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Review

Mortality in Dravet syndrome: A review

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ABSTRACT

Introduction: Premature mortality is a major issue in Dravet syndrome (DS). To improve understanding of DS premature mortality, we conducted a comprehensive literature search with a particular emphasis on SUDEP.
Methods: We searched PubMed, Embase, Web of Science, Cochrane, CENTRAL, CINAHL, PsycINFO, Academic Search Premier, and ScienceDirect on the following terms: "Dravet syndrome", "severe myoclonic epilepsy", "SMEI", "mortality", "survivors", "prognosis", and "death". DS cases or cohorts studies reporting mortality were included.
Results: The search yielded 676 articles and 86 meeting abstracts. After removing duplicates and screening titles and abstracts, full text of 73 articles was reviewed. Only 28 articles and six meeting abstracts met inclusion criteria. Five articles and four meeting abstracts were excluded, as the case(s) were also described elsewhere. After checking the references, five additional studies were included. The 30 items reported 177 unique cases. Sudden unexpected death in epilepsy was the likely cause in nearly half of the cases (n = 87, 49%), followed by status epilepticus (n = 56, 32%). Drowning or accidental death was reported in 14 cases (8%), infections in 9 (5%), other causes in six (3%), and unknown in five (3%). Age at death was reported for 142 of the 177 cases (80%), with a mean age of 8.7 ± 9.8 years (SD); 73% died before the age of 10 years.
Discussion: Dravet syndrome is characterized by high epilepsy-related premature mortality and a marked young age at death. Sudden unexpected death in epilepsy is the leading reported cause of death in DS, accounting for nearly half of all deaths. The cause of this excess mortality remains elusive but may be explained by epilepsy severity, as well as genetic susceptibility to SUDEP.

1. Introduction

Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy (SMEI), is a devastating epileptic syndrome [1]. At least 70% of cases are due to heterozygote loss-of-function mutations in the *SCN1A* gene [2,3]. The estimated incidence of DS is between 1:20,000 and 1:40,000 [4–7]. Typically, seizure onset is in the first year of life, usually with prolonged fever- or temperature-sensitive seizures, including generalized tonic–clonic and unilateral clonic seizures [8]. Before seizure onset, psychomotor development and EEGs are normal [5]. Other seizure types, including myoclonus, absences, and complex partial seizures may follow [1,8,9]. Seizures are often refractory to antiepileptic drug treatment [9,10]. A slowing of development becomes apparent after the first year of life [5]. Cognitive outcome is typically poor, and pyramidal signs and ataxia often develop [9,11].

Long-term outcome is dominated by premature mortality, estimated to affect up to 21% of those with DS [8,10]. A strong association between sudden unexpected death in epilepsy (SUDEP) and DS has been suggested [10,12]. *SCN1A* has been suggested as a possible candidate SUDEP gene [13,14]. These suggestions predominantly rely on small cohort studies or case reports. To improve understanding of DS premature mortality, we conducted a comprehensive literature search with a particular emphasis on SUDEP.

2. Methods

We used the scoping review method [15] to identify and summarize all relevant literature on DS mortality, regardless of quality or study design of included studies.

2.1. Database search

We conducted a comprehensive literature search of PubMed, Embase, Web of Science, Cochrane, CENTRAL, CINAHL, PsycINFO, Academic Search

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Premier, and ScienceDirect, with the following keywords: "Dravet syndrome", "severe myoclonic epilepsy", "SMEI", "mortality", "survivors", "prognosis", and "death". We searched all available publications up to 12 February 2016 (Appendix 1). The search strategy was developed and conducted by two authors (SS and RDT) and a librarian.

2.2. Inclusion and exclusion criteria

Inclusion criteria were 1) title and abstract available in English, 2) human DS case(s) (SMEI or severe myoclonic epilepsy of infancy borderline (SMEB)), and 3) mortality data available for these case(s). Articles describing previously published mortality data were excluded. References of all included articles were screened for additional eligible papers.

2.3. Data collection

We collected data on the following: cause of death, age at death, *SCN1A* testing (yes or no), and *SCN1A* mutation identified (yes or no). Cause of death was categorized as 1) SUDEP, 2) status epilepticus (SE), 3) accidental (including drowning), 4) infective, 5) other, and 6) unknown (i.e., not known or not reported). Sudden unexpected death in epilepsy cases were classified as definite, probable, or possible. [16]. The following clinical variables in SUDEP cases were recorded (yes or no): witnessed, from sleep, prone position, and signs of a recent seizure.

