

SUDEP-Review of Genetics

Jaishree Narayanan

Tulane University Center for Clinical Neurosciences



- I HAVE NO DISCLOSURES

SUDEP- Definition

- Sudden Unexpected Death in Epilepsy (SUDEP) is defined as “The 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 post- mortem examination, does not reveal a structural or toxicological cause for death.” (Nashef et al., 2012)

SUDEP- Classification

1. *Definite SUDEP*: Sudden, unexpected death in a patient with epilepsy. The death may be witnessed or unwitnessed, and there does not need to be evidence of a recent seizure. Postmortem examination does not reveal an alternative cause of death besides epilepsy.
2. *Definite SUDEP plus comorbidity*: This is the same as definite SUDEP with a comorbid medical condition that could contribute to death (but not a competing cause).
3. *Probable SUDEP*: Unexpected death in a patient with epilepsy for whom an autopsy was not performed.
4. *Probable SUDEP plus comorbidity*: Same as probable SUDEP with comorbidity that could contribute to death (such as a channelopathy).
5. *Possible SUDEP*: Sudden death in a patient with epilepsy for whom there is a likely alternative cause of death (such as a patient found dead in the water, but no forensic confirmation of drowning made).
6. *Resuscitated SUDEP*: A patient with epilepsy who is resuscitated and survives greater than 1 hour after cardiopulmonary arrest. No alternative cause of the arrest is discovered after evaluation.
7. *Not SUDEP*: A clear alternative cause of death was identified.
8. *Unclassified*: There is insufficient information on which to make a diagnosis.

(Sheel et al., 2022)

SUDEP- Numbers

- SUDEP accounts for about 18% of all deaths in people with epilepsy.
- By potential years of life lost, it is the second leading cause of death in neurological disorders after stroke.
(Thurman et al., 2014)
- SUDEP Incidence is estimated to be 0.58-9.0 per 1000 person years.
- In refractory epilepsy this can be as high as 35%. (Walczak et al., 2001, Mohanraj et al., 2006, Ficker et al, 1998, 2000, Sillanpaa et al 2010)
- Incidence is higher in adults than in children.
- A majority of them occur at night in sleep-mostly in the prone position.

SUDEP – Mechanism

- The mechanism is not entirely clear but is believed to be caused by a culmination of neurological, cardiac and respiratory causes.
- This is similar to cases of Sudden Cardiac Death in the general population.

SUDEP and Sudden Cardiac Death

- Genetic Cardiac Conditions like channelopathies, cardiomyopathies etc. are important predisposing contributors to sudden cardiac deaths. This knowledge helps in prevention of sudden cardiac deaths.
- Channelopathies can have an arrhythmia and seizure phenotype and the genotype may play a role in determining predisposition to SUDEP. (Johnson et al., 2009, Anderson et al., 2014)
- Cardiac Voltage gated sodium channel was found in limbic regions- could be a link between genetically predisposed cardiac arrhythmias and epilepsy. (Hartmann et al., 1999)
- Studies have shown epilepsy, cardiac arrhythmias and SUDEP in transgenic mice carrying human knock in mutations in long QT syndrome gene KCNQ1.

SUDEP – genetics

- Although mechanism of SUDEP is not known, Arrhythmogenic epilepsy is one of the hypotheses.
- Studies on large cohorts of SUDEP patients in Australia have found genetic variants encoding sodium, potassium and calcium channel subunits in neuronal and cardiac cells (Tu et al., 2011)
- These variants may work by themselves or be potentiated by environmental factors like uncontrolled seizures, ASMs (Anti-Seizure Medications), prolonged QT, non-compliance with ASMs to cause malignant arrhythmias and sudden death. (Goldman et al., 2016)

SUDEP- genetic studies

- Tu et al., 2011 studied 68 SUDEP patients specifically targeting LQT1 (KCNQ1), LQT2 (KCNH2), and LQT3 (SCN5A) and identified variants in KCNH2 and in SCN5A.
- The same group studied 61 additional cases and reported 6 cases with pathogenic variants in KCNQ1 and KCNH2.
- Cooper et al., 2016 studied mortality in Dravet syndrome(DS) patients. They studied 100 untreated people with DS. 87% were genotyped antemortem for pathogenic variants in SCN1A. 10 SUDEP events occurred with an incidence rate of 9.32 per 1000 person-years. SUDEP events were unwitnessed in 90% of cases, 60% occurred in sleep. The most frequent types of mutations in SUDEP cases were truncations(40%).

