Guest Editorial

SUDEP in adults and children

Divya K P¹, Ajith Cherian^{1,*}¹Dept. of Neurology, Sree Chitra Tirunal Institute for Medical Sciences & Technology Medical College, Trivandrum, Kerala, India

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ABSTRACT

Background: Sudden unexpected death in epilepsy (SUDEP) represents an important cause of death in patients with epilepsy and it exceeds the expected rate of sudden death in the general population by nearly 24 times.

Materials and Methods: We searched the electronic databases (Cochrane, EMBASE, Scopus, Medline, Pubmed) for studies related to etiology and risk stratification of SUDEP including data on Takotsubo cardiomyopathy (TKC) following seizures resulting in death or near death.

Results and Conclusions: SUDEP is more common among males in the fourth decade of life. Risk for SUDEP is increased by early onset of seizures, low IQ, generalised tonic clonic seizures, nocturnal seizures and seizure frequency. Nonadherence to antiepileptic medications, absence of therapeutic drug level monitoring, presence of neuropathological lesions on imaging and certain subgroups like Dravet syndrome increase its risk. The risk for premature death in patients undergoing temporal lobe resection for drug resistant epilepsy decreased over time but remained above the standard population. Prolonged postictal electroencephalographic suppression was a risk factor for SUDEP in patients with generalised seizures which may indicate a cerebral electrical shutdown. Documented ictal/postictal hypoventilation, laryngeal spasm and cardiac rhythm abnormalities prior to SUDEP may suggest central apnea, neurogenic pulmonary edema, cardiac arrhythmia, or a combination of the above as a cause. Seizure triggered TKC does not seem to play a major role in the pathogenesis of SUDEP.

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1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is defined in people with epilepsy occurring in the absence of a known structural cause.¹ A conventional definition of SUDEP would be sudden, unexpected, witnessed or unwitnessed, nontraumatic, nondrowning death in epilepsy patients, with or without evidence for a seizure excluding documented status epilepticus, in which postmortem examination does not show a toxicological or anatomical cause for death.² SUDEP is labelled as definite when there is autopsy evidence, probable in the absence of such evidence

and possible when there is insufficient data about the circumstances of death.³ We undertook a literature review for studies related to etiology and risk stratification of SUDEP.

1.1. Search strategy and selection criteria

Data for this review were retrieved from electronic databases (Cochrane, EMBASE, Scopus, Medline, Pubmed) using the search terms “SUDEP”, “seizures and sudden death” and/ or combined with “Takotsubo cardiomyopathy”. Randomized (blinded or open label) clinical trials, longitudinal studies, case series, and case reports were pondered. Only articles published in English between

* Corresponding author.

E-mail address: drjithcherian@yahoo.com (A. Cherian).

January 1, 1992, and April 30, 2020 were included.

1.2. Prevalence and risk factors for SUDEP

Probable SUDEP is an important cause of death among patients with convulsive epilepsy it exceeds the expected rate of sudden death in the general population by nearly 24 times.^{4,5} The mean incidence is 1.8/1000 and the mean percentage of SUDEP cases among deaths from epilepsy was 16.6.⁶ SUDEP is less common in children and most victims are adults with a mean age at the time of death being 35 years.⁷ Some studies suggest that it is more common among males.^{8,9} Annual incidence is maximum among epilepsy surgery candidates and those referred to epilepsy centres, intermediate in patients with mental retardation and least among children.¹⁰ The incidence in population based study in Rochester, was 0.35 per 1,000 person-years.⁵ It varies from 0.09 per 1000 patient-years in newly diagnosed patients to 9 per 1000 patient-years in candidates for epilepsy surgery suggesting the high mortality in refractory epilepsy.¹¹ The SUDEP rates are similar in patients on vagal nerve stimulation (4.1 per 1000 person years) as compared to patients on drug trials.^{12,13}

Most of the sudden deaths in patients with epilepsy are unwitnessed.³ SUDEP occurs most often in a setting of generalised tonic clonic seizures (GTCS).^{5,14} Risk factors for SUDEP are given in table 1. There is a 1.7-fold increase in risk of SUDEP for each increment in maximum number of AEDs administered, a likely surrogate for severity and persistence of seizures.⁸ Conflicting reports are there concerning postmortem blood levels in SUDEP.^{15,16} Absence of therapeutic drug level monitoring (TDM) is associated with a higher relative risk of 3.7 (95% CI: 1.0–13.1) compared to patients with epilepsy on TDM.¹⁷

