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Review

Sudden unexpected death in epilepsy: The neuro-cardio-respiratory connection

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ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is the major cause of epilepsy-related premature mortality which targets preferentially younger people. Its etiology remains unknown. Several risk factors have been identified with generalized tonic-clonic seizures as the most important one; seizure control remains the most effective measure of prevention. Although some cases may be attributable to cardiac causes, mainly undiagnosed cardiac channelopathies, the majority appear linked to epilepsy-related disruption of the functional connectivity of certain brain structures associated with the central autonomic control of cardio-respiratory function (neuro-cardio-respiratory connection). Obtaining further data on its pathophysiologic mechanisms is a cardinal step towards preventing and reducing the incidence of SUDEP. Neuroimaging and molecular genetic studies may provide insights into the causes of SUDEP and identify potential biomarkers for risk stratification of patients susceptible to SUDEP. These issues are herein reviewed with emphasis placed on the neuro-cardio-respiratory functions affected by epilepsy and their genetic control and influences.

1. Introduction

Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related premature mortality with an annual rate ranging between 0.3 and 6 cases of SUDEP per 1000 adult persons with epilepsy and 1 case of SUDEP per 4500 children [1,2]. SUDEP accounts for 8–17% of deaths in people with epilepsy. The etiology of SUDEP remains unknown. It is defined as sudden, unexpected, non-traumatic, non-drowning death in an individual with epilepsy, witnessed or unwitnessed, in which autopsy does not reveal an anatomic or toxicologic cause for the death [3,4]. A main known risk factor is recurrent generalized tonic-clonic seizures and the most effective SUDEP prevention is seizure control.

Although the definition urges that drowning cases should not be considered as SUDEP, autopsy data have suggested otherwise [5,6]. A recent review of 47 deaths of people with epilepsy including 36 definite (76.6%) and 11 possible drowning deaths (23.4%), most of which occurred in a bathtub (72.3%), and 92 cases of SUDEP, revealed no distinguishable autopsy finding between SUDEPs and epilepsy-related drownings [5]. There were no drowning-related signs and no clear evidence of submersion. The authors concluded that SUDEP could be the cause of death in such possible drowning cases. This is in agreement with suggestions for unifying the definitions of SUDEP urging that "If the death occurs in water but without circumstantial or autopsy evidence of submersion, … the death be classified as possible SUDEP" [6].

The calamity of SUDEP preferentially targets young people [7], although it has been suggested that epilepsy-related mortality is underestimated in older adults [8]. Seizures often precede SUDEP [9,10]. Obtaining insight into its pathophysiologic mechanisms is a cardinal step towards preventing and reducing the incidence of SUDEP. It has been suggested that neuronal networks producing generalized tonic-clonic seizures suppress brainstem respiratory or autonomic control centers, leading to hypoventilation, apnea and cardiovascular (CV) collapse [11–13]. Furthermore, normal arousal mechanisms appear

Abbreviations: AED, antiepileptic drug(s); ANS, autonomic nervous system; AV, atrioventricular; cQT, corrected QT (interval); CV, cardiovascular; ECG, electrocardiogram; EEG, electroencephalogram; HRV, heart rate variability; LQT, long QT; LQTS, long QT syndrome(s); MRI, magnetic resonance imaging; SCA, sudden cardiac arrest; SUDEP, sudden unexpected death of epilepsy; TdP, torsade de pointes; VF, ventricular fibrillation; VNS, vagus nerve stimulation; VT, ventricular tachycardia

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compromised in these patients. There are genetic epileptic syndromes that have a very high risk of SUDEP [14,15]. Mutations in sodium and potassium channel and other genes co-expressed in the brain and the heart have been shown to be responsible for such syndromes. Disruption of the functional connectivity of brain structures associated with autonomic respiratory and cardiac regulation conferred by spreading of seizure activity to these structures may lead to SUDEP. All these issues are herein reviewed in an attempt to summarize current knowledge on this important topic of life and death in the epileptic population.

2. Mechanisms

Although underlying cardiac pathology accounts for the majority of sudden cardiac deaths [16], and has been reported, albeit as nonspecific findings, in some cases of SUDEP (e.g. myocyte hypertrophy and cardiac fibrosis up to one fourth of cases) [17,18], specific cardiac pathology (e.g. coronary artery disease or cardiomyopathy) has not been corroborated in any significant degree in the majority of patients with epilepsy and SUDEP [19]. Furthermore, a study reviewing data regarding the effect of generalized tonic-clonic seizures on the serum levels of cardiac troponin has indicated a lack of a significant troponin elevation, thus excluding any important role of myocardial injury after uncomplicated partial or generalized seizures at least for people with a healthy CV system [20]. Comparative differences between sudden cardiac death and SUDEP are outlined in Table 1.

