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Mortality in Epilepsy: A Topic to Reflect on

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Abstract

Introduction: Epilepsy represents a global health problem and is considered one of the most frequent disorders of the Central Nervous System. Patients who suffer from this disease have a higher mortality than the rest of the population, so it is necessary for health professionals to know the possible causes of death, which is the fundamental objective of this article.

Objective: To early identify the factors that may be related to mortality in patients suffering from epilepsy, in order to direct actions that can prevent it.

Material and methods: A review of the national and international literature was carried out, selecting citations from the last 10 years related to mortality in patients with epilepsy.

Discussion: The epidemiological aspects related to mortality in patients suffering from epilepsy are described, as well as the possible etiologies described so far and preventive actions in this regard.

Conclusions: Mortality in epilepsy is frequent and knowledge of the medical professional who cares for these patients is needed in order to carry out preventive actions to minimize the devastating effects of this disease.

Keywords: Mortality; Epilepsy; Sudden unexplained death.

Introduction

Epilepsy is one of the most common brain disorders, affecting an estimated 50 to 69 million people worldwide, the majority from developing countries [1]. This disease represents a global health problem that requires an adequate response [2]. Its prevalence has been estimated at approximately 0.5-1.0% of the general population [3-5].

In turn, it can be an important cause of premature deaths, a danger that is not taken into account and could be avoidable [6,7], so it can reduce life expectancy, since mortality among people with epilepsy is significantly higher than the general population [8,9]. Some authors consider that it increases mortality by up to 10 times among affected people [10-12].

As secondary causes of epilepsy and coexisting neurological diseases become more prevalent, aging populations are expected to face increased epilepsy-related mortality [13].

International statistics show annual mortality rates of 2.1 per 100,000 inhabitants per year, varying from 1 to 8 in different countries [2].

It must be considered, however, that part of the variability in epidemiological indices arises from differences in study methodology, definitions and risk factors.

In our opinion, the epidemiology of epilepsy, and in particular its mortality, needs in-depth investigation, using uniform definitions.

However, a point of reflection to consider is that the causes of death must be identified and actions must be planned, including treatment and education, to avoid preventable deaths.

General objective

Taking into account that mortality in patients with epilepsy is higher than the rest of the population, it is necessary to early

identify the factors that may be related to this, in order to direct actions that can reduce preventable deaths.

Material and methods

A bibliographic review was carried out in various online bibliographic databases, including PubMed, Cochrane Library, Springer, MedScape and ScieLo, among others, related to mortality in patients with epilepsy. To review the avoidance of the same, for which the professionals who manage these patients must know the topic. The key words, mortality and epilepsy, were used in the literature.

Reports of original prospective or retrospective research and review works, as well as articles published in Spanish and English, were included in the information search. The period reviewed was 10 years and extended from 2014 to 2024.

Discussion

Among the different cases reviewed, a meta-analysis of mortality studies, carried out in the last 100 years, specified the Standardized Mortality Ratio (SMR) for epilepsy, which is the relationship between the deaths observed in patients with epilepsy and the deaths expected in a reference population with a similar age distribution, was found to be in a range of 1.3-9.3. The SMR for epilepsy ranges from 1.6 to 5.3 in children and adults, and is inversely correlated with age [14,15].

This, however, represents a challenge, since it is extremely difficult to analyze the mortality rate of epilepsy in the general population of a developing country, because incidence studies are difficult to carry out. Death certificates are unreliable and often unavailable, making the cause of death difficult to determine. This document does not reflect the diagnosis of epilepsy in most cases, which is why it is not useful for mortality studies.

We specified this in a study carried out over 10 years, where, in addition, it was found that the most frequent complications and direct causes of death were bronchopneumonia, status epilepticus and intracranial hypertension [15,16].

Premature mortality is a problem in low-income countries, where treatment gaps, brain infections, and traumatic brain injuries are more common than in high-income countries. Lack of indicated antiseizure medications has been associated with a higher risk of death or an increase in hospital admissions [16,17].

It can be considered, by consensus. That deaths associated with epilepsy can be classified into three main categories (1):

- That caused directly by epileptic seizures. It is the most frequent and occurs due to respiratory arrest or cardiac arrhythmias, with accidents being very common (drowning, falls from a height, traffic and domestic accidents) [18].
- That indirectly or partly associated with epilepsy, such as suicide, which is associated with 5 percent of all epilepsy deaths. Psychiatric comorbidity, and especially depression, plays an important role in the causes of premature mortality in patients with epilepsy [19].
- That which is due to other factors, including the causes of the disease or its complications.

However, some considerations can be made in relation to the patient with epilepsy and its relationship with mortality [2].

Among them can be mentioned and taken into account to analyze that:

- Epileptic seizures themselves can be a cause of death, either directly as in prolonged status epilepticus or indirectly due to the increased risk of accidental death, especially drowning. Status Epilepticus (SE) is associated with significant mortality and accounts for approximately 10% of epilepsy-related deaths [10].
- Mortality is significantly higher in people with epileptic seizures of structural or known cause [11].

Some of the risk factors for epilepsy (brain tumors, cerebrovascular disease, traumatic brain injury) are associated with increased mortality if epilepsy is present. In particular, post-stroke epilepsy is associated with high mortality in young patients.

