

Seizure-related deaths in children: The expanding spectrum

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Abstract

Although seizures are common in children, they are often overlooked as a potential cause of death. Febrile and nonfebrile seizures can be fatal in children with or without an epilepsy diagnosis and may go unrecognized by parents or physicians. Sudden unexpected infant deaths, sudden unexplained death in childhood, and sudden unexpected death in epilepsy share clinical, neuropathological, and genetic features, including male predominance, unwitnessed deaths, death during sleep, discovery in the prone position, hippocampal abnormalities, and variants in genes regulating cardiac and neuronal excitability. Additionally, epidemiological studies reveal that miscarriages are more common among individuals with a personal or family history of epilepsy, suggesting that some fetal losses may result from epileptic factors. The spectrum of seizure-related deaths in pediatrics is wide and underappreciated; accurately estimating this mortality and understanding its mechanism in children is critical to developing effective education and interventions to prevent these tragedies.

KEYWORDS

mortality, seizures, SIDS, SUDC, SUDEP

1 | INTRODUCTION

Epilepsy has a lifetime prevalence of 7.6/1000 persons; one in 11 people has at least one lifetime seizure, and 3% develop epilepsy.¹ Adults with epilepsy have a 2.5-fold higher mortality rate and 27-fold higher rate of sudden death compared to the general population.² Premature death among epilepsy patients can result from status epilepticus, sudden unexpected death in epilepsy (SUDEP), accidents (e.g., motor vehicle), falls, drowning, adverse reactions to antiepileptic drugs, comorbidities, and suicide.³

SUDEP is the most common epilepsy-related cause of death (COD)^{2,4} and can occur with or without evidence of a seizure, but does not result from injury, drowning, status epilepticus, or other known cause. If an autopsy and clinical review does not reveal an alternative COD, it is

definite SUDEP. If the setting is typical for SUDEP but autopsy is not performed, it is probable SUDEP.⁵ SUDEP is underestimated, because the COD is often attributed to other causes.

Unwitnessed deaths in sleep, with the decedent typically found prone and with male predominance, are common to SUDEP cases as well as (1) sudden unexpected infant deaths (SUIDs), which include unexplained deaths, sudden infant death syndrome (SIDS), and deaths due to presumed suffocation; and (2) sudden unexplained death in childhood (SUDC).^{6–8} Furthermore, similar genetic and neuropathological abnormalities occur in SUID, SUDC, and SUDEP.^{9–11} (Table 1) These parallels suggest that a subset of unexpected deaths in infants and children result from unrecognized seizures for which the COD is considered unexplained or is misattributed to other causes.

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TABLE 1 Shared features, genetic associations, and pathological findings in SUID, SUDC, FS, & SUDEP

Variable	FS	SUDC	SUID	SUDEP
Clinical features				
Occurrence in sleep ⁷	Unknown	+	+	+
Prone position ⁷	n/a	+	+	+
Premature birth/low weight ⁷	+	+/-	+	Unknown
Male sex ⁷	+	+	+	+
Illness/fever shortly before death ^{7,8,22,39}	n/a	+	+	-
Maternal smoking ⁷	+	+	+	Unknown
Genetic associations				
<i>SCN1A</i> ^{11,87,90,92,103,105}	+	+	+	+
<i>SCN1B</i> ^{11,87,89,90-92,104,106-108}	+	+	+	+
<i>SCN2A</i> ^{11,87,89,90-92,104,106-108}	+	Unknown	Unknown	+
<i>SCN5A</i> ^{11,87,89,90-92,104,106-108}	-	+	+	+
<i>SCN8A</i> ^{11,89-91,107-108}	-	Unknown	Unknown	+
<i>HCN1, HCN2</i> ^{11,109-110}	+	Unknown	Unknown	+
<i>KCNQ1, KCNH2</i> ^{11,90,111}	Unknown	+ ^a	+	+
<i>RYR2</i> ^{50,78,87,112-113}	Unknown	+	+	+
Neuropathology findings				
DG bilamination ^{11,22,76,79}	+/-	+	+	+
Other structural alterations of DG ^{b,76,79,81,114}	+/-	+	+	
Extrahippocampal findings ^{10,50,78,114}	Unknown	Unknown	+	
General pathology findings				
Pulmonary abnormalities ¹¹⁵⁻¹¹⁶	Unknown	+	+	+
Cardiac abnormalities ¹¹⁶⁻¹¹⁸	Unknown	+/-	+/-	+
Seizure stigmata ^{c,10,40}	+	+/-	Unknown	+

Abbreviations: – not associated; + associated; +/- associated in some studies and not in others; FS, febrile seizures; NA, not applicable; SIDS, sudden infant death syndrome; SUDC, sudden unexplained death in childhood; SUDEP, sudden unexpected death in epilepsy.