Attention has been focused on respiratory and CV dysfunction as potential mechanisms of SUDEP [11]. Alterations in brain structure, function, and connectivity have been shown in subjects with epilepsy at risk for SUDEP [12]. Disruption of the central autonomic control could play a major role in SUDEP [13]. Studies using measurements of heart rate variability (HRV) indicative of autonomic function and imaging with magnetic resonance (MRI) have indicated that brainstem atrophy occurring in patients with epilepsy impairs autonomic control and can increase the risk for SUDEP if it expands into the mesencephalon (midbrain) [13]. However, the brainstem is not the only region involved in autonomic control; hippocampus and amygdala and possibly other parts of the brain (e.g. insular cortex) also play an important role in control of the autonomic nervous system (ANS) [21–25]. Other studies have suggested a functional connection between the amygdala and medullary respiratory network in humans and seizure spread to the amygdala may cause respiratory depression that may potentially contribute to SUDEP [23]. Another study identified structural changes with increased grey matter volume in the right anterior hippocampus/amygdala and parahippocampus, and decreased posterior thalamic grey matter volume, an area mediating oxygen regulation, in sudden death cases and people at high risk, when compared to those at low risk and controls [24]. The extent of reduction correlated with disease duration in all subjects with epilepsy. Other investigators have suggested the presence of intrinsic insular lesions or acquired insular damage in patients with refractory epilepsy as a potential risk factor for SUDEP [25,26]. An association between SUDEP and insula lobe epilepsy has been suggested based on the fact that ANS dysfunction is accentuated in these patients, and ANS dysfunction and peri-ictal cardiac or respiratory abnormalities appear to be important causes of SUDEP [25].

A study employing neuroimaging in temporal lobe epilepsy patients showed differences between patients at high and low risk for SUDEP in functional connectivity of brain structures associated with autonomic respiratory and cardiac regulation [12]. A subnetwork of reduced functional connectivity was shown in several areas previously linked to increased SUDEP risk [27], including the thalamus, brain stem, anterior cingulate cortex, putamen and amygdala. Additionally, a second subnetwork was shown with significantly elevated functional connectivity, which extended to medial/orbital frontal cortex, insula, limbic areas (hippocampus, amygdala), subcallosal cortex, brain stem, thalamus, caudate, and putamen.

The posterior thalamus plays a significant role in oxygen sensing [28] and in relaying afferent activity essential for breathing [12]. A disruption of the thalamic-brain stem link in high-risk SUDEP patients is particularly worrisome due to its involvement with respiratory failure in SUDEP. Involvement of the cingulate is also important as its stimulation leads to asystole—a potential SUDEP mechanism [29]. The reduced thalamic–cingulate connectivity among patients at high risk for SUDEP reflects a disruption of key pathways involved in central modulation of cardiorespiratory and blood pressure mechanisms (with ensuing prolonged hypotension) which again may be implicated in SUDEP [30]. Ictal hypotension has also been reported in ~9% among 91 patients monitored in the epilepsy monitoring unit; nevertheless, ictal hypertension seems to be a more common finding (~26%) [31].

The putamen with its projections to insula and the limbic system has a significant autonomic and motor regulatory role and a reduced connectivity between the putamen and cingulate cortex could disrupt vital ANS communications in patients at high risk of SUDEP [12,32].

The amygdala is involved in CV and respiratory control via its connections to the brain stem [33]. A reduced functional connectivity found between the amygdala and brain stem in high-risk SUDEP patients may lead to sustained and terminal apnea due to failed amygdala influences to trigger inspiratory efforts and recover from possible hypoventilation or apnea during seizures [12].

Thus, all these depressed or enhanced connections in various brain structures characterize patients with high SUDEP risk and when detected via the use of noninvasive neuroimaging may prove possible biomarkers after their validation in larger cohorts and patients with SUDEP which could help to identify high-risk patients and enhance SUDEP risk stratification [12].

In animal models, acid reflux-induced laryngospasm has been suggested as another possible mechanism of SUDEP [34]. Other investigators have attributed laryngospasm to seizure-induced recurrent laryngeal nerve activity; the induced severe laryngospasm contributed to the seizure- and hypoxemia-induced conditions that resulted in sudden death in the animal model, and the authors suggested that this mechanism could contribute to SUDEP [35].

According with the MORTEMUS study, a retrospective survey of 147 epilepsy monitoring units indicated 29 cardiorespiratory arrests,

Table 1
Comparative features of sudden unexpected death in epilepsy (SUDEP) and sudden cardiac death (SCD).

Feature	SUDEP	SCD
Underlying SHD	+/-	CAD / HCM*
Occurrence during sleep	+ + +	+/-
Prone position	+ + +	+/-
Gender	Men > women	Men > women
Risk factors (RF)	GTCS / uncontrolled "E" (see Table 2)	CV RF
VT/VF	+/-	+ + +
Asystole	+	+/-
Apnea	+ + +	+/-
ANS dysfunction	+ + +	+
Genetics	Epilepsy/SUDEP gene mutations	+FH / Cardiac channelopathy gene mutations
Prevention	AED	ICD
Autopsy	–	+

AED = antiepileptic drug(s); ANS = autonomic nervous system; CAD = coronary artery disease; CM = cardiomyopathy; CV = cardiovascular; "E" = epilepsy; FH = family history; GTCS = generalized tonic-clonic seizures; ICD = implantable cardioverter defibrillator; RF = risk factors; SCD = sudden cardiac death; SHD = structural heart disease (coronary artery disease, cardiomyopathy, etc); SUDEP = sudden unexpected death in epilepsy; VF = ventricular fibrillation; VT = ventricular tachycardia.

* coronary artery disease (CAD) is the most common underlying heart disease in adult victims (> 35 years of age) of sudden cardiac death, while hypertrophic cardiomyopathy (CM) is the underlying disease in younger patients.

including 16 SUDEP (14 at night), 9 near-SUDEP, and 4 deaths from other causes [36]. Cardiorespiratory data, available for 10 cases of SUDEP, showed a consistent and previously unrecognized pattern whereby rapid breathing (18–50 breaths per min) developed after secondary generalized tonic-clonic seizure, followed within 3 min by transient or terminal cardiorespiratory dysfunction. In those with transient cardiorespiratory dysfunction, this dysfunction later recurred with terminal apnea occurring within 11 min of the end of the seizure, followed by cardiac arrest. SUDEP incidence in adult epilepsy monitoring units was 5.1 per 1000 patient-years, with a risk of 1.2 per 10 000 video electroencephalogram (EEG) monitorings, probably aggravated by suboptimal supervision and possibly by antiepileptic drug withdrawal.

