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RESEARCH ARTICLE

Circumstances surrounding sudden unexpected death in epilepsy in children: A national case series

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Abstract

Objective: This study was undertaken to understand the circumstances surrounding pediatric sudden unexpected death in epilepsy (SUDEP) and identify clinical factors that may be associated with SUDEP in childhood.

Methods: A retrospective case series was conducted. Pediatric SUDEP cases were collected across Canada from the Ontario Forensic Pathology Service, Canadian Pediatric Surveillance Program, and Canadian Pediatric Epilepsy Network. Demographics, epilepsy history, comorbidities, and circumstances surrounding death were analyzed.

Results: Forty-nine children with pediatric SUDEP were analyzed; 25 (51%) were females, and the median age at death was 8 years. Six children (12%) were <2 years of age at the time of death. Information on seizure types 6 months before death was known in 35 children. Twenty-two had tonic–clonic seizures within the last 6 months prior to death (63%). Seven children (18%) had no tonic–clonic seizures in their lifetime. Two thirds of children were treated with ≥2 antiseizure medications. Genetic etiologies were most common (55%). Data on global developmental delay (GDD) was known in 46 children; 12 children (26%) had no impairment, and 34 were globally delayed (74%). Children with GDD had earlier age at seizure onset ($p < .001$); however, epilepsy duration was similar to those without GDD ($p = .170$). Similar to adult cohorts, death was often unwitnessed ($n = 41/46$, 89%). Information on recent infection before death was known in 37 children. Seventeen children (46%) had a recent infection.

Significance: Our study represents the largest pediatric SUDEP case series to date. SUDEP occurred in children of all ages, including infants, with a spectrum of epilepsies with and without neurodevelopmental impairment. The circumstances around death (i.e., timing of death, witnessed/unwitnessed) were similar to previous SUDEP cohorts. A recent infection was often observed, which could decrease seizure threshold and trigger a terminal seizure and may suggest

that times of increased seizure risk could warrant heightened surveillance for SUDEP. However, further research is needed to determine the significance of this finding.

KEYWORDS
mortality, pediatric epilepsy, prevention, SUDEP, tonic–clonic seizures

1 | INTRODUCTION

Children and adults with epilepsy are at increased risk of premature and sudden death.[1–3] The risk of premature death is 2–3 times more common and the risk of sudden and unexpected death is up to 24 times more common in individuals with epilepsy than in the general population.[1–3] Death in epilepsy may be due to epilepsy-related or non-epilepsy-related causes.[2,4,5] The sudden unexpected death of an individual living with epilepsy (SUDEP) is the leading cause of epilepsy-related mortality in children and adults with epilepsy.[2,4–10]

Children with epilepsy are at increased risk of mortality compared to their adult counterparts, especially when there is associated neurological impairment.[2,4,11–15] Although SUDEP was once believed to be rare in childhood, it has been demonstrated in two population-based cohorts that the incidence of SUDEP is similar in adults and children living with epilepsy at approximately 1.2 per 1000 person-years.[16–19] The most important risk factor for SUDEP is the presence and frequency of tonic–clonic seizures (TCSs).[17,20–25] Other risk factors include failure to optimize treatment with antiseizure medications (ASMs) when patients are refractory to treatment, nocturnal seizures, and a lack of seizure freedom in the preceding 1–5 years.[17,24–28]

Overall, the pathophysiology of SUDEP remains unknown but may involve mechanisms such as cerebral shutdown following a TCS, and subsequent cardiac and respiratory dysfunction.[28] Although several studies have aimed to better understand SUDEP risk factors, they have varied in methodology and the population studied, often focusing on the adult population.[8,17,18,20–34] Few studies have focused exclusively on SUDEP in the pediatric population and/or included children with SUDEP.[18,34–47] A systematic review of SUDEP in childhood observed that children with early onset epilepsy, high seizure frequency, intellectual impairment, structural brain abnormalities, and polytherapy appeared to be most at risk for SUDEP.[45]

Overall, the clinical characteristics and circumstances surrounding pediatric SUDEP deaths are less well understood when compared to adults. The circumstances of and risk factors for SUDEP in children may differ from SUDEP in adults for many reasons, including that children with epilepsy are rarely left alone, they are believed to maintain better treatment adherence than adults, and the causes of epilepsy in childhood differ from those in adults. Careful evaluation of children with pediatric SUDEP may (1) help elicit the circumstances accompanying pediatric SUDEP deaths and (2) identify clinical characteristics that may be associated with SUDEP risk.[25] We sought to better understand pediatric SUDEP deaths through the development of a nationwide pediatric SUDEP case series.

Key points

- Genetic etiologies were most common; SUDEP occurred in well-known genetic epilepsies (i.e., *SCN1A, KCNT1*) as well as rare neurogenetic conditions (i.e., Rett syndrome).
- SUDEP occurred across the spectrum of epilepsies, from genetic generalized epilepsies (i.e., JME) to more severe epilepsies (i.e., Lennox–Gastaut syndrome).
- One eighth of the cohort were infants who died before the age of 2 years.
- One fifth of the cohort did not have a history of tonic–clonic seizures, suggesting other mechanisms may be at play in these SUDEP deaths.
- Recent infection around the time of death was observed in some children; further inquiry regarding the significance of this finding is required.

