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VIEW AND REVIEW

Sudden cardiac death in epilepsy disappoints, but epileptologists keep faith

Apesar do desapontamento com a morte súbita cardíaca nas epilepsias, os epileptologistas mantêm a fé

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ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in people with intractable epilepsy. Probably, optimization of seizure control will prevent some of these deaths. Briefly, we integrated in this paper some data about the epidemiology, risk factors, etiology, and preventative measures in the management of SUDEP.

Keywords: epilepsy; death, sudden.

RESUMO

A morte súbita nas epilepsias (SUDEP) é a causa mais comum de morte em indivíduos com epilepsia refratária. Provavelmente, o controle das crises epilépticas irá evitar algumas dessas mortes. Resumidamente, nós descrevemos nesse artigo alguns dados sobre a epidemiologia, fatores de risco, etiologia e medidas preventivas na SUDEP.

Palavras-chave: epilepsia; morte súbita.

The first formal description of sudden cardiac death (SCD) was made as early as 4th century BC by the father of medicine, Hippocrates of Kos, which stated in his aphorisms that *those who are subject to frequent and severe fainting attacks without obvious cause die suddenly*[1,2]. Presently, in most textbooks SCD is defined as an *unexpected death occurring within one hour from onset of symptoms in an individual with stable clinical conditions before the onset of the life-threatening arrhythmic event*[3,4,5]. The magnitude of the problem is reflected on the fact that more than 7 million lives per year are lost to SCD worldwide[1]. In Europe, approximately 350,000 individuals die each year due to SCD with unsuccessful out-of-hospital cardiopulmonary resuscitation[6,7]. The incidence of SCD in the United States ranges between 180,000 and 450,000 cases annually, depending on the definition used[4,5,8,9,10]. In a more specific way, prospective studies using multiple sources developed in the United States, Netherlands, Ireland, and China have shown that SCD rates ranging from 50 to 100 per 100 000 in the general population[10,11,12,13,14,15,16]. The global burden of SCD remains high despite the fact that several factors have already been described which increase the risk of SCD in the general population[9,10]. It should not be ignored that epilepsy and seizures can have a profound effect on cardiovascular function and in some cases may be fatal[17,18]. A number of questions should be raise to elucidate clearly the exact relationship between SCD and epilepsy.

WHERE? Epilepsy is one of the most common neurological conditions affecting at least 65 million people worldwide[19,20]. Individuals of all ages can be affected by it. It is treatable but often requires lifelong medication and sometimes surgery to control seizures[21,22]. Despite this, seizures in up to 40% of people with epilepsy do not respond properly to antiepileptic drugs or other treatments[23]. In these individuals with refractory epilepsy, high rates of premature death compared with the general population have recorded[24,25]. Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in those people[26]. *WHAT?* The lack of autopsy results and

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the rarely witnessed or monitored cases of SUDEP pose difficulties with regard to its pathophysiology and definitions[18,27,28,29,30]. SUDEP is generally defined as sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy, with or without evidence of a seizure and excluding documented *status epilepticus*, in which postmortem examination does not reveal a toxicologic or anatomical cause of death[31]. *WHEN?* The incidence of SUDEP is largely underestimated due to differences in patient populations, study design, incomplete level of documentation and the criteria for diagnosing SUDEP[18,27,30,32]. Over the years, further refinements to knowledge of SUDEP incidence have been made. Briefly, it has been reported that SUDEP is responsible for up to 17% of all deaths in epilepsy[33] with an incidence rate among adults between 1:500 and 1:1,000 patient-years while in children SUDEP varies on average 2/10.000 patient-years[33,34]. *WHY?* Recent research suggests that multiple risk factors may contribute for SUDEP but the by far most important clinical risk factor is the presence and the number of seizures mainly generalized tonic-clonic seizures (GTCS)[35]. Additionally, other potential risk factors for SUDEP that should not be disregarded have also been identified, including young age at epilepsy onset, longer duration of epilepsy, nocturnal seizures, dementia, absence of cerebrovascular disease, asthma, male gender, symptomatic etiology of epilepsy, alcohol abuse, and winter temperatures[35,36,37,38]. *HOW?* The precise mechanisms of SUDEP remain unknown[39]. It is also paramount to understand the mechanisms underlying SUDEP as it may lead to the identification of previously unrecognized risk factors more amenable to intervention and key to prevention[30,33,40]. Although the cause or causes of SUDEP are still unknown, human and experimental research suggest that the major domains have been attributed to autonomic system, *i.e.*, respiratory and/or cardiovascular abnormalities during and after seizures[18,27,39,40,41,42,43]. From what is known to date, different causal pathophysiological events should be highlighted such as acute cardiovascular changes during seizures (tachyarrhythmias, bradyarrhythmias and ictal asystole), neurogenic pulmonary edema and respiratory disturbances with central and obstructive apnea[17,36,40,42,43,44].

As described previously, cardiac abnormalities and autonomic dysfunction seem to be at the "heart" of the problem in SUDEP[45]. To this effect, the best approach is that of prevention. It is clear that our understanding of the best way to prevent SUDEP is still incomplete. Although strict evidence for their effectiveness is still lacking, some interesting strategies have been suggested which could be useful in reducing the risk of SUDEP[30,40]. Thus, possible preventive strategies such as good control of seizures, reduction of stress, participation in physical activity and sports, dietary management (*e.g.*, omega-3 supplementation) and supervision at night are already well formed[46]. Besides these aspects, a close convergence between neurologists and other medical specialties, especially cardiologists, it must also be present in the context and constantly encouraged by experts in the SUDEP field[41,47,48].

Considering the guidelines, we agree with suggestions that patients with epilepsy, especially those at highest risk of SUDEP, should follow the comprehensive cardiovascular screening protocols (ECG, Holter-monitoring, echocardiography, genetic analysis, ergometric exercise test and myocardial scintigraphy, and, if abnormalities were found, coronary angiography)[41,49,50]. Despite this SUDEP mechanisms are still a mystery, and the recent discoveries of genes and molecular systems involved in epilepsy and cardiovascular system[41] are a cause for optimism that this issue could be solved quicker than anticipated.

Knowledge makes us wiser. In this sense, clinical and animal research is critical to understand accurately the close association between SUDEP and seizures, and obviously, this is the primary goal of decreasing epilepsy-related deaths which figure high each year in mortality statistics.

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