2.4. Data analysis

Descriptive statistics were used to present the results. When the mean was calculated, standard deviation was added as a measure of variability.

3. Results

3.1. Database search

The search yielded 676 articles and 86 meeting abstracts. Duplicate titles were removed, leaving 427 articles and 83 meeting abstracts. After screening titles and abstracts, 354 articles and 77 meeting abstracts did not meet inclusion criteria (reasons detailed in Fig. 1). Full texts of 73 articles and six meeting abstracts were obtained. After reading full texts, 45 articles were excluded, yielding 28 articles and six meeting abstracts that met our inclusion criteria. Five articles and four meeting abstracts were excluded, as the case(s) were also described elsewhere. After checking the references of all included articles,

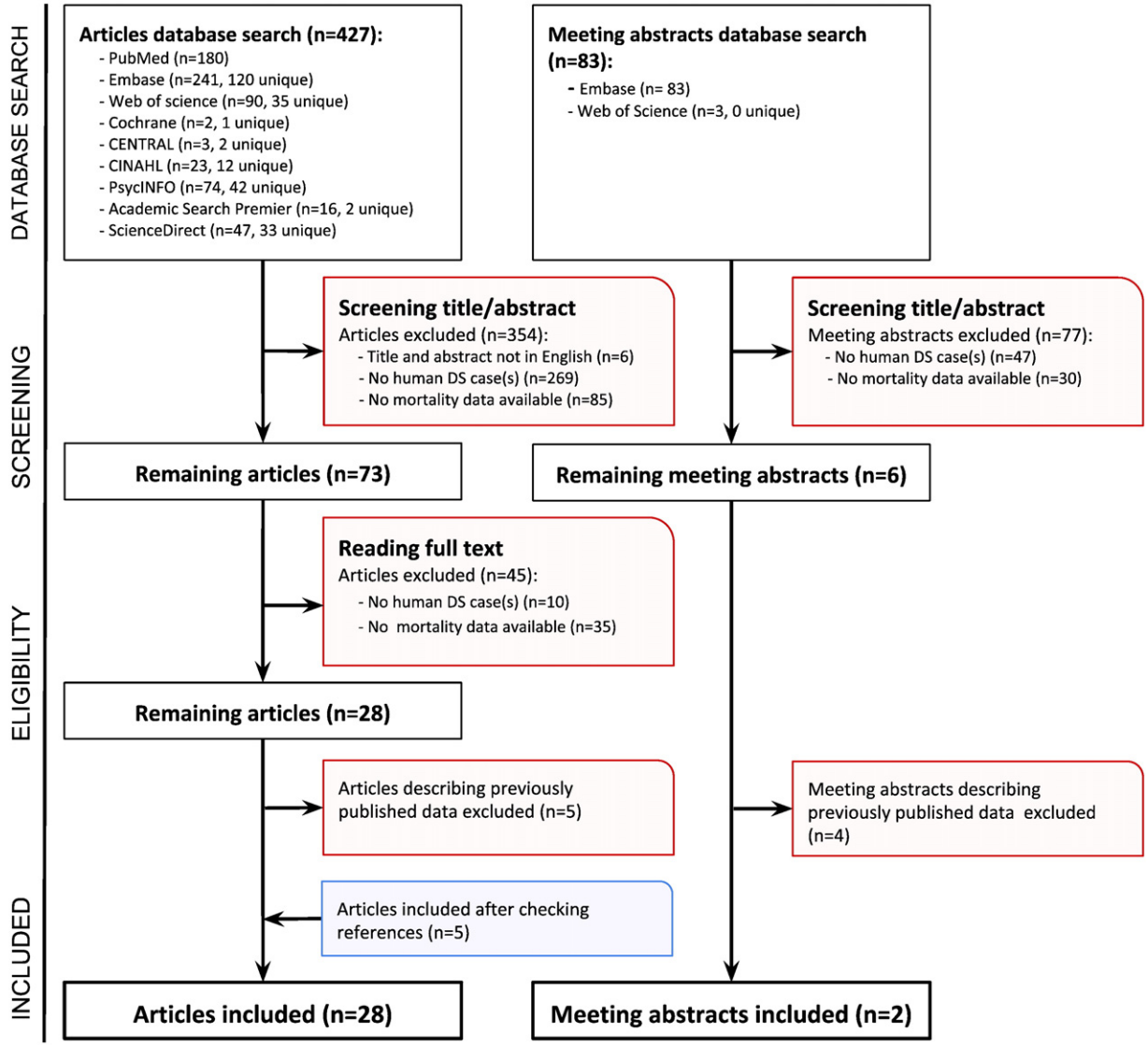

Fig. 1. Flow diagram of database search on February 12th, 2016.

five additional studies were added resulting in a total of 30 included publications (23 cohorts and 7 case reports) (Appendix 2).

