RESEARCH ARTICLE

Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies

Alice M. Donnan, BSc, MD, Amy L. Schneider, MGenCouns, Sophie Russ-Hall, BSc (Hons), Leonid Churilov, PhD, and Ingrid E. Scheffer, PhD

Correspondence
Dr. Scheffer
i.scheffer@unimelb.edu.au

Neurology® 2023;100:e1712-e1722. doi:10.1212/WNL.0000000000207080

MORE ONLINE

CME Course
NPub.org/cmelist

Abstract

Background and Objectives

The genetic developmental and epileptic encephalopathies (DEEs) comprise a large group of severe epilepsy syndromes, with a wide phenotypic spectrum. Currently, the rates of convulsive status epilepticus (CSE), nonconvulsive status epilepticus (NCSE), and sudden unexplained death in epilepsy (SUDEP) in these diseases are not well understood. We aimed to describe the proportions of patients with frequently observed genetic DEEs who developed CSE, NCSE, mortality, and SUDEP. Understanding the risks of these serious presentations in each genetic DEE will enable earlier diagnosis and appropriate management.

Methods

In this retrospective analysis of patients with a genetic DEE, we estimated the proportions with CSE, NCSE, and SUDEP and the overall and SUDEP-specific mortality rates for each genetic diagnosis. We included patients with a pathogenic variant in the genes *SCN1A*, *SCN2A*, *SCN8A*, *SYNGAP1*, *NEXMIF*, *CHD2*, *PCDH19*, *STXBP1*, *GRIN2A*, *KCNT1*, and *KCNQ2* and with Angelman syndrome (AS).

Results

The cohort comprised 510 individuals with a genetic DEE, in whom we observed CSE in 47% and NCSE in 19%. The highest proportion of CSE occurred in patients with *SCN1A*-associated DEEs, including 181/203 (89%; 95% CI 84–93) patients with Dravet syndrome and 8/15 (53%; 95% CI 27–79) non-Dravet *SCN1A*-DEEs. CSE was also notable in patients with pathogenic variants in *KCNT1* (6/10; 60%; 95% CI 26–88) and *SCN2A* (8/15; 53%; 95% CI 27–79). NCSE was common in patients with non-Dravet *SCN1A*-DEEs (8/15; 53%; 95% CI 27–79) and was notable in patients with *CHD2*-DEEs (6/14; 43%; 95% CI 18–71) and AS (6/19; 32%; 95% CI 13–57). There were 42/510 (8%) deaths among the cohort, producing a mortality rate of 6.1 per 1,000 person-years (95% CI 4.4–8.3). Cases of SUDEP accounted for 19/42 (48%) deaths. Four genes were associated with SUDEP: *SCN1A*, *SCN2A*, *SCN8A*, and *STXBP1*. The estimated SUDEP rate was 2.8 per 1,000 person-years (95% CI 1.6–4.3).

Discussion

We showed that proportions of patients with CSE, NCSE, and SUDEP differ for commonly encountered genetic DEEs. The estimates for each genetic DEE studied will inform early diagnosis and management of status epilepticus and SUDEP and inform disease-specific counseling for patients and families in this high-risk group of conditions.

From the Epilepsy Research Centre (A.M.D., A.L.S., S.R.-H., I.E.S.), Department of Medicine, The University of Melbourne, Austin Health; Melbourne Medical School (L.C.), Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville; The Florey Institute of Neurosciences and Mental Health (L.C., I.E.S.), Melbourne; and Department of Paediatrics (I.E.S.), The University of Melbourne, Royal Children's Hospital, and Murdoch Children's Research Institute, Victoria, Australia.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AS = Angelman syndrome; **CSE** = convulsive status epilepticus; **DD** = developmental delay; **DEE** = developmental and epileptic encephalopathy; **DEE-SWAS** = developmental and epileptic encephalopathy with spike and wave activation in sleep; **DS** = Dravet syndrome; **EOAE** = early-onset absence epilepsy; **GTCS** = generalized tonic-clonic seizure; **EIDEE** = early infantile DEE; **EIMFS** = epilepsy of infancy with migrating focal seizures; **EM** = eyelid myoclonus; **EEM** = epilepsy with eyelid myoclonus; **EMA** = epilepsy with myoclonic absence; **EMAtS** = epilepsy with myoclonic atonic seizures; **EOAE** = early-onset absence epilepsy; **GEFS+** = generalized epilepsy with febrile seizures plus; **IESS** = infantile epileptic spasms syndrome; **IGE** = idiopathic generalized epilepsy; **IQR** = interquartile range; **JME** = juvenile myoclonic epilepsy; **LGS** = Lennox-Gastaut syndrome; **LKS** = Landau-Kleffner syndrome; **NCSE** = nonconvulsive status epilepticus; **SeLECTS** = self-limited epilepsy with centrotemporal spikes; **SUDEP** = sudden unexplained death in epilepsy.

The developmental and epileptic encephalopathies (DEEs) are a group of severe epilepsy syndromes with a wide phenotypic spectrum, typically characterized by frequent seizures of multiple types, epileptiform EEG patterns, and developmental regression or slowing.[1] The underlying genetic defect in these epilepsy syndromes is responsible not only for the epileptic activity but also for the developmental disability, as 2 separate but interconnected components.[2] The developmental sequelae are therefore due both to direct effects of the underlying genetic variant and the epileptiform activity.

In the current age of genetic and molecular testing, our understanding of the DEEs has been transformed. More than 800 genes have been implicated, allowing for the delineation of specific genetic encephalopathies, often with a characteristic electroclinical phenotype. However, more than 1 gene can produce the same electroclinical phenotype, and conversely, the same gene can produce very different syndromes.[1]

Despite the rapid advances in our understanding of these disorders, little is known about the relative proportions of patients with status epilepticus and sudden unexplained death in epilepsy (SUDEP) for specific genetic DEEs. While the rates of status epilepticus and mortality have been well-described in Dravet syndrome, these figures are less well known in the more recently described genetic DEEs. A clear understanding of the occurrence of these events in DEEs would allow clinicians to more accurately counsel patients and families and target therapy more appropriately. This cohort study with retrospective data collection aimed to estimate the proportions of patients with convulsive status epilepticus (CSE), nonconvulsive status epilepticus (NCSE), and SUDEP associated with specific, relatively frequent, genetic DEEs.