2 | MATERIALS AND METHODS

2.1 | Study protocols and procedures

Prior to study initiation, ethics approval was obtained from the research ethics board at the Hospital for Sick Children (HSC), Toronto, Ontario, Canada and from participant centers (REB# 1000034304). HSC acted as the coordinating site for this study.

2.2 | Study population

A retrospective review of all children with pediatric SUDEP meeting the study inclusion criteria was conducted. Inclusion criteria were as follows: age at death < 18 years, history of epilepsy (≥2 seizures), death that was sudden and unexpected, and when available, an autopsy that determined no anatomical or toxicological cause of death. When the information provided was deemed to be insufficient to properly classify the cause of death, the case was excluded.

2.3 | Data sources

Pediatric SUDEP cases were collected from three sources across Canada: the Ontario Forensic Pathology Service (OFPS), the Canadian Pediatric Surveillance Program (CPSP), and the Canadian Pediatric Epilepsy Network (CPEN). The OFPS conducts all coroner-ordered autopsies in Ontario. OFPS summary reports were sequentially screened for children with a history of epilepsy and/or seizures who died unexpectedly between December 1, 2014 and December 31, 2017. Full autopsy reports were reviewed by R.W. and E.J.D. and, in the event SUDEP was identified, data were abstracted. CPSP is a national surveillance program that monitors rare childhood conditions. Pediatricians were surveyed monthly regarding pediatric SUDEP occurrences between January 1, 2014 and December 31, 2015, and when children were identified, members completed a case form related to the child's medical history and death. CPEN is a collaborative group of investigators who have a special interest in pediatric epilepsy. CPEN pediatric SUDEP cases were collected between January 1, 2000 and December 31, 2017. The medical chart was reviewed by local collaborators. All pediatric SUDEP cases collected from CPSP and CPEN were screened for inclusion. A phone interview with caregivers whose children were followed at the coordinating site (HSC) and/or had been in direct contact with the site principal investigator (E.J.D.) was conducted after consent was obtained, as per ethics approval. Phone interview with caregivers from other sources of data collection was not permitted.

2.4 | Data collection and management

Clinical data including demographics, epilepsy history, treatment, comorbidities (known prior to death), lifestyle factors, and circumstances surrounding death were collected. In addition, when available, reports of brain magnetic resonance imaging, electroencephalograms, electrocardiograms, and autopsy reports were reviewed. Study data were collected and managed using the REDCap database (Research Electronic Data Capture).[48]

2.5 | SUDEP classification and adjudication

The 2012 Nashef criteria were used to classify SUDEP deaths.[6] Definite SUDEP was applied when the death was witnessed or unwitnessed, with or without evidence of a preceding seizure, and the death was not due to trauma, drowning, or documented status epilepticus. For definite SUDEP adjudications, autopsy did not reveal an anatomical or toxicological cause of death.[6] Definite SUDEP Plus was used when definite criteria were met, but a comorbid condition was present that was felt could have contributed to the death.[6] Children who met definite criteria but lacked autopsy were classified as probable SUDEP.[6] Possible SUDEP was used when there was a clear competing cause of death.[6] Near SUDEP was used when the child survived resuscitation for >1 h and near SUDEP Plus when a concomitant condition was present.[6] When a comorbidity that may have contributed to death was present, it was considered in case adjudication. Two pediatric neurologists with extensive expertise in SUDEP (E.J.D., R.W.) independently reviewed the cases. Discrepancies were discussed until consensus was reached. Possible SUDEP cases were excluded from the analysis.

2.6 | Statistical analysis

Data are summarized using descriptive statistics, including median, mean, SD, range, and interquartile range (IQR; 25th, 75th percentile) for continuous data. Counts and percentages are reported for categorical variables. Student *t*-test was used to compare continuous variables between children who died of SUDEP with and without global developmental delay (GDD), and Fisher exact test or chi-squared test was applied for categorial variables. Factors such as mean age at death, presence of TCSs, TCS frequency, presence of ASM polytherapy, age at seizure onset, epilepsy duration, and presence of comorbidities and recent infection were compared between pediatric SUDEP with and without GDD. We also examined the lifetime frequency of TCSs in those children treated with ≥2 ASMs at time of death compared to 0–1 ASMs using the Fisher exact test. A *p*-value of <.05 was considered statistically significant. In addition, we also described the characteristics of infants (<2 years of age) who died

of SUDEP to gain better insight into the circumstances surrounding death in this unique age group. IBM SPSS version 29.01.0 was used for statistical analysis.

