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No Time to Die – Avoidable Death in Epilepsy

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Epilepsy, mortality, Death, SUDEP, mortality ratio

A National Study of Epilepsy-Related Deaths in Scotland: Trends, Mechanisms, and Avoidable Deaths

Mbizvo GK, Schnier C, Simpson CR, Chin RFM, Duncan SE. *Epilepsia*. 2021;62(11):2667-2684. doi: 10.1111/epi.17065.

Objective: This study was undertaken to investigate the trends and mechanisms of epilepsy-related deaths in Scotland, highlighting the proportion that were potentially avoidable. Methods: This was a retrospective observational data-linkage study of administrative data from 2009 to 2016. We linked nationwide data encompassing mortality records, hospital admissions, outpatient attendance, antiepileptic drug (AED) prescriptions and regional primary care attendances. Adults (aged ≥ 16 years) suffering epilepsy-related death were identified for study using International Classification of Diseases, 10th Revision coding combined with AED prescriptions. We reported epilepsy-related mortality rate (MR), age-specific mortality ratios, multiple cause-of-death frequencies and the proportion of potentially avoidable deaths (identified as those with an underlying cause listed as avoidable by the Office for National Statistics). Results: A total of 1921 epilepsy-related deaths were identified across Scotland; 1185 (62%) decedents were hospitalized for seizures in the years leading up to death, yet only 518 (27%) were seen in a neurology clinic during the same period. MR remained unchanged over time, ranging from 5.9 to 8.7 per 100 000 Scottish population (95% confidence interval [CI] = −.05 to .66 per 100 000 for annual change in MR). Mortality ratios were significantly increased in young adults aged 1654 years (2.3, 95% CI = 1.82.8), peaking at age 1624 years (5.3, 95% CI = 1.88.8). Sudden unexpected death in epilepsy (SUDEP) constituted 30% of the 553 young adult epilepsy-related deaths, with several other non-SUDEP fatal mechanisms identified including aspiration pneumonia, cardiac arrest, AED or narcotic poisoning, drowning and alcohol dependence. Seventy-six percent of young adult epilepsy-related deaths were potentially avoidable. Significance: Epilepsy-related deaths are a major public health problem in Scotland, given that they are not reducing, people are dying young and many deaths are potentially avoidable. SUDEP is only one of several important mechanisms by which epilepsy-related deaths are occurring in young adults. Services may need to be re-evaluated to improve specialist referral following seizure-related hospital admissions.

Epilepsy-Related Mortality in Children and Adults in Denmark. A Nationwide Cohort Study

Kløvgaard M, Hadberg Lynge T, Tsiropoulos I, et al. *Neurology* 2022;98(3):e213-e224. doi: 10.1212/wnl.0000000000013068.

Background and Objectives: Mortality is increased in epilepsy, but the important issue is that a proportion of epilepsy-related death is potentially preventable by optimized therapy and therefore needs to be identified. A new systematic classification of epilepsy-related mortality has been suggested to identify these preventable deaths. We applied this classification to an analysis of premature mortality in persons with epilepsy who were < 50 years of age. Methods: The study was a population-based retrospective cohort of all Danish citizens with and without epilepsy 1 to 49 years of age during 2007 to 2009. Information on all deaths was retrieved from the Danish Cause of Death Registry, autopsy reports, death certificates and the Danish National Patient Registry. The primary cause of death in persons with epilepsy was evaluated independently by 3 neurologists, 1 neuro-paediatrician and 2 cardiologists. In case of uncertainty, a pathologist was consulted. All deaths were classified as either epilepsy related or not epilepsy related, and the underlying causes or modes of death were compared between persons with and without epilepsy. Results: During the study period, 700 deaths were identified in persons with epilepsy, and 440 (62.9%) of these were epilepsy related, 169 (38%) directly related to seizures and 181 (41%) due to an underlying neurologic disease. Sudden unexpected death in epilepsy accounted for 80% of deaths directly related to epilepsy. Aspiration pneumonia was the cause of death in 80% of cases indirectly related to epilepsy. Compared with the background population, persons with epilepsy had a nearly 4-fold increased all-cause mortality (adjusted mortality hazard ratio = 3.95 [95% confidence interval [CI] = 3.644.27]; $P < .0001$) and a higher risk of dying of various underlying causes, including alcohol-related conditions (hazard ratio = 2.91 [95% CI = 2.233.80], $P < .0001$) and suicide (hazard ratio = 2.10 [95% CI = 1.183.73], $P = .01$). Discussion: The newly proposed classification for mortality in persons with epilepsy was useful in an unselected

preventable deaths. The leading causes of premature mortality in persons < 50 years of age were related to epilepsy and were thus potentially preventable by good seizure control.

Commentary

Epilepsy is a cause of avoidable death. Each year many of us experience the pain of one of our patients with epilepsy dying. Premature death in epilepsy is likely to be the condition with most years of potential life lost of any neurological disorder, due to the young age at which it occurs.[1] Our every effort should be focussed on preventing this from happening. To what extent is this possible?

Vital to our understanding is information about causes of death and whether these are preventable or not. Deserved attention has been given to SUDEP in recent years, but other causes are important such as direct epilepsy-related death from status epilepticus, drowning or accidents, or indirect epilepsy-related death from aspiration pneumonia or suicide, among others (applying the Devinsky classification).[1]

These two studies used national health system data and cause of death analysis to determine the nature of death in patients with epilepsy. Both studies used epilepsy/seizure ICD codes, cross-linked with anti-seizure medication (ASM) registries to accurately identify epilepsy patients.[2] Over 2600 deaths in patients with epilepsy were analysed in the two papers.

