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Epilepsy and its relationship to sudden death

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Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission;10 /3/ 2020

Abstract

People with epilepsy have increased risk of premature death, and their life expectancy may reduce by 2-10 yr. Population- and hospital-based studies have shown that the excess mortality in epilepsy is not entirely explained by deaths directly attributable to epilepsy such as accidents and drowning during a seizure. It is also significantly contributed by deaths from other causes such as cardiac deaths, deaths due to malignancies and other causes. It had recently been recognized that sudden unexpected deaths in epilepsy (SUDEP) contributed to a small yet important proportion of mortality in epilepsy SUDEPs are deaths (witnessed or unwitnessed) unrelated to trauma, drowning or status epilepticus and not attributable to any specific medical conditions. Several factors related to epilepsy and drug therapy have been found to be associated with higher risk of SUDEP.

Introduction

Epilepsy is a common neurological disorder of the central nervous system characterized by recurrent seizures with or without convulsions Currently, seizures are classified into four groups: simple (status epilepticus), partial (seizures in infants and young adults), complex (generalized tonic-clonic seizures (GTCS)) and unclassified seizures

Epilepsy is one of the most common neurological disorder that affect >50 million people across the world. It is now widely recognized that people with epilepsy are two to three times more likely to die early. It reduces life expectancy by 10 years for those with symptomatic epilepsy and by two years for those with idiopathic epilepsies1. Accidents, sudden unexpected deaths, status epilepticus and suicides constitute a vast majority of cause of death in epilepsy 2.

A population-based study in the UK showed that, during the period 1993-2005, the mortality from epilepsy increased by 31 per cent for males and 39 per cent for females, whereas the mortality from all causes declined by 16 per cent3. The standardized mortality ratio (SMR) for epilepsy in India varied from 2.58 to 7.64-6. The prevalence of epilepsy in low-income countries is comparable to that of high-income countries although the former has a higher incidence than the latter. This disparity between incidence and prevalence in low-income countries points towards higher mortality for epilepsy when compared to high-income countries7,In general, patients with epilepsy are two- to three-times more likely to die early than the general population Several possible causes of death have been reported in patients with epilepsy, including seizure complications, status epilepticus, or even suicide, but the main current cause is sudden unexpected death in epilepsy (SUDEP).

The excess mortality in epilepsy cannot be entirely explained by deaths directly related to epilepsy such as accidents and drowning due to seizures or status epilepticus. The proportion of deaths from suicide, malignancies and cardiac causes are also increased in people with epilepsy. Sudden unexpected death in epilepsy (SUDEP) has recently emerged as an important cause of death in people with epilepsy. Although the phenomenon of SUDEP was known as early as latter part of 19th century, it was rarely highlighted as important. Apparently, the stepdaughter of

George Washington who was suffering from epilepsy had a sudden death9. SUDEP has considerable social significance as it is still not clear how and when the issue of SUDEP need to be presented to the patient or his or her caregivers .

The first detailed definition of SUDEP was put forward by Nashef12 as 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 post-mortem examination does not reveal a toxicologic or anatomic cause for death.

Incidence of SUDEP varies according to the study population. The SMR in patients with epilepsy is 2.55 *i.e.* 2-3 times more than that of general population15. In the population-based studies, SUDEP incidence rates have been found to vary between 0.35 and 1.35/1000 person-years16,17. The incidence reported was higher for people with chronic epilepsy (1.2-5.1/1000 patient years)18-21 and for those who had undergone surgery for refractory epilepsy

The main cause of SUDEP remains unknown, and more than one mechanism seems to play a role. Several risk factors specific for SUDEP have been identified in case-control studies on SUDEP and non-SUDEP epilepsy deaths. Although identified risk factors vary due to the heterogeneity of the studies and because models cannot accurately predict the seizure risk for individual patients, some risk factors are recurrent. The strongest and most common risk factor for SUDEP is frequency of seizures, particularly GTCS Patients with ≥3 GTCS per month have a 15-fold increased risk of SUDEP. In addition, the presence of GTCS and not being seizure-free for 1–5 years are considered risk factors Lack of proper/stable antiepileptic drug treatment and polytherapy have also been associated with increased SUDEP risk

the aim of this study was to verify incidence and characteristics of sudden unexpected death (SADEP) with epilepsy .

Material and method

A literature search was performed to discover studies reviewing the correlation between epilepsy and sudden death , online sites and databases included in this report are PubMed database , and google scholar and some text book . search terms included " Seizures and " Eepilepsy" "sudden unexpected death" . Titles and were observed for significance.

Result

Several studies have identified important predictors for SUDEP. The rate is marginally higher for males, particularly for those with generalized tonic-clonic seizures (GTCS)[23]. Studies have shown that onset of epilepsy before 16 yr of age carries higher risk of SUDEP[31,32]. It is important to recognize that the presence of certain comorbidities increases the risk of SUDEP. Mental retardation, dementia, psychiatric illness, alcohol and other substance abuse are associated with increased risk of SUDEP though none has been conclusively proven

Jick *et al*[34] have pointed towards the relationship between certain aspects of pharmacotherapy Cases were aged 1.5-67 years, with 63% aged 15-45 (mean 37 years). Sixty-one percent were male. Eighty-seven percent of the deaths occurred at home, with 74% found dead in their bed or bedroom. The majority were not employed, with only 33% working or retired at the time of death; 15% were children or students. Information regarding work status was not available for 11%. Toxicology results were available for 155 cases; antiepileptic drug (AED) use was detected in 67% of these cases, with a single AED detected in 44%, two AEDs in 21%, and three AEDs in 3% of samples taken at autopsy. Approximately half who took an AED were taking either sodium valproate or carbamazepine.