3 | RESULTS

3.1 | Demographics

Fifty-two potential pediatric SUDEP were identified; two were excluded due to lack of sufficient information to classify the cause of death, and one case had complex febrile seizures but no diagnosis of epilepsy. The remaining 49 were analyzed and included 25 definite SUDEP (51%), six definite SUDEP Plus (12%), 12 probable SUDEP (25%), four near SUDEP (8%), and two near SUDEP Plus (4%). In 40 cases ($n = 40/49$, 82%), there was agreement between adjudicators (E.J.D., R.W.); consensus was reached in the remainder. Pediatric SUDEP children were collected from CPEN ($n = 16/49$, 33%), OFPS ($n = 15/49$, 31%), CPSP ($n = 7/49$, 14%), and combined sources ($n = 11/49$, 22%). Eight caregivers of children who were known to the coordinating site ($n = 8/10$, 80%) were approached and agreed to participate in an interview. No caregiver refused to participate, but two families were not approached.

Our cohort consisted of 25 females ($n = 25/49$, 51%). Demographics are summarized in Table 1. The median age at death was 8 years (IQR = 4, 15), and age at death ranged from 6 months to 17.9 years.

3.2 | Epilepsy history

Details regarding the epilepsy history are shown in Table 1. Knowledge of seizure types in the 6 months before death was available in 35 children and is shown in Table 1. Twenty-two had primary generalized/focal to bilateral TCSs within the last 6 months prior to death ($n = 22/35$, 63%). Lifetime seizure types were known in 39 children, and 32 ($n = 32/39$, 82%) had a history of TCSs, whereas seven children (18%) had no documented lifetime history of TCSs.

The lifetime frequency of primary generalized/focal to bilateral TCSs was available for 31 children and is summarized in Table 1. The timing of the last TCS was known in 19 children: within 24 h ($n = 9/19$, 47%), 2–7 days ($n = 1/19$, 5%), 14–30 days ($n = 1/19$, 5%), and >30 days ($n = 8/19$, 42%).

Three children were seizure-free in the 6 months prior to death. Among these children who were seizure-free, one child with normal cognition had juvenile myoclonic epilepsy (JME) with <10 TCSs in their lifetime and was maintained on two ASMs; epilepsy duration was between 1 and 2 years. The second child had a neurogenetic syndrome with <10 TCSs in their lifetime and was maintained on no ASMs (due to seizure freedom), and epilepsy duration was >10 years. The third child had a presumed genetic epilepsy with GDD, had 10–100 TCSs in their lifetime, and was maintained on one ASM; epilepsy duration was >5 years. Furthermore, one child with a structural etiology for their epilepsy and GDD had sustained seizure freedom for 2 years on two ASMs (epilepsy duration unknown), but seizures recurred in the week before death (seizure type unknown).

3.3 | Epilepsy syndrome/etiology

Thirty-four cases had data regarding the presence of an epilepsy syndrome. Eighteen children ($n = 18/34$, 53%) had been diagnosed with an epilepsy syndrome (Table 1), whereas 16 children ($n = 16/34$, 47%) had no identifiable epilepsy syndrome. Epilepsy etiology was classified according to the International League Against Epilepsy and is further outlined in Table 1.

3.4 | Epilepsy treatment

Forty-seven pediatric SUDEP had information regarding ASM history. Forty-three children (91%) were on ASMs at the time of death (Figure 1). The most commonly used ASMs at the time of death were levetiracetam ($n = 19/43$, 44%), valproate ($n = 16/43$, 37%), clobazam ($n = 10/43$, 23%), lamotrigine ($n = 9/43$, 21%), and topiramate ($n = 8/43$, 19%). When comparing the lifetime frequency of TCSs (>10 TCSs) and between those children currently on ≥2 ASMs (polytherapy) compared to 0–1 ASMs, no difference was found ($p = .210$; Table 2). Compliance data were available in 21 children, and five children ($n = 5/21$, 24%) had a history of poor ASM compliance. Five children ($n = 5/49$, 10%) in the cohort were treated with the ketogenic diet, two children ($n = 2/49$, 4%) with vagal nerve stimulation, and two children ($n = 2/49$, 4%) had undergone prior epilepsy surgery.

3.5 | Medical comorbidities

The presence of known medical comorbidities was considered when adjudicating SUDEP deaths (Tables 3 and 4). Data regarding cardiac comorbidities were available for 43 children, and seven children were known to have a cardiac comorbidity ($n = 7/43$, 16%). Information regarding the presence of respiratory comorbidities was available for 36 children, and nine children ($n = 9/36$, 25%) were known to have a respiratory comorbidity (sometimes multiple).

TABLE 1 Demographics, epilepsy characteristics, comorbidities, and circumstances surrounding death.

