Sudden Unexpected Death in Dravet Syndrome

Elizabeth J. Donner, MD, MSc, FRCPC

The Hospital for Sick Children

University of Toronto

Disclosures

Assistant Editor at Seizure

Editorial Board of Epilepsia Open

Honoraria from Eisai and UCB

Funded by Ontario Brain Institute, Canadian Institutes of Health Research

Learning Objectives

Following participation in this activity, learners should be able to:

1. Describe the increased risk of mortality in epilepsy, including SUDEP
2. Understand the known risk factors for SUDEP.
3. Evaluate factors that contribute to SUDEP risk in Dravet Syndrome

Mortality in Epilepsy

Standardized mortality ratio: 2.3

- 2.6 for new onset epilepsy; 3.1 for the chronic epilepsy

SMR higher for children: 5.3 - 9.0

- reflects high mortality among children with significant neurological impairment and overall low mortality rates among children

Lhatoo, et al. 2001; Rakitin, et al. 2010;
Neligan, 2011; Sillanpaa and Shinnar 2010; Nickels 2012

Mortality in Epilepsy

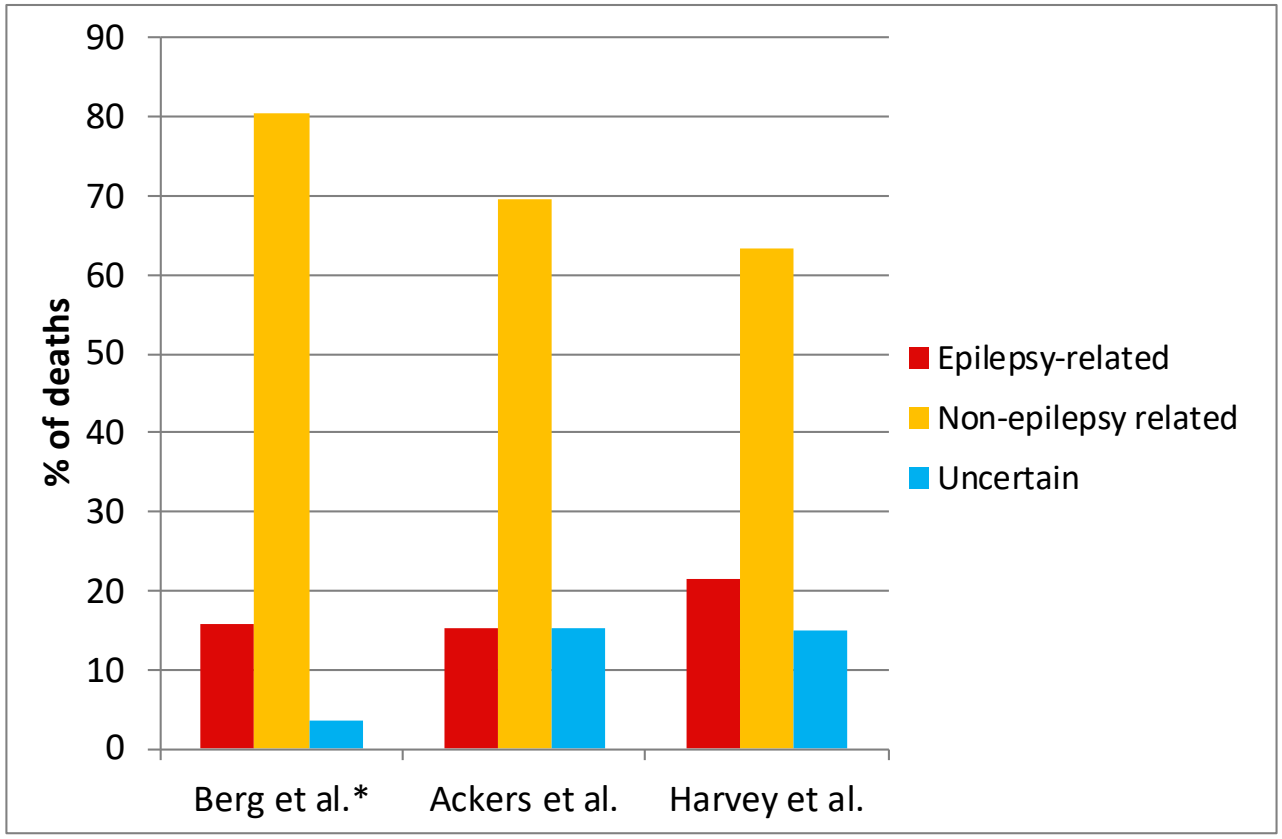
Deaths unrelated to epilepsy

Deaths related to the cause of epilepsy

Deaths due to epilepsy

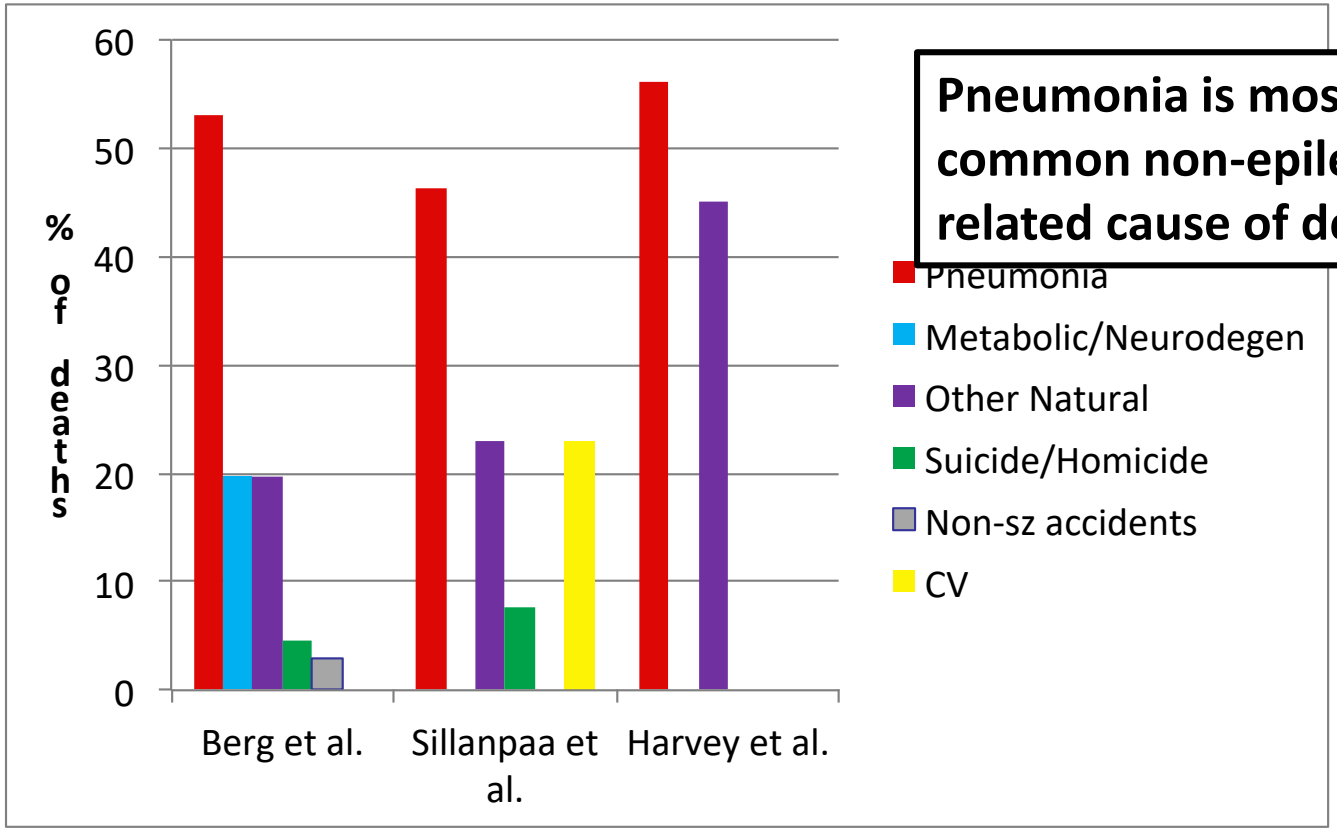
- Direct consequence of a seizure
  - Trauma, drowning, status epilepticus
- Sudden Unexplained/Unexpected Death in Epilepsy (SUDEP)