2.1. Neuro-respiratory connection

In certain cases, SUDEP may arise from primary respiratory arrest. Ictal apnea, predominantly of central origin, and resultant hypoxemia followed by bradycardia and asystole have well been documented, supporting the role of cardiorespiratory reflexes in SUDEP [37,38]. As mentioned, the MORTEMUS study showed a consistent pattern in patients with SUDEP during their postictal period with initial tachypnea and variable heart rate followed by bradycardia, transient apnea, and ensuing terminal apnea always preceding terminal asystole [36].

Respiratory depression causes hypoxemia [38] which though under normal conditions should stimulate arousal; if the arousal response to airway obstruction is also compromised, hypoxemia gets severe and may lead to death. The arousal reflex is further compromised by the *prone position* where most SUDEP victims are found. The impaired arousal in postictal patients may interfere with the brainstem autoresuscitation mechanism and prevent them from raising or turning their heads, while in the prone position their airway is obstructed by bed clothes and mattress [39]. Emerging evidence links *serotonin* to SUDEP [40]. A subset of serotonin-producing neurons, found in the midbrain serve as sensors of blood CO2 and tissue pH stimulating breathing to normalize blood gases. A defect in serotonin neurons in some epilepsy patients could explain the inadequate ventilatory response to rising CO_2 levels [41] and compromised patient arousal that under normal circumstances would have relieved airway obstruction, thus leading to patient's death in bed [42]. There are preliminary data that selective serotonin reuptake inhibitors may mitigate the severity of ictal hypoxemia [43].

There is experimental evidence that endogenous *adenosine* is a potent inhibitory neuromodulator that exerts an anticonvulsant effect [44–46]. It appears that during seizure activity, adenosine levels increase in the hippocampus, both in experimental animals and in patients with intractable complex partial seizures [44]. Central adenosine A1 receptors seem to mediate these anticonvulsant effects and their stimulation may play a role in the anticonvulsive potential of diazepam, phenobarbital, valproate and gabapentin [47]. Altered function of this purinergic system may contribute to ictogenesis and epileptogenesis. Thus, there may be a therapeutic potential of adenosine augmentation for the suppression of epileptic seizures, but more importantly for the prevention of epilepsy and its progression overall [48]. However, adenosine not only inhibits seizures, but it also inhibits cardiac and respiratory function and some investigators have implicated a surge in adenosine as a result of prolonged seizures combined with deficient adenosine clearance in the development of SUDEP [49]. Whether blockade of adenosine receptors may prevent SUDEP remains to be seen.

Seizures may induce the release of endogenous opioids which produce central hypoventilation and postictal apnea, which when severe can increase the SUDEP risk [50]. A study (ENALEPSY) is planned to evaluate the efficacy of naloxone, an opioid antagonist, in reducing postictal respiratory dysfunction in patients with epilepsy [51]. As mentioned, a functional connection has been suggested between the amygdala and medullary respiratory network in humans with evidence that seizure spread to the amygdala may cause loss of spontaneous breathing accompanied by loss of dyspnea and awareness of apnea with the potential to contribute to SUDEP [23].

Neurogenic pulmonary edema caused by generalized tonic-clonic seizures, especially of longer duration, could be a cause of SUDEP [11,14,52]. Postictal pulmonary edema is frequently (~70%) present at autopsy in cases of SUDEP [18]. Radiographic abnormalities are not uncommon following generalized tonic-clonic seizures; a study where chest X-rays were obtained in 24 patients following generalized seizures reported that 11 patients had radiographic abnormalities with signs of pulmonary edema found in 7 (29%) patients [53]. The presence of chest X-ray abnormality was significantly associated with the duration of the preceding seizures.

Animal studies have indicated that oxygenation prevents sudden death in seizure-prone mice and suggest that oxygenation might protect some seizure-prone humans at risk for SUDEP [54]. Some recent human data indicated that occurrence of postictal generalized EEG suppression noted after generalized convulsive seizures was prevented by early administration of oxygen [55]; however, whether there is a relationship of this generalized EEG suppression to SUDEP and whether we should consider routinely providing oxygen at the time of a generalized convulsive seizure remains to be seen [56].

2.2. Neuro-cardiac connection

Certain groups of patients with epilepsy may be more prone to ANS dysfunction than others, such as patients with long lasting and/or frequent seizures, patients with chronic and/or refractory epilepsy, untreated or non-compliant patients, patients using alcohol and/or recreational drugs, and patients with cardiac dysautonomia [57,58].

As mentioned, enhanced functional connectivity of certain brain structures may be involved in SUDEP patients leading to increased vagal modulation, conferred by increased functional connectivity between the right anterior hippocampus and the ventral medial prefrontal cortex [59]; hypotension may follow increased connectivity between the insulae and the orbitofrontal cortex/frontal medial cortex; the high functional interconnectivity among high-risk patients between the amygdalae and hippocampi poses a risk of deleterious influences on both breathing (apnea) and blood pressure (hypotension) [12]. High functional connectivity of subcallosal cortex with the amygdala, orbitofrontal cortex, and thalamus, may also produce hypotension [12,60]. The basal ganglia participate heavily in autonomic regulation, which likely follows from their prominent projections to the lateral hypothalamus and nuclei in the brain stem [12].

