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Epileptic Disorders

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ILAE Genetic Literacy Series: Postmortem Genetic Testing in Sudden Unexpected Death in Epilepsy

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Abstract

A 24-year-old man with non-lesional bitemporal lobe epilepsy since age 16 years was found dead in bed around midday. He was last seen the previous night when he was witnessed to have a tonic–clonic seizure. Before his death, he was experiencing weekly focal impaired awareness seizures and up to two focal-to-bilateral tonic–clonic seizures each year. He had trialed several antiseizure medications and was on levetiracetam 1500 mg/day, lamotrigine 400 mg/day, and clobazam 10 mg/day at the time of death. Other than epilepsy, his medical history was unremarkable. Of note, he had an older brother with a history of febrile seizures and a paternal first cousin with epilepsy. No cause of death was identified following a comprehensive postmortem investigation. The coroner classified the death as "sudden unexpected death in epilepsy" (SUDEP), and it would qualify as "definite SUDEP" using the current definitions.[1] This left the family with many questions unanswered; in particular, they wish to know what caused the death and whether it could happen to other family members. Could postmortem genetic testing identify a cause of death, provide closure to the family, and facilitate cascade genetic testing of first-degree family members who may be at risk of sudden death? While grieving family members struggle with uncertainty about the cause of death, we as clinicians also face similar uncertainties about genetic contributions to SUDEP, especially when the literature is sparse, and the utility of genetic testing is still being worked out. We aim to shed some light on this topic, highlighting areas where data is emerging but also areas where uncertainty remains, keeping our case in mind as we examine this clinically important area.

KEYWORDS
arrhythmia, risk factor, SUDEP

[Correction added on 19 July 2023, after first online publication: The word Postmorterm has been changed to Postmortem in the title].

See Appendix 1 for the ILAE Genetics Commission.

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1 | CASE REPORT

A 24-year-old man with non-lesional bitemporal lobe epilepsy since age 16 years was found dead in bed around midday. He was last seen the previous night when he was witnessed to have a tonic–clonic seizure. Before his death, he was experiencing weekly focal impaired awareness seizures and up to two focal-to-bilateral tonic–clonic seizures each year. He had trialed several antiseizure medications and was on levetiracetam 1500 mg/day, lamotrigine 400 mg/day, and clobazam 10 mg/day at the time of death. Other than epilepsy, his medical history was unremarkable. Of note, he had an older brother with a history of febrile seizures and a paternal first cousin with epilepsy. No cause of death was identified following a comprehensive postmortem investigation. The coroner classified the death as "sudden unexpected death in epilepsy" (SUDEP), and it would qualify as "definite SUDEP" using the current definitions.[1] This left the family with many questions unanswered; in particular, they wish to know what caused the death and whether it could happen to other family members.

Could postmortem genetic testing identify a cause of death, provide closure to the family, and facilitate cascade genetic testing of first-degree family members who may be at risk of sudden death?

While grieving family members struggle with uncertainty about the cause of death, we as clinicians also face similar uncertainties about genetic contributions to SUDEP, especially when the literature is sparse, and the utility of genetic testing is still being worked out. We aim to shed some light on this topic, highlighting areas where data is emerging but also areas where uncertainty remains, keeping our case in mind as we examine this clinically important area.

Key points

- Sudden unexpected death in epilepsy (SUDEP) can be classified as definite, definite plus, probable, or possible SUDEP.
- A major risk factor for SUDEP is the presence and frequency of generalized tonic–clonic or focal-to-bilateral tonic–clonic seizures.
- The genetic contribution to SUDEP remains unclear.
- Postmortem investigation cannot distinguish between SUDEP and unexplained sudden cardiac death.
- The utility of genetic testing in SUDEP is uncertain, and it should be performed in a research setting.

2 | SUDEP INCIDENCE, RISK FACTORS, AND POSSIBLE PATHOLOGICAL MECHANISMS

SUDEP is the most common epilepsy-related cause of death in people with epilepsy. It is defined as a "sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death."[1] As such, SUDEP is a diagnosis of exclusion of all competing causes of death since there is no specific diagnostic hallmark.[2] Postmortem investigation may show abnormal neuropathology in the brain, the heart may show minor changes, such as mild myocyte hypertrophy and myocardial fibrosis, and the respiratory system may show non-specific findings of pulmonary oedema, congestion, and hemorrhage. Still, these do not necessarily account for sudden death.[3–5] SUDEP is classified based on the circumstances of death and postmortem investigation findings.[1] "Definite SUDEP" meets the SUDEP definition, whereas "definite SUDEP plus" is used if there is a concomitant condition that may have contributed to the death, such as long QT syndrome. "Probable SUDEP" is an unexpected sudden death in a person with epilepsy for whom a postmortem examination was not performed, and "possible SUDEP" is used if there is a competing cause of death, such as the person is found dead in water but there is no confirmation of drowning found at postmortem investigation.