A total of 177 unique fatal DS cases were described (Table 1); of these, only 30 were known to have been tested for an *SCN1A* mutation, found in 28/30.

3.2. Cause of death

Causes of death for the 177 cases are shown in Fig. 2. Sudden unexpected death in epilepsy was the leading cause of death (n = 87, 49%) followed by status epilepticus (n = 56, 32%). Fatal drowning and accidents were described in 14 cases (8%) and fatal infections in nine (5%). Other causes (n = 6, 3%) included (one case each): respiratory insufficiency and generalized hypoxemia secondary to acute respiratory distress syndrome, ketoacidosis, global ischemic brain injury, brainstem tumor, found dead shortly after tonsillectomy, and postoperative multiple organ failure. In five cases, the cause of death was unknown or not reported (3%).

To test whether publication bias may have increased the proportion of SUDEP, we performed a separate analysis of cause of death in the 23 cohorts. After exclusion of all fatal case reports, the distribution of causes of death was 47% SUDEP (n = 81), 34% SE (n = 56), 8% drowning or accident (n = 14), 5% fatal infection (n = 9), 2% other cause (n = 5), and 3% unknown (n = 5). One cohort study reported only SE cases [17]. When also excluding these four deaths, the distribution was the following: total n = 166; 49% SUDEP (n = 81), 31% SE (n = 52), 8% drowning or accident (n = 14), 5% fatal infection (n = 9), 3% other cause (n = 5), and 3% unknown (n = 5).

3.3. Age at death

Age at death was reported for 142 of the 177 cases (80%). The mean age at death was 8.7 ± 9.8 years (SD); 73% occurred before the age of 10 years, and 93% occurred before the age of 20. The age distribution for all causes of death is shown in Fig. 3. Six cases (four SUDEP and two drowning) were grouped into an "18+ category" with a maximum age of 24 years [12]. We divided these cases evenly over this age category (SUDEP 18, 20, 22, and 24 years; drowning 20 and 22 years).

3.4. Characteristics of SUDEP cases

Postmortem examination was reported in 12 of 87 SUDEP cases, and autopsy was not performed in 37 cases; thus, 12 cases (14%) could be

Table 1
Data collected from the 30 included articles presenting unique DS mortality cases. Sudden unexpected death in epilepsy cases were further specified into definite and probable SUDEP when autopsy was reported. References are listed in Appendix II. The cause of death category 'other' included (from top to bottom) the following: respiratory insufficiency and generalized hypoxemia secondary to acute respiratory distress syndrome, ketoacidosis, global ischemic brain injury, brainstem tumor, found dead day after tonsillectomy, and postoperative multiple organ failure.