Although epilepsy is a genetically complex and heterogenous disease, several neuro-cardiac genes have been identified that can serve as genomic biomarkers of disease severity and outcome that could possibly predict the occurrence of SUDEP [50,61]. Other candidate genes may even appear protective. Thus, gene profiling may aid diagnosis, risk assessment and identification of patients at high SUDEP risk, and possibly specific drug selection for individual patient management.

In a study of sudden cardiac death in 490 children and young adults (ages 1–35 years) with no history of epilepsy, only 4 cases of unexplained sudden cardiac death (6%) were identified in which the person had probable pathogenic variants in epilepsy genes, suggesting that undiagnosed genetic epilepsy is uncommon in cases of unexplained sudden cardiac death [62]. On the other hand, in another study, among 61 cases of SUDEP, 25% had pathogenic or probably pathogenic variants in epilepsy genes, while a sizeable proportion (22%) had clinically relevant mutations in cardiac arrhythmia genes; specifically, 7% had mutations in the three common genes for the long-QT syndrome (LQTS), while a further 15% had candidate variants in genes potentially predisposing to malignant cardiac arrhythmia [63]. These data suggest that sudden cardiac death was probably a contributing cause of SUDEP, albeit a predictable and preventable cause should the correct

antemortem diagnosis had been rendered. Furthermore, some patients may have an unfortunate combination of epilepsy and LQTS genetic determinants [63,64]. It has been shown in the animal model that LQTS mutations, such as those in the KCNQ1 gene which encodes the cardiac KvLQT1 delayed rectifier channel and is also found in brain epileptic regions, may cause epilepsy and concurrent autonomic dysregulation of the heart, indicating a dual arrhythmogenic potential of an ion channelopathy coexpressed in heart and brain [64]. These genetic issues are further discussed below.

2.2.1. Bradyarrhythmias

Seizure-related bradyarrhythmias are relatively uncommon [65]. Ictal bradycardia occurs in 2–7%, while ictal asystole in as few as 0.3–3% of seizure patients, more commonly resulting from apnea rather than occurring as a primary event [66–69]. Approximately two-thirds of the patients with ictal bradycardia or asystole have temporal lobe epilepsy [70]. Rarely, may patients suffer from two concurrent conditions, such as intrinsic sinus node dysfunction producing long pauses and asystole necessitating pacemaker insertion and temporal lobe epilepsy requiring antiepileptic drug therapy [71].

Ictal bradycardia usually follows autonomic alterations (extrinsic sinus node dysfunction) that may result either from a sympathetic inhibition or from a parasympathetic activation probably due to the ictal discharge affecting structures of the central autonomic network. Among 63 reviewed cases of ictal bradycardia, ~76% of patients had seizures localized at the temporal or frontotemporal lobe [70]. Although a left hemispheric localization of seizure onset has been suggested [72], other investigators have reported that the majority of patients with the "ictal bradycardia syndrome" have bilateral hemispheric seizure activity at bradycardia onset [73].

In a study of neurogenic cardiac arrhythmias in 20 patients with epilepsy, an implantable loop recorder revealed ictal bradycardia (< 40 bpm) in 8 (2.1%) recorded events, in 7 patients [74]. Four patients (21%) had bradycardia or periods of asystole with subsequent permanent pacemaker insertion. Three of these four (16% of total) patients had potentially fatal asystole. In addition to sinus bradycardia and asystole, ictal atrioventricular (AV) block has also been reported, also attributable to ictal activity in central autonomic networks [75–77]. The above notwithstanding, there are no data suggesting that pacemakers can prevent SUDEP.

According to a retrospective analysis of 1244 patients with medically intractable epilepsy, ictal asystole was rare, observed in only 5 patients [67]. In these patients, 11 asystolic events, between 4 and 60 s long in a total of 19 seizures, were registered. All seizures had a focal origin identified as simple partial seizures (n = 13), complex partial seizures (n = 4), and secondarily generalized seizures (n = 2). One patient showed the longest asystole ever reported (60 s) because of a seizure. Cardiac asystole occurred in two patients with left-sided temporal lobe epilepsy and in three patients with frontal lobe epilepsy (two left-sided, one bifrontal). Two patients reported previous cardiac disease, but only one had a pathologic electrocardiogram (ECG) by the time of admission. Two patients had a simultaneous central ictal apnea during the asystole. None of the patients had ongoing deficits due to the asystole.

It has been suggested that female gender and preexisting cardiac disease could predispose to new-onset (< 1 year) ictal asystole, while male-predominant changes in neuronal networks in chronic, intractable epilepsy and concurrent autonomic dysregulation may facilitate late-onset (≥ 1 year) ictal asystole [72].

2.2.2. Tachyarrhythmias/ sudden cardiac death

Peri-ictal tachycardia is almost always occurring in the form of sinus tachycardia, however, potentially malignant ventricular tachycardias are rare [58]. Of course, in case of underlying ischemic heart disease, sinus tachycardia can precipitate ischemia with its attendant consequences, one of which might be the induction of ventricular tachycarrhythmia and sudden cardiac death. Underlying pathologic repolarization (LQTS) might be another cause of malignant ventricular tachyarrhythmias precipitated by sympathetic activation. De novo ictal/postictal ventricular tachyarrhythmias without other apparent underlying causes are very rare [66,78]. Of course in patients with epilepsy and comorbid LQTS, sudden cardiac arrest (SCA) due to ventricular arrhythmia is a plausible and probable cause of sudden death (see discussion below).

