 years)	27
Doumlele et al. 2017	USA and Canada	Retrospective case series	Adults and children	3
Geerts et al. 2010	The Netherlands	Prospective cohort follow-up of newly diagnosed patients for 15 years	Children (0–16 years)	2
Kinney et al. 2013	United States	Case report	–	1
Klassen et al. 2014	Canada	Case report	–	1
Labate et al. 2013	Italy	Case report	–	1
Langan et al. 2000	United Kingdom	Retrospective case series review	Adults and children	2
Le Gal et al. 2010	Switzerland	Case report	–	1
Lear Kaul et al. 2005		Retrospective case series/review	–	6
Leu et al. 2015	United Kingdom	Retrospective case–control DNA sample collection	Adults and children	6
McGregor et al. 2006	United States	Retrospective case series; hospital records (tertiary center)	Children 0–18 years	11
Nashef et al. 1995	United Kingdom	Prospective cohort study (learning difficulties at residential school)	Children (school age)	7
Sillanpaa et al. 2010	Finland	Prospective population cohort for 40 years follow-up	Children <16 years of age at start of study	8
Surges et al. 2010	United Kingdom	Matched pair case–control (tertiary neurology center)	Adults and children	1
Swallow et al. 2002	Wales, United Kingdom	Case report	–	1
Tu et al. 2011	Australia	Retrospective case series; postmortems	Adults and children	4
Voolswijk et al. 2007	The Netherlands	Retrospective case–control study (tertiary epilepsy center)	Adults and children	8
Weber et al. 2005	Switzerland	Retrospective case series/review of tertiary hospital records	Children (0–18 years)	4

3.5. Epilepsy characteristics

The etiology of epilepsy was reported for 81 patients, using variable terminology dependent on the year of publication. Twenty-seven children had symptomatic epilepsy, now subcategorized as either structural, metabolic, or immune (33%). Seventeen patients were described as having idiopathic epilepsy, now referred to as genetic (21%), and 13 as having cryptogenic, now referred to as unknown (16%). Twelve cases had a diagnosed epilepsy syndrome; 7 had Dravet syndrome; 5 had benign epilepsy with centrotemporal spikes (BECTS), and 5 had either Lennox–Gastaut or West Syndrome.

Among the 73 children with information regarding comorbidities, 33 were classed as having developmental delay and/or intellectual impairment (45%); six had cerebral palsy (8%); five had a clinically diagnosed intercurrent pneumonia (7%), and 26 had no comorbid conditions (36%).

3.6. Epilepsy treatment

At the time of death, patients were on a range of different AEDs. The number of AEDs used for treating epilepsy was provided for 69 children. These children were on an average of 1.4 AEDs (SD 0.9, range 0–3). Specific AEDs were reported in only 51 patients, with sodium valproate being the most frequently used (18 cases, 35%). The next most commonly used AEDs were phenobarbitone, carbamazepine, and phenytoin. Four children were not on AEDs at time of death (8%).

3.7. Neuropathological findings

Neuropathological findings on autopsy were reported in 30 cases. Chronic neuropathological lesions were present in 17 cases (57%). Seven children had evidence of acute hypoxic changes in brain (23%). An unexpected finding of perivascular lymphocytic cuffing was present in three cases (10%) in one case series despite no history of infection or inflammatory disease [7]. Pulmonary edema was noted in all 8 patients who underwent a complete autopsy, and myocardial fiber hypertrophy was noted in one case.

4. Discussion

Childhood SUDEP is rarely discussed in the literature compared with adulthood SUDEP; nevertheless it is an important subject for child neurologists, especially given our current inability to accurately identify high-risk patients, beyond those with frequent GTCS. Each study reported a small numbers of cases, likely because of the rarity of pediatric SUDEP. The majority of studies identified were retrospective case series and case control studies that used hospital records of tertiary centers in high-income countries. These studies have an inherent selection bias, being more likely to include patients with higher seizure frequency, resistance to antiepileptic drug therapy, atypical features, and longer duration of epilepsy. Our review included only one population-based study, which avoids this selection bias.

