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Highlights in clinical autonomic neurosciences: Sudden unexpected death in epilepsy

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ABSTRACT

Sudden unexplained death in epilepsy (SUDEP) is an important unresolved problem affecting many patients with recurrent seizures. Amongst the mechanisms postulated are ictal or postictal cardiac arrhythmias, central hypoventilation or apnea, and neurogenic pulmonary edema. Across these categories, a common element appears to be some form of autonomic dysregulation. Accordingly, the search for biomarkers of SUDEP risk has focused increasingly on autonomic findings. Emerging models implicate attenuated cardiac vagal modulation coupled with surging cardiac sympathetic activity, neuronal dropout in the nucleus tractus solitarii, and in some cases genetic factors affecting ion channel behavior. Explicating the crucial links between brain and heart in epilepsy benefits from collaboration amongst neurologists, cardiologists, physiologists, and other specialists with an interest in the autonomic nervous system.

Introduction

Epilepsy affects 4.9 per 1000 people in developed and 12.7 per 1000 people in developing countries (Ngugi et al., 2010). Sudden unexpected death in epilepsy (SUDEP) is defined as a sudden, unexpected, nontraumatic, witnessed or unwitnessed death while in a reasonable state of health in a person who has epilepsy with no other obvious or structural cause of death. Death may or may not coincide with a seizure, excluding status epilepticus, which if longer than 30 minutes is an exclusion criterion (Nashef et al., 2012). SUDEP is the leading cause of death in people with epilepsy, accounting for 7.5–17% of deaths. A population-based study in Rochester, Minnesota, found the incidence of SUDEP to be 0.35 per 1000 person-years, which represented a 24-fold increase in standardized mortality ratio as compared to the general population (Ficker et al., 1998).

Several recent reviews highlight the increasing interest in this syndrome with updated information, and a number of current investigations are further broadening our understanding of its pathogenesis.

Moseley, B., Bateman, L., Millichap, J.J., et al. (Rochester, MN, USA). 2013. Autonomic epileptic seizures, autonomic effects of seizures, and SUDEP. Epilepsy & Behavior 26, 375–385.

Article summary

This review positions the discussion of SUDEP within the broad framework of autonomic disturbances associated with epilepsy. The authors discuss the common autonomic manifestations of focal and generalized seizures that arise from the extensive connections linking neocortical and limbic cortices involved in seizure onset with structures that compose the central autonomic network. Of particular relevance are the insular and medial prefrontal cortices, the hippocampus and the amygdala, which relay neural activity to the hypothalamus, pons and medulla. These connections underlie ictal tachycardia, ictal bradycardia and asystole, amongst other autonomic phenomena.

Commentary

This review not only provides a comprehensive assessment of what is known of SUDEP, but it also elaborates directions for future research. A key question is whether predictive autonomic biomarkers might be identified that could be detected interictally. Enhancing EEG monitoring technology with additional polygraphic channels simultaneously assessing autonomic functions could facilitate their discovery. The authors recommend, for example, continuous measurement of chest and abdominal wall excursion, airflow, end-tidal CO_2, and oxygen saturation. To that list could be added heart rate variability analysis, baroreflex assessment, or electrodermal activity with the aim of disambiguating potentially lethal patterns from the typically benign ictal changes in heart rate. A better understanding the nature of autonomic disturbances

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in epilepsy will hopefully lead to rationales for treatment trials, which might include pharmacologic or, in cases in which a more serious risk can be predicted, consideration of more invasive strategies such as vagal nerve or deep brain stimulation or implanted cardiac pacemakers.

Tolstykh, G.P., Cavazos, J.E. (San Antonio, TX, USA). 2013. Potential mechanisms of sudden unexpected death in epilepsy. Epilepsy & Behavior 28, 410–414.

Article summary

This review summarizes the research findings in animal models of epilepsy that offer insight into SUDEP. In a baboon model, animals with spontaneous epilepsy that died suddenly were found to have neurogenic pulmonary edema. In the kainic acid model of partial epilepsy, some rats exhibit sudden unexplained death, which establishes a potential rodent model for SUDEP.

Commentary

The unique contribution of this article is the authors' hypothesis that SUDEP results from impaired integrative function due to selective decrease of neuronal populations in the nucleus tractus solitarii (nTS) involved in chemoreceptor and baroreceptor reflexes. The case for this to date is mostly hypothetical, as the cited evidence is a single unpublished presentation of postmortem changes in kainic acid-induced status epilepticus in rats. If they are correct, then ascertainment of interictal biomarkers in humans at risk for SUDEP may eventually be possible.