^aWinkel et al. 2012 (Ref.111) case series included 20–28 year old patients.

^bGranule cell dispersion, ectopic cells, irregular configuration, hyperconvolution, altered thickness, i.e. any irregularity other than DG bilamination.

^cTongue biting, incontinence, aspirated gastric contents.

2 | SUDDEN UNEXPECTED DEATH IN EPILEPSY

SUDEP has an annual incidence of 1.16/1000 in epilepsy patients, who have up to a 35% lifetime risk.¹² The strongest SUDEP risk factor is a history of convulsive seizures,¹³ as epilepsy monitoring unit-recorded and witnessed SUDEP usually follows generalized tonic-clonic seizures.^{6,14} Whereas the American Academy of Neurology (AAN) 2017 practice guideline indicated a lower SUDEP incidence in children (0.22/1000 patient-years) than adults (1.2/1000 patient-years),¹⁵ two recent population-based studies in Canada and Sweden¹⁶ found similar rates (~1.1/1000 patient-years). This variability is likely due to the AAN's meta-analysis including

studies using older SUDEP criteria,^{5,17} whereas newer studies rely on Nashef 2012.¹⁷

2.1 | SUDEP is underestimated

SUDEP is more commonly recognized by epileptologists than by medical examiners/coroners.¹⁸ Medical examiners and coroners often identify alternative causes of death in "definite" or "probable SUDEP" cases and do not consider "possible SUDEP" if competing CODs exist.^{19–21} When certifying the COD in an epilepsy patient with no alternative COD, 83.5% of pathologists accept SUDEP as a valid COD, yet only 22.9% attribute such deaths to SUDEP.²¹

Nonpathologists (e.g., coroners, nonpathologist physicians in the United States) are even less likely to diagnose SUDEP when no other COD is identified.²¹ Underrecognition of SUDEP and other epilepsy-related causes of death may result from many factors, including inadequate resources or methods to identify a history of epilepsy, lack of standardization in COD determination, and a bias toward pathoanatomic CODs demonstrable at autopsy (e.g., atherosclerotic cardiovascular disease), toxicology (e.g., low-dose benzodiazepines in a habitual user), or cardiac arrhythmias.^{19,21}

2.1.1 | Failure to identify a history of epilepsy

SUDEP may be missed as a possible COD due to a missing epilepsy history or failure to diagnose epilepsy earlier in life. Diagnosing epilepsy can be challenging, as a physician must distinguish between seizures and other neurological, medical, or psychiatric disorders, and between provoked and unprovoked seizures. Postmortem medical record review and history from close contact is often lacking, and when present, can lead to misdiagnosis. Neuroimaging and electroencephalograms (EEGs) can support or confirm epilepsy, but normal neuroimaging and EEGs occur in many epilepsy patients. In a study of sudden unexplained deaths, a seizure history was available in less than one half of cases.²² Furthermore, some patients have seizures due to psychiatric disorders—paroxysmal nonepileptic seizures—a group that also has a 2.5-fold elevated mortality rate.²³

2.1.2 | Bias toward attributing COD to a physical finding

Accurate COD determination is challenged by the need to distinguish disease processes that a patient dies with versus those that a patient dies from. The autopsy is one piece of hypothesis-directed data collected to determine COD and assess nonnatural causes. Autopsy and toxicology are heavily weighted data points, and when clinical data are meager, pathologists favor diagnoses supported by structural gross or microscopic pathological or toxicologic findings.²² This notion is supported by higher COD accuracy when there are associated physical findings,²⁴ biasing pathologists toward testable hypotheses. This diagnostic bias overrepresents CODs such as cardiovascular diseases, with large disagreement between clinical and pathological diagnoses or between pathologists in different countries.²⁵ This creates a diagnostic bias against physiological disorders that lack structural abnormalities; seizures cause no pathognomonic anatomical findings, and thus SUDEP may not be considered. When an autopsy and toxicologic studies fail to identify an anatomic COD in a person with epilepsy, the default COD is often cardiac, even in cases later determined to be SUDEP.^{21,26}