The incidence of SUDEP in children is estimated to range from .22 to 1.17 per 1000 patient-years and in adults the estimate is 1.2 per 1000 patient-years (95% CI .64–2.32), but varies according to the age range and epilepsy population studied.[6,7] Specifically, estimates range from 6.3 to 9.3 per 1000 patient-years in epilepsy surgery candidates to 1.1–5.9 per 1000 patient-years in epilepsy clinic populations and .35–2.3 per 1000 patient-years in community-based populations.[8] A major risk factor for SUDEP is the presence and frequency of generalized tonic–clonic or focal-to-bilateral tonic–clonic seizures. A systematic review found that the risk of SUDEP increased by fivefold in people with one or two tonic–clonic seizures per year and by 15-fold in people with three or more tonic–clonic seizures per year.[6] The deaths usually occur in individuals living alone, during the night, unwitnessed, in the prone position, and with an indication of a preceding seizure, supporting the critical role of lack of nocturnal supervision.[9]

The mechanisms underlying SUDEP are unknown, but current lines of investigation focus on a spectrum of neuronal, cardiac, and respiratory dysfunction, either in

isolation or combined, particularly in the immediate aftermath of a tonic–clonic seizure. The investigation of SUDEP cases occurring during video-EEG monitoring points to SUDEP primarily following an early post-ictal, centrally mediated, severe respiratory, and cardiac dysfunction induced by a tonic–clonic seizure. This can lead to immediate death or a short period of partly restored cardiorespiratory function with subsequent terminal apnea and then cardiac arrest.[10] SUDEP does not always occur in the immediate aftermath of a seizure and it is likely that there are many different contributing factors.[11]

3 | DO GENES INFLUENCE SUDEP RISK?

It is currently unclear if a genetic contribution to SUDEP risk exists. There are very few reports of more than one SUDEP case occurring within families[12,13] and no genes have been established to cause SUDEP. However, some genetic epilepsies have a high incidence of SUDEP (see below) and genetic generalized epilepsies are overrepresented in the North American SUDEP registry.[14] Several case reports and research-based cohort studies with genetic analysis of SUDEP have explored a possible genetic basis, but they come with caveats. Studies differ in the ascertainment of SUDEP cases and the extent of neurological investigations performed during life. SUDEP is rare, and the number of cases with genetic testing available, or sufficient DNA for postmortem genetic testing, is typically low. There is wide variability in the investigated genes, and under-reporting of negative findings likely occurs. Another issue is that investigations in this field often lack controls, such as matched living epilepsy patients or those who died from other causes, to compare the "background genetic noise." Despite these shortcomings, genetic studies in SUDEP might provide clues as to whether genes influence SUDEP risk.

4 | EPILEPSY GENE VARIANTS FOUND IN SUDEP

Research-based genetic studies in SUDEP occasionally find variants in genes causing epilepsies associated with frequent tonic–clonic seizures, which is perhaps not surprising given that tonic–clonic seizures are the most important identified SUDEP risk factor. A key challenge with interpreting the genetic findings in SUDEP is that it is unknown whether an identified genetic variant in an epilepsy gene heightens SUDEP risk above that contributed by the seizures alone. This is exemplified in Dravet syndrome, a severe developmental and epileptic encephalopathy with a high SUDEP rate of 9.3 per 1000 person-years (98% CI 4.4–19.4).[2] Pathogenic variants in the alpha-1 neuronal voltage-gated sodium channel subunit $Na_v1.1$ gene, *SCN1A*, are found in most Dravet syndrome patients and individuals with Dravet syndrome who died of SUDEP. While it may be tempting to speculate that *SCN1A* is a "SUDEP gene", tonic–clonic seizures are the most frequent seizure type in *SCN1A*-Dravet syndrome and they could be the primary contributing factor to SUDEP.[15] Another neuronal voltage-gated sodium channel subunit, $Na_v1.6$, encoded by *SCN8A*, is associated with developmental and epileptic encephalopathies, and these patients have a SUDEP rate of 2.8 per 1000 person-years (98% CI 2.81–2.87).[16] *SCN8A* developmental and epileptic encephalopathy is typically associated with seizures, including tonic–clonic seizures, refractory to antiseizure medications.[17] Again, this makes it challenging to distinguish between contributions to SUDEP risk by severe seizures and possible genetic contributions.

