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Ictal Cardiac Ryhthym Abnormalities

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Abstract: Cardiac rhythm abnormalities in the context of epilepsy are a well-known phenomenon. However, they are under-recognized and often missed. The pathophysiology of these events is unclear. Bradycardia and asystole are preceded by seizure onset suggesting ictal propagation into the cortex impacting cardiac autonomic function, and the insula and amygdala being possible culprits. Sudden unexpected death in epilepsy (SUDEP) refers to the unanticipated death of a patient with epilepsy not related to status epilepticus, trauma, drowning, or suicide. Frequent refractory generalized tonic-clonic seizures, anti-epileptic polytherapy, and prolonged duration of epilepsy are some of the commonly identified risk factors for SUDEP. However, the most consistent risk factor out of these is an increased frequency of generalized tonic–clonic seizures (GTC). Prevention of SUDEP is extremely important in patients with chronic, generalized epilepsy. Since increased frequency of GTCS is the most consistently reported risk factor for SUDEP, effective seizure control is the most important preventive strategy.

Keywords: Bradycardia, cardiac arrest, epilepsy, sudden unexplained death in epilepsy (SUDEP).

INTRODUCTION

Cardiac rhythm abnormalities in the context of epilepsy are a well-known phenomenon. However, they are under-recognized and often missed [1]. Ictal bradycardia and asystole are the most comorbid arrhythmias associated with epilepsy. They are usually triggered by focal seizures with or without secondary generalization. The duration and intensity of these ictal events determine the severity of symptoms associated with these events. Symptomatic events occur infrequently; typically documented in 0.27-0.4% of patients undergoing diagnostic video-electroencephalogram recordings in epilepsy monitoring units (EMU) [1 - 3].

However, the incidence may be underestimated given a selection bias of persons referred to epilepsy monitoring units (EMU). Rugg-Gunn *et al.* reported an incidence of 2.1% of ictal arrhythmias in patients suffering from intractable epilepsy utilizing implantable loop recorders for monitoring these cardiac events [4].

PATHOPHYSIOLOGY

The pathophysiology of these events is unclear [5]. Bradycardia and asystole are preceded by seizure onset suggesting ictal propagation into cortex impacting cardiac autonomic function - the insular cortex and amygdala are possible culprits in this regard [5, 6]. These events do not seem to have a lateralization bias, with cardiac events occurring equally after seizures originating from either hemisphere [7].

In vivo cortical stimulation studies have supported this notion, where stimulation of cortex regulating autonomic networks triggered parasympathetic responses leading to bradyarrhythmias [6, 8 - 11]. Central nervous system activation induced by seizures may, synergistically, have direct postganglionic effect on the heart as well [12]. However, a vast majority of patients suffering from seizures are not susceptible to these events. Factors predisposing certain individuals to ictal brady-arrhythmia remain unclear [5].

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SUDDEN UNEXPLAINED DEATH IN EPILEPSY (SUDEP)

Epilepsy is associated with increased mortality [13 - 15]. Sudden unexpected death in epilepsy (SUDEP) refers to the unanticipated death of a patient with epilepsy not related to status epilepticus, trauma, drowning, or suicide. This often occurs following a generalized convulsion in an otherwise healthy individual. SUDEP is the leading cause of death in patients with epilepsy [16]. The risk of sudden death can be as high as 24 times in patients with epilepsy compared to people without epilepsy [16].

Frequent refractory generalized tonic-clonic seizures, antiepileptic polytherapy, and prolonged duration of epilepsy are some of the commonly identified risk factors for SUDEP [17]. However, the most consistent risk factor out of these is an increased frequency of generalized tonic–clonic seizures (GTC) [16].

The cause of SUDEP is unclear but hypothesized to be due to cardiac bradyarrhythmias [17, 18]. However, respiratory depression occurring during and after a seizure can be severe enough to cause marked oxygen desaturation and hypoxia [19, 20]. Therefore, it is unclear whether the primary inciting event in the cases of SUDEP is respiratory, cardiac or a combination of both.