Details of 108 cases of pediatric SUDEP were gathered into a case series. Most of these cases were extracted from noncomparative studies, while the remainder came from comparative studies with heterogeneous control populations, which prevented any higher analysis. It is impossible to draw definitive conclusions from this noncomparative data; however, because of the paucity of data on pediatric SUDEP, narrative analysis of this case series provides new and valuable insights into possible risk factors for SUDEP in childhood, and as such can guide further research.

4.1. Risk factors for SUDEP

4.1.1. Demographics

Analysis of the case demographics of SUDEP victims reveals a heterogeneous patient group encompassing all ages and genders. The age of onset of epilepsy was low for patients in our case series; most of the children started having seizures before the age of 5 years (average 3.1 years). A large Swedish case–control study of 6880 adult patients

who had SUDEP replicated this finding that the relative risk of SUDEP was 7.7 times higher in patients with early onset epilepsy (0–15 years) than in patients with late onset (after 45 years) [40].

4.1.2. Developmental delay/intellectual impairment

Almost half of the children in the case series (45%) had cognitive or developmental delay. Intellectual impairment and developmental delay are associated with medically refractory epilepsy and a greater risk of early all-cause mortality [41]. Severe cognitive impairment has been associated with increased mortality in a study of patients with epilepsy with over 40 years follow-up [42]. However, on multivariate analysis of these data, the absence of a 5-year terminal remission was the only significant risk factor for death. Conversely, in a prospective 10-year pediatric cohort study including 53 deaths (11 of which were SUDEP), moderate or severe intellectual impairment was significantly more frequent in patients who died from causes other than SUDEP [43]. Interestingly, 33% of the children in this systematic review were reported to have no comorbidities, suggesting that SUDEP can occur in children with uncomplicated epilepsy.

4.1.3. Autopsy findings

As the autopsies were performed in different studies across multiple institutions with possible variability in classification, the review is limited by the degree of detail of neuropathological studies. There was evidence of acute hypoxic and inflammatory changes in 23% of cases, with perivascular lymphocytic cuffing present in three cases. None of these

Total n= 108	SUDEP (n)	%
Males	55	51
Females	41	38
Gender not mentioned	12	11
Definite SUDEP	66	61
Probable SUDEP	26	24
Possible SUDEP	16	15

	Mean	SD
Age at epilepsy onset	3.1	4.3
Age at death	10.2	5.4

Age at death	n (%)
<1 years	2 (2)
1–5 years	25 (23)
6–10 years	23 (21)
11–15 years	29 (27)
16–18 years	26 (24)
Not mentioned	3 (3)
Total	**108**

Gender	n (%)
Male	55 (51)
Female	41 (38)
Not mentioned	12 (11)
Total	**108**

Cause of death	n (%)
Definite SUDEP	66 (61)
Probable SUDEP	26 (24)
Possible SUDEP	16 (15)
Total	**108**

Epilepsy Syndrome	n (%)
Symptomatic	27 (25)

Age at onset of seizures	n (%)
1–4 months	13 (12)
5months–1 year	20 (19)
2 years –5 years	6 (6)
6–10 years	7 (6)
11–15 years	6 (6)
Not mentioned	56 (52)
Total	**108**

Autopsy performed	n (%)
Yes	76 (70)
No	26 (24)
Not mentioned	8 (7)
Total	**108**

Autopsy information	n
Brain histopathology findings (n= 17)	
Mesial temporal sclerosis	5
Chronic Hypoxic damage	5
Dysgenesis	7
Acute Hypoxic damage	7
Perivascular lymphocytic	3

Fig. 3. Tables of characteristics of 108 childhood SUDEP cases from 22 studies in systematic review. Abbreviations: BECTS: benign epilepsy with centrotemporal spikes, BFIS: Benign Familial Infantile Seizures, JME: Juvenile Myoclonic Epilepsy, DD: Developmental Delay, LD: Learning Difficulties, NTD: Neural Tube Defect, GOR: Gastroesophageal reflux, ADHD: Attention Deficit Hyperactivity disorder, VF: Ventricular Fibrillation.