Most deaths in children with epilepsy are not epilepsy-related



Courtesy of Elaine Wirrell

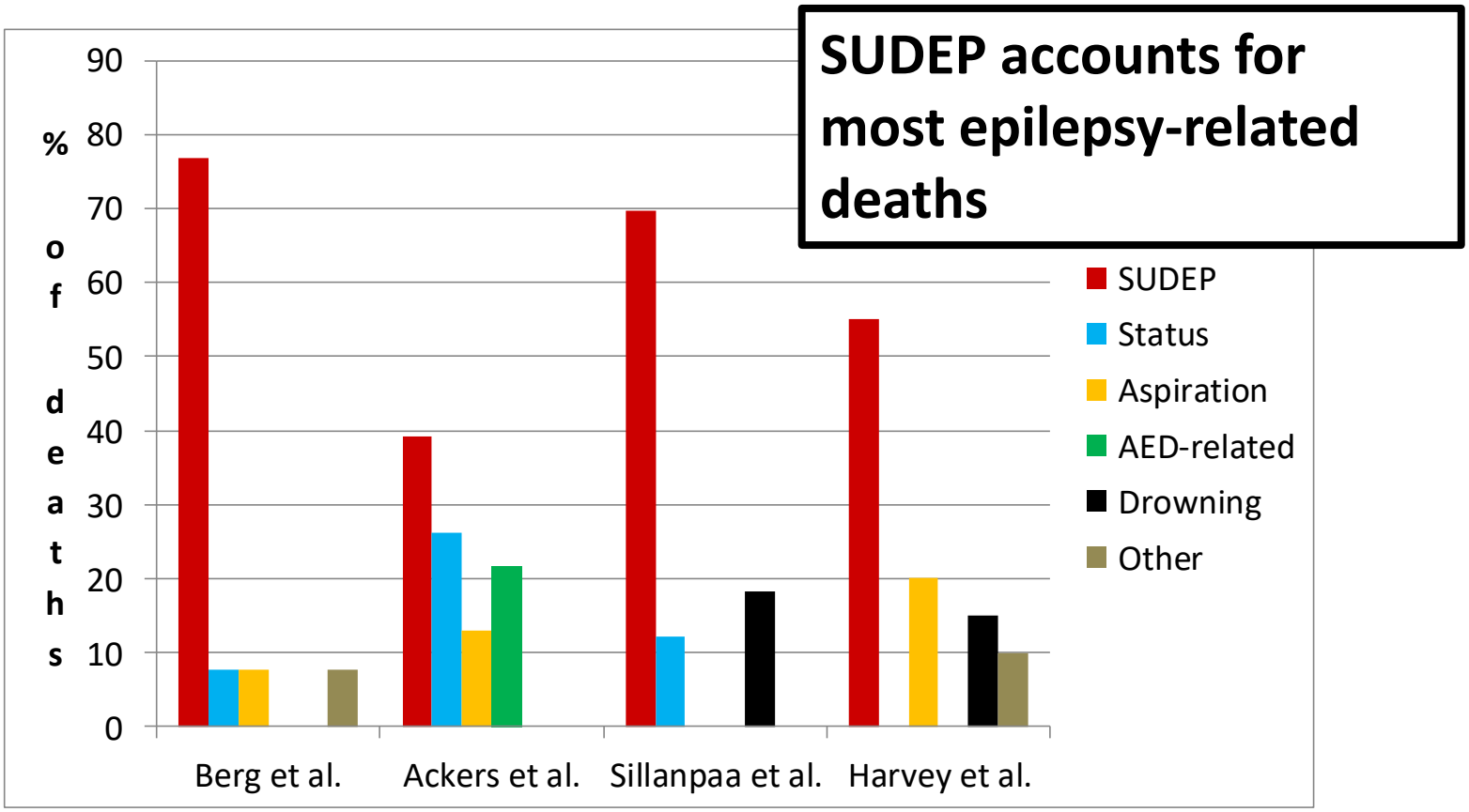
Non-Epilepsy Related Deaths



Pneumonia is most common non-epilepsy related cause of death

Courtesy of Elaine Wirrell

Epilepsy-Related Deaths



Courtesy of Elaine Wirrell

What is SUDEP?

1. Deceased had epilepsy, defined as recurrent unprovoked seizures.
2. Death occurred unexpectedly, while the person was in a reasonable state of health.
3. Death occurred suddenly, with an understanding that following successful resuscitation, a death may occur at a later time as a consequence of the fatal event.
4. Death may have been witnessed or unwitnessed.
5. Evidence of a preceding seizure is not required.
6. Death occurred during normal activities in benign circumstances.
7. Death was not the consequence of documented status epilepticus, drowning, or trauma.
8. Postmortem examination did not demonstrate a cause of death.

See Nashef, et al, Epilepsia, 2011

Sudden Unexpected Death in Epilepsy Incidence Rates and Risk Factors

Report by:
Guideline Development, Dissemination, and Implementation Subcommittee
of the American Academy of Neurology and the American Epilepsy Society

Clinical Questions

Clinical Question 1

- What is the incidence rate of SUDEP in different epilepsy populations?

Clinical Question 2

- Are there specific risk factors for SUDEP?

Conclusions for SUDEP incidence

Population	SUDEP/1,000 patient-years (CI)	Confidence level
Overall	0.58 (0.31–1.08)	Low
Childhood	0.22 (0.16–0.31)	Moderate
Adulthood	1.2 (0.64–2.32)	Low

SUDEP is more Common in Children than Previously Documented

SickKids VS Epilepsy

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

Anne E. Keller, MPH, Robyn Whitney, MD, Shelly-Anne Li, MSc, Michael S. Pollanen, MD, PhD, and Elizabeth J. Donner, MD, MSc

Neurology® 2018;0:1-5. doi:10.1212/WNL.0000000000005762

Correspondence
Dr. Donner
elizabeth.donner@sickkids.ca

17 SUDEP deaths over 2 years

11 definite, 3 probable, 2 definite plus, and 1 near plus

- 10/17 (59%) male

Incidence 1.11 (0.63, 1.79) per 1000 per year

Keller, et al *Neurology*, 2018

SUDEP is more Common in Children than Previously Documented

Definite and Probable SUDEP	Incidence/1000 patient-years
AAN Adult	1.2 (0.64–2.32)
AAN <18 years	0.22 (0.16–0.31)
All ages (Sweden)	1.2 (0.93-1.52)
< 16 years (Sweden)	1.11 (0.45-2.29)
<18 years (Ontario, Canada)	1.11 (0.63-1.79)

Harden, et al Neurology 2017; Sveinsson, et al *Neurology* 2017; Keller, et al *Neurology*, 2018

What do we know about mortality in Dravet?