#	Study	Year	Mortality (n)	Ages known (n)	*SCN1A* tested (n)	*SCN1A*+ (n)	Cause of death						Comments
							SUDEP (n)	SE (n)	Drowning or accident (n)	Fatal infection (n)	Other (n)	Unknown (n)	
1	Ogino	1989	1	1	0	0	1	0	0	0	0	0	Dravet cohort children (n = 10)
2	Renier[a]	1990	1	1	0	0	1	0	0	0	0	0	Case report
3	Miyake	1991	4	0	0	0	0	3	0	0	0	1	Children who died at neurology department (n = 237)
4	Dravet	1992	10	9	0	0	2	2	4	1	0	1	Dravet cohort all ages (n = 63)
5	Dooley	1995	1	1	0	0	0	0	1	0	0	0	Dravet cohort children (n = 7)
6	Castro-Gago[a]	1997	1	1	0	0	0	0	0	0	1	0	Case report
7	Perez	1999	1	0	0	0	1	0	0	0	0	0	Cohort of children with refractory epilepsy (n = 104, of which 21 DS)
8	Oguni	2001	12	6	0	0	3	7	1	1	0	0	Dravet cohort children (n = 84)
9	Ceulemans	2004	1	1	1	1	0	1	0	0	0	0	Dravet *SCN1A*+ cohort (n = 12)
10	Caraballo	2006	2	0	NR	NR	0	0	0	1	0	1	Dravet cohort children (n = 53)
11	Jansen	2006	1	1	0	0	0	0	0	0	0	1	Dravet cohort adults (n = 14)
12	Akiyama	2010	6	0	NR	NR	1	3	0	2	0	0	Dravet cohort all ages (n = 37)
13	Le Gal[a]	2010	1	1	1	1	1	0	0	0	0	0	Case report
14	Catarino	2011	8	8	6	4	4	0	0	3	1	0	Dravet cohort all ages, 3 post mortem diagnosed (n = 22)
15	Genton	2011	5	5	NR	NR	3	1	0	0	0	1	Dravet cohort adults (n = 24)
16	Sakauchi	2011	59	58	NR	NR	31	21	6	1	0	0	Questionnaire sent to pediatricians, max. age 24 (n = 623)
17	Skluzacek	2011	31	31	NR	NR	19	10	1	0	1	0	Dravet cohort all ages (n = 833)
18	Brunklaus	2012	5	0	5	5	3	2	0	0	0	0	Dravet *SCN1A*+ cohort children (n = 88)
19	Okumura	2012	4	4	2	2	0	4	0	0	0	0	Dravet children with SE (n = 15)
20	Brunklaus[b]	2013	3	0	3	3	2	1	0	0	0	0	Meeting abstract (n = 207, including 88 cases of Brunklaus et al., 2012)
21	Friedman[a]	2013	1	1	1	1	1	0	0	0	0	0	Case report
22	Nabbouti	2013	2	2	NR	NR	1	0	0	0	1		Dravet cohort max. age 24 (n = 67)
23	Wirrell	2013	2	2	NR	NR	1	0	0	0	1	0	Dravet cohort children (n = 82)
24	Barba[c]	2014	1	1	1	1	0	0	0	0	1	0	Dravet *SCN1A*+ cohort children (n = 6)
25	Klassen[a]	2014	1	1	1	1	1	0	0	0	0	0	Case report
26	Takayama	2014	2	2	0	0	1	0	1	0	0	0	Dravet cohort adults (n = 64)
27	Dede[a]	2015	1	1	1	1	1	0	0	0	0	0	Case report
28	Donner	2015	6	0	5	5	6	0	0	0	0	0	Meeting abstract; Dravet cohort all ages (n = 34)
29	Kolikonda[a]	2015	1	1	NR	NR	1	0	0	0	0	0	Case report
30	Verbeek	2015	3	3	3	3	2	1	0	0	0	0	Dravet *SCN1A*+ cohort up to age of 20 (n = 77)
	Total (n)		177	142	30	28	87	56	14	9	6	5	

SUDEP = sudden unexpected death in epilepsy; SE = status epilepticus; NR = not reported; N/A = not applicable.
[a] Case report.
[b] Five of eight reported deaths were previously described and therefore not included (Brunklaus et al., 2012).
[c] One of two mortality cases was previously described and therefore not included (Le Gal et al., 2014).

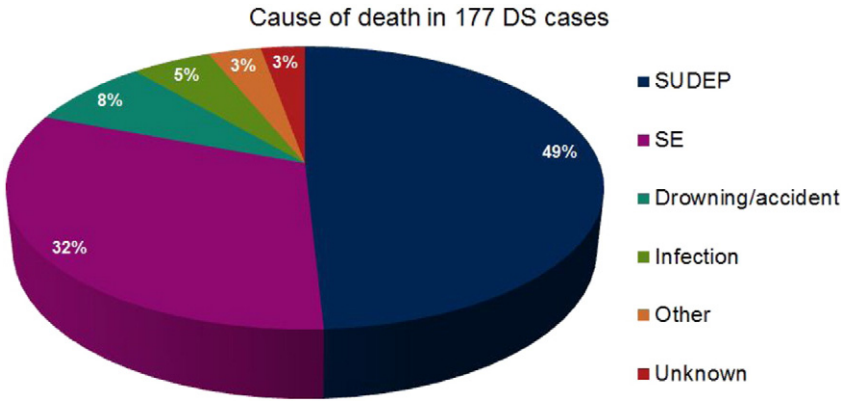

Fig. 2. Six categories of cause of death in 177 DS cases and percentage of cases in each category. DS = Dravet syndrome; SUDEP = sudden unexpected death in epilepsy; SE = status epilepticus.

classified as definite SUDEP, 37 (43%) as probable SUDEP, and 38 cases (44%) could not be classified. The following SUDEP characteristics were present when reported: six out of seven were unwitnessed (86%), 26 of 34 occurred from sleep (76%), two of three were found prone (67%), and seven of eight cases had signs of a recent seizure (88%).