Idiopathic	17 (15)
Cryptogenic	13 (12)
Dravet syndrome	7 (6)
Lennox–Gastaut/West	5 (5)
BECTS	5 (5)
Posttraumatic	2 (2)
SEMI	1 (1)
BFIS	1 (1)
JME	1 (1)
Othara	2 (2)
Not mentioned	27 (25)
Total	**108**

Medication status pre–event	**n**
Sodium Valproate	18
Phenobarbitone	13
Carbamazepine	13
Phenytoin	6
Lamotigrine	5
Clonazepam	5
Diazepam	4
No medication	4
Levetericetam	3
Topiramate	2
Chloral hydrate	1
Gabapentin	1
Ketogenic diet	1
Ethosuximde	1
Not mentioned	54

AED level at postmortem	**n**
Subtherapeutic	14
Therapeutic	12
Elevated	1
Total	**27**

cuffing	
Lipoma on corpus callosum	1
Systemic findings (n=8)	
Pulmonary oedema	8
Mycoardial fibre hypertrophy	1

Circumstances at death	**n**
Found in bed	42
Witnessed seizures/collapse	17
No witnessed seizures	16
Prone position	13
Found on floor	5
Found in shower/bath	4
Supine position	2
VF during resuscitation	1
Not mentioned	28

Seizure types	**n**
GTCS	53
Partial – simple and complex	20
Absence	4
Myoclonic	4
Atonic	3
Tonic	2
Afebrie motor (BFIS)	1
Infantile spasms	1
Not mentioned	48

Comoribidity	**n**
DD/ LD	33
None	26
Cerebral palsy	6
Genetic/Chromosomal	5
Pneumonia	5
Hydrocephalus	4
Cardiac	2
GOR	1
NTD	1
Aspergers	1
ADHD	1
Hearing loss	1
Not mentioned	35

Fig. 3 (*continued*).

Abbreviations: BECTS: benign epilepsy with centrotemporal spikes, BFIS: Benign Familial Infantile Seizures, JME: Juvenile Myoclonic Epilepsy, DD: Developmental Delay, LD: Learning Difficulties, NTD: Neural Tube Defect, GOR: Gastro-oesophageal reflux, ADHD: Attention Deficit Hyperactivity disorder, VF: Ventricular Fibrillation

patients had evidence of infection clinically prior to death. In addition, chronic lesions were present in the majority (61%) of SUDEP victims. These findings do not necessarily reveal any risk factors for SUDEP as all pathological changes identified could be related to final common terminal events prior to death.

4.1.4. Medications

Our study does not have sufficient data to examine the relationship between specific AEDs and mortality. Sodium valproate was the most commonly used AED in the case series (35%) followed by carbamazepine (25%), phenobarbitone (25%), and lamotrigine (11%). The association between specific AEDs and the risk of SUDEP is complex, and there have been contradictory reports in the adult literature. As the risk of SUDEP seems to correlate strongly with increased frequency of GTCS, the assumption that effective drug treatment would reduce its incidence seems reasonable. Poor compliance with AED treatment has been linked to increased risk of adulthood SUDEP [44]. Although early reports implicated the sodium-channel blocking agent lamotrigine

with an increased risk of SUDEP [18,45], a recent meta-analysis found no relationship between any specific drugs and SUDEP [46].