Early work from families – IDEA League

Historically limited literature

- Survey of family advocacy group
- Survey of Japanese pediatric epilepsy programs
- Hospital/clinic based cohorts
- Case reports

Risk of referral bias resulting in more severe cases

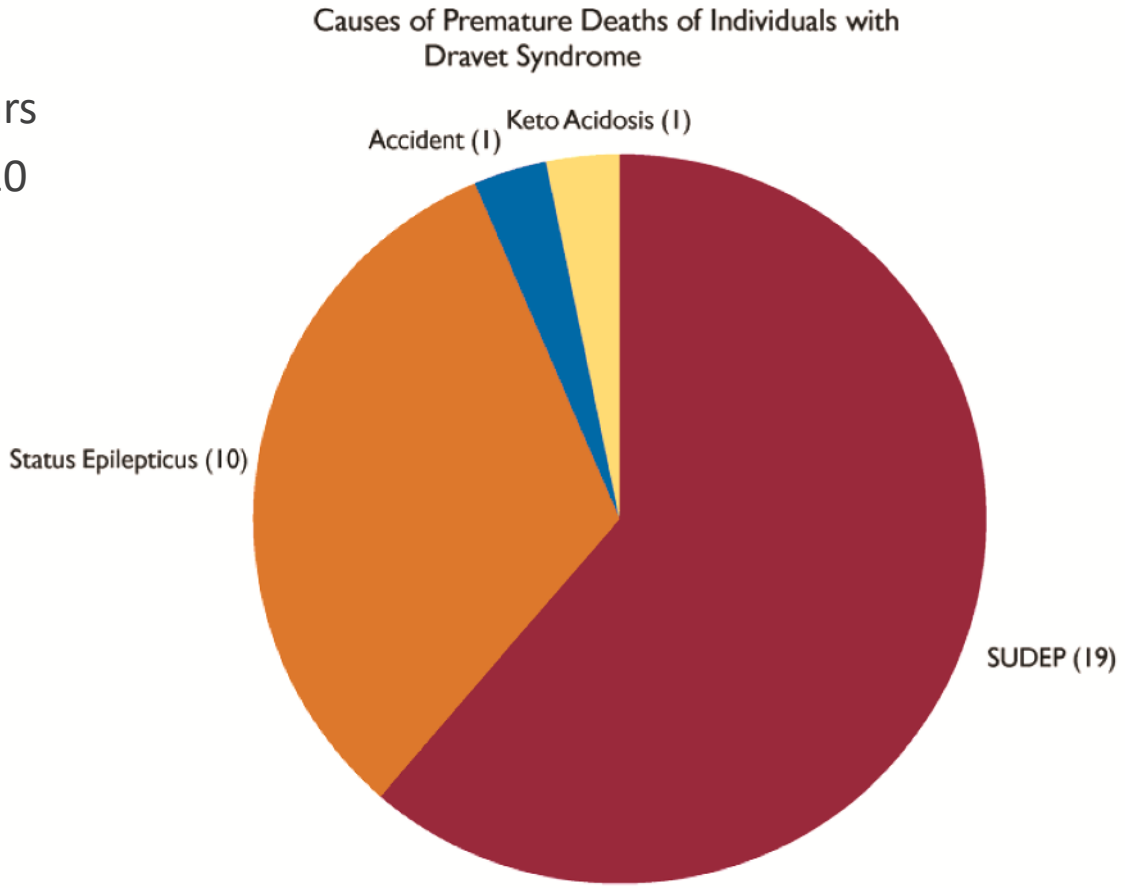
Bias towards pediatric cases

- due to missed adult diagnoses and pediatric focused research

Limited diagnostic details, genetics and post mortem data

IDEA League experience

- 31 deaths over 10 years
- Mean age 4.6 years (10 months-17 years)