2.1.3 | Variability in COD determination across regions

There is marked variability in approaching death certification across regions, leading to differences in the frequencies of reported CODs.²⁵ A comparison of two mortality reports support that SUDEP underrecognition is partially attributable to variable methods of COD determination; adult epilepsy patients in Finland with comprehensive review of clinical records, death investigations, and autopsies²⁷ found a rate of SUDEP 260 times higher than an epilepsy cohort from Ohio identified from death certificate data.²⁸

2.1.4 | Necessity of autopsies

Multiple hospital autopsy series report discrepancies between clinical and pathological diagnoses, and reveal new information in >25% of cases.²⁹ Without autopsies, forensic pathologists reach the incorrect COD in ~30% of cases, overestimating common diseases^{30,31} (e.g., cardiovascular COD prevalence is 10%–15% higher in decedents without autopsy).^{30,31} An autopsy is not always performed in adults if the circumstances indicate the manner of death is likely to be natural.³¹ Although autopsies are the diagnostic "gold standard," they are biased to identify structural CODs; ancillary testing such as molecular studies can identify pathogenic mutations (e.g., *SCN5A*, *RYR2*) in some otherwise unexplained natural deaths.³²

2.1.5 | Restrictive diagnostic systems

SUDEP excludes sudden deaths due to status epilepticus (duration > 10–30 min), febrile seizures (enriched in SUDC), a first unprovoked seizure, or a recurrent provoked (e.g., alcohol withdrawal) seizure.^{17,33,34} However, some deaths attributed to status epilepticus may be SUDEP and vice versa. This definition obscures the continuous spectrum of seizure-induced deaths. Insights into SUDEP pathophysiology could be gained by studying seizure-related deaths at the two extreme ends of severity: prolonged seizures (i.e., status epilepticus) and individuals with a single or provoked seizure (Table 1).

3 | SUDDEN UNEXPLAINED DEATH IN CHILDHOOD

SUDC affects children (1–18 years old) who die suddenly where no COD is identified after a complete clinical review of autopsy and ancillary tests.³⁵ SUDC affects ~400 US children and adolescents annually and is most common

between 1 and 4 years of age.^{35,36} SUDC is more frequent in boys between 1 and 3 years old,^{35,37,38} with an average age of 20 months.^{39,40} Deaths are rarely witnessed and usually occur in sleep with the child found in the prone position.^{7,40} Cases are more frequent during weekends and the winter.^{7,38} Illness or fever in the 72 h before death is associated with SUDC and SUID.^{7,8,22,38} A third of SUDC cases have a history of febrile seizures,^{7,35} making the febrile seizure prevalence among SUDC cases >10-fold higher than in the general population.

3.1 | SUDC is underfunded and underresearched

SUDC is underfunded and underresearched. SUID/SIDS has received about 500-fold higher funding from federal agencies than SUDC despite having a frequency only fourfold higher.⁴¹ SUID had received more than \$400 million in funding from the National Institutes of Health and Centers for Disease Control and Prevention (CDC) in the past 2 decades, whereas SUDC has never received specific funding from either institution.⁴¹ The US National Library of Medicine lists less than 50 papers on SUDC, compared to more than 16,000 on SUID/SIDS and more than 25,000 on sudden death in adults.⁴²

3.2 | Variability in autopsies and COD misattribution

Postmortem protocols to investigate and report pediatric sudden deaths vary greatly between medical examiner and coroner offices, with differences in neuropathologist involvement and extent of brain sampling.²² Children who die after a seizure may have no evidence at autopsy that a seizure occurred.¹⁹ Some pathological changes are not specific (e.g., pulmonary edema), subtle, or of uncertain significance (e.g., granule cell dispersion in hippocampus).⁴³ These factors paired with the desire for many pathologists to "find an answer" lead many SUDC cases to be misattributed to nonlethal causes such as mild upper respiratory tract infections.⁴¹

3.2.1 | Seizures are underrecognized as a cause of SUDC

Seizures affect 4%–10% of children, with ~150,000 US children experiencing a first seizure each year.⁴⁴ In young children, seizures may lack classic signs (e.g., staring, arm stiffening, mouth/eye movements, tongue-biting), making diagnosis more difficult.^{39,45,46} Febrile seizures occur with illness or fever of $\geq 100.4^{\circ}\text{F}$ in infants and children without

central nervous system infection up to ages of 5–6 years.⁴⁷ Most febrile seizures occur at between 1 and 3 years, the peak age of SUDC.³⁶ Febrile seizures preceding SUDC parallel terminal events in SUDEP, suggesting similar mechanisms. Convulsive seizures are the strongest risk factor for SUDEP, and most febrile seizures are convulsive.^{3,6} Terminal fevers or illness occurs within the 48–72 h before death in many SUDC cases,^{7,8,22,38} and terminal seizures are often observed in witnessed SUDEP.