Characteristic	number of subjects	Descriptive statistic
Demographics		
Female sex, *n* (%)	49	25 (51)
Age at death, median (25th, 75th percentile)	49	8 (4, 15)
Epilepsy history		
Age at first unprovoked seizure, months, median (25th, 75th percentile)	41	6 (3, 24)
Duration of epilepsy, years, median (25th, 75th percentile)	41	6 (2, 11)
Lifetime seizure types known, *n* (%)	39	
Presence of tonic–clonic seizures		32 (82)
No tonic–clonic seizures		7 (18)
Lifetime frequency of tonic–clonic seizures, *n* (%)	31	
<10		7 (23)
10–100		10 (32)
101–500		6 (19)
>500		8 (26)
Seizure types in 6 months prior to death, *n* (%)	35	
Focal		4 (11)
Generalized		22 (63)
Both		6 (17)
None		3 (9)
Epilepsy etiology, *n* (%)	49	
Genetic (*n* = 19)/presumed genetic (*n* = 8): Chromosomaldeletions/duplications (*n* = 3) Angelman syndrome (*n* = 1) Dravet syndrome (*n* = 6) *CDKL5*-related developmental and epileptic encephalopathy (*n* = 2) Tuberous sclerosis complex (*n* = 1) *KCNT1*-related developmental and epileptic encephalopathy (*n* = 1) *CREDL1*-related disorder (*n* = 1) Wolf–Hirschhorn syndrome (*n* = 1) Tubulinopathy (*n* = 1) Rett syndrome (*n* = 1) Klinefelter syndrome (*n* = 1) Hypomyelinating leukodystrophy (*n* = 1)		27 (55)
Structural: Malformation of cortical development (*n* = 0) Stroke (*n* = 2) Hydrocephalus (*n* = 1) Hypoxic–ischemic encephalopathy (*n* = 1)		8 (16)
Metabolic: Suspected storage disorder		1 (2)
Infectious: Meningitis		1 (2)
Immune		0 (0)
Unknown		12 (25)

(Continues)

TABLE 1 (Continued)

Characteristic	number of subjects	Descriptive statistic
Identified epilepsy syndrome, *n* (%)	18	
Dravet syndrome		6 (33)
Infantile epileptic spasms syndrome		4 (22)
Lennox–Gastaut syndrome		2 (11)
Juvenile myoclonic epilepsy		2 (11)
Genetic generalized epilepsy		2 (11)
Epilepsy of infancy with migrating focal seizures		1 (6)
Myoclonic epilepsy in nonprogressive disorder		1 (6)
Medical comorbidities, *n* (%)		
Global developmental delay	46	34 (74)
Ambulation	40	
Ambulatory without assistance		21 (53)
Ambulatory with assistance		4 (10)
Not ambulatory		15 (37)
Language	39	
Normal language development		10 (26)
Delayed language acquisition		12 (31)
Nonverbal		17 (43)
Cardiac comorbidities	43	7 (16)
Respiratory comorbidities	36	9 (25)
Circumstances surrounding death, *n* (%)		
State immediately prior to death	45	
Sleeping		42 (93)
Awake		3 (7)
Seizure [witnessed seizure or evidence suggesting seizure]	32	20 (63)
Position found	29	
Prone		16 (55)
Supine		4 (14)
Side		4 (14)
Other		5 (17)
Location at time of death	47	
At home in bed		36 (77)
At home in location other than bed [i.e., couch, chair, playpen, bathroom, bedroom floor]		6 (13)
At residential facility in bed		2 (4)
Hospital		1 (2)
Outside the family home [i.e., friend's home, holiday home]		2 (4)
CPR administered	40	28 (70)
Change in routine	34	15 (44)
Recent infection prior to death	37	17 (46)

TABLE 1 (Continued)

Characteristic	number of subjects	Descriptive statistic
Types of infections	17	
Respiratory		12 (70)
Gastrointestinal		4 (24)
Unspecified		1 (6)
Date of last seizure reported in those with infection	7	
Within 24 h		4 (57)[a]
1 week prior		1 (14)
1 month prior		1 (14)
>6 months prior		1 (14)

Abbreviation: CPR, cardiorespiratory resuscitation.

[a]Note that three of these children were also noted to have seizure clustering with infection around death.

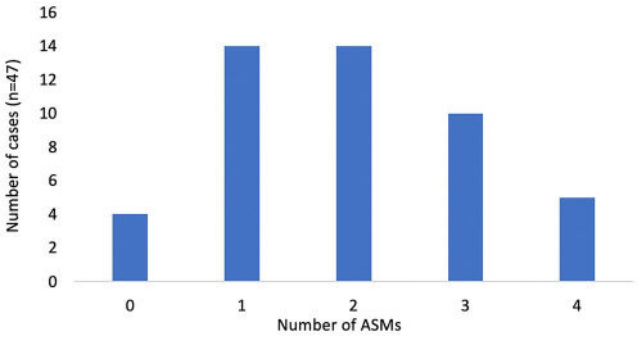

FIGURE 1 Distribution of number of antiseizure medications (ASMs) at the time of death.

3.6 | SUDEP with and without GDD

Data on the presence of GDD were available in 46 cases. Thirty-four children (74%) had GDD, whereas 12 children (26%) did not (Table 1). Details regarding seizure characteristics in those with and without GDD are shown in Table 4. When comparing the presence of TCSs, frequency of TCSs, ASM polytherapy, duration of epilepsy, and presence of infection/comorbidities, no statistically significant differences were observed between SUDEP cases with and without GDD (Table 5). However, children who had GDD had an earlier age at seizure onset when compared to those without GDD ($p < .001$; Table 5).