Skluzacek, 2011

Age and cause of death

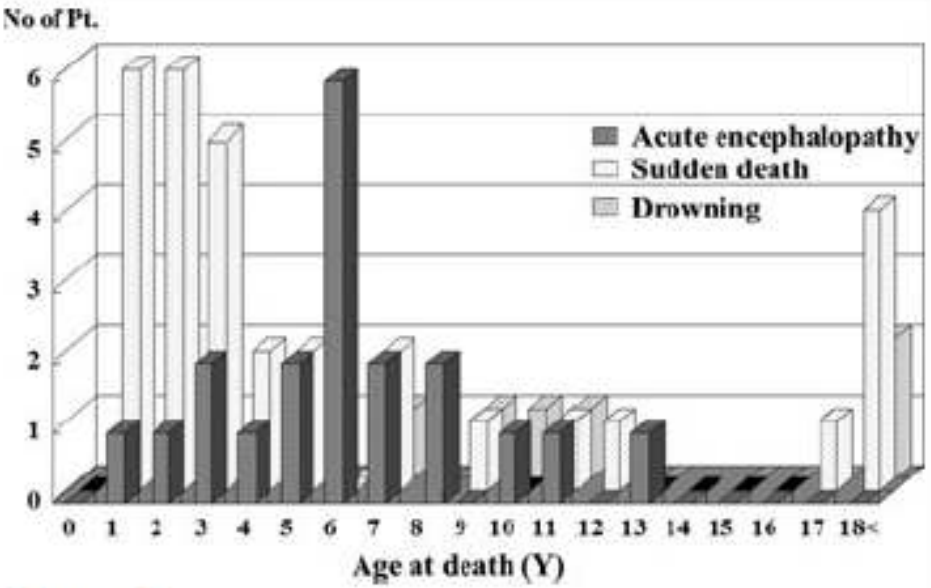
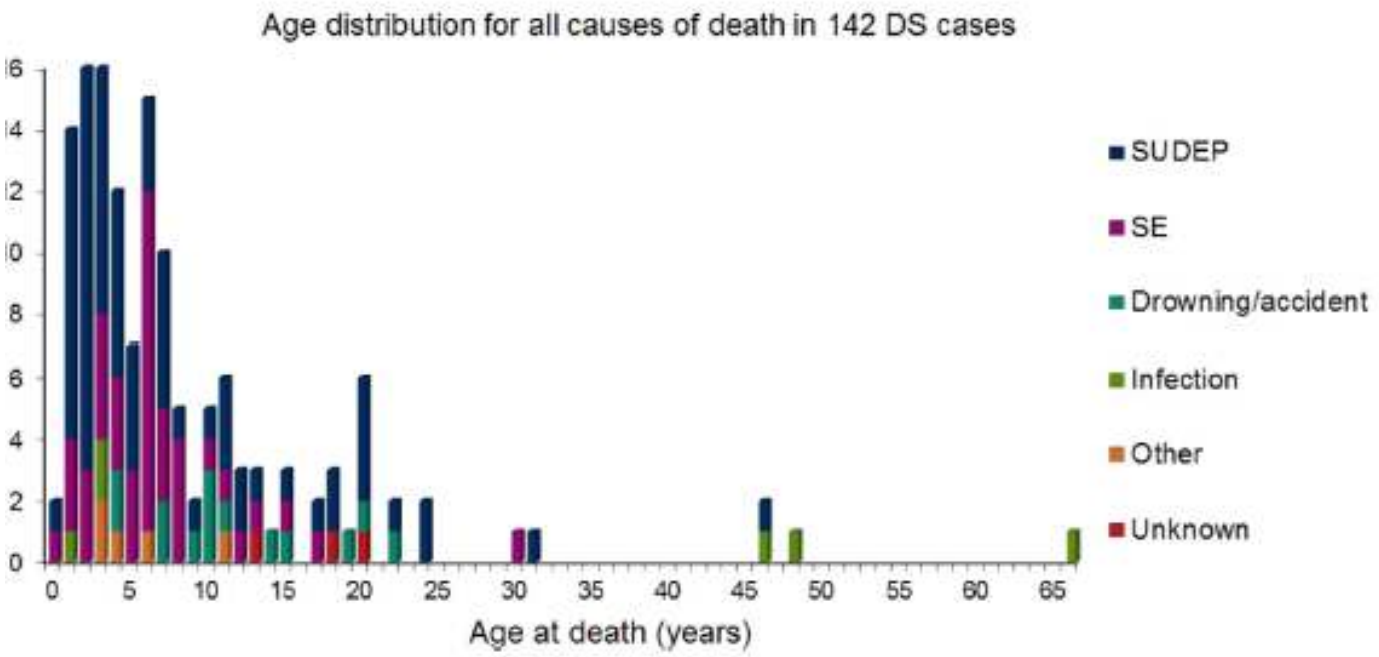


Figure 1.
Distribution of ages at death with respect to the causes of mortality. The incidence of sudden death reached a first peak at 1–3 years old and a second peak at 18 years and older. In contrast, the acute encephalopathy-related mortality rate reached a peak at 6 years old.