Terra, V.C., Cysneiros, R., Cavalheiro, E.A., Scorza, F.A. (São Paola, Brazil). 2013. Sudden unexpected death in epilepsy: from the lab to the clinic setting. Epilepsy & Behavior 26, 415–420.

Article summary

This review succinctly describes the clinical, genetic, pharmacologic, autonomic, cardiac and respiratory factors associated with SUDEP and touches on experimental animal models. The authors join Tolstykh et al. in discussing Goldman's sentinel discovery that mutations in $KCNQ_1$ at the LQT_1 locus, which underlies the most common form of long QT syndrome in humans, also cause epilepsy in mice bearing the mutation, indicating a dual arrhythmogenic and epileptogenic phenotype of an ion channelopathy coexpressed in heart and brain (Goldman et al., 2009).

Commentary

This paper explains the difficulties in predicting and understanding SUDEP due to its relatively low incidence, unpredictable occurrence, often in unwitnessed circumstances, and multitude of predisposing factors, which include generalized tonic–clonic seizure phenotype, antiepileptic drug (AED) polytherapy or drug refractoriness, onset of epilepsy at an early age, longer duration of seizure disorder, and frequent occurrence during sleep. Research into SUDEP has uncovered a number of important findings but has a long way to go toward elucidating its molecular basis, identifying predictive biomarkers, and designing effective preventative therapies.

Velagapudi, P., Turagam, M., Laurence, T., Kocheril, A. (Madison, WI, USA). 2012. Cardiac arrhythmias and sudden unexpected death in epilepsy (SUDEP). PACE 35, 363–370.

Article summary

In addition to the material covered in the above-mentioned papers, this review adds further discussion of prophylactic cardiac monitoring in high-risk epilepsy patients. In epilepsy patients with comorbid syncope or who are suspected to have cardiac arrhythmias, the authors recommend EKG, 24-hour Holter monitoring, 30-day event monitoring, or implantable loop recorders. They note, however, that no clear guidelines exist to determine which patients should undergo further cardiovascular investigations. Furthermore, no solid evidence has emerged regarding how effective interventions such as permanent pacemakers or implanted cardioverter-defibrillators are in preventing SUDEP.

Commentary

Much of the current evidence linking cardiac arrhythmias to SUDEP is based on small and retrospective studies. Prospective investigations are warranted in order to reach valid and generalizable conclusions about the value of cardiovascular monitoring and interventions in epilepsy patients at risk for SUDEP. Following up on the clues provided by small series, anecdotal cases and animal models has the potential to lead to testable hypotheses that can inform well-designed prospective investigations.

Lamberts, R.J., Laranjo, S., Kalitzin, S.N., et al. (Heemstede, The Netherlands). 2013. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. Epilepsia 54, 523–529.

Article summary

This retrospective case-control study evaluated preictal and postictal heart rate and heart rate variability (HRV) in patients with convulsive seizures. HRV as a marker of sympathetic and parasympathetic activity was analyzed using frequency domain methods during the 2 minutes preceding the seizure event and for another 2 minutes during the postictal period. Of the 50 patients, 37 exhibited postictal generalized electroencephalography suppression (PGES), which had a median duration of 28 seconds. During the seizure, heart rate and low frequency power increased, whereas high frequency power decreased. Comparisons of heart rate and HRV in patients with to those without PGES demonstrated no significant differences in autonomic instability.

Commentary

PGES, which is seen as diffuse flattening of the EEG recording, has been considered a pathophysiologic hallmark of SUDEP. PGES has been described in rare ictal recordings immediately preceding death (McLean and Wimalaratna, 2007; Carlson, 2011) and is associated with an increased risk of subsequent SUDEP (Lhatoo et al., 2010). The mechanism of PGES and its relationship to SUDEP are incompletely understood. Other investigators have hypothesized that PGES may reflect suppressed neuronal activity not only in the cerebral cortex but possibly extending also to subcortical and even brain stem systems, where disruption of autonomic reflexes or suppression of respiratory drive and arousal responses to hypercapnia might predispose to SUDEP (Carlson, 2011; Richerson and Buchanan, 2011).

PGES is not specific to SUDEP but is a common finding and was seen in 74% of the subjects in this study. Whether the autonomic parameters selected for assessment in this study are pertinent to SUDEP is uncertain, as there may be others more closely related to the mechanisms in question. The investigators did not assess the relative risk of their patients for SUDEP by standard inventories (DeGiorgio et al., 2010). Further studies of PGES might examine respiration, QT interval changes,