SUDEP- genetics

- Hata et al., 2017 reported 9 definite SUDEP cases with full autopsies and performed targeted whole exome sequencing focusing on 73 known inherited cardiovascular disease related genes.
- They identified 6 variants- LDB3, DSC2, KCNE1, MYH6, DSP, DSG2.
- One of these cases carried the KCNE1 polymorphism (pAsp85Asn) which is present in 1-24% of whites and may be considered pro-arrhythmic in the setting QT prolonging drugs.
- The study also detected variants associated with structural proteins like dystrophin (DMD) associated with cardiomyopathies, desmoglein (DSG) and desmoplakin (DSP) associated with arrhythmogenic ventricular cardiomyopathy, MYH6 associated with dilated cardiomyopathy and LDB3 associated with dilated cardiomyopathy.

SUDEP- genetics

- Anwar et al., 2020 did a systematic review of genetics of SUDEP.
- They included a total of 8 studies with 161 individuals.
- Mean age was 29 years.
- 61% were males.
- 50.7% were found prone.
- 58% of deaths were nocturnal.
- Antemortem diagnosis of Dravet syndrome was associated with 11%
- Antemortem diagnosis of autism with duplication of chromosome 15 was associated with 9% of the cases.

SUDEP- genetics

- The review revealed some important findings:
- 1) Genes encoding for sodium and potassium ion channel subunits were the most frequently reported variants by post-mortem molecular autopsy and with highest yield of pathogenic variants.
- 2) DEPDC5 which encodes for a protein in the IML1 family, involved in G-protein signaling- Associated with autosomal dominant familial focal epilepsy was the second highly ranked variant in a large series.
- 3) Although Dravet syndrome is rare, given the high SUDEP rate, these are more likely to be included in SUDEP series.

SUDEP genetics

- 4) CNVs in chromosome 15 are associated with autism, high frequency of epilepsy and SUDEP.
- 5) Most SUDEP events are oligogenic or polygenic, although 10-20% may overlap with monogenic disorders.

Lessons

- Aside from the DS cases, the most frequent pathogenic variants identified are in ion channel and arrhythmia related genes.
- The structural cardiac genes should also be considered.
- They found that there is a dearth of cases undergoing comprehensive autopsy evaluation by neuropathologist and cardiac pathologist despite guidelines recommending evaluation by subspecializing pathologists.
- Majority of studies did not report ECG data due to probable lack of availability. The importance of getting an ECG in all our epilepsy patients cannot be overemphasized.

SUDEP Counseling

- Several recent clinical practice guidelines have recommended that all individuals living with epilepsy and their caregivers be informed about SUDEP as a part of routine epilepsy counseling.
- Several studies over the last two decades have explored the state of SUDEP counseling. Patients with epilepsy and their families want to be informed about the risk of SUDEP at or near the time of diagnosis, and preferably **in person**.(Whitney et al., 2023)

SUDC

- More than 2,900 children younger than 4 years of age in the US die of unknown causes.
- In SUDC, death occurs in sleep.
- Unwitnessed
- No autopsy findings of structural abnormalities
- Disproportionate number of these children have personal or family history of febrile seizures. (Krous et al 2005)
- The febrile seizures can be associated with abnormalities in dentate gyrus- bilamination (Kinney et al., 2007,2009).
- Genetic variants have been identified in the SCN1A in some cases. (Halvorsen et al., 2015, Koh et al., 2022)
- ? Is this an epilepsy related phenotype.

SUDC

- Gould et al., 2024 in their study of “Video analysis of Sudden Unexpected Death in Toddlers” did analysis of terminal videos of 4 boys and 3 girls from ages 13-27 months.
- They found persuasive evidence of a convulsive event in the minutes before the child’s death in 6 of the videos.
- All were normally developing children with unremarkable medical histories.
- 6 of them were seen prone, one on turned to one side.
- One of them had a history of febrile seizures and family history of febrile seizures.
- 3 of 6 had abnormalities in the dentate gyrus on neuropathological evaluation.



Thanks!