SUDEP has been also reported in people with epilepsy due to variants in the *DEPDC5* gene, including a case report of a rare instance of two SUDEP cases in the same family.[13] In an exome sequencing-based study, four nonsense variants and two rare missense variants in *DEPDC5* were found in 6 out of 61 (10%) SUDEP cases, and *DEPDC5* was the top-ranked gene for having enrichment of loss of function variants in these SUDEP cases.[18] Loss-of-function variants in *DEPDC5* cause predominantly focal epilepsies with often sleep-related and drug-resistant seizures, both of which are associated with SUDEP.[19] Comparing larger cohorts of SUDEP cases to living patients with matched epilepsy phenotypes caused by genes other than *DEPDC5* will help to determine whether *DEPDC5* variants independently influence SUDEP risk. Variants in *KCNT1* cause a spectrum of epilepsies, several of which have difficult-to-control seizures such as epilepsy of infancy with migrating focal seizures (EIMFS). In a series of 17 patients with EIMFS due to *KCNT1* variants and up to 19.5 years of follow-up, all had seizure onset before age 6 months and 3 (17.6%) died from probable SUDEP.[20] This is higher than 4 out of 135 (4%) patients with EIMFS without known mutations or with mutations in genes other than *KCNT1*.[21–25]

Collectively, these findings suggest that some people who died from SUDEP had pathogenic variants causing epilepsies associated with SUDEP risk factors. It is unclear if the molecular basis of epilepsy due to variants in these genes increases SUDEP risk independent of seizure severity and frequency. In many cases, these epilepsies are also associated with varying degrees of autonomic dysfunction.[26] Until a causal link is established between an epilepsy gene and SUDEP, it will be premature to link a genetic variant that causes severe epilepsy to the underlying cause of death. Nevertheless, the heightened risk of SUDEP in people with epilepsy due to variants in the abovementioned genes should

prompt clinicians to discuss SUDEP with the families. Clinicians should reinforce the importance of interventions to reduce seizure frequency and measures to prevent SUDEP if a seizure does occur, such as nocturnal supervision.

5 | INSIGHTS FROM POSTMORTEM GENETIC TESTING IN UNEXPLAINED SUDDEN CARDIAC DEATH

While the possible genetic underpinnings of SUDEP are yet to be defined, considerable progress has been made in understanding the genetic causes of sudden cardiac death in young people. In individuals aged 1–35 years, sudden cardiac death is mainly caused by structural heart diseases; however, a complete postmortem examination fails to reveal a cause of death in 40% of cases, who are then considered cases of "unexplained sudden cardiac death".[27] There are several similarities between unexplained sudden cardiac death and SUDEP (Table 1). Postmortem genetic testing of unexplained sudden cardiac deaths over the past two decades has firmly established that some of these deaths are caused by cardiac arrhythmogenic disorders, including the long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia.[27–29] These heritable arrhythmogenic disorders are primarily due to variants in genes encoding cardiac sodium and potassium channel subunits (*SCN5A*, *KCNQ1* and *KCNH2*) and the cardiac ryanodine receptor (*RYR2*). Finding the genetic cause of unexplained sudden cardiac death with postmortem genetic testing has immediate and far-reaching implications for surviving family members. It explains the cause of death and facilitates cascade genetic testing in first-degree family members. Importantly, life-saving interventions are available for people with cardiac arrhythmias, including the implantable cardioverter defibrillator and medications, such as beta-blockers. The clear benefits of postmortem genetic testing in unexplained sudden cardiac death in the young are reflected in the current Asia-Pacific Heart Rhythm Society (APHRS) and the Heart Rhythm Society (HRS) clinical guidelines on the investigation of decedents with a sudden unexplained death, in which "arrhythmia syndrome-focused genetic testing of the proband should be considered".[30]

TABLE 1 Overlapping features of unexplained sudden cardiac death[27] and SUDEP.[9]

- Male predominance
- Death often occurs at night
- Deceased often found in bed lying in the prone position
- Death event often unwitnessed
- No cause of death found following post-mortem investigation