Methods

Participants

We identified patients with a DEE of known genetic cause who had been recruited to The University of Melbourne Epilepsy Genetics Research Program. This program has recruited patients with genetic epilepsies over the past 30 years, with ongoing clinical contact with families and their treating clinicians. Patients with 12 genetic DEEs were included in this study: *SCN1A*, *SCN2A*, *SCN8A*, *SYNGAP1*, *NEXMIF*, *CHD2*, *PCDH19*, *STXBP1*, *GRIN2A*, *KCNT1*, *KCNQ2*, and Angelman syndrome (AS)[3] because for these genes, we had a cohort of at least 10 patients. Patients were excluded where there was inadequate clinical information available.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Human Research Ethics Committee of Austin Health. Written informed consent was obtained from the patient or the parents or legal guardians of all minors or individuals with intellectual disability.

Data Collection

Episodes of status epilepticus (both CSE and NCSE) were identified through review of patient clinical records, which were collected from their individual treating team, and family interviews.[4] The records included medical letters, hospital discharge summaries, EEGs, imaging, and pathology studies. Status epilepticus was defined as an episode of continuous seizure activity for at least 30 minutes or frequent seizures over 30 minutes without regaining consciousness between seizures.[5] The 30-minute timepoint was selected as the point at which continuous seizure activity causes long-term neuronal consequences. NCSE was defined as at least 30 minutes of altered awareness, with or without myoclonic or atonic features. NCSE could be generalized (absence status epilepticus) or focal. The clinical records included details of seizure types and duration, which were cross-checked with previous publications and family interviews. In cases where the clinical details were unclear, follow-up phone calls to families were made to clarify the presence or absence of CSE and NCSE.

For each patient, we obtained their age (during the last accessible clinical record in living individuals or during death), genetic pathogenic variant, seizure types, episodes of CSE or NCSE, age at first episode of CSE or NCSE, death, and cause of death, including SUDEP category where relevant.

For the mortality study, we recorded the cause of death for all patients. Cases of SUDEP were identified through review of clinical notes, death certificates, and postmortem examinations where available. Where the cause of death was unclear from review of the clinical records, the treating clinician and/or

family was contacted for clarification. Cases were further classified into definite SUDEP, definite SUDEP plus, probable SUDEP, possible SUDEP, near SUDEP, and near SUDEP plus, based on Nashef et al.'s[6] proposed unifying definitions. Definite cases of SUDEP were those confirmed by a postmortem examination.

To compare our data with previous studies of mortality in epilepsy syndromes, we calculated person-years based on predefined study entry and exit dates. For this study, the entry date for each included patient was defined as their birth date. The exit date was the date of death for deceased individuals or the date of the most recent accessible medical record in the database for living individuals.

We then provided an overall anticipated risk of CSE, NCSE, mortality, and SUDEP for each studied genetic DEE. We defined genetic DEEs as being at low risk for CSE and NCSE if there were less than 10% of patients affected, at moderate risk if there were between 10% and 30% affected, and high risk if more than 30% were affected. We defined mortality risk as high if any patients in the cohort had died.

Statistical Analysis

Demographic variables were presented as numbers, percentages, and median values with respective interquartile ranges (IQRs) where appropriate. Estimated population proportions of patients with CSE, NCSE, and SUDEP for each genetic DEE were presented with respective 95% CIs. For the mortality study, we estimated all-cause mortality rates and SUDEP rates per 1,000 person-years for each genetic DEE, with 95% CIs. Statistical analyses were performed using Stata software, version 16IC (StataCorp, College Station, TX).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

We identified 545 patients with a DEE and known pathogenic variant. Of these patients, 35 were excluded from subsequent data analysis because of insufficient data. The cohort then comprised 510 individuals with a median age of 10 years (range 1 month–79 years; IQR 26.8 years) (Table 1); 308/510 (61%) were female and 393/510 (77%) were younger than 18 years.

Of this large DEE cohort, 239/510 (47%) had an episode of CSE, with the first recorded episode occurring at a median age of 8 months, and 96/510 (19%) had NCSE, with the first recorded episode at a median age of 5 years (Table 2). Many patients with *SCN1A* DEEs had CSE, affecting 181/203 (89%; 95% CI 84–93) of patients with Dravet syndrome and 8/15 (53%; 95% CI 27–79) of patients with other *SCN1A* DEEs (Table 2 and Figure 1). Among our cohort, notable proportions of patients with pathogenic variants in *KCNT1* (6/10; 60%; 95% CI 26–88), *SCN2A* (8/15; 53%; 95% CI 27–79), and *STXBP1* (6/17; 35%; 95% CI 14–62) had CSE.

CSE was more common than NCSE among patients with pathogenic variants in *SCN1A*, *SCN2A*, *SCN8A*, *STXBP1*, *KCNT1*, *KCNQ2*, and *PCDH19*. Conversely, NCSE was more common than CSE in patients with DEEs related to *SYNGAP1*, *NEXMIF*, and *CHD2* and with AS.

NCSE was common in patients with non-Dravet *SCN1A* DEEs (8/15; 53%; 95% CI 27–79) compared with those with Dravet syndrome (46/203; 23%; 95% CI 17–29). NCSE was also noted in patients with *CHD2* variants (6/14; 43%; 95% CI 18–71) and AS (6/19; 32%; 95% CI 13–57). The estimated population proportions of CSE and NCSE are summarized with 95% CIs in Table 2; wide CIs were observed for most specific genetic DEEs.

A total of 42 deaths were observed in the cohort of 510 patients. Cases of SUDEP accounted for 19/42 (48%) deaths (Table 3). Figure 2 shows the causes of and age at death, highlighting the affected gene for the cases of SUDEP. The observed cases of SUDEP were highest in the *SCN1A* DEEs including patients with Dravet syndrome (12/203; 5.9%) and other *SCN1A* DEEs (3/15; 27%). Deaths due to SUDEP occurred only among patients with pathogenic variants in 4 genes: *SCN1A, SCN2A, SCN8A*, and *STXBP1*. Among the total 19 cases of SUDEP, 4 were classified as definite SUDEP, 2 were definite SUDEP plus, 10 were probable SUDEP, 1 was possible SUDEP, 1 near-SUDEP and 1 near-SUDEP plus. There were no cases of SUDEP identified among patients with pathogenic variants in *SYNGAP1*, *NEXMIF*, *PCDH19*, *CHD2*, *GRIN2A*, *KCNT1*, *KCNQ2*, or AS.

The overall estimated population mortality rate was 6.1 per 1,000 person-years (95% CI 4.4–8.3), when calculating years from birth date to study exit, over a total of 6,805 person-years (510 patients). The estimated population SUDEP rate for all genetic DEEs was 2.8 per 1,000 person-years (95% CI 1.6–4.3). The Dravet-specific estimated population SUDEP rate was 4.4 per 1,000 person-years (95% CI 2.3–7.8), over a total of 2,675 person-years (203 patients).