4.1.5. Etiology of epilepsy

Thirty-three percent of the children in our case series had symptomatic epilepsy, encompassing structural, metabolic, and immune causes. Idiopathic epilepsy (or genetic epilepsy as per ILAE Revised Terminology [21]), which is most common in the general population, was diagnosed in just 21% of children in our case series. The association between SUDEP and symptomatic epilepsy in our case series could be attributed to selection bias; however, the association has been more reliably identified in the adult literature, primarily for epilepsy resulting from traumatic brain injury or encephalitis/meningitis [42]. Several pediatric cohorts have also identified the association; analysis of four cohorts of children with newly diagnosed epilepsy found those whose disease was associated with neurodisability or an underlying brain condition had a SUDEP rate 2–3 times higher than other patients [23]. A further prospective cohort study found that children with symptomatic epilepsy had a standardized mortality ratio of 31.6 [95% CI 18.4–50.6] versus 0.8 [95% CI 0.02–4.2] for idiopathic epilepsy [39]. In contrast, a Dutch cohort of patients with epilepsy in a tertiary neurology center showed no correlation between SUDEP and type of epilepsy for the 55 SUDEP cases included over a 5-year period [37].

In addition, 7% of the children in our series had Dravet syndrome, an SCN1A mutation-related infantile epilepsy syndrome. This is the most well-described pediatric genetic epilepsy syndrome with increased SUDEP risk [28], and the channelopathy resulting from SCN1A mutation may confer an increased risk of sudden cardiac death, compared with other epilepsy causes.

4.1.6. Seizure type

The majority of patients (88%) in our review had GTCS, supporting previous studies that have found GTCS to be a major risk factor for both adults and children [5,11,43]. Increased seizure burden has been previously associated with a higher SUDEP risk; a case–control study reported that people who were not seizure-free had a 23-fold increased risk of SUDEP compared with people with fully controlled seizures [38]. Other population-based studies found that adulthood SUDEP was associated with high seizure frequency (especially >50 seizures/year), multiple AEDs, and early onset epilepsy [9]. In this review, children had on average 16.3 seizures per month.

4.2. Future directions

Recently, there has been an increased interest in the molecular mechanisms underlying SUDEP, driven by whole exome sequencing (WES) studies. Mutations in ion channels expressed in the brain and the heart have been shown in animal and clinical case studies [21,47]. The WES data from patients who had SUDEP and control patients with epilepsy demonstrated a significantly increased genome-wide polygenic burden per individual in the SUDEP group, but no one single gene emerged as common to all cases [26].

The North American SUDEP Registry in the United States and Canada has been set up for prospective surveillance of SUDEP cases and currently acts as a repository for clinical, imaging, tissue, genetic, and physiological data [48]. A similar SUDEP registry in the United Kingdom with a pediatric focus would provide a more population-based approach for establishing incidence and risk factors of SUDEP in the UK. We thus propose a multidisciplinary approach to allow collection of high-quality clinical information, tissue, and deoxyribonucleic acid (DNA) samples from UK epilepsy-related mortality cases as possible to help in our search for understanding the mechanisms that lead to SUDEP.

5. Conclusions

In summary, from the limited evidence available, it is apparent that a constellation of features associated with severe epilepsy such as early age of onset, high seizure frequency, intellectual impairment, and developmental delay; multiple AED therapy; and structural abnormalities are associated with a higher risk of SUDEP [5,32,49,50]. Although many of these are not necessarily modifiable risk factors, knowledge that they are associated with SUDEP can nonetheless be valuable for clinicians when counselling parents and families.

There is a clear need for multiple large-scale, prospective, international community-based studies of both adulthood and childhood SUDEP to explore its pathogenesis, underlying risk factors, and possible preventative measures; current single center studies have not identified sufficient numbers of SUDEP cases. Inconsistent and inaccurate death certification, the lack of agreed definitions, and use of different terminologies have historically hampered research into mortality in epilepsy [16]. This has led to a probable under-appreciation of the public health burden of SUDEP, and there is a strong need to raise awareness of SUDEP. This implies that it is not just clinicians who need to talk more about SUDEP, but also health policy makers, researchers, and the public health community.

Acknowledgments

We would like to thank all corresponding authors of studies included for providing details on their published pediatric SUDEP cases needed for this systematic review.