Febrile seizures occur in ~3% of children between the ages of 6 months and 6 years,^{7,48} but approximately one third of SUDC cases have a history of febrile seizures.^{7,35,40,49} At the median age of SUDC, less than 2% of children in the general population have febrile seizures, making their rate in the SUDC population ~15-fold higher. This high relative risk (e.g., lung cancer develops 15–30-fold more often in smokers) suggests a pathogenic relationship between febrile seizures and SUDC, although selection bias cannot be excluded. This relation is also supported by similarities in demographics (male predominance), scenario (death in sleep, found prone), and neuropathological findings (see below) between SUDC and SUDEP. Just as convulsive seizures precede SUDEP, we hypothesize that febrile seizures precede many cases of SUDC.

4 | SUDDEN UNEXPECTED INFANT DEATH

SUID is the sudden and unexpected death of an infant less than 12 months old without an obvious COD before investigation. The CDC defines SUID as including accidental asphyxiation or suffocation, unknown causes, and SIDS, in which the COD remains unexplained after a review of the clinical history, circumstances of death, and autopsy. Of the 3,500 SUID cases in the United States annually, SIDS is a leading cause, affecting ~1300 children each year. Among SUID cases, 95% occur in the first 6 months of life, with a peak at 2–4 months.⁵⁰ Like SUDEP and SUDC, SUID is unexpected in nature, often unwitnessed, most frequent in sleep with the infant found prone, and with no alternative COD on autopsy.^{51,52} Like SUDC, SUID has an association with illness or fever before death.^{7,8}

4.1 | Seizures are underrecognized as a cause of SUID

SUID case investigations may not satisfy current guidelines for comprehensive investigations. These lapses may result from investigation by nonpathologists, lack of autopsy, or missing toxicology, microbiology, and radiology reports.^{53–56} A cause other than SUID could be listed in $\geq 25\%$ of cases,^{57,58}

suggesting seizures may represent a subset of these misdiagnosed deaths.

4.1.1 | Neuropathological review is variable and frequently inadequate

SUID cases often do not undergo comprehensive neuropathological examination because of nonuniform access to neuropathology expertise, financial restraints, and nonstandardized postmortem analyses.^{22,59} Among SUID cases in which brains were examined by neuropathologists, 38% had abnormalities that could have contributed to death.⁶⁰ By contrast, when nonneuropathologists were primarily involved in brain examinations, only 6% had findings that contributed to death.⁶¹ This suggests that brain findings implicating seizures as a COD are underrecognized when examinations are performed by nonexperts.

4.1.2 | Seizures in infancy are atypical in nature

Seizures in infancy are often atypical and more difficult to diagnose. Neonatal seizures often lack the clinical signs present in older children and adults, with generalized tonic-clonic activity infrequently observed.⁶² The only signs of epileptic activity in infants may be subtle eye and mouth movements, hypoxemia, or apnea.⁶² These minor motor or nonmotor features can also occur in febrile seizures.

Febrile seizures

Researchers have long hypothesized that infant cot deaths could be attributed to overheating that provokes febrile apnea or seizures.⁶³ Sleep states modify the hypothalamic regulation of temperature⁵¹; these temperature changes can impact respiration, trigger apnea, and increase seizure risk. For example, in young rats, raising the temperature in hippocampal slices induces epileptic activity.⁶⁴ Hyperthermia can result from infection, sleeping in the prone position, or heavy wrapping of infants, common findings in SUID cases.⁶³

Elevated temperature in fever and febrile illness can cause convulsions and other seizure types in children older than 6 months. Similar to their role in SUDC, febrile seizures may underlie a subset of SUID cases, with infants younger than 6 months not showing overt clinical signs of febrile seizure despite a similar mechanism leading to death. Similarly, young kittens develop fever leading to lethal apnea without clinical or EEG signs of convulsions.⁴⁷ However, fever has differential effects depending on age, with younger kittens dying suddenly and older kittens first showing convulsive activity,⁴⁷ consistent with mild or absent ictal clinical signs in infants compared to older children. Autopsy of young kittens' brains

showed no cellular changes, suggesting not enough time had passed for histological changes to develop.⁴⁷ The absence of cellular changes despite the febrile seizure-induced death suggests that if a febrile seizure caused an infant death, it could be indistinguishable from other SUIDs.

