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Summary

Epilepsy is one of the most common neurological conditions, with an overall good prognosis for seizure control. Despite this, people with epilepsy have an increased risk of premature death compared to the general population. A practical classification of causes of death in epilepsy distinguishes causes directly related to epilepsy and seizure activity (status epilepticus, accidents and sudden unexpected death in epilepsy), structural underlying causes of epilepsy and causes indirectly related to epilepsy. This aetiological heterogeneity contributes to a polyphasic trend of increased risk of death throughout a person's life, even when seizures are in remission. In the first years after diagnosis of epilepsy, causes directly related to the pathogenesis of seizures are the most important determinants of premature death, while indirect causes and comorbidities have a stronger role in the long term. Psychiatric disorders, cardiovascular diseases and cancer are the main comorbidities that have been found to raise the risk of mortality on long-term follow-up studies. Premature mortality in epilepsy is an underestimated, complex and multifactorial problem with major public health impact. As such, it would be important to increase awareness among clinicians and researchers about the magnitude of the problem and the potentially preventable causes.

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Key words: Causes of death, SUDEP, seizure, comorbidities

Mort prématurée chez les personnes atteintes d'épilepsie

L'épilepsie est une des maladies neurologiques la plus commune avec globalement un bon pronostic pour le control des crises. Malgré cela, les personnes souffrant d'épilepsie ont un risque augmenté de mortalité prématurée en comparaison avec la population générale. La classification pragmatique des causes de décès distingue des causes directement en relation avec l'épilepsie et son activité en termes de crises (état de mal épileptique, mort accidentelle et mort subite inattendue dans l'épilepsie), les conséquences des causes structurelles sous-jacentes de l'épilepsie et les causes avec un lien indirect avec l'épilepsie. Cette hétérogénéité étiologique contribue à une distribution polyphasique du risque de décès tout au long de la vie du patient, même si les crises sont en rémission. Dans les premières années suivant le diagnostic d'épilepsie, les causes directement liées à la pathogénèse des crises sont le déterminant le plus important de la mortalité précoce, alors les causes indirectes et les comorbidités ont plus de poids dans le long terme. Les maladies psychiatriques, cardiovasculaires et néoplasiques sont les comorbidités principales qui ont été démontrées comme étant la cause du risque de mortalité dans les études de suivi à long terme. La mortalité prématurée dans l'épilepsie est un problème sous-estimé, complexe multifactoriel avec un impact major en termes de santé publique. En tant que tel, il est important de sensibiliser les cliniciens et chercheurs sur la magnitude du problème et sur ses causes potentiellement évitables.

Mots clés : Causes de mort, mort subite et inexpliquée du patient épileptique, saïse, comorbités

Vorzeitige Sterblichkeit bei Menschen mit Epilepsie

Epilepsie ist eine der häufigsten neurologischen Erkrankungen, mit einer insgesamt guten Prognose bezüglich der Anfallkontrolle. Dennoch haben Patienten, die an einer Epilepsie leiden, ein erhöhtes Risiko vorzeitiger Sterblichkeit, verglichen mit der Allgemeinbevölkerung. Die pragmatisch orientierte Klassifikation der epilepsieassoziierten Todesursachen unterscheidet zwischen direkt in Zusammenhang mit der Epilepsie und der Anfallsaktivität stehenden Ursachen (Status epilepticus, Unfälle und plötzlicher unerwarteter Tod bei Epilepsie (SUDEP)), der Epilepsie zugrundeliegenden strukturellen Ursachen und Ursachen, die in indirekter Verbindung zur Epilepsie stehen. Diese Heterogenität bezüglich der Ursachen trägt, selbst bei anfallsfreiem Verlauf, zu einer polyphasischen Verteilung des Sterblichkeitsrisikos im Laufe des Lebens der Patienten bei. In den ersten Jahren nach der Diagnose der Epilepsie sind die Ursachen, die in direkter Verbindung zur Pathogenese der Anfälle stehen, die wichtigsten Determinanten von vorzeitiger Sterblichkeit, während die indirekten Ursachen und die Begleiterkrankungen die wichtigere Rolle im Langzeitverlauf darstellen. Psychiatrische, kardiovaskuläre und Krebserkrankungen konnten in Langzeit-Verlaufsstudien als wichtigste Begleiterkrankungen bezüglich des erhöhten Sterblichkeitsrisikos aufgezeigt werden. Frühzeitige Sterblichkeit bei Epilepsie ist ein unterschätztes, komplexes und multifaktorielles Problem, mit wichtigen Auswirkungen auf das Gesundheitswesen. Daher erscheint es als wichtig, sowohl klinisch als auch wissenschaftlich tätige Kollegen für die Tragweite des Problems und die potenziell vermeidbaren Ursachen zu sensibilisieren.