4. Discussion

Dravet syndrome is characterized by high epilepsy-related premature mortality and a marked young mean age at death. Sudden unexpected death in epilepsy is the leading cause of death in DS, causing nearly half of all deaths in this condition.

Epilepsy-related deaths (SUDEP and SE) account for the vast majority of premature mortality in DS (up to 81%). This contrasts with previous cohorts of new-onset epilepsies (up to 3%) [18,19]. In chronic epilepsy cohorts, the proportion of epilepsy-related deaths is higher, varying from 46 to 73% of all cases of premature mortality [20]. Even compared with those cohorts, DS stands out with remarkably high epilepsy-related premature mortality.

Up to a third of all deaths in DS are the results of episodes of SE. In other epilepsy cohorts, the proportion of fatal SE is much lower; 0.2–1% in population-based cohorts [19,21] and up to 14% in chronic cohorts [22–24]. The age at death for SE in DS (86% ≤10 years; 98% ≤20 years) was remarkably lower than seen in other epilepsies; 4% ≤10 years [25] and 3% <20 years [26].

The leading cause of death in DS, SUDEP, accounts for nearly half of overall mortality (49%). This figure contrasts with population-based cohorts of people with epilepsy (2–4%) [21,27] and some cohorts of people with intractable epilepsy (20–25%) [28,29]. Other studies of chronic epilepsy cohorts show similar SUDEP proportions of overall mortality (42–44%) [22,24], up to 50% in cohorts with chronic intractable epilepsy and learning difficulties [23].

Sudden unexpected death in epilepsy in DS tends to occur at a younger age (73% before the age of 11) than in other epilepsy cohorts (3–9% ≤10 years) [23,30–32]. In these cohorts, SUDEP risk peaks in early adulthood (45–56% 20–40 years vs. 6% 20–40 years in DS) [30,32,33]. Sudden unexpected death in epilepsy characteristics in DS seem quite similar to those reported in other epilepsies [34–37], but often, details were not reported.

High SUDEP rates in DS may be explained by epilepsy severity. The main SUDEP risk factors, including high frequency of convulsions and antiepileptic drug polytherapy [35–39], relate to epilepsy severity; these factors are often seen in DS. Young age at death may also, at least partly, be explained by epilepsy severity, as the tendency for SE and high frequency of convulsions in those with DS seems to peak in childhood [40,41]. The number of convulsions often gradually decreases over time, and SE rarely occurs after the age of 10 [40,41]. In other epilepsies, SE appears to have a bimodal age distribution, with the highest frequency in children and the elderly [26,42], but this does not apply to the mortality figures: despite the high frequency of SE in children, its mortality in non-DS children is low, whereas in the elderly, both a high incidence rate and high mortality rate of SE have been reported [25,26].

The association between DS and SUDEP is supported by animal studies. Mutant *SCN1A* knock-out or knock-in mice were often found

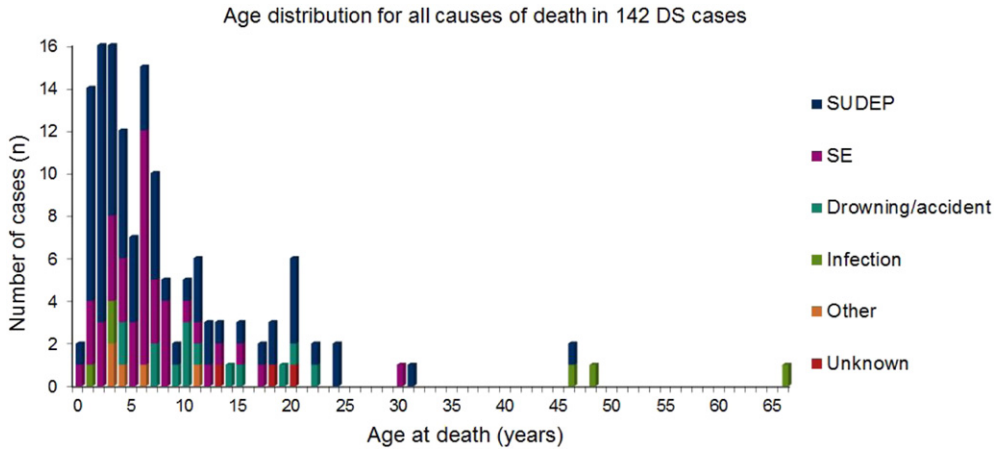

Fig. 3. Age distribution for all causes of death in 142 DS cases. DS = Dravet syndrome; SUDEP = sudden unexpected death in epilepsy; SE = status epilepticus.

