Epilepsy Currents
2020, Vol. 20(1) 16-18

DOI: 10.1177/1535759719892220
journals.sagepub.com/home/epi
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Mortality in Epilepsy: Referral to a Specialty Center Makes a Difference

Association of Levels of Specialized Care With Risk of Premature Mortality in Patients With Epilepsy

Lowerison MW, Josephson CB, Jetté N, et al. *JAMA Neurol*. 2019;76:1352-1358.

Importance: Patients with epilepsy are at an elevated risk of premature mortality. Interventions to reduce this risk are crucial. Objective: To determine if the level of care (non-neurologist, neurologist, or comprehensive epilepsy program) is negatively associated with the risk of premature mortality. Design, Setting, and Participants: In this retrospective open cohort study, all adult patients 18 years or older who met the administrative case definition for incident epilepsy in linked databases (Alberta Health Services administrative health data and the Comprehensive Calgary Epilepsy Programme Registry [CEP]) inclusive of the years 2002 to 2016 were followed up until death or loss to follow-up. The final analyses were performed on May 1, 2019. Exposures: Evaluation by a non-neurologist, neurologist, or epileptologist. Main Outcomes and Measures: The outcome was all-cause mortality. We used extended Cox models treating exposure to a neurologist or the CEP as time-varying covariates. Age, sex, socioeconomic deprivation, disease severity, and comorbid burden at index date were modeled as fixed-time coefficients. Results: A total 23 653 incident cases were identified (annual incidence of 89 per 100 000); the mean age (SD) at index date was 50.8 (19.1) years and 12 158 (50.3%) were women. A total of 14 099 (60%) were not exposed to specialist neurological care, 9554 (40%) received care by a neurologist, and 2054 (9%) received care in the CEP. In total, 4098 deaths (71%) occurred in the nonspecialist setting, 1481 (26%) for those seen by a neurologist, and 176 (3%) for those receiving CEP care. The standardized mortality rate was 7.2% for the entire cohort, 9.4% for those receiving nonspecialist care, 5.6% for those seen by a neurologist, and 2.8% for those seen in the CEP. The hazard ratio (HR) of mortality was lower in those receiving neurologist (HR, 0.85; 95% CI, 0.77-0.93) and CEP (HR, 0.49; 95% CI, 0.38-0.62) care. In multivariable modeling, specialist care, the age at index, and disease severity were retained in the final model of the association between specialist care and mortality. Conclusions and Relevance: Exposure to specialist care is associated with incremental reductions in the hazard of premature mortality. Those referred to a comprehensive epilepsy program received the greatest benefit.

Commentary

Mortality related to epilepsy is a concerning issue. There is increasing interest in sudden unexpected death in epilepsy (SUDEP),[1] defined as sudden unexpected death in a person diagnosed with epilepsy, in which trauma, status epilepticus, or drowning was excluded, and there are no other likely causes of death.[2] Recent research efforts, on both basic science and clinical levels, have resulted in better understanding of the etiology and risk factors for SUDEP. Poorly controlled generalized tonic–clonic seizures are a leading risk factor. Other important risk factors include overall high seizure burden, prone position at the time of death, intellectual disability, and lack of antiepileptic drug treatment.[2] Nocturnal supervision and use of nocturnal listening devices can decrease the risk of SUDEP.[3] Despite our advances in the understanding of SUDEP and advances in treatment for patients with epilepsy, overall mortality rates in patients with epilepsy are rising.[2]

The incidence of SUDEP varies widely in different studies. A recent systematic meta-analysis reviewed studies reporting the incidence of SUDEP in different epilepsy populations. While the authors estimated incidence of SUDEP per 1000 person-years at 0.58 overall, 0.22 in childhood, and 1.2 in adulthood, they also found significant unexplained heterogeneity in studies reporting SUDEP incidence, suggesting the presence of unknown or unexplored risk factors.[3] Despite the difficulties in objectively defining SUDEP incidence, the overall findings in studies follow typical neuroepidemiological trends, with lower incidence of SUDEP in primary care, population-based studies and higher SUDEP incidence in studies conducted in the tertiary care setting, theoretically reflecting the greater severity of epilepsy in referral centers. For

