Sudden unexpected death in epilepsy (SUDEP) accounts for 5-30% of deaths in patients with epilepsy. Past research has attempted to reveal these mechanisms, but the specific risk factors and pathophysiology have not been established. Inherited lethal cardiac arrhythmias can be erroneously diagnosed as epilepsy. A diagnosis of coexistent epilepsy cannot be completely excluded in the inherited cardiac arrhythmias but the differential diagnosis is often challenged. SUDEP may be attributed to seizure-induced fatal cardiac arrhythmias or cardiopulmonary dysfunction as a secondary cause. The expanding knowledge base has increased the understanding of the structure-function and genotype-phenotype relationships of ion channels and has provided insights into the pathophysiological basis of common diseases such as cardiac arrhythmias and epilepsy. In this review, the mechanisms for SUDEP and the possible relationships between epilepsy and inherited cardiac arrhythmias as “neuro-cardiac channelopathy” have been discussed based on clinical and genetic evidence.

Keywords: Inherited cardiac arrhythmia; Epilepsy; Sudden unexpected death; Channelopathy


Sudden unexpected death in epilepsy and inherited cardiac arrhythmia

Sudden unexpected death in epilepsy (SUDEP) has been receiving increased attention. SUDEP events are not uncommon and are regularly encountered by clinicians. Although SUDEP accounts for 5-30% of deaths in epileptic patients [1], the pathophysiological mechanisms behind SUDEP have not been confirmed. Past research has attempted to reveal these mechanisms, but the specific risk factors and pathophysiology have not been established. Poor incident case reporting, inaccurate death certification and fewer post-mortem examinations have limited the accuracy of data on the epidemiology of SUDEP. The mechanisms behind SUDEP include cardiac arrhythmias, cardiopulmonary dysfunction and autonomic dysregulation induced by epilepsy.

Recently, coexistence of inherited cardiac arrhythmias in epilepsy has been proposed as a concept called "neuro-cardiac channelopathy". This proposed primary cause affecting both lethal cardiac arrhythmias and epilepsy has been hypothesized [2]. These findings highlight the benefits of risk factor modification for the prevention of premature and sudden unexpected death in patients with epilepsy [3]. The expanding knowledge base has considerably increased the understanding of the structure-function and genotype-phenotype relationships of voltage-gated sodium channels and has provided insights into the pathophysiological basis of common diseases such as cardiac arrhythmias and epilepsy [4].

This review will discuss the mechanisms behind SUDEP and the possible relationships between epilepsy and inherited cardiac arrhythmias as neurocardiac
channelopathy.

**Misdiagnosis of inherited cardiac arrhythmias as epilepsy**

Before the concept of neurocardiac channelopathy is deliberated, prior reports of misdiagnosis of cardiac arrhythmias as epilepsy should be reviewed.

It has been demonstrated that inherited lethal cardiac arrhythmias can be erroneously diagnosed as epilepsy. Pignata et al. reported that neurologic paroxysmal symptomatology, wrongly considered idiopathic epilepsy, should be interpreted as a consequence of an underlying cardiac abnormality [5]. Pediatric cases have also often been reported [6]. Ballardie et al. showed that Romano-Ward syndrome characterized by QT interval prolongation was presented as an epileptic seizure [7]. Hunt et al. reported that long QT syndrome (LQTS) often presents as epilepsy, delaying treatment and increasing the risk of sudden cardiac death [8].

Cardiac channelopathies can be misdiagnosed as refractory epilepsy when in fact, these events similarly represent convulsive syncope [9]. Rutter et al. reported a familial case. A mother and her three children presenting with syncope induced by exercise and emotions were diagnosed with epilepsy. Ambulatory electrocardiography showed frequent ventricular and supraventricular tachyarrhythmia [10]. A 21-month-old infant presented with episodes of decreased consciousness and seizures during fever. During a typical episode, rapid ventricular tachycardia was documented. Resting 12 lead electrocardiography revealed Brugada type electrocardiogram [11]. Febrile seizures mimic manifestation of Brugada syndrome; syncpe and seizures during high fever. The seizure episodes in the most misdiagnosed cases were judged to be cardiac arrhythmias. A diagnosis of coexistent epilepsy cannot be completely excluded in the inherited cardiac arrhythmias but the differential diagnosis is often challenged. Epilepsy, a disorder of neural function, is also associated with abnormal channel function. We reported a LQTS type2 case with a history of epilepsy [12]. The possibility that some channelopathies can manifest as both inherited cardiac arrhythmias and epilepsy has also been discussed.