Hypoxemia and apnea as signs of seizure

Hypoxemia and apnea are implicated in SUID pathophysiology, and can be primary seizure manifestations in infants and young children.^{45,46} Apnea may escape parental detection if brief, unwitnessed, or lacking cyanosis, making these seizures difficult to diagnose and sometimes only identified with concurrent EEG and respiratory monitoring.

Acute/apparent life-threatening events (ALTEs), SUID, and seizures share connections. ALTEs include episodes of apnea, changes in complexion or in muscle tone, and choking or gagging. ALTEs are involved in ~12% of SUID cases,⁶⁵ and seizures in 6%–16% of ALTEs.⁴⁶ Epilepsy-induced hypoxemia may be associated with an initial EEG change followed by apnea, then hypoxemia, and sometimes sinus tachycardia.⁴⁶ If a child in a hospital setting suddenly stops breathing with oxygen desaturation and tachycardia before death, the COD is likely determined to be cardiac arrhythmia. However, EEG monitoring may have revealed seizures discharges correlating with the apneic period even without clinical signs of epilepsy.⁶⁶ This subset of SUID cases closely mirror the sequence in SUDEP in which a seizure provokes respiratory distress and/or cardiac arrhythmia.^{52,65} Some SUID deaths may result from seizures, especially if seizures are predominantly in sleep, of febrile nature, or first instance, or have subclinical or atypical features.

The role of terminal unwitnessed seizures in SUID is supported by several cases. One healthy 8-month-old boy was discovered seizing and in respiratory distress while sleeping prone, brought to the hospital where seizures were diagnosed, and declared brain dead 2 days later.⁶⁷ In another case, a 20-month-old girl with a chromosomal disorder was admitted with febrile status epilepticus.⁶⁸ Her sudden death 2 days later was recorded on video-EEG; 10 min before death, her EEG showed diffused attenuation similar to the EEG changes before SUDEP.^{14,68} However, these cases are unique in that they were either witnessed or recorded with video-EEG. We hypothesize that many other sudden infant and toddler deaths result from similar epileptic mechanisms, yet escape recognition.

5 | PRENATAL CORRELATES

Spontaneous abortions occur in 10%–20% of all pregnancies,^{69,70} but are enriched in those of women with a personal and/or family history of epilepsy. Compared to their same-sex siblings, men and women with epilepsy have higher rates

of spontaneous abortions if their epilepsy was early onset, and risk decreased with increasing parental age of onset.⁷¹ In a study of 75 families with a child with seizures, 60% had at least one fetal or infant death.⁷²

5.1 | Does genetic susceptibility to epilepsy increase risk of spontaneous abortions?

A maternal history of spontaneous abortions is associated with increased epilepsy risk in future offspring. Comparing mothers of children with febrile or nonfebrile seizures before age 6 years to controls whose children had no seizures, mothers of children with seizures had more early fetal deaths (19.1% in febrile group vs. 12.2% of their controls, 16.8% in nonfebrile group vs. 7.9% of their controls).⁷³ Another group found that children of women with a history of spontaneous abortions had a 4.5-fold higher risk of developing epilepsy than children of women without a history of spontaneous abortion. Among mothers with histories of spontaneous abortion and family epilepsy, the cumulative incidence of epilepsy in their offspring was fivefold higher than among mothers who had neither history.⁶⁹

There are several potential explanations for increased spontaneous abortions among women with epilepsy. Intrauterine exposure to antiseizure medications and gestational seizures may increase risk, although evidence refutes that either factor could fully account for the association.⁷⁴ An alternative explanation is the in utero death of fetuses with a genetic susceptibility to epilepsy, manifesting in spontaneous abortions. However, most genetic epilepsy variants permit full-term pregnancies with children who have an increased risk of epilepsy. We hypothesize a weak to modest selection against fetuses harboring epilepsy genes, with milder variants allowing full-term pregnancies with children who have an increased risk of epilepsy, and more pathogenic variants increasing the rate of spontaneous abortion. This is supported by the finding that spontaneous abortion risk decreased with increasing age of parental epilepsy onset, linking later onset (less severe genotype) with lower risk of in utero death.⁷¹