6 | CARDIAC ARRHYTHMIA GENE VARIANTS FOUND IN SUDEP

The overlapping circumstances of unexplained sudden cardiac death and SUDEP have prompted researchers to look for gene variants causing cardiac arrhythmia syndromes in SUDEP. A few studies have found in SUDEP cases pathogenic or likely pathogenic deletions, nonsense variants, and missense variants in *SCN5A* and *KCNQ1*, which raise the risk for long QT syndrome or Brugada syndrome.[18,31–34] This raises the question of whether the underlying cause of death in these cases was a fatal cardiac arrhythmia in people with epilepsy. Additional *SCN5A*, *KCNQ1* and *KCNH2* variants reported in SUDEP cases are often too common in the general population to cause long QT syndrome.[35,36] However, recent functional studies indicate that both rare and common *SCN5A* and *KCNQ1* variants found in SUDEP cases display varying degrees of loss or gain of function. Furthermore, *KCNH2* loss of function variants with a general population allele frequency <5% show a four-fold enrichment in SUDEP cases when compared to an alive epilepsy population older than 50 years, who are considered at low risk of SUDEP.[37,38] It has been postulated that common variants with subclinical impact could potentially increase the risk of sudden death in people with epilepsy.[39] The distinction between unexplained sudden cardiac death in people with epilepsy and SUDEP cannot be made by postmortem investigation alone as there are no morphological or histological markers indicative of prior cardiac arrhythmias at the postmortem examination. However, this is an important distinction to make as sudden cardiac death in people with epilepsy would prompt clinical investigations of first-degree relatives, including physical examination, electrocardiogram, cardiac imaging, and cascade genetic testing.

In those SUDEP cases with cardiac arrhythmia gene variants, it is likely that the epilepsy was unrelated to the cardiac arrhythmia genes. Less likely, long QT syndrome may have been misdiagnosed as a seizure disorder, as has occasionally been reported,[40,41] since seizures may be secondary to cerebral hypoxia during episodes of cardiac arrhythmia. A more controversial suggestion is that the genes associated with cardiac arrhythmia, *KCNQ1*, *KCNH2* and *SCN5A*, can also be implicated in epilepsy themselves since they are co-expressed in the brain and heart and a few families with nonsense variants in these genes reportedly have long QT syndrome and epilepsy.[42–45] In one case series, 10 out of 610 (1.6%; 95% CI .8%–3%) people with long QT syndrome were diagnosed with a seizure disorder by an epileptologist on the basis of the clinical findings and EEG studies.[46] Of these 10 cases, 7 were found in 190 (3.6%) people with a pathogenic variant in *KCNH2*, causing long QT syndrome type 2, which shows high expression levels in the brain.[47] Whether

the cardiac arrhythmia genes increase susceptibility for recurrent seizures outside the episodes of ventricular arrhythmias is yet to be established.

7 | RESPIRATORY GENE ANALYSIS IN SUDEP

Another possible mechanism involved in SUDEP is a fatal compromise in breathing. This notion stems from reports of breathing difficulties in witnessed SUDEP,[48] instances of terminal apnoea preceding cardiac arrest in monitored SUDEP cases,[10] and potential airway obstruction in SUDEP cases found lying face-down or with fluid in the lungs at autopsy.[9] The regulation of breathing is a complex process that influences multiple factors including the respiratory rate and the response to blood carbon dioxide levels. Decreased levels of serotonin, a neurotransmitter that regulates the breathing rate in response to blood carbon dioxide levels, may increase the likelihood of seizures.[49] Studies on mice with deleted serotonin receptors have shown that they are prone to generalized tonic–clonic seizures, respiratory arrest, and death.[50] Although research studies have looked for clinically relevant variants in serotonin receptor genes in some SUDEP cases, none have been found thus far. Respiratory compromise is also a prominent feature of congenital central hypoventilation syndrome, a condition that typically presents within the first few months of life. It is characterized by shallow breathing during sleep, resulting in elevated blood carbon dioxide levels, decreased oxygen levels, and potentially life-threatening cardiac arrhythmias that can lead to sudden death. Most cases of congenital central hypoventilation syndrome are caused by an expansion of a repeated glutamine sequence in the *PHOX2B* gene; however, these expansions were not found in a series of 68 SUDEP cases.[51] Furthermore, the analysis of additional genes implicated in respiratory control has not revealed any pathogenic variants in SUDEP cases so far.[18]