**Epilepsy-induced cardiac arrhythmia as a secondary cause**

Sudden unexplained deaths may be attributed to seizure-induced fatal cardiac arrhythmias or cardiopulmonary dysfunction. Prior studies have discussed secondary pathophysiological causes of SUDEP. Cardiac arrhythmias and conduction abnormalities are common during seizures in intractable epilepsy, particularly those that are prolonged or generalized. These conduction abnormalities have been shown to contribute to SUDEP [13]. Long-term epilepsy can cause physiological and anatomical autonomic instability resulting in lethal cardiac arrhythmias. A wide range of cardiac arrhythmias is commonly seen during ictal, interictal, and postictal phases in epilepsy patients [14]. Clinical characteristics of patients with pericardial cardiac abnormalities are similar to those at greatest risk of SUDEP. Cardiac arrhythmias have been proposed as mechanisms of SUDEP although subsequent autopsies often prove negative [15, 16].

Misdiagnosis of inherited cardiac arrhythmias as epilepsy should be reviewed. Deliberated, prior reports of misdiagnosis of cardiac arrhythmias as epilepsy have cardiac effects that can contribute to SUDEP [17]. Multiple seizures induced in rats by hippocampal kindling resulted in QT interval prolongation and increased susceptibility to cardiac arrhythmias. These data suggest that multiple, self-limiting seizures of intractable epilepsy have cardiac effects that can contribute to SUDEP [18]. Singh et al. suggested that potentially life-threatening cardiopulmonary abnormalities such as bradycardia, apnea, and hypoxemia induced by pediatric epileptic seizures are associated with sudden unexpected death and particular seizure characteristics, including seizure subtype and duration [19]. Desaturation was more prevalent in longer-duration seizures and may be one of the secondary causes of sudden unexpected death. Simona et al. demonstrated precise pathological features of SUDEP. These cases displayed significant fibrosis of the myocardium that may have been caused by myocardial ischemia resulting from repetitive epileptic seizures, which could cause lethal arrhythmias when associated with the ictal sympathetic storm [20].

Devinsky summarized sudden unexpected death in 8 patients with epilepsy. Respiratory problems were noted in all 8 patients, such as postictal hypoventilation, apnea, laryngospasm and pulmonary edema. Brain function failure with severe diffuse EEG attenuation was considered the primary cause of death in 2 cases; patient experienced ventricular fibrillation that came close to causing sudden death. In 2 patients, these multiple mechanisms may have led to sudden death [21]. Nei et al. revealed increased autonomic stimulation associated with seizures, particularly in sleep, in patients with sudden unexpected death compared with that in a clinically similar group of patients with refractory epilepsy [22]. Autonomic instability during sleep may be associated with sudden unexpected death and arrhythmogenic properties [23]. In differential diagnosis for SUDEP, simultaneous dual EEG and ECG monitoring can reveal the mechanisms. EEG and ECG monitoring during a seizure has been shown to reveal a left temporal
Inherited Cardiac Arrhythmia in Epilepsy

Chikaya Omichi

Paroxysmal discharge and ictal cardiac arrhythmia \(^{[24]}\). Temporal seizure can be related to an ictal cardiac arrhythmia and sudden unexpected death \(^{[25]}\). An implantable loop recorder has recently been made available for monitoring ECG in patients with epileptic seizures. This device can reveal mechanisms of sudden unexpected death in a syncopal attack. Rugg-Gunn et al researched 20 epilepsy patients who received an implantable loop recorder. Asystole may have been the cause of death in many of these deaths, which would have important implications for the investigation of similar patients and affect cardiac pacing policies \(^{[26]}\). Antiepileptic medications can induce potentially fatal cardiac arrhythmias such as torsades de pointes in patients with epilepsy. In particular, the potential for these medications, either alone or in combination, to prolong the QT interval should be considered \(^{[27]}\). During sleep, sudden death can occur in patients with epilepsy. Different mechanisms including cardiac arrhythmias, respiratory dysfunctions, and dysregulation of systemic or cerebral circulation have been suggested as potential pathophysiological mechanisms \(^{[28]}\). Although these secondary causes may be attributed to sudden unexpected death in some epilepsy patients, primary coexistence of inherited cardiac arrhythmia in epilepsy as neuro-cardiac channelopathy should be taken under consideration.