An investigation, part of the Amsterdam Resuscitation Studies (ARREST) in the Netherlands, was designed to assess the risk of SCA in the general population [79]. A diagnosis of active epilepsy was ascertained in all cases and controls. A total of 1019 cases of SCA with ECG-documented ventricular fibrillation (VF), were identified and matched to 2834 controls. There were 12 people with active epilepsy among cases and 12 among controls. Epilepsy was associated with a 3-fold increased risk for SCA (adjusted odds ratio - OR 2.9; p = 0.034). The risk for SCA in epilepsy was particularly increased in young and females. The authors concluded that epilepsy in the general population seems to be associated with an increased risk for SCA. It should be noted that in the majority of the SCA cases (11/12) there was no evidence of seizure activity preceding SCA, indicating that sudden death in epilepsy may not always be seizure-related.

2.2.3. Long QT syndrome and epilepsy

The long QT-syndrome (LQTS), either congenital or acquired, is characterized by polymorphic ventricular tachycardia (VT), syncope and sudden cardiac death [80]. Ventricular tachycardia appears in the distinctive form of self-terminating episodes or runs of rapid polymorphic VT, designated as torsade de pointes (TdP), due to its gradual change (twisting) in the QRS morphology and axis. The arrhythmia episodes self-terminate but recur frequently, however they may occasionally degenerate into VF causing SCA. The TdP episodes produce syncope during which seizure-like (epileptiform) activity is quite common (convulsive syncope), and patients with LQTS have been occasionally erroneously diagnosed with epilepsy [81]. However, there may be some overlap between the congenital LQTS and epilepsy, since mutations within the LQTS genes have also been found in patients with epilepsy; this has been reported for the *KCNQ1* gene causing congenital LQTS type 1 (LQT1) which has been shown to also cause epilepsy [82]. On the other hand, a seizure phenotype has been more commonly ascribed to patients with LQT2 compared to other types of LQTS, resulting in having these patients labelled as having epilepsy in up to ~40% of the cases and thus treated with antiepileptics [83]; whether some of the epileptiform episodes represent true epileptic activity has not been entirely clear in the absence of EEG recordings. In other studies, EEGs were reported positive in ~1.6% of LQTS patients with a higher (~4%) representation of LQT2 patients, and even higher prevalence (~15%) of positive EEGs among LQTS patients presenting with seizures or seizure-like episodes; thus, a hypothesis emerges that certain ion channels, like the KCNH2-encoded potassium channel responsible for LQT2, which are co-expressed in both the heart and the brain, may be the shared pathogenetic link [84]. Abnormal EEGs, but not typical of epilepsy, have been reported in up to ~70% of LQTS patients, again indicating a possible link between cardiac and cerebral channelopathy [85].

An important issue regarding the overlap of LQTS and epilepsy relates to the acquired form of LQTS, which may even develop as a complication possibly of anti-epileptic but more commonly of other QT-prolonging drugs employed for common comorbid conditions, such as infections or psychiatric disorders, which may lead to potentially fatal arrhythmias (TdP), thus clouding the diagnosis of SUDEP [86,87].

2.2.4. Heart rate variability / T-wave alternans

A reduced heart rate variability (HRV) has been shown to predict arrhythmic mortality in conditions other than epilepsy, e.g. after acute myocardial infarction, in heart failure, diabetic neuropathy, and stroke

[88]. Subsequent studies have also shown that patients with drug-resistant epilepsy have both increased heart rates and lower HRV measures, which indicate a high probability that sudden cardiac death may be the cause of SUDEP in some patients [89]. Other investigators have indicated that epilepsy patients with sodium channel (SCN) gene mutations have severe ANS dysfunction characterized by lower HRV, suggesting HRV as a potential biomarker for SUDEP risk [90]. However, newly diagnosed patients with epilepsy, as compared to patients with chronic epilepsy, have normal HRV values [91]. Finally, a meta-analysis of 39 studies indicated that there is a sympathovagal imbalance in epilepsy, as shown by lower HRV values compared to controls, suggesting that a lower vagal and higher sympathetic tone may be predictors of CV morbidity and mortality in epilepsy patients [92]. Thus, some investigators consider a low HRV as a potential risk factor for SUDEP [92], while others have proposed HRV as a potential biomarker for monitoring a progressive decline of the ANS in patients with epilepsy [93]. T-wave alternans, also considered a marker of risk of sudden cardiac death and CV mortality, albeit with a low positive predictive value, has been found to be increased postictally; however, its value for risk stratification in epilepsy patients remains doubtful [94].

In *summary*, various brady- and/or tachy-arrhythmias have been reported in patients with epilepsy during or after seizure activity, attributable to seizure activity arising in or spreading to autonomic neural networks. There is some evidence from clinical observations of hemispheric lateralization, with right-sided seizures causing peri-ictal tachycardia, and left-sided seizures resulting in peri-ictal bradycardia and asystole [67,95]. Postictal arrhythmias may be more prone to induce SUDEP according to a recent systematic literature search [66]. This search identified 7 distinct patterns of ictal/postictal cardiac arrhythmias; ictal asystole (103 cases), postictal asystole (13 cases), ictal bradycardia (25 cases), ictal AV block (11 cases), postictal AV block (2 cases), (post)ictal atrial flutter/atrial fibrillation (14 cases) and postictal VF (3 cases). Ictal asystole had a mean prevalence of 0.318% in people with refractory epilepsy who underwent video-EEG monitoring. Ictal asystole, bradycardia and AV-conduction block were self-limiting in all but one of the cases and seen during focal dyscognitive seizures. Seizure onset was mostly temporal (91%) without consistent lateralization. Postictal arrhythmias were mostly found following convulsive seizures and often associated with (near) SUDEP [66].