Authors' contributions

OA conceptualized and designed the systematic review, drafted the initial manuscript, carried out the initial analyses, and approved the final manuscript as submitted. HT assisted with designing the systematic review and made a substantial contribution to the manuscript, carried out the initial analyses, and approved the final manuscript as submitted. ED and AS conceptualized the systematic review, supervised the team, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding

There is no funding associated with this work.

Declarations of interest

We declare no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.11.006.

References

[1] Appleton R. Sudden unexpected death in epilepsy in children. Seizure 1997;6:175–7.
[2] Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997;38(Suppl. 11):S6–8.
[3] Nashef L, So E, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53:227–33 [1].
[4] Annegers J, Coan S, Hauser W, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000;41:549–53.

[5] Ficker DM, So EL, Shen WK, Annegers JF, O'Brien PC, Cascino GD, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology 1998;51:1270–4.
[6] Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88:1674–80.
[7] Berg A, Nickels K, Wirrell E, Geerts AT, Callenbach PM, Arts WF, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics 2013;132:124–31.
[8] Appleton R. Mortality in paediatric epilepsy. Arch Dis Child 2003;88:1091–4.
[9] Timmings P. Sudden unexpected death in epilepsy: a local audit. Seizure 1993;2: 287–90.
[10] Jick S, Cole T, Mesher R, Jick H. Sudden unexpected death in young persons with primary epilepsy. Pharmacoepidemiol Drug Saf 1992;1:59–64.
[11] Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case–control study. Epilepsia 2001;42:667–73.
[12] Walczak T, Leppik I, D'Amelio M, Rarick J, So E, Ahman P, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 2001;56:519–25.
[13] Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64: 1131–3.
[14] Ficker D. Sudden unexplained death and injury in epilepsy. Epilepsia 2000;41: S7–12.
[15] Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–77.
[16] Lhatoo S, Johnson A, Goodridge D, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Ann Neurol 2001;49:336–44.
[17] Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. Epilepsy Behav 2007;10:138–41.
[18] Ackers R, Besag F, Hughes E, Squier W, Murray ML, Wong IC. Mortality rates and causes of death in children with epilepsy prescribed antiepileptic drugs. Drug Saf 2011;34:403–13.
[19] Aurlien D, Larsen J, Gjerstad L, Taubøll E. Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case-control study. Epilepsia 2012;53:258–66.
[20] Bagnall R, Crompton D, Cutmore C, Regan BM, Berkovic SF, Scheffer IE, et al. Genetic analysis of PHOX2B in sudden unexpected death in epilepsy cases. Neurology 2014; 83:1018–21.
[21] Berg A, Scheffer I. New concepts in classification of the epilepsies: entering the 21st century. Epilepsia 2011;52:1058–62.
[22] Donner EJ, Smith CR, Snead OC. Sudden unexplained death in children with epilepsy. Neurology 2001;57:430–4.
[23] Doumlele K, Friedman D, Buchhalter J, Donner EJ, Louik J, Devinsky O. Sudden unexpected death in epilepsy among patients with benign childhood epilepsy with centrotemporal spikes. JAMA Neurol 2017;74:645–9.
[24] Geerts A, Arts WF, Stroink H, Peeters E, Brouwer O, Peters B, et al. Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch study of epilepsy in childhood. Epilepsia 2010;51:1189–97.
[25] Kinney HC, McDonald AG, Minter ME, Berry GT, Poduri A, Goldstein RD. Witnessed sleep-related seizure and sudden unexpected death in infancy: a case report. Forensic Sci Med Pathol 2013;9:418–21.
[26] Klassen T, Bomben V, Patel A, Drabek J, Chen TT, Gu W, et al. High-resolution molecular genomic autopsy reveals complex sudden unexpected death in epilepsy risk profile. Epilepsia 2014;55:e6–12.
