Sudden Unexpected Death in Epilepsy

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Epilepsy is a common neurological disorder associated with increased morbidity and mortality. Sudden unexpected death in epilepsy, also known as SUDEP, is the main cause of death in patients with epilepsy. SUDEP has an incidence of 1.2 per 1000 person-years in adults and 0.2 per 1000 person-years in children.

SUDEP epilepsy genetics

1. Introduction

Epilepsy is a common neurological disorder of the central nervous system characterized by recurrent seizures with or without convulsions [1]. Currently, seizures are classified into four groups: simple (status epilepticus), partial (seizures in infants and young adults), complex (generalized tonic-clonic seizures (GTCS)), and unclassified seizures. Those associated with an altered state of consciousness, particularly GTCS and uncontrolled repetitive seizures or status epilepticus, are associated with increased morbidity and mortality, especially in infants and young populations [2][3].

In general, patients with epilepsy are two- to three-times more likely to die early than the general population [4]. Several possible causes of death have been reported in patients with epilepsy, including seizure complications, status epilepticus, or even suicide, but the main current cause is sudden unexpected death in epilepsy (SUDEP). Today, SUDEP is defined as a “sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy with or without evidence for a seizure, and excluding documented status epilepticus, in which postmortem examination does not reveal a structural or toxicological cause of death” [5].

The concept of SUDEP was first defined in the 1990s based on whether an autopsy was performed and competing factors were present [6][7]. A new classification by Nashef et al. in 2012 helped refine SUDEP definitions and classification [5]. The authors introduced definite SUDEP plus and probable SUDEP plus, which are classifications that consider cases in which the individual had other concomitant conditions. The authors also defined near SUDEP, identifying resuscitated cases after a cardiopulmonary arrest of unidentified origin with survival of >1 h (**Table 1**). Today, SUDEP is likely underestimated; thus, improved criteria to classify the cause of death would allow more accurate tracking of this condition. Devinsky et al. recently suggested additional clinical and pathological criteria for more consistent and reliable classification of epilepsy-related mortality [8]. Lamberts et al. [9] observed that 62% of SUDEP cases happened between midnight and noon, and that 58% of SUDEP cases were sleep-related. Further, they found that individuals whose deaths were associated with SUDEP were two-times more likely

to have nocturnal seizures than those without SUDEP [9]. SUDEP occurs at night likely because of multiple factors, including both situational factors (absence of caregivers) and physiological modifications (circadian rhythms) [10].

Table 1. Proposed sudden unexpected death in epilepsy (SUDEP) definition and classification [5].

Classification	Definition
Definite sudden unexpected death in epilepsy (SUDEP)	Sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death that occurs in benign circumstances in an individual with epilepsy, with or without evidence for a seizure, and excludes documented status epilepticus, in which post-mortem examination does not reveal a cause of death.
Definite SUDEP plus	Death satisfying criteria for definite SUDEP, if a concomitant condition other than epilepsy is identified before or after death, if the death might have been due to the combined effect of both conditions, and if autopsy or direct observations or recording of the terminal event did not prove the concomitant condition to be the cause of death.
Probable SUDEP or probable SUDEP plus	Same definition as definite SUDEP or SUDEP plus, but without autopsy.
Possible SUDEP	A competing cause of death is present.
Near-SUDEP or near-SUDEP plus	A patient with epilepsy who survives resuscitation for more than an hour after cardiorespiratory arrest and has no structural cause identified after investigation.
Not SUDEP	A clear alternative cause of death is identified.
Unclassified	Incomplete information available; impossible to classify.

2. Sudden Unexpected Death in Epilepsy (SUDEP) Pathophysiology

Recent studies have extensively investigated the pathophysiology of SUDEP in different groups, proposing four main mechanisms for SUDEP: cardiac dysfunction, respiratory dysfunction, brainstem arousal system dysfunction, and dysregulation in the neurotransmitter and neuromodulator system [11]. Most results suggest a complex and multifactorial model. The MORTality in Epilepsy Monitoring Unit Study (MORTEMUS) study focused on deaths occurring during video electroencephalogram monitoring to ascertain the possible mechanisms of SUDEP on an international scale. The study results suggest that the crucial mechanism leading to SUDEP starts with an early, centrally mediated, severe alteration of both respiratory and cardiac functions after GTCS, which the authors consider as an early postictal neurovegetative breakdown. Depending on the intensity, this mechanism might lead to instant death or cardiorespiratory arrest after several minutes of altered cardiorespiratory function, most likely intensified by profound hypoxia. It has been hypothesized that intrinsic mechanisms leading to or associated with seizure termination are the origin of this centrally mediated neurovegetative breakdown and postictal generalized electroencephalogram (EEG) suppression [12].

3. Genetics of SUDEP

Definite evidence has recently emerged concerning genetic susceptibility to SUDEP, suggesting a highly polygenic contribution [13]. A gene associated with SUDEP should include a definite pathogenic alteration that causes epilepsy, increasing SUDEP risk [14]. Numerous neurocardiac genes have been identified as genomic biomarkers of disease severity and outcome, helping predict SUDEP incidence [15]. Moreover, several pathogenic alterations in different genes have been reported to increase SUDEP risk through different pathophysiological mechanisms. These genes encode proteins related to epilepsy and the cardiorespiratory system [13][16]. Until now, few genes have been analyzed in genetic testing (**Table 2**), but with next-generation sequencing and the low cost of these high-throughput technologies, candidate genes can now be interrogated to explore new genetic causes.

Table 2. Genes associated with SUDEP (adapted from Reference [17]).