Lamotrigine, which inhibits the cardiac rapid delayed rectifier potassium current, use as a risk factor was allayed as there was no increased risk of SUDEP in patients treated with it compared to active comparators and placebo in randomised controlled clinical trials.¹⁸ Similar conclusions have been drawn from large clinical development program.¹⁹ Similarly though use of carbamazepine was thought to be associated with SUDEP,²⁰ this too could not been confirmed by other studies.^{15,21,22} Mortality in antiepileptic drug development programs is related to the severity of the disease and not to drugs.^{22,23} SUDEP is more common in some epileptic syndromes like Dravet again confirming that the disease severity plays an important factor.²⁴

Antiepileptic blood levels are either low or absent indicating poor compliance in patients with SUDEP.²⁵ It is hypothesised that low drug levels may lead to increased interictal or ictal epileptiform activity which may lead to increased autonomic activity leading to changes in heart rate, rhythm and blood pressure that would partially explain the sudden death. Meta-analysis showed that the risk of

SUDEP was less in patients on efficacious dose of AEDs compared to patients on placebo.²⁶

The risk for premature death in patients undergoing temporal lobe resection for temporal lobe epilepsy decreased over time but remained above the standard population. Men had a slightly higher risk than women, as did right-sided resections for mesial temporal lobe sclerosis. Although lower, the risk of SUDEP remained despite temporal lobe resection.²⁷ Elimination of seizures after surgery reduces mortality rates in people with epilepsy to a level indistinguishable from that of the general population, whereas patients with recurrent seizures continue to suffer from high mortality rates. This suggests that uncontrolled seizures are a major risk factor for excess mortality in epilepsy.²⁸ The presence of neuropathological lesions increases the risk for SUDEP.⁹

1.3. Pathogenesis

Prolonged postictal electroencephalographic suppression was a risk factor for SUDEP in patients with generalised seizures.²⁹ Electroencephalographic suppression may indicate a cerebral electrical shutdown. Patients with regional cerebral oxygen saturation (rSO₂) decrease of $\geq 20\%$ tended to have higher SUDEP inventory scores.³⁰ SUDEP is probably caused by central apnoea, cardiac arrhythmia, or neurogenic pulmonary edema. Case reports suggest that ictal/postictal hypoventilation,³¹ malignant arrhythmia,³² asystole,³³ laryngeal spasm³⁴ can lead to SUDEP. Patients with epilepsy who have survived cardiac arrest have a higher risk of life-threatening ventricular tachyarrhythmia, cardiac death and all cause mortality.³⁵ This data also suggests that cardiac arrhythmia could be one of the causes of SUDEP. Seizure related respiratory dysfunction (RD), duration of postictal generalized electroencephalography (EEG) suppression (PGES) and duration of postictal immobility may contribute to SUDEP. Postictal immobility was associated with lower and longer duration of oxygen desaturation.³⁶

Ictal maximal heart rate (HR) particularly for nocturnal seizures was more in SUDEP patients compared to others with refractory epilepsy indicating increased autonomic stimulation.³⁷ Postictal autonomic dysregulation in the form of sympathetic activation (recorded by electrodermal activity) and parasympathetic suppression (detected by high-frequency power of heart rate variability) correlates with postictal EEG suppression after tonic-clonic seizures.³⁸ Though this may be relevant in the pathogenesis of SUDEP it was refuted in another study which did not show any relation between postictal generalised EEG suppression and periictal cardiac autonomic instability in persons with convulsive seizures.³⁹ Abnormal shortening of corrected QT interval (QTc) occurred in early postictal phase and significantly more often in secondarily GTCS.⁴⁰ Ictal asystole can occur in patients with temporal lobe

epilepsy manifesting as loss of tone and collapse late in the course of seizure.⁴¹ There is a suggestion of cardiac ischemia during seizures in drug refractory epilepsy patients.⁴² Dysfunction in serotonin axis has been proposed as a cause for SUDEP due to depression of respiration and arousal.^{43,44} Adult mouse model for SUDEP suggest over activation of adenosine receptors as cause of SUDEP.