3.7 | Living environment

Information regarding room sharing was available in 23 pediatric SUDEP, and nine children shared a room ($n = 9/23$, 39%), whereas 14 did not ($n = 14/23$, 61%). Room sharing was with an adolescent/adult in all children but one, where this information was missing. Information regarding the presence of regular nocturnal checks was available in 17 pediatric SUDEP cases, and checks were performed in seven children ($n = 7/17$, 41%). Two caregivers who performed regular nocturnal checks also used a listening device monitor ($n = 2/7$, 29%). Data regarding the use of listening device monitors (i.e., infant monitor) were available in 12 pediatric SUDEP cases, and monitors were used in four children ($n = 4/12$, 33%). The death was unwitnessed in all children who used listening devices.

3.8 | Circumstances surrounding death

Circumstances surrounding death are summarized in Table 1. The state before death was available in 45 children, and 42 were asleep ($n = 42/45$, 93%). Data regarding whether the death was witnessed or unwitnessed were available in 46 children. Death was unwitnessed in 41 children ($n = 41/46$, 89%) and witnessed in five ($n = 5/46$, 11%). A seizure was observed preceding death in three of five witnessed deaths; all were asleep immediately prior. In the other witnessed children, one child had difficulty breathing prior to cardiac arrest, and in the other there was ambiguity about how the death was witnessed. All witnessed deaths received cardiorespiratory resuscitation.

3.9 | Change in routine and infection status

Data regarding changes in routine before death were available in 34 cases. Fifteen children ($n = 15/34$, 44%) were reported to have a change in their routine before death; seven children in the cohort had a change in sleeping environment ($n = 7/34$, 47%), seven had ASM

TABLE 2 Lifetime tonic–clonic seizure frequency versus ASM use.

	Children on ≥2 ASMs, $n=29$		Children on 0–1 ASMs, $n=18$		
Lifetime frequency of tonic–clonic seizures, $n=20$, n (%)	<10	3 (15)	Lifetime frequency of tonic–clonic seizures, $n=11$, n (%)	<10	4 (36)
	10–100	6 (30)		10–100	4 (36)
	101–500	5 (25)		101–500	1 (9)
	>500	6 (30)		>500	2 (18)

Abbreviation: ASM, antiseizure medication.

TABLE 3 Cardiovascular and respiratory comorbidities within the cohort.

Cardiovascular/respiratory comorbidity	Children, n[a]
Arrythmia	3/7 (43%)
Structural heart defects	3/7 (43%)
Obstructive sleep apnea	3/9 (33%)
Chronic lung disease	2/9 (22%)
Recurrent aspiration	2/9 (22%)
Asthma/reactive airway disease	2/9 (22%)
Apnea	1/9 (11%)
Previous arrest/resuscitation	1/7 (14%)
Upper airway stridor	1/9 (11%)

[a]$n=7/43$ had cardiac comorbidities; $n=9/36$ had respiratory comorbidities.

dose reduction/missed doses ($n=7/34$, 47%), and one case had a change in their sleeping schedule ($n=1/34$, 6%). Of the 43 children on ASMs at the time of death, it was known whether ASMs were taken 24 h before death for 33 children. Seven children ($n=7/33$, 21%) missed an ASM dose or received a reduced ASM dose in the 24 h prior to death. The remaining 26 children took their ASMs as prescribed ($n=26/33$, 79%). The presence of a recent infection was evaluated prior to death, and data were available in 37 children. Seventeen children ($n=17/37$, 46%) were reported to have had a recent infection before death, and details are summarized in Table 1. The exact pathogen was only specified in four children and included influenza in two children and enterovirus and echovirus in one child each.

TABLE 4 Clinical characteristics with/without GDD.

Characteristic	Children without GDD, $n=12$			Children with GDD, $n=34$		
Mean age at death, years	11.5, SD 5.1			8.3, SD 6.5		
Mean age at seizure onset, months	75.7, SD 73.5			9.7, SD 13.4		
Mean duration of epilepsy, years	5.2, SD 5.1			7.7, SD 5.1		
Known epilepsy syndrome, n (%)	$n=6$	DEE	2 (33)	$n=11$	DEE	11 (100)
		Non-DEE [JME, GGE]	4 (67)		No DEE	0 (0)
Cardiac comorbidities, n (%)	$n=11$	Yes	2 (18)	$n=31$	Yes	5 (16)
		No	9 (82)		No	26 (84)
Respiratory comorbidities, n (%)	$n=11$	Yes	2 (18)	$n=25$	Yes	7 (28)
		No	9 (82)		No	18 (72)
Infection prior to death, n (%)	$n=9$	Yes	2 (22)	$n=27$	Yes	14 (52)
		No	7 (78)		No	13 (48)
Lifetime seizure types known, n (%)	$n=11$	Presence of TCSs	10 (91)	$n=27$	Presence of TCSs	21 (78)
		No TCSs	1 (9)		No TCSs	6 (22)
Lifetime frequency of TCSs, n (%)	$n=10$	<10	3 (30)	$n=20$	<10	3 (15)
		10–100	3 (30)		10–100	6 (30)
		101–500	3 (30)		101–500	3 (15)
		>500	1 (10)		>500	8 (40)
ASMs at time of death, n (%)	$n=12$	None	0 (0)	$n=32$	None	4 (13)
		1 ASM	6 (50)		1 ASM	6 (19)
		2 ASMs	3 (25)		2 ASMs	11 (34)
		≥3 ASMs	3 (25)		≥3 ASMs	11 (34)

Abbreviations: ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy; GDD, global developmental delay; GGE, genetic generalized epilepsy; JME, juvenile myoclonic epilepsy; TCS, tonic–clonic seizure.

