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Risk of mortality among patients with epilepsy in southern Taiwan

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ABSTRACT

Objective: Previous studies suggested a higher risk of all-cause mortality in patients with epilepsy than in the general population. However, information on the age- and sex-specific risk of mortality, as well as on the cause-specific risk of mortality has been sparse. This study aims to determine sex-, age-, and cause-specific risk of mortality among patients with epilepsy from southern Taiwan.
Methods: A total of 2180 patients treated in a tertiary hospital in southern Taiwan between 1989 and 2008 were compared to the general population of Taiwan for age-, sex- and cause-specific mortalities. The age-, sex-, and calendar year-standardized mortality ratios (SMRs) were calculated to estimate the relative risks of mortality associated with the epilepsy.
Results: There are 266 (12.2%) deaths noted in the study period. The patients with epilepsy experienced a significantly increased SMR of all-cause mortality (SMR, 2.5; 95% confidence interval (CI), 2.2–2.8). The most significantly elevated age-specific SMR was 51.8 (95% CI, 6.2–187.2) and 8.6 (95% CI, 4.4–14.9) for male patients aged 0–9 years and female patients aged 20–29 years, respectively. Additionally, the most increased cause-specific SMR was noted for brain tumor (SMR, 21.4; 95% CI, 9.23–23.1), followed by accidental drowning (SMR, 8.8; 95% CI, 3.5–9.6) and falls (SMR, 5.7; 95% CI, 2.2–6.1).
Conclusion: Younger epilepsy should be the object of aggressive treatments. Advancement in treating brain tumors and prevention of accidental injuries may help improve the survival of patients with epilepsy.

1. Introduction

Mortality in people with epilepsy exceeds that in the general population,[1–5] which is especially true for certain causes of death including cerebrovascular disease (CVD),[2,3,6] neoplastic disorders,[2,3,6] pneumonia,[2,3] poisoning,[7] and suicide.[8–10] In a recent review, Neligan et al. examined the temporal trends in the mortality of people with epilepsy and noted that the standardized mortality ratio (SMR) of mortality is highest in the initial years after diagnosis[11]; and there is no evidence that either the overall SMR or the mortality rate of people with epilepsy has changed significantly over time. Compared to the general population, the SMR for all-cause deaths varied from 1.6 to 5.3,[12] and the variation in cause-specific SMRs is usually grater. Common causes of deaths were also observed in certain selected epilepsy populations where patients with frequent and severe seizures are more common, and the SMRs for these selected epilepsy populations are three to six fold higher compared to those noted in population-based studies.[7,13–18] Although an increased mortality risk of all accidents was also noted in patients with epilepsy,[2,7,14,19] information concerning risk of death from specific cause of accidental death, such as drowning[20] and driving fatalities[21] has been neither comprehensive nor consistent, mainly due to certain methodological problems including small sample size and employment of patients with varying frequency of seizures.

Despite that the excess mortality in people with epilepsy has been well documented in the literature, most of studies were conducted in European and North American nations.[12,13,22] While there were data on prevalence of epilepsy from some developing countries, there is little information on the mortality of epilepsy in these populations. Limited information concerning mortality from epilepsy was available in developing countries, which was mainly due to the fact that death certificates are usually unreliable and often unavailable, and the cause of death is difficult to determine in many developing countries.[23] Meanwhile, information on mortality risk associated with epilepsy has also been rarely reported in Asian nations including Taiwan.[24,25] A community-based survey of 13,663 subjects aged 30 years or older reported an active epilepsy prevalence of 3.8/1000 in Taiwan, and the lifetime prevalence rate

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of epilepsy (including active epilepsy and epilepsy in remission) was estimated at 3.14/1000 for age above 30 years. In comparison with prior surveys, the study also indicated that the prevalence rate of epilepsy was rather stable over the in recent two decades.[26] Concerning the mortality risk, there have been only two hospital-based studies carried out to investigate the risk of mortality in Taiwanese patients with epilepsy.[24,25] Due to small sample size, interpretation of cause-specific mortality risk is rather limited, and reliable mortality risk estimates for detailed age and sex stratifications were not likely. We therefore conducted this cohort study with a larger cohort of people with epilepsy recruited from a tertiary hospital in southern Taiwan. With a sufficient number of study subjects, this study aims to investigate the sex, age, and cause-specific mortality risk associated with epilepsy in Taiwan. Results from this study were also compared with findings from other nations globally.

2. Subjects and methods

Between 1989 and 2008, a total of 2180 prevalent epilepsy patients, including 1214 men and 966 women, were treated at a tertiary hospital in southern Taiwan. We reviewed medical charts of those patients for their demographic characteristics and clinical manifestations of the disease. The charts included personal identification number (PIN), gender, date of birth, and date of the initial diagnosis of epilepsy. Information on seizure type and diagnosis was ascertained according to the guidelines recommended by the Commission on Epidemiology and Prognosis of the International League against Epilepsy.[27]

The cohort was then linked, using PIN, to Taiwan Death Register (TDR) between 1989 and 2008. The TDR is considered accurate and complete because it is mandatory to register all deaths in Taiwan and for physicians to complete all death certificates.[28] The linkage showed that 266 patients died by the end of 2008. Information on date of death and underlying cause of death (UCOD) coded according to the International Classification of Diseases 9th or 10th Clinical Modification (ICD-9-CM for 1988–2007 and ICD-10-CM for 2008) were retrieved from the TDR.