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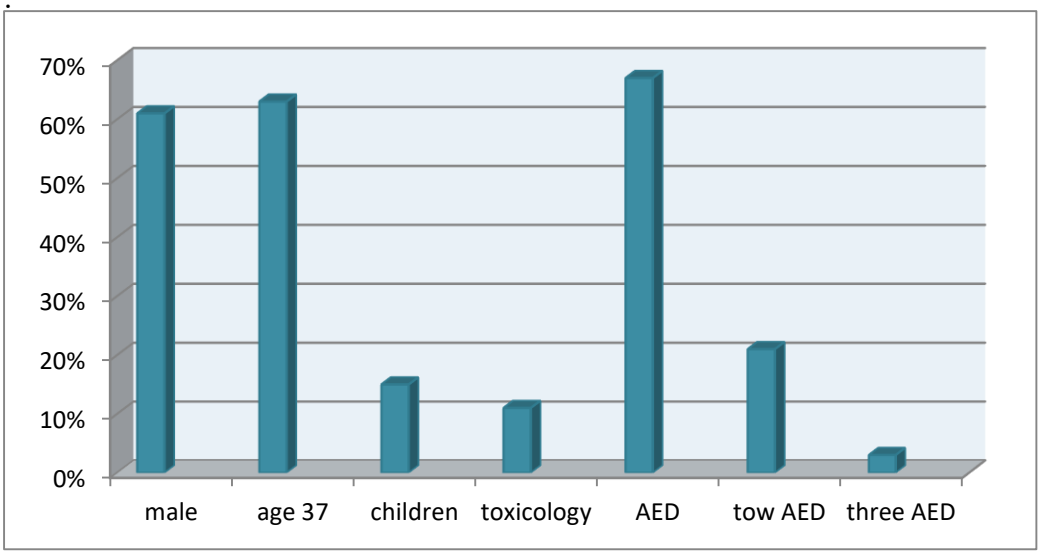

Discussion:

The long term follow up study indicated that Epilepsy-related causes of death world wild its have a really high risk of SUDPE defined as the sudden and unexpected, nontraumatic and nondrowning death of a person with epilepsy

The study revealed that SUDEP incidence is highest among young adults, while it is considerably lower in the pediatric population. In individuals <14 years of age, SUDEP chiefly accounts for high-risk cases, such as individuals with major neurological impairment or injury If the onset of epileptic seizures occurs early and never fully remits, the risk of death is about 8% by 70 years of age. this risk might vary substantially in different populations, depending on seizure type and extent of seizure control

Wail Holst et al. reported that the adjusted hazard ratio for death in young patients with epilepsy was 5.4-times higher than in the general population, and the adjusted hazard ratio for sudden death was 16.3-times higher than in the general population

Definite evidence has recently emerged concerning genetic susceptibility to SUDEP, suggesting a highly polygenic contribution A gene associated with SUDEP should include a definite pathogenic alteration that causes epilepsy, increasing SUDEP risk Numerous neurocardiac genes have been identified as genomic biomarkers of disease severity and outcome, helping predict SUDEP incidence Moreover, several pathogenic alterations in different genes have been reported to increase SUDEP risk through different pathophysiological mechanisms

Some genetic epilepsy syndromes have a high risk of SUDEP, and the associated pathogenic variants may be appropriate biomarker a study group that included 20 epilepsy patients with personal or family history of heart rhythm disturbance/cardiac arrhythmia/sudden death identified

In 2016, Bagnall et al performed an exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in SUDEP. They analyzed 61 SUDEP cases and found one previously described pathogenic mutation and five candidate pathogenic variants in DEPDC5. They also identified a variant in sodium channel

gene SCN1A, related to genetic epilepsy plus febrile seizures and a rare cause of Brugada syndrome, and SCN2A, associated with epileptic encephalopathies .

The duration and severity of epilepsy have an association with risk of SUDEP. People who suffered SUDEP had a longer duration of epilepsy than others in case-control studies39 The risk of SUDEP was 15-fold higher for people with >50 GTCS per year39. Nocturnal seizures were more common amongst the SUDEP group.

Patients suffering from GTCS have been found to have increased risk of SUDEP39 when compared to patients with complex partial seizures and absences.

Conclusion:

Epilepsy is a common chronic neurological condition study indicated that Epilepsy-related causes of death world wild it have a really high risk of SUDPE defined as the sudden and unexpected Sudden death from epilepsy

SUDEP is an important yet under recognized aspect of epilepsy care. Several risk factors and possible predictors of SUDEP have been identified through epidemiological, clinical and experimental studies. Nevertheless, the precise mechanisms and possible preventive measures are yet to be found out. Health care professionals need to be aware of this condition and need to discuss regarding SUDEP with patients and their relatives for the better treatment and prevention of the same.

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