6 | NEUROPATHOLOGY ASSOCIATED WITH SUDDEN DEATH

Neuropathological studies of SUID and SUDC reveal findings in some cases that are consistent with prior seizures, even in cases without a history of epilepsy or witnessed seizure. Most abnormalities involve the hippocampus, which is implicated in up to 40%–60% of SUID and SUDC^{9,11,22,40,75–77} as well as SUDEP.²²

6.1 | Dentate gyrus of the hippocampus

The most common hippocampal changes in seizure-related pediatric deaths involve the dentate gyrus (DG), a region involved in episodic memory formation. The DG has three cell layers, with the granule cell layer in the middle. DG abnormalities in unexplained pediatric deaths include ectopic cells in the molecular layer or hilus, granule cell dispersion, irregular configuration, bilamination (two layers of granule cells), granule cell loss, hyperconvolution, and altered thickness.^{9,40,78}

The most frequent hippocampal change in one series of sudden death across the age spectrum of SIDS and SUDC was DG bilamination,⁹ a finding also associated with SUDEP. In a SUID-specific series, bilamination was found in 41.2% of unexplained infant deaths and in 7.7% of explained deaths.⁷⁵ In a 10-month-old boy whose death resembled SUID (sleep-related, prone position, illness within 2 days of death) with unrevealing autopsy and clinical investigation, neuropathology revealed hippocampal asymmetry and DG microdysgenesis with focal bilamination.⁷⁹ In a retrospective study of SUDC cases, DG bilamination was found in 43.5% of SUDC cases compared to 13% of controls.⁴⁰ These DG changes mirror histologic findings in adult cases of temporal lobe epilepsy and SUDEP.^{22,80}

6.2 | Hippocampal alterations and sudden death

Hippocampal alterations are the most common neuropathologic finding associated with SUDC, and in some cases are associated with a history of febrile seizures and fever shortly before death.^{9,22,40,75,78,81} One hypothesis characterizes a constellation of histological changes as “hippocampal malformation associated with sudden death” (HMASD) and draws connections between hippocampal maldevelopment, febrile seizures, and sudden death. Among 151 SUDC cases, the most frequent observations were focal DG granule cell bilamination, hippocampal asymmetry, and malrotation in 48% of SUDC cases versus in 13% of cases with an explained COD.⁷⁸ Febrile seizures were enriched in HMASD, with 62% having a personal or family history of febrile seizures.⁷⁸ An earlier study found that 82% of children with hippocampal and temporal lobe abnormalities had an individual or family history of febrile seizures.⁷⁶ A related hypothesis characterizes hippocampal lesions in sudden unexplained death as “hippocampal formation maldevelopment in SUDP” (sudden unexplained death in pediatrics–hippocampal focal malformation [SUDP-HFM]), with abnormalities in the hippocampus (often focal dentate bilamination) or subiculum (inferior hippocampal formation).⁹

However, many studies linking DG bilamination to SUID or SUDC are retrospective and suffer selection bias as well as a lack of suitable controls, with most reports coming from a single group. A prospective and blinded SUDC study from another group found hippocampal alterations were common, but did not find a significant difference between hippocampal pathology in explained versus unexplained cases.⁴⁹ Thus, hypotheses linking hippocampal abnormalities and sudden unexplained deaths remain unproven, and the differences between SUID/SUDC cases and explained cases has yet to be replicated in a prospective blinded study.

The neuropathologic changes in SUDP may correlate with mechanisms of seizure-related death. For instance, hippocampal alterations may cause or result from a developmental susceptibility to seizures. The alterations seen in HMASD and SUDP-HFM could be due to migration of granule cells without subsequent proliferation; over time, these abnormalities may predispose to seizures and epilepsy in susceptible children.⁷⁸ Alternatively, hippocampal changes may result from febrile seizures, but this cannot explain the 38% of children with HMASD without a personal or family history of febrile seizures,⁷⁸ unless seizures were unwitnessed or had subtle manifestations. Mouse models support DG pathology as either a cause or consequence of seizures; granule cell abnormalities can cause defective synaptic connectivity, leading to hyperexcitability and increased risk of seizure activity⁸²; alternatively, inducing seizures can cause granule cell dispersion.⁸³

7 | KEY GENETIC ASSOCIATIONS

Several genes may contribute to epilepsy and sudden unexpected death in children and adults, with specific variants enriched in SUDEP, SUDC, and SUID.