Finally, the overlap between LQTS and epilepsy needs to be considered by paying particular attention to measure the corrected QT (QTc) interval in all patients diagnosed with epilepsy and to obtain detailed family history from each patient (congenital LQTS), while monitoring the QTc when therapies with QT-prolonging drugs are prescribed (acquired LQTS).

3. Risk factors

Several risk factors predisposing to SUDEP have been considered (Table 2, Fig. 1). The most important clinical risk factor for SUDEP is the frequency of generalized tonic-clonic seizures [96]. There is also a strong association of SUDEP with sleep and nocturnal seizures, with ~70% of cases of SUDEP noted during sleep [97]. Younger (< 40 years) patients are also more likely to die in sleep. The prone body position is also an important contributory factor [39]; patients with nocturnal seizures appear to have a 6-fold higher likelihood to die in a prone position than those with diurnal seizures [97]. Other risk factors for SUDEP include refractory epilepsy, tonic-clonic seizures, longer seizure duration, periods during which the patient is not observed or monitored, antiepileptic drug (AED) polytherapy and the lack of therapeutic AED levels at death have all been correlated with increased SUDEP risk; in most studies, no relation has been found between SUDEP risk and a specific AED [1,11]. Ictal and postictal effects on autonomic functioning and accidental suffocation are commonly considered potential factors. As mentioned, low HRV values may be a potential risk factor for SUDEP [92].

Table 2
SUDEP risk factors.

- Generalized tonic–clonic seizures
- Young age (15–45 years old)
- Early onset of epilepsy
- Male gender
- Subtherapeutic antiepileptic drug (AED) levels
- Chronic uncontrolled epilepsy
- Frequent seizures / unobserved seizures
- Sleep / Nocturnal seizures
- Prone position
- Long duration of seizure disorder / Status epilepticus
- AED polytherapy
- Insula lobe epilepsy
- Alcohol and recreational drugs
- Concomitant channelopathies (e.g. LQTS)
- Specific genomic biomarkers (neurocardiac or neurorespiratory epilepsy gene variants)
- Low HRV
- Comorbid mental disorder or psychosis

AED = antiepileptic drug(s); HRV = heart rate variability; LQTS = long QT syndrome; SUDEP = sudden unexpected death in epilepsy.

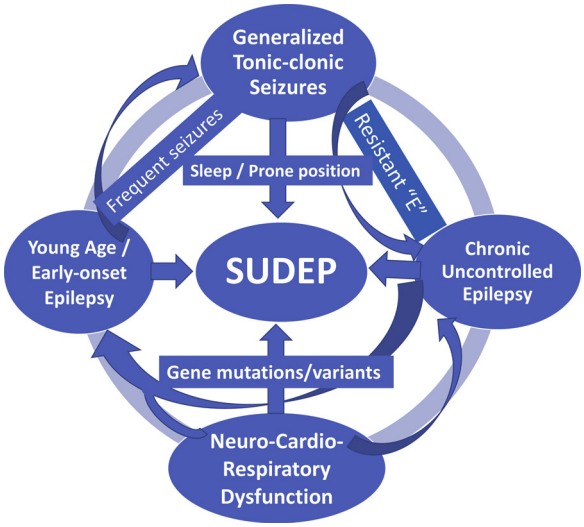

Fig. 1. The schema depicts the inter-relationship of clinical and genetic risk factors leading to sudden unexpected death in epilepsy (SUDEP). Among the potential mechanisms involved in SUDEP, the epilepsy-related disruption of the central autonomic control leading to cardio-respiratory dysfunction predominates, with resultant respiratory and/or cardiac arrest. Various brady- and/or tachy-arrhythmias have been reported in patients with epilepsy during or after seizure activity, attributable to seizure activity arising in or spreading to autonomic neural networks. Several risk factors predisposing to SUDEP have been considered, with frequent generalized tonic-clonic seizure activity being the most important clinical risk factor, followed by young age and early-onset epilepsy, chronic uncontrolled or resistant epilepsy, with a strong association with seizures occurring during sleep and in a prone position. Although epilepsy is a genetically complex and heterogenous disease, several neuro-cardiac genes have been identified that can serve as genomic biomarkers of disease severity and outcome that could possibly predict the occurrence of SUDEP and help decrease its incidence (see text for further discussion). "E" = epilepsy.

Although a score, the SUDEP-7 Inventory score (that includes varying numbers and types of seizures, duration of epilepsy, number of anti-epileptic drugs and retardation), or the use of independent SUDEP risk factors have been proposed to risk-stratify epilepsy patients for SUDEP, these tools have not been clinically validated [98]. Thus, currently our ability to apply this information clinically and predict SUDEP risk in individual patients or patient groups remains limited.