Table 4 summarizes an estimate of the risk of CSE, NCSE, mortality, and SUDEP among the studied genetic DEEs. Of the 510 patients, 416 have been previously reported in article describing their genetic DEE[4,7–18] (eTable 1, links.lww.com/WNL/C641). Of the 35 patients we excluded because insufficient data, 11 (31%) had a genetic variant in *KCNQ2*, 7 (20%) in *PCDH19*, 5 (14%) in *STXBP1*, 4 (11%) in *SYNGAP1*, 2 (6%) in *CHD2*, and 1 patient had a variant in each of *SCN1A, SCN2A, SCN8A, KCNT1* and AS. Compared with the included patients, there was a slightly higher median age of 16 years in the excluded patients (range 5.1–60.3, IQR 15.6) and a similar proportion (22/35; 63%) were female.

Discussion

A critical clinical question when faced with an individual with a genetic DEE is whether they are at risk of life-threatening emergencies such as CSE, NCSE, or death. With more than 800

Table 1 Demographic Information of Our Cohort of 510 Patients

Genetic DEE	Female, N (%)	Age at study (y)		Seizure type(s)	Epilepsy syndrome(s)
		Median	Range (IQR)		
***SCN1A* (Dravet)** N = 203	116 (57)	10.1	0.9–60.2 (11.6)	Generalized Hemiclonic Focal Myoclonic Absence	DS[a]
***SCN1A* (other DEE)** N = 15	5 (33)	11.9	4.2–48.6 (6.6)	Generalized Myoclonic Infantile Spasms Absence Atonic	EIDEE; EIMFS; LGS; EMAtS
SCN2A N = 15	6 (40)	4.9	0.1–27.2 (9.2)	Focal tonic GTCS Epileptic spasms	DEE; EIDEE; EIMFS; IESS; LGS
SCN8A N = 13	8 (62)	8.5	0.6–51.0 (20.8)	Focal clonic GTCS Infantile spasms Absence	DEE; EIDEE; EIMFS; focal; GEFS+
KCNT1 N = 10	5 (50)	8.0	0.8–22.4 (7.4)	Tonic Clonic Focal Epileptic spasms	DEE; EIMFS; focal
STXBP1 N = 17	6 (35)	9.0	1.5–26.7 (7.9)	Refractory epileptic spasms	EIDEE; EMA; focal; IESS; LGS; DS
PCDH19 N = 53	53 (100)	17.5	1.7–79 (15.2)	Febrile GTCS Focal Absence Myoclonic	*PCDH19* clustering epilepsy
CHD2 N = 14	8 (57)	16.9	9.6–44.0 (11.8)	Myoclonic Absence Atonic-Myoclonic Absence	EMA; JME; LGS; EMAtS; EOAE
KCNQ2 N = 28	16 (57)	3.7	0.5–16.6 (5.8)	Tonic Apneic Focal clonic Autonomic	DEE; EIDEE; EIMFS; IESS; LGS
GRIN2A N = 14	5 (36)	12.9	12.0–57.9 (11.8)	Focal Focal-to-generalized tonic-clonic	SeLECTS; DEE-SWAS; focal; LKS
NEXMIF N = 49	37 (76)	11.0	1.7–42.0 (11.0)	Absence Myoclonic Myotonic	IGE; IESS; JME; EMAtS
AS[b] N = 19	11 (58)	7.1	1.3–26.3 (10.5)	Febrile Tonic-clonic Atypical absence Myoclonic Focal	AS
SYNGAP1 N = 60	29 (48)	8.9	1.6–33.7 (22.6)	Focal Focal-to-generalized tonic clonic	SeLECTS; DEE-SWAS; focal; LKS
Total N = 510	308 (61)	10.0	0.1–79 (26.8)	—	—

Abbreviations: AS = Angelman syndrome; DD = developmental delay; DEE = developmental and epileptic encephalopathy; DEE-SWAS = developmental and epileptic encephalopathy with spike-and-wave activation in sleep; DS = Dravet syndrome; EOAE = early-onset absence epilepsy; GTCS = generalized tonic-clonic seizure; EIDEE = early infantile DEE; EIMFS = epilepsy of infancy with migrating focal seizures; EM = eyelid myoclonus; EEM = epilepsy with eyelid myoclonus; EMA = epilepsy with myoclonic absence; EMAtS = epilepsy with myoclonic atonic seizures; EOAE = early-onset absence epilepsy; GEFS+ = generalized epilepsy with febrile seizures plus; IESS = infantile epileptic spasms syndrome; IGE = idiopathic generalized epilepsy; IQR = interquartile range; JME = juvenile myoclonic epilepsy; LGS = Lennox-Gastaut syndrome; LKS = Landau-Kleffner syndrome; SeLECTS = self-limited epilepsy with centrotemporal spikes.
[a] One patient in our cohort initially presented with DS but, after an immersion injury at age 3 y, developed an LGS phenotype.
[b] Patients with AS included those with deletions involving maternal chromosome 15q11.2-q13, abnormal methylation of maternal chromosome 15q11.2-q13, uniparental disomy of paternal chromosome 15q11.2-q13, and pathogenic variants in the maternally derived *UBE3A* gene.

Table 2 Estimated Population Proportions of CSE/NCSE and Age at First Episode of CSE/NCSE in Our Cohort of Patients With Genetic DEEs

Genetic DEE	CSE, N	CSE % (95% CI)	Median age at first episode of CSE (range; IQR)	NCSE, N	NCSE % (95% CI)	Median age at first episode of NCSE (range; IQR)
***SCN1A* (Dravet)** N = 203	181	89% (84–93)	8 mo (3 mo–11 y; 6.5 mo)	46	23% (17–29)	3.6 y (10 mo–25 y; 4.8 y)
***SCN1A* (other DEE)** N = 15	8	53% (27–79)	7 mo (2 mo–9 mo; 5.5 mo)	8	53% (27–79)	2.1 y (2 y–5 y; 1.7 y)
SCN2A N = 15	8	53% (27–79)	3 mo (17 d–18 mo; 10.5 mo)	1	6.7% (0.16–31)	—
SCN8A N = 13	4	31% (9.1–61)	8 mo (13 d–18 mo; 15 mo)	3	23% (5.0–54)	4.3 y (21 mo–9.8 y; 4.0 y)
KCNT1 N = 10	6	60% (26–88)	5 mo (2 mo–2.6 y; 3 mo)	0	—	—
STXBP1 N = 17	6	35% (14–62)	19 mo (12 mo–3.5 y; 2 y)	4	24% (6.8–50)	6.4 y (4.3 y–7 y; 2 y)
PCDH19 N = 53	14	26% (15–40)	17 mo (6 mo–4 y; 13 mo)	1	1.9% (0.048–10.1)	—
CHD2 N = 14	3	21% (4.6–51)	8.8 y (8 y–8.8 y; 5 mo)	6	43% (18–71)	16.9 y (5 y–28 y; 14.7 y)
KCNQ2 N = 28	5	18% (6.1–37)	8 mo (2 d–3.3 y; 16 mo)	2	7.1% (0.88–24)	2.1 y (7 mo–3.5 y; 1.5 y)
GRIN2A N = 14	2	14% (1.7–43)	4.8 y (3.9 y–5.6 y, 10 mo)	2	14% (1.7–43)	4.9 y (4.1 y–5.7 y; 9.5 mo)
NEXMIF N = 49	1	2% (0.1–10)	—	14	29% (17–43)	9.8 y (18 mo–14 y; 5.9 y)
Angelman syndrome N = 19	1	5% (0.13–26)	—	6	32% (13–57)	2.7 y (5 mo–8.3 y; 3.4 y)
SYNGAP1 N = 60	0	0% (0–59)[a]	—	3	5.0% (1.0–14)	15.6 y (6 y–18 y; 6.2 y)
Total N = 510	239	47%	8 mo (2 d–11 y; 10.3 mo)	96	19%	5 y (5 mo–28 y; 6.1 y)