7.1 | Voltage-gated sodium channels

Voltage-gated sodium channels (VGSCs) are a conserved family of genes coding for ion channel proteins in the nervous system and heart. The family is comprised of nine pore-forming α -subunits (*SCN1A–5A*, *SCN8A–11A*) and five β -subunits (*SCN1B–4B*, fetal *SCNB1B*). VGSC pathologic variants are associated with neurological and cardiac disorders and have been implicated in SUDEP, SUID, and SUDC.

7.1.1 | VGSC variants are associated with epilepsy

SCN1A is an important epilepsy gene expressed in both the brain and heart. It encodes the VGSC Na_v1.1 and can cause

a range of epilepsies, from mild febrile seizures to genetic epilepsy with febrile seizures plus to the severe epileptic encephalopathy Dravet syndrome. Dravet syndrome usually results from truncating or other loss-of-function *SCN1A* mutations and is associated with a 20% mortality rate by early adulthood, mainly from SUDEP and status epilepticus.^{11,84} *SCN1A* mutations are enriched in SUDEP cases,^{85,86} and mouse models of Dravet syndrome with *SCN1A* mutations (as well as potassium channel gene mutations) show a lower threshold for seizures resulting in death.^{85,87} Beyond *SCN1A*, variants in the VGSC genes *SCN1B*, *SCN2A*, *SCN5A*, and *SCN8A* also occur in SUDEP cases.^{11,86,88–90}

7.1.2 | VGSC variants are associated with sudden unexpected death in pediatrics

Pathogenic VGSC variants occur in SUID and SUDC and may contribute to death via effects on the heart and brain. *SCN5A*, *SCN1B*, and *SCN1A* are most often found in SUID and SUDC.^{11,86,88–90} In a very small SUID cohort, 60% had *SCN1A* mutations and most showed lower current density consistent with a partial loss of function.¹¹ VGSC variants, especially in *SCN5A*, may predispose children to sudden death via cardiac arrhythmias.⁹⁰ In whole-exome sequencing analysis of 73 cases of pediatric sudden unexpected death, "pathogenic" or "likely pathogenic" variants were found in 11 brain/cardiac VGSC genes.⁹¹

7.1.3 | VGSC variants are associated with neuropathologic changes implicated in sudden death

VGSC-related epilepsies are also associated with neuropathologic abnormalities. Of the 11 VGSC variants in sudden unexpected pediatric deaths, seven subjects had hippocampal abnormalities and one had a history of febrile seizures.⁹¹ *SCN1A* in particular has been linked to hippocampal sclerosis and DG granule cell dispersion. In two thirds of the SUID cases with *SCN1A* mutations, infants also showed DG bilamination.¹¹ These findings tie the VGSC family of genes to the neuropathological features associated with sudden unexplained death.

Given the deepening connections between VGSCs, hippocampal lesions, seizures, and sudden death, it is likely that SUID and SUDC cases with pathogenic VGSC mutations died from seizures, arrhythmias, or both. Yet many SUID and SUDC cases with DG lesions or *SCN1A* mutations do not have a history of epilepsy.^{9,11,91} It is possible that some of these cases had unwitnessed or unrecognized seizures, implicating them in sudden childhood death even when never observed or diagnosed. Biomarkers of prior lifetime seizure,

such as alterations in DNA methylation or DG abnormalities, may support our hypothesis that a subset of sudden pediatric deaths result from unrecognized seizures. However, there are currently no molecular biological pathognomonic signatures of seizures that can be identified from brain tissue examination.

Other brain–heart genes

Other genes implicated in epilepsy and SUDEP include *KCNA1*, which encodes the voltage-gated potassium channel $K_v1.1$; *HCN1* and *HCN2*, which encode hyperpolarization-activated cyclic nucleotide-gated cation channels; and *PRRT2*, which encodes a proline-rich transmembrane protein identified in an early onset seizure disorder.⁹² Other genes implicated in cardiac arrhythmias and SUDEP include long QT syndrome genes such as *KCNQ1* and *KCNH2*, which encode potassium channels; and *RYR2*, which encodes a ryanodine receptor for intracellular calcium release.⁹² *KCNQ1* encodes the cardiac K_vLQT1 delayed rectifier channel, in which mutations can cause both long QT syndrome and epilepsy.⁹³ The terminal sequence of events in SUDEP often involves changes in the brain and heart, linking these genes to the mechanism of sudden unexpected death.

