Understanding the Sources of Excess Mortality in Epilepsy

Premature Mortality in Epilepsy and the Role of Psychiatric Comorbidity: A Total Population Study.

BACKGROUND: Epilepsy is associated with high rates of premature mortality, but the contribution of psychiatric comorbidity is uncertain. We assessed the prevalence and risks of premature mortality from external causes such as suicide, accidents, and assaults in people with epilepsy with and without psychiatric comorbidity. METHODS: We studied all individuals born in Sweden between 1954 and 2009 with inpatient and outpatient diagnoses of epilepsy (n=69,995) for risks and causes of premature mortality. Patients were compared with age-matched and sex-matched general population controls (n=660,869) and unaffected siblings (n=81,396). Sensitivity analyses were done to investigate whether these odds differed by sex, age, seizure types, comorbid psychiatric diagnosis, and different time periods after epilepsy diagnosis. RESULTS: 6155 (8.8%) people with epilepsy died during follow-up, at a median age of 34.5 (IQR 21.0-44.0) years with substantially elevated odds of premature mortality (adjusted odds ratio [aOR] of 11.1 [95% CI 10.6-11.6] compared with general population controls, and 11.4 [10.4-12.5] compared with unaffected siblings). Of those deaths, 15.8% (n=972) were from external causes, with high odds for non-vehicle accidents (aOR 5.5, 95% CI 4.7-6.5) and suicide (3.7, 3.3-4.2). Of those who died from external causes, 75.2% had comorbid psychiatric disorders, with strong associations in individuals with co-occurring depression (13.0, 10.3-16.6) and substance misuse (22.4, 18.3-27.3), compared with patients with no epilepsy and no psychiatric comorbidity. INTERPRETATION: Reducing premature mortality from external causes of death should be a priority in epilepsy management. Psychiatric comorbidity plays an important part in the premature mortality seen in epilepsy. The ability of health services and public health measures to prevent such deaths requires review.

Commentary
Those of us involved in the lives and care of people with epilepsy know that epilepsy can erode quality of life and cause great disability. Epilepsy is projected to be the fourth leading contributor to neurologic burden of disease in 2015, after stroke, Alzheimer and other dementias, and migraine (1). Efforts to reduce this burden rightly capture much of our attention.

It is also well known, if less often discussed, that epilepsy is associated with excess mortality. The excess mortality in people with epilepsy relative to the population from which they are derived (standardized mortality ratio) depends on a number of factors. Important variables include the epilepsy population being studied (e.g., institution based, hospital based, population based), sex, etiology of epilepsy, and duration and severity of epilepsy (2). Standardized mortality ratio estimates range from 1.9 to 5.1 in institutionalized people with epilepsy to 1.3 to 3.1 in population-based cohorts (2).

The causes of excess mortality in epilepsy are several and include those related to the underlying cause of epilepsy (e.g., neoplasms), those directly related to seizures (e.g., SUDEP), and others that may or may not have a direct relationship with epilepsy (e.g., accidents, suicide). The independent contributions of epilepsy and psychiatric disease to this latter group have been debated and are less well defined. The study by Fazel and colleagues aims to better describe the causes of excess mortality in epilepsy including the relationship with psychiatric comorbidities.

The authors studied people with epilepsy born between 1954 and 2009 in Sweden, a total of nearly 70,000 people, and compared them with more than 660,000 age- and sex-matched general population controls and more than 81,000 unaffected siblings. The inclusion of a sibling comparison arm, adjusted for sex and age, allowed them to address potential confounding factors of environment and genetics. To accomplish this immense task, the authors relied on national registries for census data, medical diagnoses, and causes of death. Although use of administrative data can be a source of bias, previous studies using Swedish patient registry data have shown excellent diagnostic validity (3). The databases are also comprehensive: the cause of death register is estimated to capture more than 99% of the deaths that occurred in Sweden over this time period.

By combining these databases, people with epilepsy were identified and tracked (retrospectively) for an average of 9
years. A total of 6,155 people with epilepsy (8.8%) died before the end of follow-up, compared with 4,892 (0.7%) of controls. After adjusting for age, sex, and sociodemographic confounds, the mortality odds ratio (OR) for people with epilepsy was 11.1 (95% CI: 10.6–11.6) and was higher in men than women. Most deaths were owing to conditions underlying the epilepsy such as brain neoplasms, but 15.8% were judged to be due to "external causes," inclusive of various types of accidental death and suicide. The OR for external cause of death in people with epilepsy compared with controls was elevated, including for all external causes (3.6), suicide (3.7), assault (2.8), and especially nonvehicular accidents (5.5). Compared with their siblings, these ORs were elevated in a similar range (2.9–6.3). There was no evidence of familial confounding—the siblings appeared similar to the background general population on these measures. As noted in previous work, the highest OR for mortality, including for external causes of death, was seen in the early period after epilepsy diagnosis.

As expected, psychiatric comorbidity was common, seen in 18% prior to epilepsy diagnosis and 22.7% following, with depression and substance use especially common. Remarkably, of those who died of external causes, 75% had a comorbid psychiatric diagnosis: 56% were substance abusers and 23% suffered from major depression. The timing of the psychiatric diagnosis (before or after epilepsy diagnosis) did not appear to influence mortality risk. Those who died of other causes such as neoplasms did not show an association with psychiatric comorbidity.

Clearly, there is a high rate of premature mortality in epilepsy. Although prior reports assessing the direct role of epilepsy have been mixed, the present work clarifies an independent contribution of epilepsy to all cause and external cause mortality. It also emphasizes the potent additional risk of psychiatric comorbidity: in those with epilepsy and depression, the OR for suicide was 23 compared with the general population without depression, and more than double that of depression in people without epilepsy. Similarly, epilepsy combined with substance abuse showed a markedly elevated OR (21) for suicide. The combination of epilepsy and substance abuse conferred an OR of 43 for nonvehicular accidental death; again more than double that of substance abuse without epilepsy.

The study has some limitations, including reliance on administrative databases that have potential for misclassification bias in diagnoses or causes of death, and study of a single, relatively homogenous population that limits generalizability. Nonetheless, this careful assessment of a large population provides important new data on causes of excess mortality in epilepsy and the role of psychiatric comorbidity.

Psychiatric comorbidity is well established as an influence on perceived cognitive function and quality of life in epilepsy (4–6). In addition, psychiatric disease contributes to excess mortality in epilepsy. Recognition of the role of psychiatric comorbidity is critically important because many of these associated conditions are potentially treatable. The findings from this study suggest that enhanced efforts to screen for, identify, and treat psychiatric comorbidity are warranted. Epilepsy itself is an independent risk factor for premature mortality, and efforts to render our patients seizure-free and prevent SUDEP must continue. However, this study by Fazel and colleagues reminds us that we must not ignore the important contribution of psychiatric comorbidity to premature mortality in epilepsy.

by David Spencer, MD

References
**American Epilepsy Society**

**Epilepsy Currents Journal**

Disclosure of Potential Conflicts of Interest

**Instructions**

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   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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3. **Relevant financial activities outside the submitted work.**
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<th>Money to Your Institution*</th>
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David Spencer, MD

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