Gene	Description	Evidence for Association with SUDEP
SCN1A	Sodium Voltage-Gated Channel Alpha Subunit 1	Animal model; de novo variants found in SUDEP cases
SCN2A	Sodium Voltage-Gated Channel Alpha Subunit 2	De novo variants found in SUDEP cases
SCN5A	Voltage-Gated Sodium Channel Subunit Alpha Nav1.5	De novo variant found in SUDEP case
SCN8A	Sodium Voltage-Gated Channel Alpha Subunit 8	Animal model; de novo variants found in SUDEP cases
KCNA1	Potassium Voltage-Gated Channel Subfamily A Member 1	Animal model; variant found in SUDEP case
KCNQ1	Voltage-Gated Potassium Channel Subunit Kv7.1	Variants found in SUDEP cases
KCNH2	Voltage-Gated Potassium Channel Subunit Kv11.1	Variants found in SUDEP cases
DEPDC5	DEP Domain-Containing Protein 5	De novo variants found in SUDEP cases

3.1. Cardiac Arrhythmia Genes in SUDEP

Epilepsy can have damaging effects on cardiac function, which may play an important role in the pathophysiology of SUDEP [18][19]. Epileptic seizures can induce malignant cardiac arrhythmias, possibly due to seizure-related effects on the autonomic nervous system [17].

Mutations of ion channel genes have a major role in the pathogenesis of several epilepsies, confirming that these are due to the impairment of ion channel function (channelopathies). Voltage-gated channels play an essential role

in neuronal excitability and it is not surprising that most mutations associated with epilepsy have been identified in these genes [20].

In 2009, Aurlien et al. identified the first *SCN5A* mutation in a patient with idiopathic epilepsy, suggesting that ion channel mutations are co-expressed in the brain and heart and predispose to both epileptic seizures and cardiac arrhythmias [21]. In 2011, a larger retrospective analysis of autopsies of SUDEP cases in a forensic center in Australia during a 16-year period identified 86 SUDEP cases. The genetic analyses revealed six genetic mutations in voltage-gated ion channel genes *KCNH2* and *SCN5A*, as previously reported in long QT syndrome (LQTS) [22]. Sequencing of a family of four hyperpolarization-activated cyclic nucleotide-gated cation channel genes (*HCN1*, *HCN2*, *HCN3*, and *HCN4*) in the same cohort identified three non-synonymous variants (Phe738Cys and Pro802Ser in *HCN2*, and Gly973Arg in *HCN4*).

The largest genetic study of SUDEP was done by Bagnall et al. in 2016 using exome sequencing-based analysis of 61 SUDEP cases [23]. They analyzed cardiac arrhythmia, respiratory control, and epilepsy genes, identifying four pathogenic and two candidate pathogenic variants of cardiac arrhythmia genes: a de novo *SCN5A* Ile397Val variant, a Gly924Ala and Arg744* nonsense variant in *KCNH2*, and a Tyr662* nonsense variant in *KCNQ1*. The variants in *KCNQ1* and *KCNH2* were previously reported in patients diagnosed with LQTS, and these three variants were absent in more than 60,000 population controls. The de novo variant in *SCN5A* is located in a highly conserved transmembrane domain. All these variants are classified as likely pathogenic for LQTS. In addition, the variants were found in one coronial SUDEP case and three SUDEP cases from the Melbourne Epilepsy Research Centre cohort [17].

3.2. Genetic Epilepsy Syndromes and SUDEP Risk

Some genetic epilepsy syndromes have a high risk of SUDEP, and the associated pathogenic variants may be appropriate biomarkers [17]. Pathogenic alterations in *SCN1A* (associated with Dravet syndrome, a genetic epileptic encephalopathy in which a *SCN1A* loss-of-function mutation is found in 80% of cases) or in *SCN8A* (associated with early-infantile encephalopathy) are examples of variants co-expressed in both brain and heart that increase the risk of SUDEP [24]. However, it remains to be determined why these epilepsies caused by genetic variants should have a high risk of SUDEP.

3.3. Respiratory Genes and SUDEP Risk

The association between neuronal regulation of respiratory function and SUDEP came from functional in vivo models. DBA/1 and DBA/2 (Dilute Brown Non-Agouti) mice are useful animal models to study SUDEP because these mice exhibit generalized convulsive seizures followed by respiratory arrest [25]. Respiratory arrest can be prevented by treatments that activate serotonin (5-HT) receptors, as subtypes of 5-HT help regulate normal respiration [26]. Further, congenital heart hypoventilation syndrome is a disorder characterized by increased frequency of bradyarrhythmia and is mainly caused by expansion of an alanine repeat in *PHOX2B*. This gene could be a good target for SUDEP, although no studied SUDEP cases carry a variant in this gene [27]. Moreover, no

genetic variants in respiratory control genes (*ASCL1*, *BDNF*, *EDN3*, *GDNF*, and *RET*) were identified in exome analysis of 61 SUDEP cases [23].

3.4. Future Directions

Although considerable progress has been made in SUDEP in recent years, there is much work to be done on the genetic diagnosis of this condition. Several genes responsible for inherited channelopathies are linked to SUDEP, and several recently identified potential candidate genes with positive segregation indicate that a common cardiac neuron gene expression may underlie the basis of sudden death in epilepsy. Although in silico tools are being used to predict the possible pathogenicity and could help classify some variants, it is not recommended that these predictions be used as the sole source of evidence to make a clinical assertion. Moreover, larger cohorts as well as in vivo and in vitro studies will be required to ascertain the pathogenicity of these variants. Molecular genetic screening also needs to become an inherent part of the post-mortem examination in cases labeled as SUDEP. This genetic testing will enhance the ability to screen SUDEP victims' family members, who may be at-risk carriers of fatal cardiac disorders. Genetic interpretation requires multidisciplinary groups, including geneticists working together with clinicians, forensic pathologists, and genetic counselors. To best manage families, close interdisciplinary collaboration is essential.

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