4. Genetics

Data on the genetics of SUDEP are slowly emerging and relate to mutations or variants of cardiac, epilepsy and respiratory genes [14,99]. Apart from gene mutations responsible for cardiac channelopathies that have also been implicated in neuronal channelopathies, such as LQTS gene variants involved in SUDEP, already discussed, there are other epilepsy and respiratory genes that confer a high incidence of SUDEP, according to data mainly emanating from studies of animal models [15]. Some genetic mutations in genes implicated in SUDEP may not be directly responsible for increased SUDEP risk independent of seizure severity and frequency, but they are rather causes of severe and refractory epilepsy with general tonic-clonic seizure activity known to predispose to SUDEP (e.g. SCN1A, DEPDC5, SCN8A, dup15q).

Genetic disorders causing epileptic encephalopathies and other severe forms of epilepsy confer high rates of SUDEP and status epilepticus, e.g. in Dravet syndrome [100,101]. In Dravet syndrome (severe myoclonic epilepsy of infancy), a SCN1A neuronal channelopathy, triggered by hot temperatures or fever [102], the mortality rate/1000-person-years was found high at 15.8, as was the SUDEP rate at 9.3/1000 person-years, much higher than other pediatric epilepsies and even higher than the 5.1 SUDEP rate/1000-person-years for adults with refractory epilepsy [100]. A high incidence of SUDEP has also been reported in children with early-infantile epileptic encephalopathies caused by mutation of the SCN8A gene; but, again, this syndrome causes seizures typically refractory to medical treatment that may account for the high SUDEP risk, rather than a direct effect on cardiorespiratory function [103].

Genes encoding components of the amino acid–sensitive branch of the mechanistic target of rapamycin (mTOR) signaling pathway have been implicated in familial focal epilepsies [104]. The GATOR1 (GAP activity towards rags complex 1) complex, comprising DEPDC5 (DEP domain containing protein 5), NPRL2 (nitrogen permease regulator-like 2) and NPRL3, is a repressor of the mTOR complex 1 (mTORC1) pathway. Variants of the GATOR1-encoding genes are found in ~1/3 of familial focal epilepsies, whereby the phenotypic spectrum ranges from sporadic to familial focal epilepsies, with key features early-onset, sleep-related and drug-resistant epilepsies, with SUDEP occurring in ~10% of the families [104].

SUDEP is not limited to treatment resistant epilepsies. Thus, the suspicion remains that there are other epilepsy genes that increase SUDEP risk beyond the increased risk related to epilepsy severity. As mentioned, seizure-related respiratory compromise during sleep, followed by bradyarrhythmia and apnea, is a common scenario in monitored SUDEP. Many ion channel genes regulating the central control of cardiac and respiratory function are expressed within the brain epileptogenic networks; they include sodium channels (SCN1A/ SCN2A/ SCN3A/SCN9A/SCN8A/SCN1B), or potassium channels (KCNA1/ KCNQ2). Mutations in these genes may contribute to the mechanism of death by disrupting autonomic function, leading to cardiac and/or respiratory dysfunction, more prolonged postictal depression of arousal and interfering with post-ictal autonomic recovery [105,106].

As detailed above, SUDEP is also associated with variants and mutations of neuro-cardiac channelopathy genes [58]. The presence of LQT gene mutations in SUDEP suggests that a seizure could provoke a lethal cardiac arrhythmia, or SCA could occur independently of a seizure. Both possibilities may occur in some cases.

As mentioned, in certain cases, SUDEP may arise from primary respiratory arrest leading to apnea, where the arousal reflex is further compromised by the prone position where most SUDEP victims are found. Emerging evidence links serotonin to this process responsible for a dysfunctional arousal mechanism culminating into SUDEP [40,42]. There are some data that polymorphisms in serotonin genes may contribute to susceptibility to obstructive sleep apnea [107]; whether they can also produce ictal/postictal apnea remains to be seen. As already mentioned, there are preliminary data that selective serotonin reuptake inhibitors may mitigate the severity of ictal hypoxemia [43].

As mentioned, central hypoventilation and apnea may be related to seizure-induced release of endogenous opioids [108]. Epilepsy patients with polymorphisms (e.g. in the ARRB2 gene, which encodes beta-2-arrestin, a protein that is involved in modulating desensitization response in G-protein-coupled receptors, including opioid receptors) which impair desensitization of brainstem opioid receptors in response to seizure-related endogenous opioid release may suffer from more severe postictal apnea, thereby increasing SUDEP risk [50]. Gene variants related to glutamateric and GABAergic neurotransmission have also been identified that could influence excitatory/inhibitory balance and increase risk of epilepsy, seizure severity or centrally mediated autonomic dysfunction [50].

In *summary*, evidence is emerging for a genetic susceptibility to SUDEP, suggesting a highly polygenic contribution to SUDEP causation [99]. Genetic analysis in patients at high SUDEP risk for mutations or variants in cardiac arrhythmia, epilepsy and respiratory genes [15,99], together with post-mortem genetic testing (molecular autopsy) [14,50] may provide insights into the causes of SUDEP and identify potential genetic biomarkers for risk stratification of patients prone to SUDEP with the aim towards reducing the individual patient's risk of SUDEP.

5. Prevention

Freedom from recurrent seizures and particularly generalized tonic-clonic seizures has been advocated as the best strategy to mitigate the risk of SUDEP [109]. A meta-analysis of 112 randomized controlled trials (RCTs) assessing the risk of SUDEP in patients given adjunctive antiepileptic treatment for refractory seizures indicated that definite or probable SUDEP, all SUDEP, and all causes of death were significantly less frequent in the efficacious antiepileptic drug group than in the placebo group, with odds ratios of 0.17 ($p = 0.0046$), 0.17 ($p = 0.0046$), and 0.37 ($p = 0.0131$), respectively [110]. Rates of definite or probable SUDEP per 1000 person-years were 0.9 in patients who received efficacious antiepileptic drug doses and 6.9 in those allocated to placebo. The authors concluded that treatment with adjunctive antiepileptic drugs at efficacious doses may have reduced the incidence of definite or probable SUDEP by more than 7-fold compared with placebo in patients with previously uncontrolled seizures.