[27] Labate A, Tarantino P, Palamara G, Gagliardi M, Cavalcanti F, Ferlazzo E, et al. Mutations in PRRT2 result in familial infantile seizures with heterogeneous phenotypes including febrile convulsions and probable SUDEP. Epilepsy Res 2013;104:280–4.
[28] Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. J Neurol Neurosurg Psychiatry 2000;68:211–3.
[29] Le Gal F, Korff C, Monso-Hinard C, Mund MT, Morris M, Malafosse A, et al. A case of SUDEP in a patient with Dravet syndrome with SCN1A mutation. Epilepsia 2010;51: 1915–8.
[30] Lear-Kaul KC, Coughlin L, Dobersen MJ. Sudden unexpected death in epilepsy: a retrospective study. Am J Forensic Med Pathol 2005;26:11–7.
[31] Leu C, Balestrini S, Maher B, Hernández-Hernández L, Gormley P, Hämäläinen E, et al. Genome-wide polygenic burden of rare deleterious variants in sudden unexpected death in epilepsy. EBioMedicine 2015;2:1063–70.
[32] McGregor A, Wheless J. Pediatric experience with sudden unexplained death in epilepsy at a tertiary epilepsy center. J Child Neurol 2006;21:782–7.
[33] Nashef L, Fish D, Garner S, Sander JW, Shorvon SD. Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. Epilepsia 1995; 36:1187–94.
[34] Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med 2010;363:2522–9.
[35] Surges R, Adjei P, Kallis C, Erhuero J, Scott CA, Bell GS, et al. Pathologic cardiac repolarization in pharmacoresistant epilepsy and its potential role in sudden unexpected death in epilepsy: a case–control study. Epilepsia 2010;51:233–42.
[36] Swallow R, Hillier C, Smith P. Sudden unexplained death in epilepsy (SUDEP) following previous seizure-related pulmonary oedema: case report and review of possible preventative treatment. Seizure 2002;11:446–8.
[37] Tu E, Bagnall R, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathol 2011;21:201–8.
[38] Vlooswijk M, Majoie H, De Krom M, Tan IY, Aldenkamp AP. SUDEP in the Netherlands: a retrospective study in a tertiary referral center. Seizure 2007;16:153–9.
[39] Weber P, Bubl R, Blauenstein U, Tillmann BU, Lütschg J. Sudden unexplained death in children with epilepsy: a cohort study with an eighteen-year follow-up. Acta Paediatr 2005;94:564–7.
[40] Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet 1999;353:888–93.
[41] Shinnar S, Pellock JM. Update on the epidemiology and prognosis of pediatric epilepsy. J Child Neurol 2002;17(Suppl. 1):S4–S17.
[42] Johnson J, Hofman N, Haglund C, Cascino GD, Wilde AA, Ackerman MJ. Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy. Neurology 2009;72:224–31.
[43] Terra V, Scorza F, Arida R, Fernandes RM, Wichert-Ana L, Machado HR, et al. Mortality in children with severe epilepsy: 10 years of follow-up. Arq Neuropsiquiatr 2011; 69:766–9.
[44] Téllez-Zenteno JF, Ronquillo LH, Wiebe S. Sudden unexpected death in epilepsy: evidence-based analysis of incidence and risk factors. Epilepsy Res 2005;65:101–15.
[45] Nashef L, Garner S, Sander JW, Fish DR, Shorvon SD. Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. J Neurol Neurosurg Psychiatry 1998;64:349–52.
[46] Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52:1150–9.
[47] Annegers JF, Coan SP. SUDEP: overview of definitions and review of incidence data. Seizure 1999;8:347–52.
[48] Donner E, Devinsky O. Registries for SUDEP research. In: Hanna J, Panelli R, Jeffs T, Chapman D, editors. Continuing the global conversation [online]. SUDEP action, SUDEP aware & epilepsy Australia; 2014 [retrieved 05/09/16]. Available from: https://www.sudepglobalconversation.com.
[49] Nickels K, Grossardt B, Wirrell E. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County, MN. Epilepsia 2012;53:2164–71.
[50] Pedley T, Hauser W. Sudden death in epilepsy: a wake-up call for management. Lancet 2002;359:1790–1.