to die prematurely, mostly following seizures — a death resembling SUDEP [43–46]. Mice were found to have decreased heart rate variability (HRV) [45]. Several mice died from bradycardia at seizure offset and from seizure-triggered ventricular fibrillation [43,45]. Interictal human DS studies demonstrated lower HRV [47] and increased QT-dispersion [48] in DS compared with those with other epilepsies and healthy controls suggesting an increased arrhythmia vulnerability; ictal proof is lacking and is the subject of an ongoing project (ClinicalTrials.gov Identifier: NCT02415686).

SCN1A has been suggested as a possible candidate SUDEP gene [13,14,49,50]. This hypothesis predominantly relies on the abovementioned animal studies and postmortem genetic analyses of SUDEP cases [13,14,51]. Potentially deleterious variants in the *SCN1A* gene have been found in SUDEP cases without a clinical diagnosis of DS [13,14,50]. Whether *SCN1A* is a 'SUDEP gene' is debatable, as this would require a proof that *SCN1A* independently confers SUDEP risk beyond epilepsy severity.

Our findings may have been affected by differences in methodology and reporting. Publication bias on epilepsy-related mortality reporting, especially SUDEP, may also have played a role. Sudden unexpected death in epilepsy, however, remained the major cause of death even after exclusion of case reports. It is likely that more severe DS phenotypes were included, as most cases were seen at tertiary centers. This referral bias may have led to an overestimation of epilepsy-related mortality. This may also apply to the time frame: most cases were identified in a period when DS was still diagnosed by strict clinical criteria [8]. Several factors may have influenced the age distribution found. Underdiagnosis is a recognized problem in DS. In the last 10 to 15 years, genetic testing for DS has been widely implemented, and this has likely led to increased diagnosis in children rather than adults, as DS is seen as a pediatric syndrome. Awareness of DS is also recent, as it was only described about four decades ago [1]. Adults may have thus missed out on a diagnosis [52,53]. The reported DS population is likely to be biased toward younger cases, thus affecting our results as most studies describe pediatric cohorts (Table 1). The peak of deaths at young age was, however, consistent and also seen in those cohorts with longer follow-up into adulthood [40,54].

Another limitation includes diagnostic accuracy: clinical features of most DS cases were poorly described, and in the majority of cases, no information was provided whether cases had been tested for an *SCN1A* mutation. Another potential limitation is that most SUDEP cases did not have a postmortem examination.

These factors all underscore the need for further studies. Reliable figures are crucial to inform health care professionals, individuals with the condition, and their carers.

Future studies are warranted to confirm and update these findings and should involve long-term follow-up of large, properly genetically detailed, DS cohorts. Preferably, nationwide genetic databases should be used for recruitment to avoid referral bias [55] and should include complete documentation of the full clinical DS spectrum, as well as detailed reporting of the circumstances of death, including autopsy reports. These studies would provide better estimates of mortality and SUDEP frequency in people with DS. Genetic studies may elucidate the potential role of the variety of *SCN1A* mutations in premature mortality and provide markers to estimate SUDEP risks.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.09.007.

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Conflict of interest

SS and WGB report no conflict of interest. SMS is a member of Scientific Advisory Board of Dravet Syndrome UK. JWS reports personal fees from Lundbeck and Teva, grants and personal fees from UCB, Eisai, grants from GSK, WHO and Dutch National Epilepsy Fund, outside the submitted work; his current position is endowed by the Epilepsy Society, he is a member of the Editorial Board of the Lancet Neurology and receives research support from the Marvin Weil Epilepsy Research Fund. RDT receives research support from the Dutch National Epilepsy Fund, NUTS Ohra Fund, Medtronic, and AC Thomson Foundation, and has received fees for lectures from Medtronic, UCB and GSK.

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