Abbreviations: CSE = convulsive status epilepticus; DEE = developmental and epileptic encephalopathy; IQR = interquartile range; NCSE = nonconvulsive status epilepticus.
[a] One-sided, 97.5% CI.

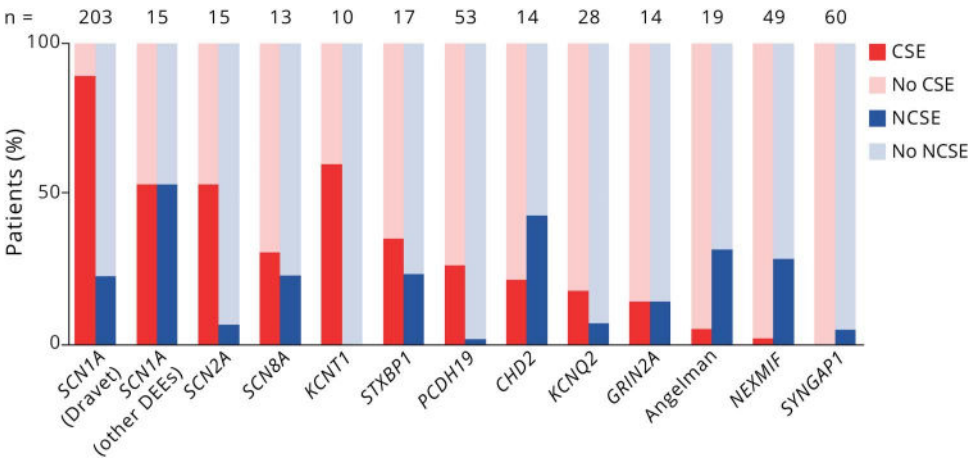
genetic causes of DEEs, each disease is not likely to carry an equal risk of these serious complications. In a large cohort of 510 patients with DEEs, we estimated the occurrence of CSE, NCSE, mortality risk, and SUDEP among the more common genetic DEEs.[19,20] Of the 12 genetic DEEs analyzed, CSE was most frequent among the sodium channelopathies (*SCN1A, SCN2A,* and *SCN8A*), potassium channelopathies (*KCNT1* and *KCNQ2*), *PCDH19, STXBP1, CHD2,* and *GRIN2A.* Conversely, different genetic etiologies or syndromes were associated with a higher risk of NCSE, such as *CHD2,* non-Dravet *SCN1A,* AS, and *NEXMIF*. Different genetic DEEs varied markedly regarding mortality and SUDEP rates. These data will inform clinical discussions and management for individuals in whom a genetic diagnosis is established for their DEE.

Overall, 239 of 510 (47%) patients with a genetic DEE had at least 1 episode of CSE, with onset at a median age of 8 months (range 2 days–11 years). CSE is the most common pediatric neurologic emergency and is associated with significant morbidity and mortality.[21] CSE is a well-recognized feature of Dravet syndrome,[4,22] observed in 89% of our 203 patients. In patients with non-Dravet *SCN1A,* such as those with the early infantile DEE,[10] EIMFS,[11] MAE,[23] and LGS,[24] 53% had CSE, noting that these diseases include both loss-of-function and gain-of-function pathogenic variants.[25]

The frequency of CSE in other genetic DEEs or epilepsy syndromes is not as well understood. Notably, other sodium channelopathies also carried a substantial rate of CSE with individuals with *SCN2A* (53%) posing a higher proportion than those with *SCN8A* (31%).[9,13,26–28] Potassium channel DEEs due to *KCNT1* and *KCNQ2* were associated with 60% and 18% rates of CSE, respectively.[15,18,19,29,30]

The median age at first episode of CSE varied between the genetic DEEs studied, informing families when their child

Figure 1 Proportion of Patients With Episodes of CSE and NCSE for Each Studied Genetic DEE



CSE = convulsive status epilepticus; DEE = developmental and epileptic encephalopathy; NCSE = nonconvulsive status epilepticus.

may be at greater risk. Indeed, the median onset of CSE in *SCN1A*-DEEs was 8 months for Dravet and 7 months for non-Dravet *SCN1A*-DEEs, compared with 3 months for *SCN2A*, 8 months for *SCN8A*, 4 years for *GRIN2A*, and 8 years for *CHD2*-DEEs. This likely reflects heterogeneity in the underlying neurobiology of these genetic diseases.

Other genes previously reported to have a strong association with CSE or NCSE (although these subtypes of status epilepticus were often not differentiated) are *CHD2*, *PCDH19*, *SCN8A*, *STXBP1*, and *SYNGAP1*.[12,13,16,31–33] In our cohort, CSE occurred in all these genes aside from *SYNGAP1*, which was, however, associated with NCSE. The genetic variants that were least associated with CSE are related to synaptic signaling pathways (*SYNGAP1*)[12] or neuronal migration in early brain development (*NEXMIF*).[14] The underlying molecular mechanisms of the genetic DEEs are likely to predispose to (or protect against) the development of CSE.

There were fewer patients with NCSE compared with CSE across all genetic DEEs studied. NCSE was most common in patients with pathogenic variants in *SCN1A* (23% in Dravet syndrome; 50% in other *SCN1A*-DEEs) and *CHD2* and in patients with AS (32%). Our findings are consistent with previous descriptions of AS, where NCSE has been described in 25%–50% of patients,[34–36] comprising both absence and myoclonic status.[37] Both CSE and NCSE are late features of *CHD2* myoclonic DEE,[16] and this is reflected in our cohort of 14 individuals, in whom the median age at onset was 8.8 years and 16.9 years for CSE and NCSE, respectively.