TABLE 5 Analysis of clinical characteristics with/without GDD.

Characteristic	Without GDD, $n=12$	With GDD, $n=34$	p
Mean age at death, years	11.5, SD 5.1	8.3, SD 6.5	.094
Mean age at seizure onset, months	75.7, SD 73.5	9.7, SD 13.4	<.001
Mean duration of epilepsy, years	5.2, SD 5.1	7.7, SD 5.1	.170
Children with epilepsy syndromes who had DEE, *n* (%)	2/6 (67)	11/11 (100)	.006
Children with cardiac comorbidities, *n* (%)	2/11 (18)	5/31 (16)	1.0
Children with respiratory comorbidities, *n* (%)	2/11 (18)	7/25 (28)	.690
Children with tonic–clonic seizures, *n* (%)	10/11 (91)	21/27 (78)	.648
Children on ≥2 ASMs, *n* (%)	6/12 (50)	22/32 (69)	.303
Children with infection prior to death, *n* (%)	2/9 (22)	14/27 (52)	.245
Children with lifetime frequency of tonic–clonic seizures >100, *n* (%)	4/10 (40)	11/20 (55)	.439

Note: Student *t*-test was used to compare continuous variables between children who died of sudden unexpected death in epilepsy with and without GDD, and Fisher exact test or chi-squared test was applied for categorial variables.

Abbreviations: ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy; GDD, global developmental delay.

3.10 | Infants with SUDEP

Six children in the cohort died before the age of 2 years ($n=6/49$, 12%). Four were males ($n=4/6$, 67%). Median age at death was 1.2 years (IQR = 1.1, 1.6). Seizure onset ranged from birth to 5 months of age. Four infants were diagnosed with an epilepsy syndrome: Dravet syndrome, epilepsy of infancy with migrating focal seizures, West syndrome, and myoclonic epilepsy in a nonprogressive disorder. One child was diagnosed with Wolf–Hirschhorn syndrome, and another had epilepsy secondary to stroke. Developmental status was known in five infants, and four had GDD ($n=4/5$, 80%). Four infants were treated with ≥2 ASMs ($n=4/6$, 67%), and two infants were treated with monotherapy. Four infants had a previous history of TCSs ($n=4/6$, 67%), whereas seizure types were unknown in one infant and the other infant had a history of epileptic spasms. Lifetime frequency of TCSs was reported as <10 in two infants, 10–100 in one infant, and >500 in the other infant. All infants were asleep prior to death. Sleeping environment was known in five infants, and all slept in a crib. Information regarding room sharing was available in three infants, and all shared a room.

4 | DISCUSSION

We identified 49 cases of SUDEP in children, constituting the largest pediatric SUDEP case series to date. Case ascertainment in our series utilized three sources to identify pediatric SUDEP cases, as reliance on a single method may lead to underrecognition of SUDEP deaths.[7,10,18,25] Several studies have aimed to better understand the circumstances of death and clinical characteristics associated with SUDEP, although few have focused exclusively on children.[18,25,34–47] Our findings consolidate what is known about the circumstances surrounding pediatric SUDEP deaths.

Pediatric SUDEP deaths in our cohort occurred across the lifespan, which has been observed previously.[37,46,47] Six children in our cohort were younger than 2 years at the time of death. Descriptions of SUDEP in children younger than 2 years are fairly limited in other SUDEP cohorts.[37,42,46] Most infants in our cohort had GDD, were diagnosed with a developmental and epileptic encephalopathy (DEE) and were receiving ASM polytherapy. However, not all infants had a documented history of TCSs, and in at least one infant there was no prior history. This finding may be important for SUDEP counseling in infancy, where TCSs may not always occur. Similar to older children and adults, infant SUDEP deaths were unwitnessed and occurred from sleep even in the presence of nocturnal supervision.