Schlüsselwörter: Todesursachen, plötzlicher unerwarteter Tod bei Epilepsie, Anfall, Begleiterkrankungen

Introduction

Epilepsy is one of the most common neurological conditions [1], with prevalence between 5 and 10 per 1000 people, and overall incidence of 50 per 100 000 people [2]. Most people developing epilepsy have a good prognosis for seizure control [3] and will achieve terminal remission on monotherapy [4].

Despite the overall good prognosis for seizure control, having epilepsy is potentially life-threatening as it is associated with an increased risk of premature death [2]. Epilepsy-related mortality remains underestimated and, although sometimes it is potentially preventable, public health interventions are lacking [2].

Premature mortality in epilepsy is a complex, multifactorial phenomenon. The death of a person with epilepsy may be totally unrelated to epilepsy or to the causes of epilepsy. A pragmatic classification of the causes of death in people with epilepsy distinguishes causes directly related to the epilepsy and seizure activity (status epilepticus, accidents and sudden unexpected death in epilepsy), deaths related to the underlying causes of epilepsy and deaths indirectly related to epilepsy [5]. It has been shown that the underlying organic causes such as brain tumours, cerebrovascular diseases and metabolic conditions are the main determinants of increased mortality in the early years after onset [6]. It is also true, however, that people with epilepsy have an increased risk of premature death throughout their life and this is the case even when seizures are in remission [7]. The pathophysiological mechanisms underlying this long-term risk have not yet been elucidated, although comorbidities as well as genetic factors have been postulated to play a role [8].

Accidental death

Accidents and injuries are more frequent among people with epilepsy than in the general population; although they are usually minor in severity, involving soft tissue contusions and lacerations, particularly in the context of a generalized tonic-clonic seizure some may be fatal [9]. The risk of fracture, either resulting from a seizure or predisposed by drug-induced bone mineral density loss, is elevated twofold; burns due to seizures may also be related to increased morbidity [10]. Drowning is increased twenty-fold in people with epilepsy, usually happening in the context of swimming or bathing [11].

Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP is defined as a sudden unexpected death in an individual with epilepsy with or without evidence of a seizure, and excluding documented status epilepticus, where post-mortem examination does not reveal an anatomical or toxicological cause of death [12]. The incidence is higher in adults than in children. The risk in children from 0 to 17 years with epilepsy is 0.22/1,000 patient-years (95% confidence interval [CI] 0.16-0.31); in adults this risk increases to 1.2/1,000 patient-years (95% CI 0.64-2.32) [13]. The frequency of generalized tonic-clonic seizures (GTCS) appears to be the major risk factor, in direct relationship with the frequency of GTCS (the higher the frequency, the greater the risk). Nocturnal convulsions are potentially dangerous, especially when unwitnessed, as they may culminate in prolonged postictal respiratory depression. The presence of a witness who could detect seizures and promote proper stimulation could avoid the respiratory