We expected to find higher proportions of patients with NCSE in *SYNGAP1*-DEE, which is a generalized DEE with intellectual disability, behavioral issues, and ataxia. Frequent seizure types include eyelid myoclonia with absence, myoclonic, and atonic seizures.[12] Clinically, although we have seen many children with *SYNGAP1*-DEE in NCSE, this was not captured in our data. These children typically have very frequent, if not constant, absence seizures with eyelid myoclonias associated with epileptiform activity through much of the day, but some clinicians may not consider this a form of NCSE. Therefore, we may have underestimated the true existence of NCSE among a number of the genetic DEEs, particularly in those with subtle, frequent, nonconvulsive seizure types.

The median age at first episode of CSE was typically younger than the age at first episode of NCSE for each genetic DEE studied. This likely reflects differences in biochemical or neurologic mechanisms relating to CSE and NCSE. While we were able to record the age of first episode of status epilepticus for our cohort, we were not able to accurately document the number of episodes of CSE or NCSE that occurred in each patient. Therefore, while this study provides an estimate of the overall rate of patients with specific genetic DEEs developing CSE or NCSE, and the median age at which this occurs, we cannot comment on how frequently these events might occur in an individual.

Death occurred in 42/510 (8.2%) patients in our cohort, with an estimated population mortality rate of 6.1 per 1,000 person-years (95% CI 4.4–8.3). This is broadly comparable with the mortality rate of 4.06 per 1,000 person-years (95% CI 3.24–5.08) recently reported in Danish children (younger than18 years) with all types of epilepsy.[38] Causes of death in our cohort included SUDEP, status epilepticus, cerebral edema,[8] respiratory infection, and drowning (Table 3). SUDEP accounted for almost half (19/42; 45%) of all deaths, which was higher than the 19% rate in a recent surveillance study of all children with epilepsy in the UK and Ireland.[39] The high mortality and SUDEP rates in our cohort likely reflects the more severe prognosis of the DEEs.

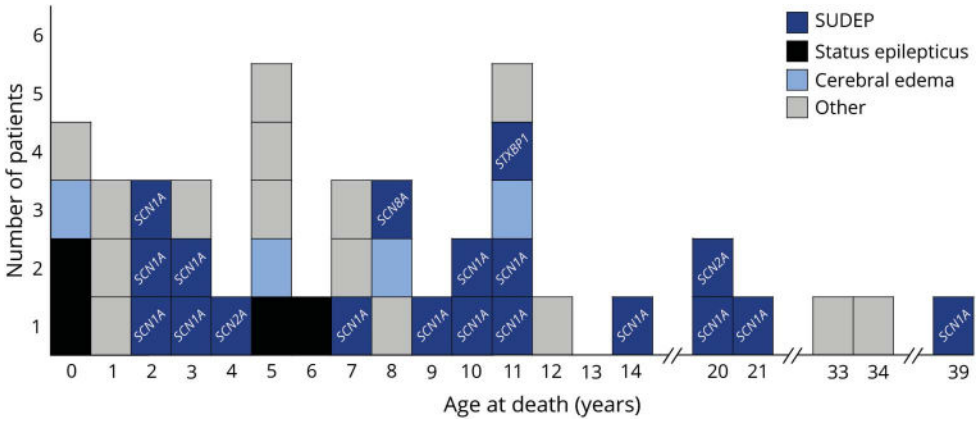
The SUDEP rate was 2.8 per 1,000 person-years across the genetic DEEs studied. This compares with adult epilepsy studies that show SUDEP rates between 0.35 and 5.1 per 1,000 person-years[40,41] and pediatric studies between 0.22 and 1.17

Table 3 Mortality and SUDEP in Our Cohort of 510 Patients With Genetic DEEs

Genetic DEE	Deceased, N (%)	All-cause mortality per 1,000 person-y (95% CI)	Median age at death in y (range; IQR)	Causes of death (N)	SUDEP, N (%)	SUDEP level (N)	SUDEP per 1,000 person-y (95% CI)	Proportion of deaths from SUDEP	Median age SUDEP in y (range; IQR)
***SCN1A* (Dravet)** N = 203	23 (11)	8.6 (5.4–13)	9.7 (0.9–49.8; 11.4)	SUDEP (12) SE (3) Cerebral edema (4)[a] Drowning (4)	12 (5.9)	Definite (3) Definite plus (2) Probable (5) Possible (1) Near plus (1)	4.4 (2.3–7.8)	52%	8.9 (2.7–39; 9.3)
***SCN1A* (other DEE)** N = 15	5 (33)	19 (5.3–45)	11.2 (9.6–34.1; 5.4)	SUDEP (3) Pneumonia (2)	3 (20)	Definite (1) Probable (2)	11 (2.4–34)	60%	10 (9.6–21; 5.7)
SCN2A N = 15	6 (40)	53 (19–116)	5.0 (0.1–20.9; 12.4)	SUDEP (2) Pneumonia (2) Withdrew care (1)[a] Unknown (1)	2 (13)	Probable (2)	17 (2.1–64)	33%	12.9 (4.9–20; 7.9)
SCN8A N = 13	3 (21)	14 (2.9–42)	7.3 (0.2–8.4; 6.7)	SUDEP (1) Pneumonia (1) Withdrew care (1)[a]	1 (7.7)	Near plus (1)	4.7 (0.12–26)	33%	8.5
KCNT1 N = 10	2 (20)	22 (2.7–82)	9.7 (7.5–11.9; 5.9)	Pneumonia (1) Unknown (1)	0	—	—	—	—
STXBP1 N = 17	1 (5.9)	5.9 (0.15–33)	11.8	SUDEP (1)	1 (5.9)	Probable (1)	5.9 (0.15–33)	100%	11.8
PCDH19 N = 53	0	—	—	—	0	—	—	—	—
CHD2 N = 14	0	—	—	—	0	—	—	—	—
KCNQ2 N = 28	1 (3.6)	6.3 (0.02–36)	5.6	Pneumonia (1)	0	—	—	—	—
GRIN2A N = 14	0	—	—	—	0	—	—	—	—
NEXMIF N = 49	0	—	—	—	0	—	—	—	—
Angelman syndrome N = 19	0	—	—	—	0	—	—	—	—
SYNGAP1 N = 60	1 (1.7)	1.5 (0.04–8.7)	33.7	Complications post-dental surgery (1)	0	—	—	—	—
All genes N = 510	42 (8.2)	6.1 (4.4–8.3)	7.4 (0.1–39; 11.9)	—	19 (3.7)	—	2.8 (1.6–4.3)	45%	9.8 (2.7–39; 8.1)

Abbreviations: DEE = developmental and epileptic encephalopathy; IQR = interquartile range; SUDEP = sudden unexplained death in epilepsy.
[a] Withdrawal of care in infancy due to severe epileptic encephalopathy.