The majority of children in our cohort had TCSs in their lifetime, and TCSs are the most important risk factor for SUDEP.[8,17,21,24,25,34,49] In a recent nationwide population-based case–control study, having 1–3 TCSs in the previous year was associated with a 22-fold risk, and having 4–10 TCSs was associated with a 32-fold risk. Eighteen percent of children in our cohort, however, had no documented history of TCSs. Furthermore, for those children who had sufficient information regarding the lifetime frequency of TCSs, 23% had fewer than 10 TCSs in their lifetime. Our findings emphasize that SUDEP may occur in those without a history of TCSs and those with low TCS frequency. This was similarly observed in the North American SUDEP Registry (NASR) study, in which 33% of the cohort had fewer than 10 lifetime TCSs and 4% had no history of TCSs.[34] In contrast, in a nationwide population-based case–control study of children and adults from Sweden only 1.6% of the cohort had no history of TCSs.[49] It is

possible that because the Swedish study was population based and our study was not, that this led to a higher number of pediatric SUDEP children without a history of TCSs in our cohort due to selection bias.

SUDEP may occur when there are periods of sustained seizure freedom; however, a lack of seizure freedom in the preceding 1–5 years has been associated with SUDEP risk.[17] Three children (9%) in our cohort were seizure-free for at least 6 months before death, and one child had been seizure-free for 2 years but had a seizure recurrence in the week before death. In the NASR cohort, 15% of SUDEP cases were seizure-free in the year before death.[34] The aforementioned observations reinforce the need to counsel all patients regarding SUDEP risk, even for those with periods of seizure freedom and weaning off ASMs.

Most children in our cohort were treated with ASMs (91%), and 70% percent were treated with polytherapy. However, we were unable to demonstrate that the seizure burden of TCSs (lifetime frequency) was statistically different between those on monotherapy and polytherapy. Furthermore, when comparing the rates of ASM polytherapy in pediatric SUDEP with and without GDD, we were unable to detect a difference between the two groups. A relationship between polytherapy and SUDEP has been suggested in some pediatric SUDEP case series[38,39] but not all.[37] A systematic review of SUDEP in children documented ASM polytherapy and severe epilepsy as being linked to SUDEP risk in childhood.[46] However, more recent data suggest that monotherapy and polytherapy with ASM treatment may be protective against SUDEP.[49] Seven children (21%) in our cohort missed an ASM dose or received a reduced dose before death, and there were five children in whom compliance was reported to be incomplete (24%). Similarly, nonadherence was documented in the NASR cohort, and only 37% of the cohort took their last ASM dose, which included pediatric and adult cases.[34] Nonadherence to ASM therapy has been associated with a 2.75-fold increased risk of SUDEP.[50] This is an important finding, as children with epilepsy may be believed to maintain better treatment adherence than adults with epilepsy.

The epilepsy etiology in our cohort was heterogeneous. Several genetic etiologies were observed, highlighting that SUDEP may occur in other neurogenetic conditions (i.e., Klinefelter syndrome, tuberous sclerosis complex) in addition to the genetic DEEs (i.e., *SCN1A, KCNT1*) more commonly associated with SUDEP. SUDEP also occurred in patients with progressive neurological conditions (i.e., Rett syndrome, leukodystrophy), and this is an important finding when it comes to counseling caregivers. Previous studies have suggested that developmental impairment and cryptogenic/symptomatic etiologies may be more common in pediatric SUDEP, and this was also supported by a systematic review of SUDEP in children.[37–39,42,46] Mortality is known to be increased in children with epilepsy and associated neurological impairment.[2,4,11–15,45] However, it is important to emphasize that 26% of our cohort had no history of GDD. An analysis of previously reported SUDEP cases in children demonstrated that 33% had uncomplicated epilepsy.[46] Moreover, intellectual disability was found not to be associated with SUDEP after adjustment for generalized tonic–clonic seizure frequency in a nationwide case–control study from Sweden.[49] Overall, our findings further demonstrate the spectrum of children lost to SUDEP, including children without significant neurological impairment.

The spectrum of epilepsy syndromes in our cohort ranged from syndromes with a better prognosis such as JME with normal cognition (two cases) to more severe DEEs. Six children had Dravet syndrome, reflecting their heightened risk of SUDEP.[25] Previous studies have similarly shown that "benign" pediatric onset epilepsy syndromes are not immune to SUDEP, with SUDEP reported in JME and self-limited epilepsy with centrotemporal spikes.[34,35] The prevalence of epilepsy syndromes should be taken into context when evaluating the occurrence risk of SUDEP and counseling patients (i.e., JME is a more common epilepsy than Dravet syndrome). However, given that SUDEP can occur across the spectrum of epilepsies, the discussion of SUDEP should not be tailored based on the perceived severity of an epilepsy syndrome alone.