arrest and is correlated with a decreased risk [2, 14]. Studies of long-term outcome of chronic epilepsy suggest that SUDEP is an important cause of death, but does not fully explain early mortality, to which comorbidities contribute [15]. The pathophysiology of SUDEP is still unexplained. Prolonged postictal generalized electroencephalographic suppression is related to sympathetic and parasympathetic dysregulation, and may lead to seizure-related respiratory depression [14]. Results from neuroimaging studies led to speculations that right-sided increased amygdala-hippocampal grey matter volume reflects an asymmetric central influence on autonomic outflow, which may contribute to cardiac arrhythmia; on the other hand, pulvinar damage may influence hypoxia regulation [16]. The genetic susceptibility to SUDEP is complex, polygenic and possibly a result of interaction with an increased burden of deleterious variants [17].

Status Epilepticus

Another cause of death directly associated with seizure activity is status epilepticus, a severe condition that can have long-term consequences and even fatal outcome [18]. In people with refractory status epilepticus, mortality is mainly related to prolonged mechanical ventilation, older age and aetiology [19, 20]. Seizure control without suppression-burst or isoelectric electroencephalogram is associated with better functional outcome [19]. It should be noted that most cases of refractory status epilepticus are not in people with established epilepsy but occur “de novo”.

Comorbidities

While in the first years after epilepsy diagnosis causes directly related to the pathogenesis of seizures prevail [21], follow-up studies have suggested that indirect causes and causes associated with comorbidities have a stronger role in determining increased mortality in the long term [22]. A large-cohort study prospectively assessed the long-term risk of premature mortality associated with epilepsy in a large cohort of people with epilepsy in the UK, with a median follow-up of 22.8 years [22]. It showed that the Standardised Mortality Ratio (SMR) may follow a triphasic time course, with the highest risk in the first five years, then a plateau in the next ten years of follow-up and a suggestion of a further peak in premature mortality twenty years after the initial diagnosis. All-cause mortality was found to be elevated, and this trend was confirmed in all the periods of disease history. Cancers (including lung cancer), cerebrovascular diseases, pneumonia and ischaemic heart disease were the most common causes of death. Unlike findings from previous studies from the same cohort [23], even those with cryptogenic/idiopathic

epilepsy were found to have a slight increase in the risk of all-cause mortality in the last ten years of follow-up. Notably, as over 70% of people in the cohort were seizure free at last follow up, the long-term increase in the risk of mortality seems independent of seizure control.

Ischaemic heart disease has been recognized as an important cause of death in epilepsy since 1984, when an increased SMR for heart disease mortality among young (< 65 years) people with idiopathic epilepsy who survived 10 years after diagnosis was found [24]. More recent studies [22, 25] confirmed this trend. A higher prevalence of cardiovascular risk factors in people with epilepsy compared to the general population has been reported [26].

The relationship between epilepsy and cancer is also of interest. All types of cancer were found to contribute to increased mortality in epilepsy [22, 25], even after exclusion of primary brain tumours [27]. The association between epilepsy and late-onset cancer is not clear from a pathogenic point of view [28]. Controversy exists about any association between prolonged use of antiepileptic drugs and increased risk of cancer. Some have found such associations [29, 30] whilst this was disputed by others [31].

Psychiatric comorbidity is common in epilepsy. Depression, anxiety disorders, psychosis and substance abuse have been recognized as the most prevalent psychiatric disorders in epilepsy [32]. A recent large Swedish cohort study [25] reported an increase in the risk of successful suicide amongst people with epilepsy, particularly if associated with a psychiatric diagnosis. In particular, the adjusted Odds Ratio for suicide was 23 in people with both epilepsy and depression. The study also highlighted that substance misuse contributed to the increased risk of suicide, highlighting the importance for clinicians to identify and address this problem early.

Conclusions

A large group of causes, either directly or indirectly related to seizures, contributes to premature mortality in people with epilepsy. For clinicians it is fundamental to be aware of the magnitude of the phenomenon and identify preventable conditions, in particular cardiovascular risk factors and psychiatric comorbidity.

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