Figure 2 Causes of and Age at Deaths in the Studied Genetic DEEs, Including the Affected Gene for the Cases of SUDEP



DEEs = developmental and epileptic encephalopathies; SUDEP = sudden unexplained death in epilepsy.

per 1,000 person-years.[42,43] Although SUDEP is less common in children than adults,[44] this is not the case for DEEs. Of our 19 patients who died of SUDEP, 15 (79%) were younger than 18 years at time of death. The median age at SUDEP was 9.8 years (range 21 months–39 years). Our findings of high SUDEP rates and a young median age of SUDEP highlights the increased risk of SUDEP in patients with genetic DEEs compared with the general population with epilepsy.

Table 4 Seizure Onset, Estimated Status Epilepticus Risk, and Estimated Mortality Risk for the Studied Genetic DEEs

Genetic DEE	Typical age at seizure onset	Status epilepticus risk	Mortality risk
KCNQ2[2,15,30]	Neonatal	CSE moderate NCSE low	High
KCNT1[18,29,46]	Neonatal-infancy	CSE high NCSE low	High
STXBP1[2,33]	Neonatal–early infancy	CSE high NCSE moderate	High SUDEP+
SCN2A[9,47]	Neonatal–early infancy	CSE high NCSE low	High SUDEP+
SCN8A[13,26,27]	Within first 18 mo	CSE high NCSE moderate	High SUDEP+
SCN1A **(Dravet phenotype)**[4,10]	Within first 19 mo	CSE high NCSE moderate	High SUDEP+
SCN1A **(other phenotypes)**[10,23,25]	Early infancy–childhood	CSE high NCSE high	High SUDEP+
SYNGAP1[12]	6 mo–6 y	CSE low NCSE low	High
PCDH19[32,48]	6–36 mo	CSE moderate NCSE low	—
NEXMIF[14]	1–2 y	CSE low NCSE moderate	—
CHD2[16]	1–4 y	CSE moderate NCSE high	—
Angelman syndrome[34,49]	1–5 y	CSE low NCSE high	—
GRIN2A[50]	3–6 y	CSE moderate NCSE moderate	—

Abbreviations: CSE = convulsive status epilepticus; DEE = developmental and epileptic encephalopathy; NCSE = nonconvulsive status epilepticus; SUDEP = sudden unexplained death in epilepsy.

SUDEP occurred only in patients with pathogenic variants in the sodium channel genes, *SCN1A*, *SCN2A*, *SCN8A*, and in *STXBP1*, which affect synaptic vesicle docking and fusion. Of interest, the single SUDEP death in *STXBP1*-associated DEE occurred in a patient with a clinical diagnosis of Dravet syndrome.[45] Two genes associated with high proportions of CSE, *SCN1A* and *SCN2A*, were also associated with SUDEP.

The Dravet-specific estimated SUDEP rate was 4.4 per 1,000 person-years (23 deaths in 203 patients), which differs from the rate of 9.32 per 1,000 person-years (17 deaths in 100 patients) we previously described in the study conducted by Cooper et al.[7] Some of this disparity in estimations may be accounted for by different methodology in calculating patient years. While we included patients from their date of birth to date of death or last medical record, Cooper et al. defined patient years from a set study entry point (age 1 year or February 2002) to a set exit point. The 2 cohorts were not identical: the first cohort of 100 patients in the study conducted by Cooper et al. included 13 without *SCN1A* pathogenic variants because recruitment occurred before wide availability of molecular testing. Furthermore, in our current cohort, 5 of the deaths occurred in patients included in the cohort of the study conducted by Cooper et al. who died after the study concluded. As genetic testing has become more accessible and accurate with time, it is likely that we are now diagnosing more *SCN1A* pathogenic variants among less severely affected patients.[4] We do not know whether these less severely affected patients have a reduced risk of SUDEP. Our current estimate, which includes recent data, may therefore more accurately reflect the SUDEP rate in patients with Dravet syndrome, accounting for a wider phenotypic spectrum.[4]

KCNT1-DEE has early infantile onset associated with the syndrome of EIMFS, with a 47% (8/17) mortality rate at a median age of 3 years and 17% rate of SUDEP.[29] In our cohort, 2 of 20 patients with *KCNT1*-DEE died, 1 of pneumonia and 1 of unknown cause (Table 3). There were no cases of SUDEP. The difference in our results compared with previous reports likely represents sampling error, given the small sample sizes.[18,29] A recent review of *KCNT1*-associated epilepsies did not report any mortalities among a novel cohort of 50 individuals with *KCNT1*-DEE.[46]

More broadly, the small sample size of patients with particular genetic DEEs in our cohort has limited our ability to accurately estimate the occurrence of CSE, NCSE, mortality, and SUDEP. This is reflected in the wide CIs observed for our estimations. A disproportionate number experience Dravet syndrome in our cohort, accounting for 203/510 (40%) patients. The large numbers of patients with Dravet syndrome improves the reliability of our Dravet syndrome results and highlights that large cohort studies of specific diseases are necessary to draw definitive conclusions regarding risks for each genetic disease. It will, however, have skewed our overall results relating to the rates of CSE, NCSE, and SUDEP in the entire cohort. More accurate estimates of the proportions of patients with CSE, NCSE, and SUDEP in the less common genetic DEEs will require further multicenter research.

This was a cohort study with retrospective data collection, and therefore, differences in the quality of available patient data and loss of follow-up in some cases may have contributed to bias. We cannot draw epidemiologic conclusions from these data because our cohort was based on referral to the Epilepsy Genetics Research Program and would not have captured all patients with these diseases in our region. Referrals came from a wide range of sources including physicians, support groups, and directly from patients or families. Referral bias is therefore possible and may have skewed our findings.

Despite these limitations, this study allows for an initial estimation of the risks of status epilepticus and SUDEP for the more common genetic DEEs. Further multicenter research is needed to confirm these estimates, which can be used to provide counseling to patients and families about the risks of status epilepticus and SUDEP. Early counseling about these features in patients with DEEs is particularly important because the risk in this cohort is much higher than in the general pediatric epilepsy population. This will enable rapid recognition of NCSE and CSE by families, enabling prompt therapy, which in turn could improve long-term outcomes because status epilepticus can be associated with developmental regression. Targeted counseling regarding the specific risks of each genetic DEE will provide more accurate information to families and treating clinicians.