8 | MECHANISMS OF DEATH

The presence of hippocampal abnormalities coupled with genetic variants underlying epilepsy and cardiac arrhythmias suggests that sudden death may result from aberrant excitability in either the brain or heart. A diathesis toward fever-induced or non-fever-related seizures could cause death directly from ictal or postictal hypoxia, which can be complicated by cardiac arrhythmias. Hippocampal maldevelopment could be a primary problem predisposing to epilepsy, a consequence of seizures, or both. An epileptiform hippocampal lesion triggering sudden death without clinical seizures may be “epilepsy in situ.”⁹⁴ However, once it develops, it may increase the probability of ictal/postictal-related autonomic dysfunction with apnea, and impaired arousal and reflexive responses to hypercapnia. The subtlety of seizures in infants and young children, the tendency toward ictal-induced apnea in this age group, and the vulnerability during sleep when arousal is depressed make this a “perfect and lethal storm.”^{6,95,96}

8.1 | Respiratory dysfunction

When SUDEP is recorded in epilepsy monitoring units, the typical pattern is one or more generalized tonic–clonic seizure(s), tachycardia, and hyperventilation, then decreased respiration rate, and finally bradycardia and EEG suppression

with terminal apnea and asystole.¹⁴ SUDEP, SUDC, and SUID patients are often found prone during sleep, a position that reduces the threshold for postictal hypoxemia and EEG suppression, classic correlates of depressed brain function.⁹⁷

8.2 | Cardiac arrhythmias

Seizures can cause tachycardia, bradycardia, shortening or prolongation of QT intervals, and more serious atrial and ventricular tachyarrhythmias. Bradycardia is followed by apnea in monitored pediatric SUDEP⁶⁸ and occurs with seizures in animal models.⁸⁵ QT prolongation is associated with increased susceptibility to cardiac arrhythmias and sudden death.⁹⁸ Long QT syndrome has similarities to SUDEP, with both showing a male predominance, a pathologically normal heart after death, and QT interval changes on electrocardiograms obtained during earlier hospital stays.^{89,99} Arrhythmias occur in sudden cardiac death (SCD), and one study found a twofold higher frequency of febrile seizures in cases of SCD in children and young adults, with the most common COD after negative autopsy listed as an arrhythmia.¹⁰⁰

8.3 | Hypothesized sequence of events

Unwitnessed or rarely witnessed seizures during sleep may lead to some SUDC and SUID deaths as well as SUDEP cases misattributed to other CODs. Precipitating events include fevers and/or febrile seizures, sleep in the prone position (increased risk of hypoxemia and seizures), and even sleep itself (altered hypothalamic control),^{9,78,81} factors that are reflected in the circumstances of sudden unexplained deaths. The precise brain mechanisms, such as spreading waves of depression⁸⁵ or ictal spread to brain stem structures,¹⁰¹ are well supported in animal models but remain uncertain in children with epilepsy or febrile seizures.

In seizure-related pediatric deaths, the terminal seizure may be followed by autonomic dysfunction with apnea, impaired arousal and reflexive responses to hypercapnia/hypoxia, and finally cardiorespiratory arrest. This well-established SUDEP sequence is supported by the high frequency of DG abnormalities and ~15-fold increased febrile seizure prevalence in SUDC, but remains speculative in the cases of SUID and miscarriage.

9 | CONCLUSIONS

Seizures may be a more frequent cause of sudden pediatric deaths than is recognized. SUDEP rates are underestimated in all epilepsy patients, including infants and children. In children without a diagnosis of epilepsy or those with

well-controlled or infrequent seizures, seizures may not be considered as a COD or contributing COD. Yet the striking clinical overlaps between the settings of SUDEP, SUDC, and SUID and the parallel abnormalities in neurocardiac genes and neuropathology suggest that shared mechanisms apply across the spectrum of childhood, and perhaps extend into uterine life. It is essential that we begin to more accurately estimate the role of seizures in pediatric mortality, elucidate their mechanisms, and develop effective interventions to prevent these tragedies. We recommend that future prospective studies follow large complex febrile seizure cohorts to identify subsequent sudden deaths for a nested case–control series. Once neuropathological biomarkers of epilepsy or recent seizures are identified, these could provide more direct evidence of seizure-induced deaths.

CONFLICT OF INTEREST

J.H. has nothing to disclose. L.C., D.M., and O.D. are involved in the New York University Sudden Unexplained Death in Childhood Registry and Research Collaborative study, but there is no financial compensation.

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How to cite this article: Harowitz J, Crandall L, McGuone D, Devinsky O. Seizure-related deaths in children: The expanding spectrum. *Epilepsia.* 2021;62:570–582. <https://doi.org/10.1111/epi.16833>