1.4. Takotsubo cardiomyopathy and SUDEP

Seizure-associated takotsubo cardiomyopathy (TKC) manifests frequently as sudden hemodynamic deterioration, which could result in death in the absence of adequate help. Probably some cases of SUDEP are attributable to takotsubo cardiomyopathy.⁴⁵ Patients with seizure-associated TKC differ from TKC patients due to other causes in being younger (61.5 vs. 68.5 years, $p < 0.0001$), more frequently male, suffer less frequently from chest pain, have a more serious course with a higher rate of cardiogenic shock and a higher recurrence rate. Most often TKC occurred following an acute symptomatic seizure rather than due to an underlying epilepsy raising concerns regarding its contribution to SUDEP. The pathogenetic mechanisms of TKC include coronary artery vasospasm, microcirculatory dysfunction, and transient obstruction of the left ventricular outflow tract. An excessive release of catecholamines seems to have a pivotal role in the development of TKC.⁴⁶ Compared with other emotional or physical triggers of TKC, catecholamine release due to seizures might be more excessive and last longer. If postictal TKC occurs outside the hospital, however, it may not be recognized promptly by the patient or his caregivers, and in the absence of medical assistance could be fatal.⁴⁷ However of the 44 cases reviewed from literature linked to TKC only 2 cases of documented SUDEP could be identified while all others recovered.^{48,49} One case of near SUDEP of cardiac origin with anteroseptal and anterior wall hypokinesia was believed to be secondary to chest compression during cardiopulmonary resuscitation (CPR) following ventricular fibrillation and not due to TKC.⁵⁰ Features of these 3 cases are given in table 2. Twelve case reports of TKC following electroconvulsive therapy (ECT) were available but none resulted in SUDEP. There were 7 documented cases of TKC, 4 cases of myocardial stunning, and 1 case of cardiogenic shock following ECT. Although TKC was not mentioned in 5 of the cases, some clinical characteristics were consistent with this diagnosis.⁵¹

1.5. Prevention of SUDEP

There is general agreement that a seizure control especially of generalised tonic clonic seizure is important to reduce SUDEP risk.^{14,21,43,55} There is evidence from meta-analysis that use of antiepileptic drugs (AEDs) to control epilepsy reduce the risk of SUDEP.⁵⁸ Use of efficacious dose of

Table 1: Factors that affect SUDEP risk

Factors	SUDEP risk
Age	Risk increases with advancing age compared to children. ⁷
Sex	Risk more among males compared to females. ^{8,9}
Habitual seizure onset	Risk increases with early onset of seizure Vs later onset ²¹
Intelligence quotient	Risk more among low IQ Vs normal intelligence ⁵²
Seizure frequency	Risk more among those with high seizure frequency Vs those in remission ^{21,28}
Seizure type	Risk more with GTCS compared to partial seizures ^{2,14,21,52,53}
Time of occurrence of seizure	Risk more with nocturnal seizures Vs daytime seizures ^{54,55}
AED therapy	Risk more with polypharmacy* than monotherapy ^{8,9,21,52,56}
AED compliance	Risk more with nonadherence ^{6,9,57}
Absence of TDM	Increases risk ¹⁷
Specific epilepsy syndromes	Dravet syndrome has an increased risk. ²⁷

* may be a surrogate marker for severity of disease, TDM= Therapeutic drug level monitoring

Table 2: Features of 2 cases of SUDEP and one case of near SUDEP with cardiac pump failure from literature

Author	Year	Sex	Age	Type of seizure	Duration of epilepsy	Interval between seizure and cardiac event	Cause of epilepsy/seizures	Type of TKC	Final outcome
Espinosa et al.	2009	F	51 y	Complex partial seizures of right temporal origin with secondary generalization	4 decades	immediately	Right mesial temporal sclerosis	No TKC*	Ventricular fibrillation-Recovered with CPR
Stoßlberger et al	2009	F	71	Generalised tonic clonic seizures	9 months	48 hours	Parahippocampal cavernoma	Apical	Died due to myocardial rupture
Kurisu et al	2010	M	78	NK	NK	NK	Epilepsy after brain infarction	Apical	Cardiogenic shock leading to in-hospital death