Acknowledgment

The authors thank the patients and their families for participating in their research program.

Study Funding

The authors gratefully acknowledge support provided by the Australian Epilepsy Research Foundation grant, Australian National Health and Medical Research Council (NHMRC) Center for Research Excellence Grant (GNT2006841), and NHMRC Synergy Grant (GNT2010562). Professor Scheffer is also supported by a NHMRC Senior Investigator Fellowship (GNT1172897).

Disclosure

I.E. Scheffer has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Rogcon, Takeda Pharmaceuticals, UCB, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, Liva Nova, Nutricia, Zuellig Pharma, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, and Eisai; has served as an investigator for Anavex Life Sciences, Cerecin Inc, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma, Marinus, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and

Zynerba; has consulted for Care Beyond Diagnosis, Epilepsy Consortium, Atheneum Partners, Ovid Therapeutics, UCB, Zynerba Pharmaceuticals, BioMarin, Encoded Therapeutics, and Biohaven Pharmaceuticals; and is a Nonexecutive Director of Bellberry Ltd and a Director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies Limited. She may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for SCN1A testing held by Bionomics Inc and licensed to various diagnostic companies; and has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) (PRRT2) 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009). The remaining authors do not have any disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* August 6, 2022. Accepted in final form January 5, 2023. Submitted and externally peer reviewed. The handling editor was Associate Editor Barbara Jobst, MD, PhD, FAAN.

Appendix Authors

Name	Location	Contribution
Alice M. Donnan, BSc, MD	Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Amy L. Schneider, MGenCouns	Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia	Drafting/revision of the article for content, including medical writing for content; and study concept or design
Sophie Russ-Hall, BSc (Hons)	Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia	Drafting/revision of the article for content, including medical writing for content
Leonid Churilov, PhD	Melbourne Medical School, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Parkville, Australia; The Florey Institute of Neurosciences and Mental Health, Melbourne, Victoria, Australia	Drafting/revision of the article for content, including medical writing for content; and analysis or interpretation of data
Ingrid E. Scheffer, PhD	Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Melbourne, Australia; The Florey Institute of Neurosciences and Mental Health, Melbourne, Victoria, Australia; Department of Paediatrics, The University of Melbourne, Royal Children's Hospital, and Murdoch Children's Research Institute, Victoria, Australia	Drafting/revision of the article for content, including medical writing for content; and study concept or design

References

1. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol.* 2016;15(3):304-316. doi:10.1016/s1474-4422(15)00250-1.
2. El Kosseifi C, Cornet M-C, Cilio MR. Neonatal developmental and epileptic encephalopathies. *Semin Pediatr Neurol.* 2019;32:100770. doi:10.1016/j.spen.2019.08.006.
3. Specchio N, Wirrell EC, Scheffer IE, et al. International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: position paper by the ILAE Task Force on Nosology and Definitions. *Epilepsia.* 2022;63(6):1398-1442. doi:10.1111/epi.17241.
4. Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: an essential pre-requisite for precision medicine trials. *Epilepsia.* 2021;62(9):2205-2217. doi:10.1111/epi.17015.
5. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus—report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia.* 2015;56(10):1515-1523. doi:10.1111/epi.13121.
6. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. *Epilepsia.* 2012;53(2):227-233. doi:10.1111/j.1528-1167.2011.03358.x.
7. Cooper MS, Mcintosh A, Crompton DE, et al. Mortality in Dravet syndrome. *Epilepsy Res.* 2016;128(1):43-47. doi:10.1016/j.eplepsyres.2016.10.006.
8. Myers KA, McMahon JM, Mandelstam SA, et al. Fatal cerebral edema with status epilepticus in children with Dravet syndrome: report of 5 cases. *Pediatrics.* 2017;139(4):e20161933. doi:10.1542/peds.2016-1933.
9. Howell KB, McMahon JM, Carvill GL, et al. SCN2A encephalopathy. *Neurology.* 2015;85(11):958-966. doi:10.1212/wnl.0000000000001926.
10. Sadleir LG, Mountier EI, Gill D, et al. Not all SCN1A epileptic encephalopathies are Dravet syndrome: early profound Thr226Met phenotype. *Neurology.* 2017;89(10):1035-1042. doi:10.1212/wnl.0000000000004331.
11. Burgess R, Wang S, McTague A, et al. The genetic landscape of epilepsy of infancy with migrating focal seizures. *Ann Neurol.* 2019;86(6):821-831. doi:10.1002/ana.25619.
12. Vlaskamp DRM, Shaw BJ, Burgess R, et al. SYNGAP1 encephalopathy. *Neurology.* 2019;92(2):e96-e107. doi:10.1212/wnl.0000000000006729.
13. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of SCN8A encephalopathy. *Neurology.* 2015;84(5):480-489. doi:10.1212/wnl.0000000000001211.
14. Stamberger H, Hammer TB, Gardella E, et al. NEXMIF encephalopathy: an X-linked disorder with male and female phenotypic patterns. *Genet Med.* 2021;23(2):363-373. doi:10.1038/s41436-020-00988-9.
15. Weckhuysen S, Ivanovic V, Hendrickx R, et al. Extending the KCNQ2 encephalopathy spectrum: clinical and neuroimaging findings in 17 patients. *Neurology.* 2013;81(19):1697-1703. doi:10.1212/01.wnl.0000435296.72400.a1.
16. Thomas RH, Zhang LM, Carvill GL, et al. CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures. *Neurology.* 2015;84(9):951-958. doi:10.1212/wnl.0000000000001305.
17. Carvill GL, Regan BM, Yendle SC, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. *Nat Genet.* 2013;45(9):1073-1076. doi:10.1038/ng.2727.
18. Møller RS, Heron SE, Larsen LHG, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. *Epilepsia.* 2015;56(9):e114-e120. doi:10.1111/epi.13071.
19. Symonds JD, Zuberi SM, Stewart K, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain.* 2019;142(8):2303-2318. doi:10.1093/brain/awz195.
20. Symonds JD, Elliott KS, Shetty J, et al. Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. *Brain.* 2021;144(9):2879-2891. doi:10.1093/brain/awab162.
21. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet.* 2006;368(9531):222-229. doi:10.1016/s0140-6736(06)69043-0.
22. Dravet C. The core Dravet syndrome phenotype. *Epilepsia.* 2011;52(suppl 2):3-9. doi:10.1111/j.1528-1167.2011.02994.x.
23. Scheffer IE, Wallace R, Mulley JC, Berkovic SF. Clinical and molecular genetics of myoclonic–astatic epilepsy and severe myoclonic epilepsy in infancy (Dravet syndrome). *Brain Dev.* 2001;23(7):732-735. doi:10.1016/s0387-7604(01)00272-8.
24. Singh R, Andermann E, Whitehouse WPA, et al. Severe myoclonic epilepsy of infancy: extended spectrum of GEFS+? *Epilepsia.* 2001;42(7):837-844. doi:10.1046/j.1528-1157.2001.042007837.x.
25. Berecki G, Bryson A, Terhag J, et al. SCN1A gain of function in early infantile encephalopathy. *Ann Neurol.* 2019;85(4):514-525. doi:10.1002/ana.25438.
26. Ohba C, Kato M, Takahashi S, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. *Epilepsia.* 2014;55(7):994-1000. doi:10.1111/epi.12668.
27. Wagnon JL, Meisler MH. Recurrent and non-recurrent mutations of SCN8A in epileptic encephalopathy. *Front Neurol.* 2015;6:104. doi:10.3389/fneur.2015.00104.
28. Kong W, Zhang Y, Gao Y, et al. SCN8A mutations in Chinese children with early onset epilepsy and intellectual disability. *Epilepsia.* 2015;56(3):431-438. doi:10.1111/epi.12925.
29. Kuchenbuch M, Barcia G, Chemaly N, et al. KCNT1 epilepsy with migrating focal seizures shows a temporal sequence with poor outcome, high mortality and SUDEP. *Brain.* 2019;142(10):2996-3008. doi:10.1093/brain/awz240.
30. Micelli F, Soldovieri MV, Joshi N, Weckhuysen S, Cooper E, Taglialatela M. KCNQ2-related disorders. In: Adam M, Pagon R, Ardinger H, eds. *GeneReviews [online].* University of Washington; 2018. ncbi.nlm.nih.gov/books/.
31. Bhatnagar M, Shorvon S. Genetic mutations associated with status epilepticus. *Epilepsy Behav.* 2015;49:104-110. doi:10.1016/j.yebeh.2015.04.013.
32. Trivisano M, Pietrafusa N, Terracciano A, et al. Defining the electroclinical phenotype and outcome of PCDH19-related epilepsy: a multicenter study. *Epilepsia.* 2018;59(12):2260-2271. doi:10.1111/epi.14600.