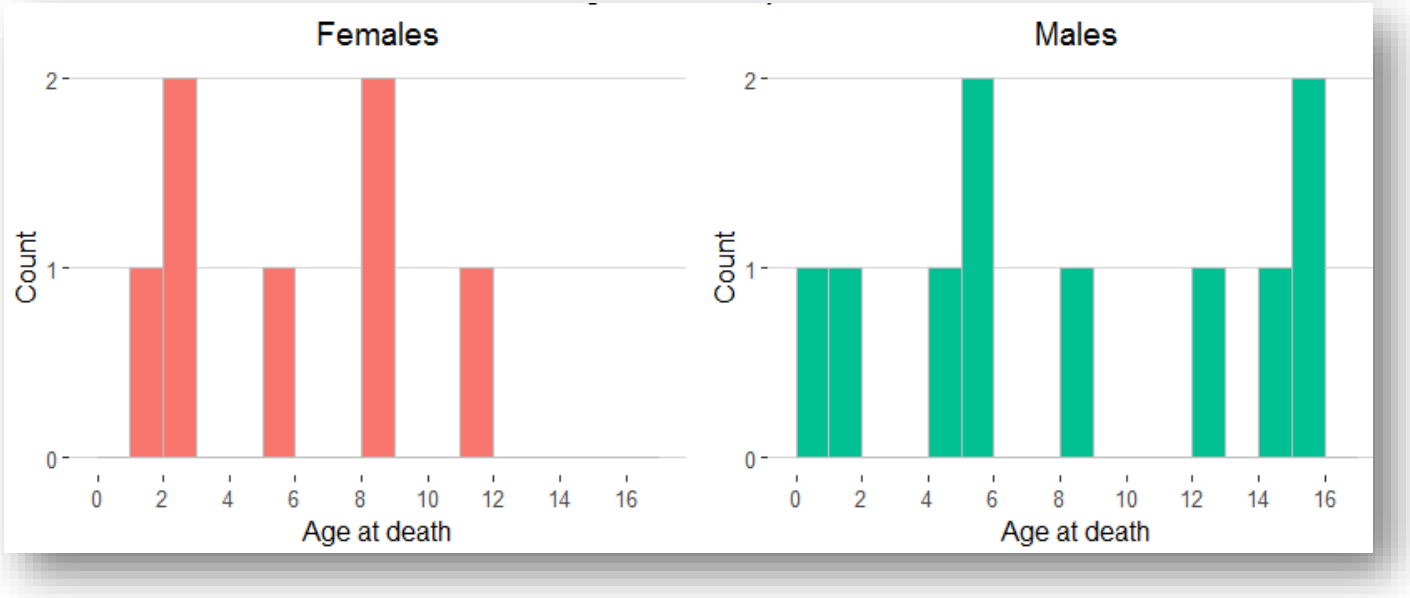
Sakauchi, 2011

Age at death



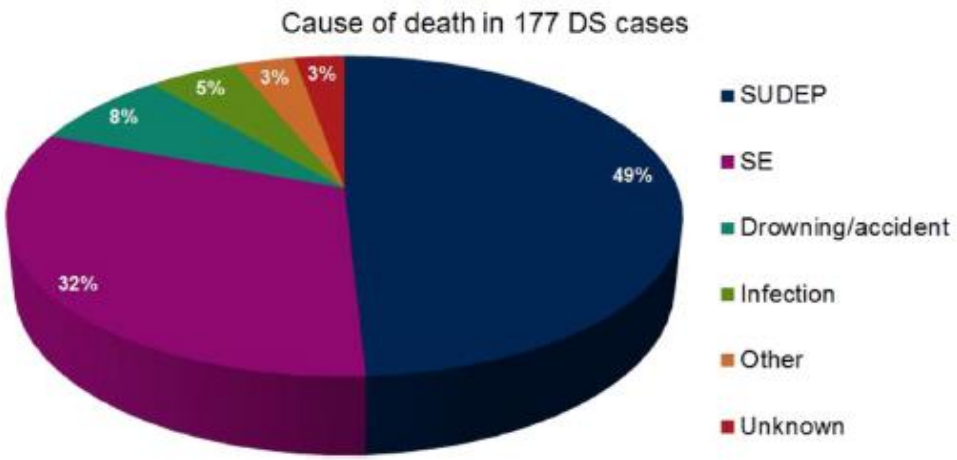
Shmuely, 2016

Age at Pediatric SUDEP



Keller, 2018

Cause of Death in Dravet Syndrome



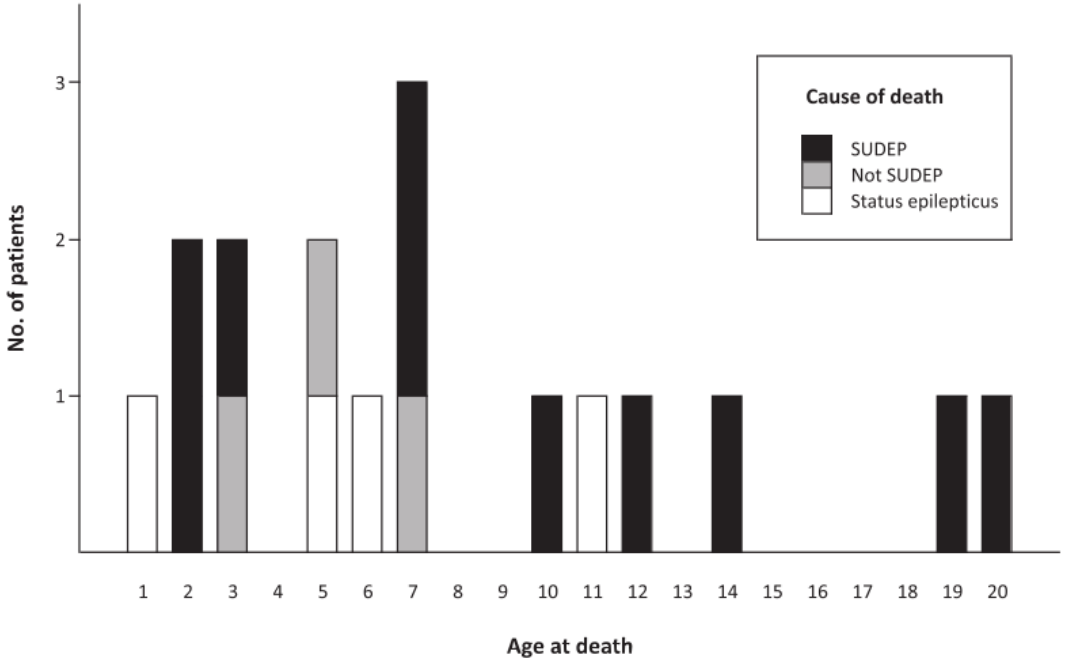
177 Dravet deaths from published papers and abstracts