Mbizvo and colleagues from Scotland, conducted a multiple cause of death analysis (MCOD) in an all-nation cohort of adult patients with epilepsy. MCOD analysis incorporates not only the death certificate cause, but also other contributory causes and mechanisms. They also cross-linked other national datasets to strengthen case ascertainment. There were a total of 1921 deaths over a 7-year period.

Kløvgaard and colleagues from Denmark, another country with a strong national health database, cross-linked data on epilepsy hospitalizations and outpatient contacts with death certificates in patients aged 1-49 years. There were a total of 700 deaths over the 2-year period.

Both studies found a significant degree of 'avoidable mortality' in patients with epilepsy. Avoidable mortality is defined as unnecessary untimely deaths in a disease where effective intervention should make this rare or not happen at all, for example, death from poliomyelitis. Some mortality may be 'preventable' by public health measures (i.e. smoking cessation), and a portion is 'amenable' mortality; amenable to an effective treatment.[3] Epilepsy is included on the list of avoidable causes of death.[4] We have effective treatments for epilepsy. Some of the deaths due to epilepsy should be avoidable.

Mbizvo identified SUDEP and non-SUDEP epilepsy-related deaths and standardized mortality ratios (MR) in adults over 16 years during a retrospective 7-year period of 2009-2016. While some of the deaths in patients with epilepsy would be hard pressed to be called epilepsy related (e.g those due to non-neurological cancer), the majority of avoidable death was linked to seizures.

The overall MR was 5.9-8.7/100 000 population, with no significant change over time and no difference between males and females.

Age-specific mortality ratios showed that epilepsy-related deaths were more common in young adults (16-54). Peak deaths were during the vulnerable transition ages of 16-24 years. These patients had a MR of 5.3, meaning they are 5.3 times more likely to die than the expected rate in their age group, a shocking statistic that should change the way we talk to our young epilepsy patients and bring mortality to the forefront of our discussion, no matter how uncomfortable that is.

Another concerning statistic was that 1185 patients (62%) had at least one hospital admission during the study period, but only 518 (27%) were seen in a neurology clinic. 360 of those seen in the clinic, were also in the hospital group, meaning 825 seen in hospital were never followed as an outpatient.

In 62 cases, primary care data was available to analyse, and showed significant rates of mental health issues in 50%, and alcohol/drug abuse in 44% of patients.

Of patients aged 16-54 ('young adults'), 421 of 553 deaths had a cause (some of which were not neurological) listed in the avoidable death list. However, 70% of these 553 deaths were directly epilepsy related. Thirty percent of deaths were due to SUDEP, and the majority lived in socially deprived areas. Lower epilepsy-related MR in older patients repeats concerns regarding underreporting of epilepsy-related deaths in the elderly, although could also be due to methodological issues (comparing observed deaths to expected deaths from population means in the elderly).

In Kløvgaard's study, the MR was 8.57 per 1000 patient years. MR was more common in adult males (higher numbers of accidents or drownings), with the highest MR of 16.48 in the 40-49 age group. The most frequent causes of death were brain tumour (21%), SUDEP (19.3%) and aspiration pneumonia (10.3%). 440 of the total number of deaths (62.9%) were epilepsy related, and were increased compared with the background population. Almost 40% of deaths were directly due to epilepsy (the leading cause being SUDEP). Adjusting for co-morbid conditions, the mortality hazard ratio was 3.95 (CI = 3.64-4.27). Aspiration pneumonia was more frequent than previously thought in patients with developmental disabilities.

The two studies are similar whole-population, registry-linked retrospective studies. Kløvgaard reported on the baseline epilepsy population, and thus reports MR per 1000 person years and controlled for co-morbidities. They also included paediatric cases. Both showed elevated epilepsy-related MR with a majority consisting of avoidable deaths. SUDEP rates were 30%

and 19.3%, respectively. Autopsy rates were similar across both studies at around 19%.

National large-scale datasets generated in modern healthcare systems, provide opportunities for research, without having to recruit large numbers of patients.[5] These datasets can be confounded by diagnostic errors, missing deaths due to first seizures and those without a pre-existing diagnosis of epilepsy, unwitnessed deaths and sudden deaths in the elderly, partially due to inaccurate death certificate reporting. For example, cause of death may be falsely attributed to alcohol or substance abuse, and cardiac death in the elderly. Both studies use different definitions of 'epilepsy-related' deaths. Mbizvo includes all causes of death in anyone who fulfilled their criteria for an epilepsy diagnosis. Kløvgaard at least excludes non-neurological deaths from being 'epilepsy related'. However, both studies still serve to highlight higher mortality rates, particularly for directly seizure-related causes.

What can we do to avoid death in our patients? Seizures cause most mortality directly linked to the epilepsy itself. We should treat seizures at every stage and opportunity, from timely identification of epilepsy and prompt initiation of treatment to monitoring medication adherence. These studies also highlight the high prevalence of mental health issues and substance abuse, in these most vulnerable of patients. We need to pay attention to groups that are socially deprived and developmentally disabled. These two studies were done in resource-rich European nations; mortality is estimated to be several times higher in non-Western populations, and a study of this type in a third-world country would, I suspect, shock us even more. A Kenyan study found a mortality ratio of 33.1/1000 person years in patients with epilepsy and a seizure in the previous 12 months.[6] We, as advocates of patients with epilepsy, need to provide the leadership to guide further study and ultimately find better ways to save the lives of our patients with epilepsy.

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