**Neuro-cardiac Channelopathy**

To support the emerging concept of a genetically determined neurocardiac channelopathy, various clinical and genetic approaches are needed. Primary coexistence of inherited cardiac arrhythmias in epilepsy patients as neuro-cardiac channelopathy is considered when cardiac arrhythmias, secondary-induced in epileptic seizure, are excluded. Coexistence of inherited cardiac arrhythmias in epilepsy has been recently reported to support the concept of neurocardiac channelopathy. Anderson et al. evaluated a case report for the possibility of coexistent epilepsy with LQTS. Approximately 15% of patients with LQTS, type 2 who presented with seizures and seizure-like episodes had EEG-identified epileptiform activity, and epilepsy is more common in patients with LQTS, type 2 further supporting the shared pathogenetic link hypothesis of this KCNH2-encoded potassium channel that is expressed in both the heart and the brain \(^{[29, 30]}\). Haugaa et al. showed that abnormal electrical cerebral activity was identified more frequently in subjects with LQTS secondary to a potassium channel mutation as compared to healthy controls. They indicated a possible link between cardiac and cerebral channelopathy \(^{[31]}\). Jehi et al. suggested that cardiac arrhythmia generally observed in seizures is a risk factor for sudden unexpected death \(^{[32]}\). In genotype-phenotype analysis, Zamorano-Leon showed a potential link between epilepsy and LQTS. This report indicates the possibility that R863X alteration in KCNH2-encoded potassium channels may confer susceptibility to epilepsy and LQTS, type 2 arrhythmia \(^{[33]}\). Nashef et al. showed the potential of coexisting genetic mutations that predispose a patient to cardiac arrhythmias as a contributing factor to SUDEP, while acknowledging that clear evidence bridging cardiac inherited gene determinants and sudden unexpected death is lacking \(^{[34]}\). Parisi et al. reported a family showing an association between Brugada syndrome and epilepsy in which a known mutation in the SCN5A gene was identified \(^{[35]}\). They suggested that the mutation was responsible for cardiac and brain involvement at different developmental ages in the same individual. This observation suggests the possibility that SCN5A mutations may confer susceptibility to recurrent seizures, supporting the concept of neurocardiac channelopathy. Sandorfi et al. showed the possibility of coexistent epilepsy with Brugada syndrome. Although Brugada syndrome was discovered incidentally, most of the clinical features of epilepsy shared the risk factor characteristics of sudden unexplained death. The case report provided additional information on the potential interaction between ion channel abnormalities in the heart and in the brain \(^{[36]}\). Patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) have been initially diagnosed with epilepsy in many cases \(^{[37]}\). Johnson et al. reported the first postmortem molecular diagnosis of CPVT in a patient with SUDEP. A novel and sporadic missense mutation of CPVT-susceptibility genes was found in an 8-year-old patient with SUDEP in epilepsy \(^{[38]}\). Lehnart et al. showed that CPVT associated mutant leaky Ryr2-R2474S channels in the brain could cause seizures in mice, independent of cardiac arrhythmias. CPVT is a combined neurocardiac disorder in which leaky RyR2 channels in the brain cause epilepsy. This study suggested that the same leaky channels in the heart cause exercise-induced sudden cardiac death \(^{[39]}\). Paziaud et al. reported that a polymorphic ventricular tachycardia started before epileptic seizure occurred \(^{[40]}\). In this case the cardiac arrhythmia was not secondary to epileptic seizure but spontaneous cardiac arrhythmia independently occurred in a patient with epilepsy. Goldman et al. showed that neuro-cardiac channelopathy was recently proved in animal model. Epilepsy occurred in mouse lines bearing dominant human LQTS type1 mutations. LQTS mutations in KCNQ1 that cause epilepsy have the dual arrhythmogenic potential of an ion channelopathy co-expressed in the heart and brain \(^{[41]}\). Although syncope in patients with LQTS is common and often secondary to cerebral hypoxia after protracted ventricular arrhythmia,
this study demonstrated the importance of preventing "tunnel vision" as patients with LQTS could also have a primary seizure disorder. The concept of neurocardiac channelopathy in LQTS is that type 2 mutations could increase a patient’s susceptibility to cardiologic and neurologic phenotypes [42]. Johnson et al. indicated that a seizure phenotype was often seen in 29% LQTS probands. A seizure phenotype was more common in LQTS, type 2 than other LQTS types. The novel LQTS, type 2-causing perturbations in the KCNH2-encoded potassium channel may confer susceptibility to recurrent seizures [43]. One gene for LQTS, encoding a cardiac sodium ion channel associated with lethal cardiac arrhythmia is coexpressed in certain limbic regions of brain [44]. Single ion channelopathy accounts for the pleiotropic phenotype in the heart and brain in Timothy Syndrome, in which a gene mutation underlies both cardiac arrhythmia and autism [45]. This likely induces intracellular Ca\(^{2+}\) overload in multiple cell types. In the heart, prolonged Ca\(^{2+}\) current delays cardiomyocyte repolarization and increases risk of arrhythmia and implicates Ca\(^{2+}\) signaling in autism. The ion channelopathy is coexpressed in the heart and in the brain. These data support that mutations in inherited cardiac arrhythmias such as LQTS, Brugada syndrome and CPVT and their interacting subunits expressed in the brain may similarly cause epilepsy with an increased risk of sudden death.

Conclusion

Further interdisciplinary approaches are needed to prove the hypothesis. Advanced screening techniques for known epilepsy associated mutations in inherited cardiac arrhythmias will be required to address whether epilepsy commonly occurs concurrently with inherited cardiac arrhythmias. The links between the brain and the heart in epilepsy should be extensively studied by a collaboration between cardiologists, neurologists, and geneticists with a common interest in ion channels in both the heart and brain.

Disclosures

Conflict of interest: None

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