81% epilepsy-related deaths

Shmuely, 2016

Age and Cause of Dravet

100 consecutive patients with Dravet
Dravet Mortality Rate: 1584 / 1000 person-years
SUDEP mortality rate: 9.32/1000 person-years



Cooper, 2016

What factors may contribute to an increased risk of SUDEP in Dravet?

Clinical Questions

Clinical Question 1

- What is the incidence rate of SUDEP in different epilepsy populations?

Clinical Question 2

- Are there specific risk factors for SUDEP?

Most concerning risk factors

Factor	Odds ratio (CI)	Confidence level
Presence of GTCS vs lack of GTCS	10 (7–14)	Moderate
Frequency of GTCS	OR 5.07 (2.94–8.76) for 1–2 GTCS per y, and OR 15.46 (9.92–24.10) for >3 GTCS per y	High
Not being seizure free for 1–5 y	4.7 (1.4–16)	Moderate
Not adding an AED when patients are medically refractory	6 (2–20)	Moderate
Nocturnal supervision (risk reduction)	0.4 (0.2–0.8)	Moderate
Use of nocturnal listening device (risk reduction)	0.1 (0.0–0.3)	Moderate

Do Dravet characteristics increase SUDEP risk?

SickKids VS Epilepsy

Frequency of GTC is most important risk factor for SUDEP

- Japanese series of 59 Dravet deaths found seizure severity not a factor for any cause of mortality
- Limited cohort and data collection

Early age of epilepsy onset

Comorbid cognitive impairment

Early SUDEP in Dravet does not fit with known SUDEP risk factor of longer epilepsy duration

Is there something specific about Dravet that increases SUDEP risk?

Cardiac dysfunction associated with SCN1A mutations?

SickKids VS Epilepsy

20 pts with DS compared to controls with/without epilepsy and without

- No difference in RR, QT, or QTc intervals
- Lower HRV in DS group, regardless of SCN1A status

15 pts with SCN1A mutation compared to healthy controls

- Significantly higher P wave, QT and QTc dispersion
- Holter ECG showed all HRV parameters were significantly lower in DS patients than controls

40 SCN vs. 40 non-SCN epilepsy

- Awake HRV differed significantly, trends in other measures

Delogu, 2007; Ergul, 2013, Myers, 2018

Evidence from animal models

SCN1A knock in mice with phenotype

- QT prolongation, ventricular ectopic foci, idioventricular rhythms, beat-to-beat variability, ventricular fibrillation, and focal bradycardia
- Altered cardiac electrical function suggesting risk for arrhythmogenic SUDEP

SCN1A knock out mice with SUDEP immediately following GTC

- History of multiple seizures was strong risk factor for SUDEP;
- Suppressed interictal HRV
- Ictal bradycardia with the tonic phases of GTC
- Prolonged atropine-sensitive ictal bradycardia preceded SUDEP and atropine or N-methyl scopolamine treatment reduced the incidence of ictal bradycardia and SUDEP

Auerbach, 2013:Kalume, 2013

How can we reduce the risk of SUDEP in Dravet?