- An increase in mortality has been reported in patients with intellectual disabilities.
- Long-term use of Antiseizure Medications (ACMs) has been linked to increased incidence of malignancies and osteoporosis, potentially affecting long-term mortality rates in people with epilepsy, especially in younger adults (ages 15-49).
- There is an increased risk of sudden unexplained death in epilepsy (SUDEP) [10], with an estimated incidence of 1.8 per 1000 patients/year. Overall mortality in patients with epilepsy is 2 to 3 times higher than in the general population, while the risk of sudden death is increased 20 to 25 times [20].

Sudden unexpected death in epilepsy is responsible for approximately 7,000 deaths each year in the United States and Europe, being the most common cause of premature death in people with epilepsy, and even more so if it is difficult to control and, in turn, ranks second place, after stroke, as a neurological cause of years of life lost in the general population [21,22].

It is defined as death that occurs suddenly, unexpectedly, not traumatic, or due to asphyxiation in patients with epilepsy, without considering the presence of witnesses or evidence of a previous epileptic seizure as relevant, but deaths secondary to status are excluded epileptic. In these patients, the postmortem pathological study should not reveal signs of an underlying toxicological or anatomical cause of death [23].

To date, the mechanisms involved in SUDEP, why it affects some patients and what relationship exists with the identified risk factors have not yet been fully elucidated. However, some comments can be made on the most recent studies.

It is agreed that the most important predisposing factor is the history of generalized motor onset seizures and nocturnal seizures. The risk has been estimated 24 times higher in young people, especially between 20 and 40 years of age, without a gender predilection [2,19].

Poor control of epileptic seizures has also been invoked, as well as maintaining low plasma levels of anticonvulsant medication (MAC). The onset of the disease before the age of 16, and its duration for more than 15 years to a lesser extent, are also related.

Other studies have associated polytherapy and frequent changes in MAC with SUDEP, which is related to treatment refractoriness. Concomitant pathologies are also mentioned, with

alcohol abuse having the greatest impact and others reported such as dementia and asthma [24].

Alterations have been identified mainly in 3 mechanisms; cardiovascular (tachy and bradyarrhythmias, asystole during crisis), respiratory (central apnea, neurogenic pulmonary edema), and in the autonomic system (sympathetic predominance and sustained vagal dysfunction) [23].

A landmark study of physiological changes immediately preceding SUDEP identified a consistent pattern of cardiorespiratory collapse [21].

The high frequency of focal to bilateral tonic-clonic seizures has been associated with hypermetabolism in regions of the diencephalon, cerebellum, midbrain, and pons. These findings suggest a possible association between SUDEP risk and functional changes in brain regions that serve a variety of critical functions, including cardiorespiratory regulation [25].

Epileptic seizures originating from the left hippocampus seem to be related to greater changes in cardiac repolarization and Atrioventricular (AV) conduction. These alterations are subtle, but underscore the notion of asymmetric lateralization of cortical cardiac control, which in turn may reflect an elevated risk of AV conduction disturbance in people with left mesial temporal lobe epilepsy [26].

In addition, certain severe epilepsy syndromes, such as epileptic encephalopathies, including Dravet Syndrome, expose people to an increased risk of sudden death [27].

Recent findings indicate that preventing deaths from external causes, such as suicide, unintentional injuries or homicides, could be one of the priorities when seeking to improve survival in this group of patients [28].

A five-fold increased risk of alcohol-specific deaths has been observed in people with epilepsy compared to those without epilepsy. Therefore, in people with epilepsy, a sensitive and systematically applied assessment of alcohol consumption, with rapid access to quality treatment services, should be mandatory and play a key role in reducing health harms and mortality [29].

Pharmacological and surgical efforts dedicated to achieving seizure freedom may decrease the risk of SUDEP, but additional measures (e.g., psychological consultations) could complement care for patients with epilepsy who are nonadherent to treatment or have refractory epilepsy treatment.

Therefore, it is necessary to better understand the main preventable causes of death, beyond SUDEP.

Drug resistance

On the other hand, drug resistance represents a significant problem for the patient, with devastating consequences, including persistence of seizures and morbidity derived from epilepsy, medication, social isolation, unemployment and decreased quality of life.

Intractable chronic epilepsy, in turn, carries a poor prognosis, with a mortality rate of 1/200 inhabitants/year as a direct consequence of the seizures [15].

Some authors point out that mortality rates in cases refractory to medical treatment for all causes are lowest in children aged 1-14 years (4.1 deaths/1000 inhabitants/year) and increase with age (32.1 deaths per 1000 inhabitants /years between 55-72 years) [30].

In patients who are refractory to treatment, an increased risk of sudden death is also described, as well as a significant health cost derived from the use of new and multiple medications and a greater need for health care.

For all these reasons, it is imperative to comprehensively manage the patient with this disease and the need to take into account possible prevention measures, such as adequate control of epileptic seizures, thus avoiding the possibility of drowning, status and accidents [16].

The appropriate use of antiepileptic medication and the timely and early use of surgery for patients with criteria must be taken into account. Lifestyle changes must also be adequately guided and psychiatric disorders, including possible suicides, depression, psychosis and impulsivity, must be timely managed [31].

Conclusion

Mortality in patients suffering from epilepsy is frequent and in-depth knowledge of the medical professional who cares for them is necessary in order to take preventive actions to minimize the devastating effects of this disease, including death. This leads us to reflect and take into account that comprehensive management of the disease is essential.

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