Risk of Unnatural Mortality in Epilepsy

Risk of Unnatural Mortality in People With Epilepsy.

Gorton HC, Webb RT, Carr MJ, DelPozo-Banos M, John A, Ashcroft DM [published online ahead of print April 9, 2018]. *JAMA Neurol* doi: 10.1001/jamaneurol.2018.0333

IMPORTANCE: People with epilepsy are at increased risk of mortality, but, to date, the cause-specific risks of all unnatural causes have not been reported. OBJECTIVE: To estimate cause-specific unnatural mortality risks in people with epilepsy and to identify the medication types involved in poisoning deaths. DESIGN, SETTING, AND PARTICIPANTS: This population-based cohort study used 2 electronic primary care data sets linked to hospitalization and mortality records, the Clinical Practice Research Datalink (CPRD) in England (from January 1, 1998, to March 31, 2014) and the Secure Anonymised Information Linkage (SAIL) Databank in Wales (from January 1, 2001, to December 31, 2014). Each person with epilepsy was matched on age (within 2 years), sex, and general practice with up to 20 individuals without epilepsy. Unnatural mortality was determined using International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes V01 through Y98 in the Office for National Statistics mortality records. Hazard ratios (HRs) were estimated in each data set using a stratified Cox proportional hazards model, and meta-analyses were conducted using DerSimonian and Laird random-effects models. The analysis was performed from January 5, 2016, to November 16, 2017. EXPOSURES: People with epilepsy were identified using primary care epilepsy diagnoses and associated antiepileptic drug prescriptions. MAIN OUTCOMES AND MEASURES: Hazard ratios (HRs) for unnatural mortality and the frequency of each involved medication type estimated as a percentage of all medication poisoning deaths. RESULTS: In total, 44 678 individuals in the CPRD and 14 051 individuals in the SAIL Databank were identified in the prevalent epilepsy cohorts, and 891 429 (CPRD) and 279 365 (SAIL) individuals were identified in the comparison cohorts. In both data sets, 51% of the epilepsy and comparison cohorts were male, and the median age at entry was 40 years (interquartile range, 25-60 years) in the CPRD cohorts and 43 years (interquartile range, 24-64 years) in the SAIL cohorts. People with epilepsy were significantly more likely to die of any unnatural cause (HR, 2.77; 95% CI, 2.43-3.16), unintentional injury or poisoning (HR, 2.97; 95% CI, 2.54-3.48) or suicide (HR, 2.15; 95% CI, 1.51-3.07) than people in the comparison cohort. Particularly large risk increases were observed in the epilepsy cohorts for unintentional medication poisoning (HR, 4.99; 95% CI, 3.22-7.74) and intentional self-poisoning with medication (HR, 3.55; 95% CI, 1.01-12.53). Opioids (56.5% [95% CI, 43.3%-69.0%]) and psychotropic medication (32.3% [95% CI, 20.9%-45.3%)] were more commonly involved than antiepileptic drugs (9.7% [95% CI, 3.6%-19.9%]) in poisoning deaths in people with epilepsy. CONCLUSIONS AND RELEVANCE: Compared with people without epilepsy, people with epilepsy are at increased risk of unnatural death and thus should be adequately advised about unintentional injury prevention and monitored for suicidal ideation, thoughts, and behaviors. The suitability and toxicity of concomitant medication should be considered when prescribing for comorbid conditions.

Commentary

Individuals with epilepsy have at least twice the risk of premature death than the rest of the population. While sudden unexpected death in epilepsy (SUDEP) is the leading cause of mortality in individuals with chronic epilepsy and has been the focus of high-volume recent research, it accounts for fewer than half of deaths due to epilepsy (1). Therefore, there is a need to understand unnatural causes of mortality in epilepsy, defined as deaths that result from external causes, which can be intentional, such as suicide or homicide, or unintentional, such as in accidents. Counseling individuals with epilepsy typically incorporates education about seizure precautions, including exercising water safety and avoiding driving among other potentially risky behaviors. It also includes recommendations about the importance of adherence to antiseizure medications. However, it is important to take into consideration that many people with epilepsy have major comorbid mental illnesses and social difficulties that may limit their ability to follow these recommendations. Psychiatric comorbidities are associated with increased risks of death in epilepsy, both due to unnatural causes as well as SUDEP. A recent population-based cohort

Epilepsy Currents, Vol. 18, No. 6 (November/December) 2018 pp. 365–366

study in Sweden found that female patients with psychiatric comorbidities had a 5-fold increased incidence of SUDEP (1), and another study found that 75.2% of all unnatural death in epilepsy was associated with comorbid psychiatric disorders (2). In the latter study, the odds ratios for mortality were 13 for coexistent depression and 22.4 for substance misuse, when compared with patients who had no epilepsy or psychiatric illness. In addition, some authors have established that the incidence and prevalence of epilepsy are strongly associated with deprivation (or low socio-economic status), which, in one study, remained unchanged for a decade after the diagnosis (3).