Dravet SUDEP Registry

SickKids VS Epilepsy

nasr north american sudep registry

Pediatric SUDEP Registry

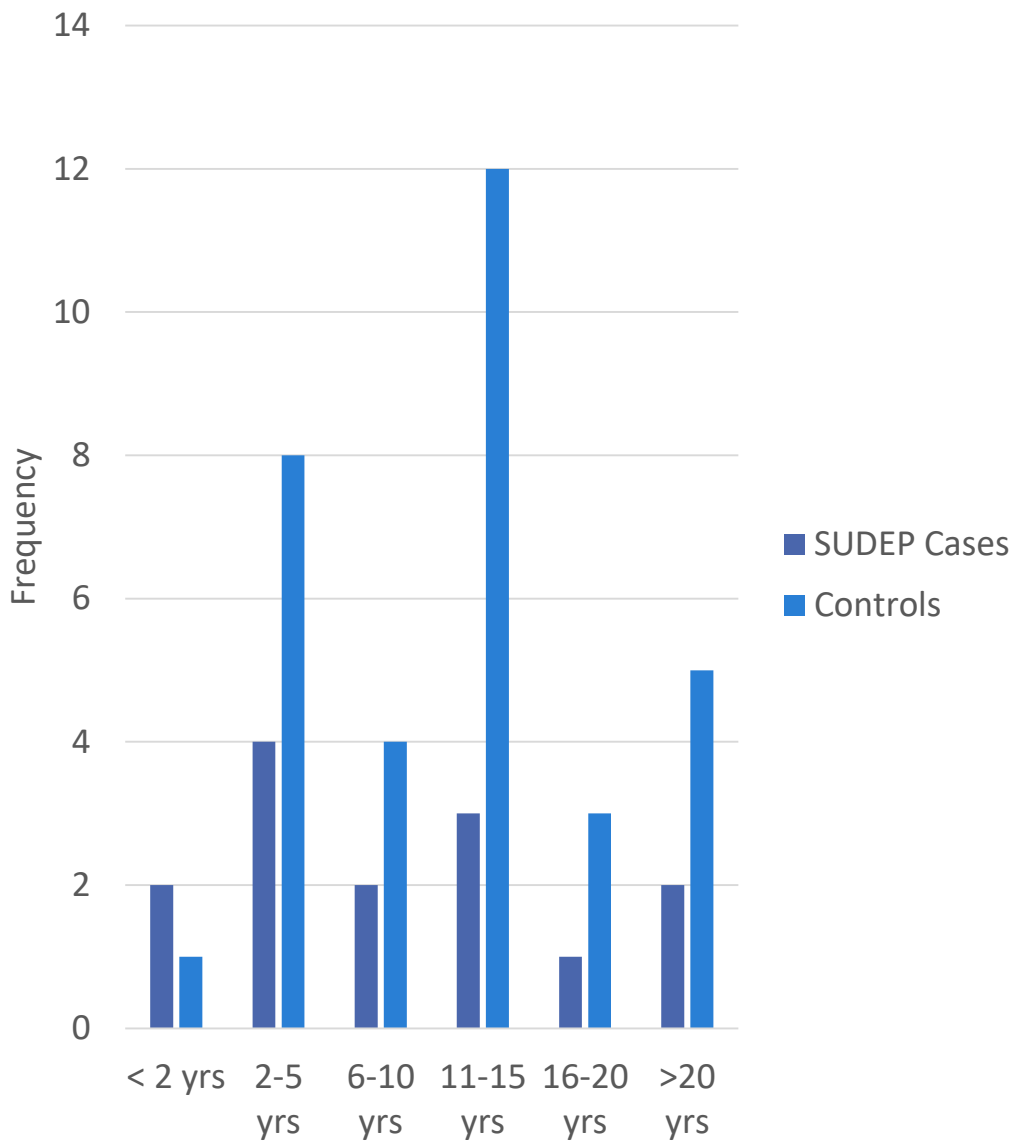
SUDEP in Dravet

Cases

- 14 Total
- 5 Definite SUDEP
- 7 Probable SUDEP
- 2 Data collection in progress
- 9 Female
- 5 Male

Controls—living Dravet or deceased from other cause

- 33 Controls
- 17 Female
- 16 Male



Circumstances around death

Characteristic	N (%)
Death was witnessed	2 / 11 (18)
Prone Position at death	6 / 10 (60)
Awake immediately prior to death	4 / 10 (40)
Recent infection, illness, or fever	4 / 11 (36)

Lifestyle Factors

Characteristic	Cases, N (%)	Controls, N (%)
Pillow Usage	11 / 12 (92)	25 / 30 (83)
Room Sharing – “Always or Often”	8 / 12 (67)	20 / 29 (69)
Bed Sharing – “Always or Often”	7 / 12 (58)	18 / 29 (62)
Video Surveillance or Baby Monitor	6 /11 (55)	16 / 31 (52)

What do we know about SUDEP in Dravet?

Premature mortality epilepsy-related mortality beyond that seen in general childhood onset epilepsy.

SUDEP appears to account for nearly half of deaths in Dravet Syndrome.

- Similar to rates in cohorts of severe drug resistant epilepsy
- Dravet SUDEP occurs at a younger age

Relationship between SUDEP and Dravet supported by animal models

Why SUDEP is more common in Dravet is not yet clear

More work is needed!

Dravet SUDEP Registry

SUDEP.registry@sickkids.ca

elizabeth.donner@sickkids.ca

Thanks to families that share their stories

And also:

Research team:

Anne Keller

Robyn Whitney

Jordan Ho

Shelly-Anne Li

Collaborators:

Canadian Pediatric Epilepsy Network

North American SUDEP Registry, Orrin Devinsky, Daniel Friedman

Michael Pollanen, OFPS

Funding:

Citizens United for Research in Epilepsy

Dravet Canada

Kivinen Family

Montanera Family

Ontario Brain Institute

SUDEP Aware

Hadyen

Eric

Jordan

Lisa

Henry