The circumstances surrounding death in our series is consistent with observations from previous SUDEP cohorts, with a prevalence of unwitnessed deaths occurring in sleep.[18,22–24,27,34,37–42,46,47] When position at death was known, more than half (55%) of children were found prone. Seven children had a change in sleeping environment at the time of death, which could have resulted in sleep deprivation and a terminal seizure. Fifteen percent of cases were sleep-deprived in the NASR cohort.[34] It has been suggested that sleep deprivation be considered a risk factor for SUDEP.[51] Three children in our cohort had a seizure witnessed at the time of death, and the majority had evidence of a preceding seizure, underscoring the role of a terminal seizure in SUDEP pathophysiology. Although, two children had witnessed deaths with no preceding seizures, and the mechanism of SUDEP death in these children is unknown. A recent interaction analysis demonstrated that patients who had a TCS in the past year and did not share a bedroom had a 67-fold increase of SUDEP compared to those without TCSs and with nocturnal supervision.[49]

Although nocturnal supervision may protect against SUDEP, deaths still occurred in the presence of supervision

and listening devices, similar to previous reports.[17,18,24,34,49] The use of supervision and seizure detection devices is particularly common in children with DEEs, such as Dravet syndrome, as demonstrated in a recent multicenter study from Germany.[52] Critical incidents and the need for resuscitation often associated with seizures are frequently reported in Dravet syndrome. This may be related to the higher rates of SUDEP and mortality in this population.[52] However, it is important to highlight that not all SUDEP deaths can be prevented by resuscitation efforts even with the best supervision practices and seizure surveillance.

Finally, a recent infection before death was reported in 46% of children in our cohort, when infection status was available ($n = 17/37$). This is not completely surprising, given that our cohort was composed exclusively of children. In the NASR cohort of children and adults, recent infection was reported in 17%.[34] Generally, younger children are most at risk of infection, with children 0–2 years old having up to six infections per year.[53] This number subsequently decreases with age (i.e., at 5–9 years, four infections per year).[53] Infection rates are considerably higher in those who attend daycare, up to 9–10 per year.[53] Infection frequency in our cohort therefore may not necessarily be elevated but rather may represent normal rates in childhood. However, it is plausible that infection could decrease seizure threshold and trigger a terminal seizure, which could favor increased supervision or the use of seizure detection devices around illness. Three children in our cohort were documented to have observed seizure clustering with intercurrent illness. However, in most cases, there was insufficient documentation with regard to the date of last seizure with illness. Ultimately, the relationship between SUDEP and infection (if any) requires additional investigation.

4.1 | Limitations

Our study has several limitations. First, our study lacked non-SUDEP controls, limiting our ability to identify SUDEP risk or protective factors. A strength of our study was the use of three different sources to identify SUDEP cases; however, cases were collected over different time periods, and the completeness of data was variable. Autopsy reports often lacked data when compared to data obtained from medical chart review. In addition, we were unable to interview all caregivers. Our cohort was small, which likely prevented our ability to detect significant differences between children with/without GDD and SUDEP. Bias may have occurred in the form of recall bias, especially where practitioners were asked to recall details about a patient's medical history but had not had recent contact with them. Finally, our cohort had a large portion of children with GDD, which could affect the generalizability of the findings.

5 | CONCLUSIONS

Overall, our study represents the largest pediatric SUDEP case series to date. We highlight that SUDEP affects children with epilepsies with a better prognosis (i.e., JME, GGE) as well as those with severe DEEs and rare neurogenetic conditions. SUDEP may also occur in early infancy. Twenty-six percent of our cohort had no associated neurological impairment. Although TCSs were frequently reported, they were not documented in one fifth of the cohort and lifetime frequency of TCSs was considered low (i.e., <10) in one quarter. Importantly, being seizure-free did not protect against SUDEP in our cohort. A recent infection prior to death was uniquely observed in our cohort, which in some cases resulted in seizure clustering. Recent infection could decrease seizure threshold and cause a terminal seizure, and may suggest that times of increased seizure risk could warrant heightened surveillance for SUDEP. However, the relationship of recent infection with SUDEP (if any) requires further investigation.

AUTHOR CONTRIBUTIONS

Robyn Whitney: Data acquisition/interpretation; formal analysis; preparation of the first manuscript draft; writing—review and editing; final approval. **Anne Keller:** Data acquisition/interpretation; formal analysis; writing—reviewing and editing; final approval. **Shelly-Anne Li:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Anita N. Datta:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Matthew MacDonald:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Maryam Nabavi Nouri:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Daniela Pohl:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Erick Sell:** Data acquisition/interpretation; writing—reviewing and editing; final approval. **Gabriel M. Ronen:** Data acquisition/interpretation; analysis; writing—reviewing and editing; final approval. **Mandeep Sidhu:** Data acquisition/interpretation; analysis; writing—reviewing and editing; final approval. **Elisabeth Simard-Tremblay:** Data acquisition/interpretation; analysis; writing—reviewing and editing; final approval. **Michael S. Pollanen:** Data acquisition/interpretation; analysis; writing—reviewing and editing; final approval. **Elizabeth J. Donner:** Study conceptualization; methodology and design; data acquisition/interpretation; formal analysis; writing—review and editing; final approval.

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R.W. has received consulting fees from Jazz Pharmaceuticals. E.J.D. has received consulting fees from Eisai, Pendopharm, Tilray, UCB and Jazz Pharmaceuticals. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Further details may be made available on reasonable request for academic purposes as guided by the institutional research ethics board.

ETHICS APPROVAL STATEMENT

The Hospital for Sick Children in Toronto, Ontario, Canada acted as the research coordinating site; local ethics approval was obtained. Other individual participant centers also obtained ethics approval according to respective hospital policies. 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.

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