33. Stamberger H, Nikanorova M, Willemsen MH, et al. STXBP1 encephalopathy. *Neurology*. 2016;86(10):954-962. doi:10.1212/wnl.0000000000002457.
34. Valente KD, Koiffmann CP, Fridman C, et al. Epilepsy in patients with Angelman syndrome caused by deletion of the chromosome 15q11-13. *Arch Neurol*. 2006;63(1):122-128. doi:10.1001/archneur.63.1.122.
35. Uemura N, Matsumoto A, Nakamura M, et al. Evolution of seizures and electroencephalographical findings in 23 cases of deletion type Angelman syndrome. *Brain Dev*. 2005;27(5):383-388. doi:10.1016/j.braindev.2004.01.009.
36. Hamad AP, Ferrari-Marinho T, Caboclo LO, Thomé U, Fernandes RMF. Nonconvulsive status epilepticus in epileptic encephalopathies in childhood. *Seizure*. 2020;80:212-220. doi:10.1016/j.seizure.2020.06.024.
37. Laan LAEM, Renier WO, Arts WFM, et al. Evolution of epilepsy and EEG findings in Angelman syndrome. *Epilepsia*. 1997;38(2):195-199. doi:10.1111/j.1528-1157.1997.tb01097.x.
38. Kløvgaard M, Lynge TH, Tsiropoulos I, et al. Epilepsy-related mortality in children and young adults in Denmark. *Neurology*. 2022;98(3):e213-e224. doi:10.1212/wnl.0000000000013068.
39. Abdel-Mannan O, Sutcliffe AG. A national surveillance study of childhood epilepsy mortality in the UK and Ireland. *Eur J Neurol*. 2020;27(2):327-333. doi:10.1111/ene.14081.
40. Ficker DM, So EL, Shen WK, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. *Neurology*. 1998;51(5):1270-1274. doi:10.1212/wnl.51.5.1270.
41. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. *Lancet Neurol*. 2013;12(10):966-977. doi:10.1016/s1474-4422(13)70214-x.
42. Keller AE, Whitney R, Li S-A, Pollanen MS, Donner EJ. Incidence of sudden unexpected death in epilepsy in children is similar to adults. *Neurology*. 2018;91(2):e107-e111. doi:10.1212/wnl.0000000000005762.
43. Harden C, Tomson T, Gloss D, 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. *Epilepsy Curr*. 2017;17(3):180-187. doi:10.5698/1535-7511.17.3.180.
44. Abdel-Mannan O, Taylor H, Donner EJ, Sutcliffe AG. A systematic review of sudden unexpected death in epilepsy (SUDEP) in childhood. *Epilepsy Behav*. 2019;90:99-106. doi:10.1016/j.yebeh.2018.11.006.
45. Carvill GL, Weckhuysen S, McMahon JM, et al. GABRA1 and STXBP1: novel genetic causes of Dravet syndrome. *Neurology*. 2014;82(14):1245-1253. doi:10.1212/wnl.0000000000000291.
46. Bonardi CM, Heyne HO, Fiannacca M, et al. KCNT1-related epilepsies and epileptic encephalopathies: phenotypic and mutational spectrum. *Brain*. 2021;144(12):3635-3650. doi:10.1093/brain/awab219.
47. Reynolds C, King MD, Gorman KM. The phenotypic spectrum of SCN2A-related epilepsy. *Eur J Paediatric Neurol*. 2020;24:117-122. doi:10.1016/j.ejpn.2019.12.016.
48. Kolc KL, Sadleir LG, Scheffer IE, et al. A systematic review and meta-analysis of 271 PCDH19-variant individuals identifies psychiatric comorbidities, and association of seizure onset and disease severity. *Mol Psychiatry*. 2019;24(2):241-251. doi:10.1038/s41380-018-0066-9.
49. Clayton-Smith J, Laan L. Angelman syndrome: a review of the clinical and genetic aspects. *J Med Genet*. 2003;40(2):87-95. doi:10.1136/jmg.40.2.87.
50. Lesca G, Rudolf G, Bruneau N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. *Nat Genet*. 2013;45(9):1061-1066. doi:10.1038/ng.2726.

Rates of Status Epilepticus and Sudden Unexplained Death in Epilepsy in People With Genetic Developmental and Epileptic Encephalopathies

Alice M. Donnan, Amy L. Schneider, Sophie Russ-Hall, et al.

Neurology 2023;100;e1712-e1722 Published Online before print February 7, 2023
DOI 10.1212/WNL.0000000000207080