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Editorial

Sudden unexpected death in epilepsy: Rethinking the unthinkable

Epilepsy affects approximately 70 million people worldwide; it is the commonest, chronic, serious neurological disease [1–4]. A very well conducted systematic review and meta-analysis of international studies demonstrated that the prevalence of epilepsy is 6.4 cases per 1000 persons and that the annual incidence is 67.8 cases per 100,000 person-years [1,5]. In approximately one-third of the patients with epilepsy, seizures cannot be sufficiently controlled with currently available antiepileptic drugs (AEDs), which represents a major challenge for treating physicians [2,6,7]. Unfortunately, high seizure frequency and severity are considered a major cause of disability, comorbidities, stigma, costs, and mortality [2,3,6]. Among patients with epilepsy, mortality is highest for those with drug-resistant epilepsy [6]. Accordingly, patients with epilepsy have a 1.6- to 11.4-times higher mortality rate than expected [6,8–10]. Sudden unexpected death in epilepsy (SUDEP) is a leading epilepsy-related cause of death in patients with epilepsy [11]. Over the last decade, more precise figures about the frequency of SUDEP have been achieved [12]. More precisely, it has been demonstrated that SUDEP is responsible for up to 15% of all deaths in epilepsy [11,13–15], and a recent practice guideline showed that SUDEP affects 1 in 4500 children per year and 1 in 1000 adults with epilepsy per year [16]. However, recent data have shown that SUDEP may be even more common in children than previously thought, with an incidence similar to that found in adults (1.11 per 1000 person-years) [11,17]. After consensus about the definitions of SUDEP has been achieved [18,19], a classification of unified definitions was evaluated seven years ago [20]. Although this most recently proposed system involves specific criteria in each SUDEP category [20], the most widely used definition of SUDEP is "the sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure, and excluding documented *status epilepticus*, in which postmortem examination does not reveal a toxicological or anatomical cause for death" [18]. Investigations have demonstrated that the risk factors for SUDEP are complex and heterogeneous [21]. Undoubtedly, the most important clinical risk factor is the presence and the number of seizures (nocturnal) mainly generalized tonic–clonic seizures, and the most effective SUDEP prevention is good seizure control (reduce seizures to a frequency of less than 3 per year) [21–23]. Although the precise etiology of SUDEP is still unknown [24,25], advances of translational studies suggest that SUDEP is a culmination of a multifactorial mechanism, such as cardiac arrhythmia, respiratory dysfunction, dysregulation of systemic, or cerebral circulation and seizure-induced hormonal and metabolic changes during and after seizures [21,26]. The best way on how to prevent SUDEP is still under discussion. However, several important studies clearly demonstrated that prevention of seizures prevents SUDEP [27,28]. Though recent studies suggested some promising measures against SUDEP [21], seizure control is still the most effective measure [23,27]. It should be noted that reduction of stress, participation in physical activity and sports, dietary management (e.g., omega-3 supplementation), supervision at night, or living with a dog are very promising actions [29].

The joint effort of epileptologists, conducting experimental studies (from the molecular aspects to physiological mechanisms) and clinical/therapeutic applications in order to understand and even prevent as much as possible the phenomenon of SUDEP has resulted in spectacular indices. On the other hand, an extremely important subject and still little explored by neuroscientists (which we include in this context as well) are the educational aspects of SUDEP. As previously shown in other studies, less than 15% of patients with epilepsy, parents, and caregivers receive systematic information about SUDEP and epilepsy-related mortality whereas more than 90% want SUDEP education [27,30,31].

Following these considerations, there is apparently an educational problem with SUDEP. The disease (even more chronic) saddens people. This is why it seems more shocking when it is embedded with high rates of premature mortality in childhood and among young adults, when there is nothing more incomprehensible and "out of place". This is the time to improve education in SUDEP. Educating is an arduous and complex task, but it is the only way to provide access to human emancipation and social transformation. We need to educate everyone about SUDEP. Epileptologists and neuroscientists (and physicians in general) need to be encouraged to publish all cases of SUDEP. We, neuroscientists, understandably frustrated because our patient with epilepsy died prematurely, need to understand that our mission transcends the unfortunate loss and continues in the effort to uncover risk factors, mechanisms, and preventive measures to try to save our patients. In a very technological world, we urgently need a shock of compassion. The excellent article recently published by Nashef and Leach describes this reality elegantly [32]. In addition, after carefully evaluating Professor Camargo's sensitive and real words [33], one of the world's references to lung transplantation, we think it convenient to parallel his observations to the SUDEP field. Thus, our tendency to interpret death as a predictable and unchanging phenomenon is unquestionable. However, we must never forget that these rationalizations are devoid of affection, since death will always appear sad, cruel, and painful in the eyes of those who love [33]. Why do humans act in this direction? Because love is not a feeling that is rationalized and obviously, parents and caregivers will always "die together" with the patients who have died from SUPEP. And finally, it is always good to say: if there is anything I can do to help, I am here with you.

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Disclosure

The authors report no conflicts of interest.

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