We compared patients' risks of overall and age- and sex-specific mortality to those of the general population. We also compared the risks of mortality from various causes including malignant neoplasms (ICD codes: 140–208 & C00-C97), heart disease (ICD code: 398, 402, 416, 425, 427–428 & I09, I11, I27, I42, I49, I50), ischemic heart disease (ICD codes: 410–414 & I20-I25), cerebrovascular disease (ICD codes: 430–438 & I60-I69), pneumonia (ICD codes: 480–486 & J12-J18), liver cirrhosis (ICD codes: 571 & K70, K73-K74), and injury (ICD code: E800-E999 & V01-Y89) between the patients with epilepsy and the general population. The expected number of death for the epileptic cohort was calculated from the person-year approach, using the age (10-year intervals) and sex-specific annual mortality rates with reference to the general population. We first calculated the number of person-years being observed for each study subject. The date of study entry was the date of initial primary or secondary diagnosis as epilepsy during the study period, i.e., 1989–2008. The date of completion of follow-up was the date of death encountered by the study subjects who died prior to the end of 2008. For those who were intact during the study period, the date of end-of-follow-up was set to be December 31, 2008. The annual age-sex-specific population sizes for the general population during the study period were derived from the national annual household registration statistics published by Ministry of the Interior of Taiwan. Standardized mortality ratios (SMRs) were calculated as relative risk estimates. The average annual average size of the general population over the study period was 21,769,198. The 95% confidence interval (CI) for SMR was estimated using the exact estimation.[29,30] The analysis was performed using SAS (version 9.1; SAS Institute, Cary, NC), and level of significance was set at a p-value of 0.05. The National Cheng Kung University Medical School IRB has approval of this study (ER-98-065).

3. Results

The study cohort consisted of 1214 male subjects and 966 females. The age ranged from 0 to 82 years at the first appearance in the cooperative hospital, with a median and mean (±SD) age of 15 and 21 ± 16 years old, respectively. Over a maximum of nearly 20 years of follow-up, a total of 22,617 person-years were accumulated. The length of follow-up varied, ranging from 0 to 4 years (n = 423), 5 to 9 years (n = 601), 10 to 14 years (n = 664), and 15 years and longer (n = 492). Totally, 266 deaths (193 men and 73 women) were noted at the end of follow-up. The mean age at death was 50 years (SD = 19 years) for all 266 deceased subjects.

Table 1 shows the overall and age- and sex-specific SMRs of all-cause mortality. The overall SMR was significantly increased for patients with epilepsy (SMR, 2.5; 95% CI, 2.2–2.8). Both male and female patients had a very similar risk estimate. The age-specific SMR was also significantly increased in patients with epilepsy of all age groups except those aged 10–19 and 70+ years. The most elevated SMR was noted in young children epilepsy aged 0–9 (SMR, 34.0; 95% CI, 4.1–122.8) followed by those aged 20–29 years (SMR, 6.3; 95% CI, 4.4–8.7). The age-sex-specific analysis showed that the most increased SMR for male patients was noted in children patients aged 0–9 years (SMR, 51.8; 95% CI, 6.2–187.2) followed by those aged 20–29 years (SMR, 5.6; 95% CI, 3.5–8.2), while patients aged 20–29 years were at the most elevated risk of mortality (SMR, 8.6; 95% CI, 4.4–14.9) in females.

The cause-specific SMRs are shown in Table 2. The SMR of all malignant neoplasm was significantly increased at 1.7 (95% CI, 1.2–1.7). The cancer-specific analysis further indicated a substantially and significantly increased SMR for brain tumor (SMR, 21.4; 95% CI, 9.2–23.1). We also noted a significantly increased SMR for liver cancer (2.6; 95% CI, 1.4–2.7). In addition to malignant neoplasm, heart disease (SMR, 2.6; 95% CI, 1.2–2.7), cerebrovascular disease (SMR, 2.6; 95% CI, 1.6–2.6) and pneumonia (SMR, 2.5; 95% CI, 1.1–2.7) were all significantly and positively associated with epilepsy mortality. On the other hand, we found no significant association of epilepsy with mortality from ischemic heart disease or liver cirrhosis. Patients with epilepsy were also at a significantly increased SMR for all injuries (SMR, 3.6; 95% CI, 2.7–3.6), as well as for certain injuries including transport accidents (SMR, 2.5; 95% CI, 1.4–2.6), accidental falls (SMR, 5.7; 95% CI, 2.2–6.1), accidental drowning (SMR, 8.8; 95% CI, 3.5–9.6), and suicide (SMR, 4.0; 95% CI, 2.4–4.1).

4. Discussion

4.1. Main findings

In 22,617 person-years observed over nearly 20 years, we noted an SMR of 2.5 for all-cause mortality in our sample patients, with a slightly higher risk estimate for men (SMR = 2.6) than for women (SMR = 2.2). In the age-specific analysis, our study noted a remarkably increased risk of mortality in younger patients with epilepsy. Like findings from the studies of many developed nations, our study also noted that Taiwanese people with epilepsy were also at significantly elevated risk of mortality from non-injury causes including malignant neoplasm (especially form brain tumor), cerebrovascular disease, pneumonia, and suicide, with an SMR ranging from 1.7 for malignant neoplasm (21.4 for brain tumor) to 2.6 for cerebrovascular disease. Additionally, SMRs for certain injury related causes, such as drowning (8.8) and fall (5.7)