example, in a population-based study of newly diagnosed epilepsy followed for the first 11 to 14 years after diagnosis, involving a cohort of 792 patients and 11,400 person-years, there were only 5 epilepsy-related deaths, one of which was due to SUDEP.[4] Ficker et al[5] retrospectively reviewed all deaths in patients diagnosed with epilepsy in Rochester, Minnesota, from 1935 to 1994, and compared findings with the expected rate of sudden death in the general population. They found SUDEP was a rare cause of death in the epilepsy population, with an incidence of 0.35 per 1000 person-years. This rate, however, was 24 times the expected sudden death rate in the general population. In contrast, results from studies in tertiary referral centers show higher rates of SUDEP. In a study evaluating sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral center, investigators reviewed records from 601 outpatients accounting for 1849 person-years, finding 11 unexpected deaths. The resultant incidence of SUDEP was 5.9 per 1000 person-years.[6]

Sudden unexpected death in epilepsy is an important, specifically defined syndrome. However, mortality in epilepsy overall is a much broader issue. There are many possible determinants of increased incidence of premature mortality in patients with epilepsy,[7] with major determinants including cerebrovascular disease, heart disease, neoplasms, pneumonia, suicide, accidents, seizure-related mortality (ie, status epilepticus), and SUDEP.[8] The percentage of SUDEP as a cause of mortality in patients with epilepsy overall varies depending on the study population. Ficker et al[5] found SUDEP accounted for 1.6% of all deaths in their population-based epilepsy cohort, while Aurlien et al[8] found SUDEP as the cause of death in 7.1% of all patient deaths in their hospital-based cohort of patients with epilepsy. Therefore, SUDEP accounts for a relatively small proportion of the overall mortality in patients with epilepsy.

Given the risks of mortality in patients with epilepsy beyond SUDEP, the study by Lowerison et al provides important information about overall mortality in patients with epilepsy, especially in relationship to level of specialized epilepsy care. This Canadian-based study used the Alberta Health Services administrative health data and the Comprehensive Calgary Epilepsy Programme Registry databases to evaluate 23 653 incident cases of epilepsy in adult patients 18 years or older. They used a validated administrative case definition to identify epilepsy cases and subsequently divided cases into 3 groups depending on level of care by exposure to a (1) non-neurologist, (2) neurologist, and (3) epileptologist. A total of 14 099 (60%) received care from a non-neurologist, 9554 (40%) received care by a neurologist, and 2054 (9%) received care by an epileptologist. Using the most recent published mortality rate of 5.7 deaths per 1000 person-years for Alberta, the standardized mortality ratio was 7.2 for the entire cohort, 9.4 for those unexposed to neurological care, 5.6 for those who received care by a neurologist, and 2.8 for those who received epileptologist care. Compared with those who did not receive neurological care, mortality rates were significantly lower among those who received care from neurologists and were lower still for those receiving care from an epileptologist.

Importantly, the investigators carefully controlled for age, sex, sociodemographic factors, disease severity, and comorbidities in the study. As discussed in relationship to SUDEP, findings in mortality outcome studies are often confounded because of the preponderance of greater disease severity at the tertiary care level. In this study, there is a clear demonstration of benefit of epileptologist care in relationship to mortality outcome, despite the potential bias of a greater disease severity in the group referred for epileptologist care. The findings of the study support the authors' conclusion about the importance of timely referral to neurology specialists and epileptologists for optimal survival benefit for patients with epilepsy.

Mortality in epilepsy remains a major public health concern. While SUDEP remains an important issue, especially in clinical research, it accounts for only a small portion of overall mortality in patients with epilepsy. The current study looks beyond SUDEP and evaluates overall outcomes in epilepsy mortality based on level of specialist care, showing convincing evidence that specialist referral reduces overall mortality. The study does not address why specialist referral decreases mortality. However, considering the multifactorial etiologies for mortality in patients with epilepsy, comprehensive evaluation by an epilepsy specialist actively addressing individual needs for care conceptually offers a framework to address the multiple issues which affect a patient's health and subsequent outcomes, including mortality. Given the many effective proven treatments for epilepsy, including medications, and advanced treatments such as epilepsy surgery, the study provides further evidence of the importance of specialty epilepsy care. In an era of increasing limitations of resources and reimbursements for specialty services, this study also speaks to the importance of maintaining allocations of resources to epilepsy specialty centers for patients with epilepsy to have access to specialty care.

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