F= female; M= male; NK =not known; TKC= Takotsubo cardiomyopathy; *anteroseptal and anterior wall hypokinesia in this patient was believed to be secondary to chest compression during cardiopulmonary resuscitation (CPR) and not due to TKC.

adjuvant AED reduces the risk of SUDEP. Avoidance of polytherapy may also reduce the risk of SUDEP.²¹

Video-EEG data shows that early periictal nursing interventions reduce duration of respiratory dysfunction and reduces duration of PGES.³⁶ Duration of seizure was less with intervention.³⁶ Nursing interventions include administration of supplemental oxygen, oropharyngeal suction, and patient repositioning to prevent periictal suffocation and apnoea.

Patients with nocturnal seizures benefit from night supervision.^{14,52} Supervision includes sharing the same bedroom, and use of listening devices.^{14,52} Sleeping on the sides or back compared to prone position may reduce SUDEP risk which is an extrapolation from the sudden infant death syndrome (SIDS) recommendation. Surgery reduces the risk of SUDEP in patients who are surgical candidates.⁵⁹ Use of antiarrhythmic medication and implantation of combined cardiac pacemaker-defibrillator devices is not recommended as of now.⁶⁰

1.6. SUDEP in Children

SUDEP is rare among children.^{44,61} Two-thirds of death in children with epilepsy is not due to epilepsy. The SUDEP rates ranges between 1.1 and 4.3/10,000 patient years.⁵⁹ The risk factors include neurologic impairment^{7,44,61} poorly controlled epilepsy,⁶¹ children with learning disability,³ symptomatic or presumed symptomatic seizure.⁵¹ Polypharmacy and low AED levels are not risk factors in children.⁶⁰

Ictal hypoxia was seen in half of children with seizures and was more common during generalized seizures and while tapering antiepileptic medications. Ictal hypoxia was also associated with prolonged complex partial seizures. In contrast children had lower prevalence of ictal bradycardia.⁶² Cardiac dysregulation is seen in children with temporal lobe epilepsy especially right sided lesions.⁶³ Treatment following first episode of seizure is unlikely to alter the mortality in children with first unprovoked seizures.⁶⁴

1.7. Disclosure of SUDEP risk to patients and caregivers

Disclosure of the risk of SUDEP to patients is not routinely done even though UK National Institute for Health and Clinical Excellence (NICE) as well as Scottish Intercollegiate Guidelines Network (SIGN) guidelines for epilepsy recommend it. SUDEP discussion was done in only 4% of patients with epilepsy especially if they had ongoing seizures.⁶⁵ Only 8.76% of the Italian epileptologists discussed SUDEP with all their patients while 19.59% discussed with majority of their patients.⁶⁶ The American Epilepsy society and the Epilepsy Foundation Joint Task Force recommended that information should be provided to

people with epilepsy according to person's risk of SUDEP as part of the general epilepsy education. These include patients with generalised seizure, patients who are not compliant and patients who are candidates for epilepsy surgery. The discussion about SUDEP with those seeking the information is better done in the subsequent physician visits rather than at the first encounter. Majority (91%) of the parents of children with epilepsy wish to have discussions about mortality.[67]

2. Conclusions

Seizure associated TKC often occurs following the first episode of an acute symptomatic seizure raising concerns regarding its contribution to SUDEP. Seizure associated TKC patients have a more serious course with a higher rate of cardiogenic shock, and higher recurrence rate than TKC due to other causes. Though only 2 out of the 44 reported cases to date of TKC following seizure had resulted in death expert opinion argues that more cases of SUDEP can be attributed to it, probably going unreported. Treatment with adjunctive AEDs at efficacious doses and avoidance of polypharmacy where possible can reduce the incidence of definite or probable SUDEP. The discussion about SUDEP should be done by the physician with those seeking the information, preferably at subsequent visits rather than at the first encounter.

3. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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None.

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Ajith Cherian, Associate Professor <https://orcid.org/0000-0001-8743-9793>

Author biography

Divya K P, Assistant Professor <https://orcid.org/0000-0002-4695-8842>

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