Surgery for drug-refractory epilepsy might reduce mortality, including deaths from SUDEP. Among 215 patients with temporal lobe epilepsy undergoing surgery, patients who were seizure-free ($n = 148$) had a 2% death rate compared with the 11.9% of patients who still had seizures after surgery [111]. In another surgical series of 306 epilepsy patients, the risk for premature death decreased over time but remained above the standard population (6 SUDEP cases / observed rate of 1 in 595 person-years) [112].

Monitoring medication adherence and avoidance of triggering factors may effectively prevent SUDEP [8,113]. Treating psychiatric comorbidities, such as depression and substance abuse, may also promote treatment compliance and prevent SUDEP [114]. Also, avoiding proarrhythmic drugs and conditions (e.g. electrolyte disturbances) will be beneficial by preventing potentially fatal arrhythmias [86].

As mentioned, some cases of SUDEP may be mistaken for epilepsy-related drownings, albeit with no distinguishable autopsy finding between SUDEPs and epilepsy-related drownings, suggesting that SUDEP could be the cause of death in such possible drowning cases [5]. As most of such drowning/possible SUDEP cases occur in the bathtub, supervision and specific bathing precautions could be effective prevention strategies. Also, nocturnal supervision and monitoring of patients with a history of nocturnal epilepsy with tonic-clonic seizures or other high-risk patients might help prevent SUDEP [11,39,115].

Dietary and healthy lifestyle measures have also been proposed to mitigate the occurrence of epilepsy and SUDEP; these include consumption of ω-3 fatty acid supplements, avoidance of alcohol, and engagement in physical activity [116]; however, the data on the effects

of ω-3 fatty acids remain inconclusive and non-convincing [117,118].

Although accumulated data support the effectiveness of vagus nerve stimulation (VNS) in patients with refractory epilepsy, its role and impact on mortality and SUDEP remains unsettled [119,120]. Some data suggest that it might reduce the risk of SUDEP [121,122], but not consistently [123]. Furthermore, studies reporting a decline of SUDEP during follow-up lack a control group [122], thus making it impossible to ascribe this effect to VNS treatment or simply to the natural course of SUDEP risk, which other studies have shown to be decreasing overtime with duration of follow-up [124].

With regards to the occurrence of post-ictal asystole, a possible suspect as a potential cause of SUDEP in some cases, there are no data suggesting that pacemakers can prevent SUDEP [125,126]. A reflex mechanism with excessive vagal tone has been implicated in these instances [125], and modification of anti-epileptic drugs for a more effective control of seizures may be the best preventive method, with pacemaker implantation reserved for particularly long periods of asystole [126], associated with significant morbidity (falls and accidents) [127,128].

Seizure detection systems have been used to alert observers to intervene when seizures start [129]. The gold standard for seizure monitoring is the video/EEG, which though is used in controlled environments such as epilepsy monitoring units (EMUs). Home-based seizure monitoring devices are also available; both non-EEG systems that combine detection methods for movement and heart rate [130], as well as automatic computer-based seizure detection and warning multimodal systems (EEG, ECG, electromyography, oximetry, etc.) have been introduced [131]; however, despite sensitivities over 70% provided by most of these systems, specificity expressed as false alarm rates still lags behind.

As mentioned, administration of oxygen at the time of a generalized convulsive seizure to prevent generalized EEG suppression has been suggested as a potential preventive measure of SUDEP, however, this still remains speculative [55,56].

Finally, genetics appear promising in identifying neuro-cardio-respiratory genes implicated in SUDEP and may possibly lead to targeted preventive therapies in some of these epilepsy patients who are at high risk for SUDEP [104].

6. Conclusion

The incidence of sudden death is many-fold higher in an epilepsy population than for the general public. SUDEP is the major cause of epilepsy-related premature mortality which targets preferentially young people. SUDEP risk increases with the severity of epilepsy. The central autonomic network includes reciprocally connected cortical limbic areas and subcortical regions. Seizures can arise in any cortical region and spread to involve other cortical and subcortical regions of the central autonomic network. Ictal activity that arises in or spreads to the central autonomic network, can disrupt functional connectivity of this network by inhibiting or activating autonomic areas, causing diverse autonomic manifestations, including respiratory and cardiovascular dysfunction, which are potential mechanisms of SUDEP (neuro-cardio-respiratory connection).

Several SUDEP risk factors have been identified with generalized tonic-clonic seizures as the predominant risk factor. Seizure control remains the most effective measure of prevention. Cardiac causes, mainly undiagnosed cardiac channelopathies, may be the cause in some cases of SUDEP. However, the majority appear linked to epilepsy-related cardio-respiratory autonomic dysfunction. Control of epilepsy, and particularly control of generalized tonic-clonic seizures is the initial best strategy to reduce the risk of SUDEP.

Advancing our knowledge on the pathophysiologic mechanisms of SUDEP is a most important first step towards preventing and reducing its incidence. Neuroimaging and molecular genetic studies may provide insights into the causes of SUDEP and identify potential biomarkers for risk stratification of patients susceptible to SUDEP that may help reduce the individual patient's risk of SUDEP.

Conflict of interest

None to be declared.

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