CARDIAC DYSFUNTION LEADING TO SUDEP

Impairment of autonomic regulation of cardiac rhythm has been implicated in the development of SUDEP. Hyperactivity of the sympathetic nervous system leads to increased secretion of adrenomedullary catecholamines which facilitates the occurrence of various cardiac arrhythmias that can cause SUDEP [14]. Studies have shown reduction in cardiac uptake of meta-iodobenzylguanidine (MIBG) during ictal events suggesting a postganglionic cardiac catecholamine disturbance or impaired postganglionic sympathetic cardiac innervation in patients with epilepsy [21]. Heart rate variability (HRV) is a measure of the beat-to-beat variability of the heart rate and low HRV is a predictor of mortality in patients with heart disease [22]. Similarly, low HRV might be a risk factor for SUDEP [23]. Studies with larger cohorts are needed to confirm the validity and utility of this variable as a predictor of SUDEP.

ANTI-EPILEPTIC MEDICATION LEADING TO SUDEP

Ionotropic effects of antiepileptic drugs (AEDs) on cardiac musculature have been implicated in the pathophysiology of SUDEP, however there is limited supportive literature. The mechanism of action as phenytoin is central blockade of sodium channels impairing propagation of depolarization. Phenytoin induces similar blockade in cardiac myocytes leading to cardiac rhythm dysfunction [24, 25]. Carbamazepine has also been shown to impair cardiac conduction through its effect on the autonomic nervous system [26, 27] Lamotrigine may impair repolarization potentials due to its effect on potassium channels leading to comorbid arrhythmias [28, 29].

Many persons with epilepsy take multiple anticonvulsants and polypharmacy has also been hypothesized as a risk factor for SUDEP [30]. However, this position is controversial as SUDEP appears to have a higher incidence in patients with sub-optimal seizure control [31, 32].

GENETIC SYNDROMES ASSOCIATED WITH SUDEP

Several genes have been identified which may increase likelihood of SUDEP. A combination of single nucleotide polymorphisms in genes expressed in both neuro-cardiac and respiratory control pathways have been implicated in the development of SUDEP: *SCN1A, KCNA1, RYR3*, and *HTR2C* [33].

Long QT syndrome is known to cause fatal cardiac arrhythmias [34]. This syndrome has been attributed to mutations in 13 or more genes that are expressed in the heart. Clinical seizures are observed in upto 29% of these patients, and epileptiform activity on electroencephalography is present in upto 15% of patients with long QT syndrome [35, 36]. Therefore, it is important to evaluate seizures in these patients and effectively treat them to prevent SUDEP.

Dravet syndrome manifests itself in childhood as a severe form of epilepsy progressing from febrile seizures to refractory epilepsy [37]. The genetic cause of Dravet syndrome is a loss-of-function mutation in SCN1A in approximately 80% of cases [38]. Mouse models of Dravet syndrome have revealed cardiac arrhythmias similar to those observed in humans during seizures. These findings support the notion of a channelopathy leading to SUDEP in these patients [37, 39].

RESPIRATORY DYSFUNCTION LEADING TO SUDEP

Respiratory dysfunction is well documented during seizures [19, 20, 39]. Apnea, severe oxygen desaturation and

pulmonary edema has been observed in patients during and after ictal events [19, 20, 39]. Consequently, respiratory depression is hypothesized to lead to SUDEP.

The Mortality in Epilepsy Monitoring Units Study (MORTEMUS) is a landmark study aimed at evaluating the cardiorespiratory mechanism involved in SUDEP. The patients were enrolled from multiple epilepsy monitoring units (EMU) internationally. Interestingly, all the SUDEPs were preceded by a GTC and, the majority, occurring at night while patients were prone. Cardiopulmonary resuscitation (CPR) was only successful when started immediately after the event. Post-ictal tachypnea near 18-50 breaths per minute seemed to progress to apnea, bradycardia and cardiac arrest. This study improved our understanding of SUDEP and physicians began to understand it as a combination of cardio-respiratory dysfunction which is centrally mediated [14].

CONCLUSION

Prevention of SUDEP is extremely important in patients with chronic, generalized epilepsy. Since increased frequency of GTCS is the most consistently reported risk factor for SUDEP, effective seizure control is the most important preventive strategy. Non-pharmacological approaches such as nocturnal checks and supervision, as well as family or care-giver CPR training have the potential to decrease the incidence of SUDEP. Cardiac monitoring with routine, as well as, long term holter monitors is suggested in high risk epilepsy patients to prevent SUDEP. Pacemakers have been implanted to prevent death in high-risk epilepsy patients but the clinical utility of this is currently controversial [39] Vagus nerve stimulation (VNS) has the potential to reduce the incidence of SUDEP by decreasing seizure frequency [39]. Therefore, it should be considered in patients with medically intractable, non-lesional epilepsy [39].

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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