8 | GENETIC ANIMAL MODELS OF SUDEP

It is difficult to study the genetic basis of SUDEP or investigate neuronal, cardiac, and respiratory mechanisms in humans when it is such a rare and usually unwitnessed event. Therefore, genetic animal models that exhibit symptoms similar to human SUDEP, including spontaneous seizures, cardiorespiratory failure, and sudden death, offer useful avenues for SUDEP research. Some SUDEP mouse models have genetic modification of the same epilepsy genes that show rare variants in human SUDEP cases. These including *Scn1a*,[52] *Scn8a*,[53] *Depdc5*,[54] and *Kcn1a*,[55] and the genetic modifications can be global or targeted specifically to neurons. A particular benefit with mice is that they can be studied with continuous video, EEG and ECG monitoring that captures the events leading up to sudden death. Genetic modifiers that reduce seizure frequency and improve survival have been identified in *Scn1a* and *Kcna1* SUDEP mice,[56,57] as have drug treatments that prolong survival in *Scn1a* and *Depdc5* mice.[52,54] These models have advanced our understanding of genetic factors associated with seizures and SUDEP and potential strategies to prevent SUDEP.

9 | CASE RESOLUTION

DNA was extracted from the deceased's postmortem blood following genetic counseling with the next-of-kin and approval of consent to perform postmortem genetic testing as part of a research study. Exome sequencing was performed as this allows analysis of a panel of epilepsy genes and cardiac arrhythmia genes. No rare variants were found in epilepsy genes, but a nonsense variant was found in the cardiac potassium channel subunit gene, KCNH2 p.Arg744Ter, causing long QT type 2. This represents a rare case of sudden death that could be considered as SUDEP or as sudden cardiac death in a person with epilepsy. Importantly, direct action should be taken with the surviving family members, including a detailed family history of cardiac events and sudden unexpected deaths, with baseline cardiac evaluation screening for long QT syndrome and cascade genetic testing for the KCNH2 nonsense variant in first-degree relatives. The identification of a nonsense variant in KCNH2 has no relevance to the family history of seizures, which currently has no known genetic cause in this family.

10 | CONCLUDING REMARKS

The outcome of genetic testing in this SUDEP case is atypical, as most genetic research studies of SUDEP do not find variants that can be considered to cause death. Occasionally, a pathogenic variant in an epilepsy gene is found, which currently does not explain the underlying cause of death but can be used for segregation analysis within the family. However, it should be emphasized that there remains much uncertainty about the value and purpose of genetic testing in SUDEP, and therefore it is primarily performed as part of research studies. If clinical genetic testing is undertaken, it should be performed in a multidisciplinary setting that includes pre- and post-test genetic counseling of the family, including a frank discussion about the very low expectations of finding answers to the family's many questions.

A clinical genetic test should be performed only if the potential outcomes are deemed useful for the clinical management of the family; in this case, a history of seizures in a first degree relative, and should only include those genes with established clinical validity to avoid the return of ambiguous, incorrect, or uninformative results.[58] Clinical genetic testing should prioritize genes that have a well-established and definitive association with epilepsy or cardiac arrhythmias. In research studies, it may be permissible to consider additional genes having moderate evidence of association with epilepsy or cardiac arrhythmia, but caution and restraint must be exercised before attributing clinical relevance to variants found in these genes.

This manuscript in the Genetic Literacy series maps to Learning Objective 1.2 of the ILAE Curriculum for Epileptology.[59]

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

FULL LIST OF ILAE GENETICS COMMISSION MEMBERS

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Test yourself

1. The definition of definite sudden unexpected death in epilepsy (SUDEP) includes
   A. Drowning
   B. Status epilepticus
   C. Post-mortem examination
   D. Mandatory evidence of a witnessed seizure
2. Regarding genetic testing in SUDEP
   A. Genetic testing is routinely performed as part of the clinical evaluation
   B. When genetic testing is performed in the research setting, a pathogenic variant in an epilepsy gene is found in 85%–90% of patients
   C. If a pathogenic variant in *SCN1A* is found in a patient with SUDEP, it confirms the variant as the cause of SUDEP
   D. When genetic testing is performed in the clinical setting for SUDEP, it should be done in a multidisciplinary setting, emphasizing the low yield of testing
3. SUDEP and unexplained sudden cardiac death can be differentiated by
   A. Postmortem investigation
   B. A pre-morbid clinical history of epilepsy in the deceased
   C. The circumstances of death
   D. A family history of sudden cardiac death

Answers may be found in the supporting information