Gorton et al. mined two large general practice data sets in England and Wales with the goals of studying cause-specific unnatural mortality risks in epilepsy and identifying whether antiseizure medications versus other drugs were most involved in poisoning deaths. One data set was the Clinical Practice Research Datalink (CPRD), which covers 7% of the UK population and represents age, sex, and ethnicity of all the UK population. The CPRD contains anonymous data, such as demographic characteristics, diagnoses, and treatments. The other data set was the Secure Anonymised Information Linkage (SAIL) Databank, which contains data from 13 health and social care databases in Wales that are anonymized and linked through unique identifiers. The authors matched individuals with epilepsy from each of these data sets with up to 20 individuals without epilepsy based on sex, year of birth, and general practice. The two data sets also included deprivation levels by quintiles, which helped the authors assess the role of that factor. From the CPRD, collected over approximately 16 years, 44,678 individuals with epilepsy were included in the analysis and the comparison cohort from the same data set consisted of 891,429 individuals. From the SAIL databank over approximately 15 years, 14,051 individuals with epilepsy and 279,365 individuals without epilepsy were included.

The epilepsy cohort had a higher risk of unnatural mortality with a hazard ratio (HR) of 2.77 when adjusted to the deprivation level. This increased risk was observed for both unintentional death (HR 2.97) and suicide (HR 2.15). Even infrequent causes of death, such as homicide and iatrogenic fatalities, were also more common in the epilepsy cohorts. Regarding the medication types most associated with poisoning deaths, opioids and psychotropic medications were the most common, whereas antiseizure medications were associated with relatively fewer poisoning deaths. Additionally, the results corroborated prior findings of increased prevalence of comorbidities in epilepsy, including alcohol misuse, anxiety, bipolar disorder, depression, eating disorder, migraine, personality disorder, schizophrenia, self-harm, and substance misuse. The epilepsy population had more frequent use of psychotropic medications and higher levels of deprivation than controls. The results also supported prior findings that low socioeconomic status and comorbid psychiatric conditions in epilepsy were particularly associated with increased mortality (4).

Unlike hospital-based data sets, which are likely to be skewed toward the more acute presentations of epilepsy, the data sets used in the study are general practice–based and mortality linked. Therefore, the results broaden our views about the epidemiology of premature death in epilepsy, and call for a change in physicians' practices and public health interventions to prevent it.

What are the reasons for increased risk of unnatural death in epilepsy? The increased prevalence of mental illness in the epilepsy population, regardless whether it is a cause or effect, certainly plays a major role. The results of this study further urge the physician to evaluate such comorbidities with the same focus as evaluating and treating seizures. Despite the stigma associated with epilepsy and mental illness and the resistance of some patients to establish care with a psychiatrist, the neurologist must not shy from evaluating the patient's mental health and work hand-in-hand with a psychiatrist to screen and treat any associated psychiatric illnesses. Epilepsy was defined in a 2005 report by the International League Against Epilepsy as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures *and by* the neurobiologic, cognitive, psychological, and social consequences of this condition" (5). Therefore, both clinical practice and public health policies must not reduce epilepsy to seizures, but deal with it as a constellation of associated problems, neurological, psychological, and social alike, in an attempt to help reduce its tragic consequences. Finally, the finding that psychotropic medications and opiates pose a higher risk of poisoning death than antiseizure medications should prompt the physician to pay special attention to individuals on polypharmacy with these medications. Education, soliciting social support for administration of medications (if possible), engaging a psychiatrist and a pain specialist, and using pill boxes can only be the beginning.

by Mohamad Koubeissi, MD

References

1. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. *Neurology* 2017;89:170–177.
2. Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* 2013;382:1646–1654.
3. Pickrell WO, Lacey AS, Bodger OG, Demmler JC, Thomas RH, Lyons RA, Smith PE, Rees MI, Kerr MP. Epilepsy and deprivation, a data linkage study. *Epilepsia* 2015;56:585–591.
4. Devinsky O, Spruill T, Thurman D, Friedman D. Recognizing and preventing epilepsy-related mortality: a call for action. *Neurology* 2016;86:779–786.
5. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–472.