

Excess Mortality in Remote Symptomatic Epilepsy

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Background.—Published estimates of excess mortality associated with epilepsy vary greatly. How much, if any, of the excess is attributable to the seizures themselves as opposed to an underlying condition causing the epilepsy is not clear from the literature. This article offers evidence that epilepsy per se is associated with excess mortality. The excess varies according to severity and frequency of seizures.

Materials and methods.—The authors studied mortality rates of developmentally disabled persons in California with and without epilepsy. In order to focus on the effect on mortality risk of epilepsy per se, they included only persons with good motor function (able to walk and climb stairs) and at worst moderate mental retardation (MR). The data were 506,204 person-years and 1523 deaths among 80,682 California subjects of age 5 to 65 years during the 1988-1999 study period. Mortality rates for persons with epilepsy were compared to rates for persons with no history of epilepsy.

Results.—Mortality rates were higher for persons with epilepsy than for those without. Excess death rates (EDRs) varied according to type and frequency of seizures. Combined EDRs were 6 (deaths per 1000 person-years) for persons with recent (<12 months) history of status epilepticus, 5 for recent history of generalized tonic-clonic (GTC) seizures, 3 for recent history of seizures but no recent GTC seizures, and less than 1 for a history of seizures but no recent events.

Conclusions.—The data presented here are evidence that epilepsy per se is associated with increased mortality. The EDRs reported here may be better measures of excess mortality due to epilepsy than previously published estimates.

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Epilepsy is a significant issue for life insurance underwriting. The Centers for Disease Control and Prevention estimate the prevalence of epilepsy in the United States to be 4.7 cases per 1000 persons.¹ This estimate is based on self-reported cases, and the true prevalence may be higher. It is a well established finding in medical²⁻⁷ and actuarial literature⁸⁻¹¹ that persons who experience epi-

leptic seizures are subject to greater mortality than the general population. The estimates of excess risk given in these sources vary widely, ranging from as low as 1 death per 1000 person-years for generalized tonic-clonic (GTC) seizures^{11(p 12-28)} to as high as 7 per 1000 implicit in a large Dutch study for epilepsy of undifferentiated type or etiology.² Some of the variation in estimated excess risk may be

attributable to: (1) lack of a controlled comparison group—mortality in persons with epilepsy, many of whom may have conditions such as cerebral palsy or traumatic brain injury, was compared to that of the general population, (2) failure to differentiate among persons with epilepsy according to type or frequency of seizures.

SUBJECTS AND MATERIALS

The database of the California Department of Developmental Services is compiled from annual Client Development Evaluation Reports¹² (CDERs) on over 235,000 persons with developmental disabilities.

From the 190,154 persons with developmental disabilities who received services from the State of California between January 1988 and December 1999, the authors identified persons age 5 to 65 years who (a) could walk well alone and climb stairs without assistance or the need for a hand rail, and (b) had at worst moderate mental retardation. They excluded persons with idiopathic epilepsy or with degenerative illnesses or conditions. The resulting population consisted of 80,682 persons.

Demographic characteristics are summarized by percentages in Table 1. As the table indicates, the majority of the subjects in this study were young. Overall, 10% of the subjects had at least a history of epilepsy by the end of the follow-up. Therefore, the prevalence of epilepsy (10%) was at least 10 times higher than in the general population.

Reliability of the functional items in the CDER has been assessed previously and judged satisfactory.¹³⁻¹⁷ Details reported in the CDER on seizure type and frequency are determined retrospectively from a patient's caregivers. In a comparison of these data to information taken from case records of a random sample of clients, discrepancies were found in 4% of cases for type and 6% for frequency of seizures.¹⁷

See the source article¹⁸ for details on the follow-up methods. These yielded a total of 506,204 person-years and 1523 deaths. Epi-

Table 1. Demographic Characteristics of 80,682 Persons With at Worst Moderate Mental Retardation who Could Walk Well Alone and Climb Stairs Without the Need for a Hand-Rail in the 1988-1999 Registry of the California Department of Developmental Services

| Characteristic | Percentage |
|--|------------|
| Sex | |
| Male | 60 |
| Female | 40 |
| Age at first evaluation | |
| 5-14 | 39 |
| 15-24 | 30 |
| 25-34 | 17 |
| 35-44 | 9 |
| 45-65 | 5 |
| Etiology | |
| Autism | 12 |
| Cerebral palsy | 5 |
| Chromosomal anomaly | 10 |
| Traumatic brain injury | 2 |
| Other/unknown | 71 |
| Epilepsy status at end of follow-up* | |
| History of status epilepticus | 1 |
| History of GTC | 6 |
| History of seizures other than status epilepticus or GTC | 6 |
| No history of epilepsy | 90 |

* The percentages do not sum to 100% because the first 3 categories overlap.

lepsy was identified by type, frequency and by whether there had been an episode of status epilepticus in the past year. Subjects with at least a history of epilepsy contributed 46,807 person-years of data and 266 deaths.

"Status epilepticus in the last 12 months," regardless of seizure type, was analyzed as a separate entity. The following severity scale was used:

1. No history of epilepsy
2. History of epilepsy (any type), but no event in the last 12 months
3. Seizures in the last 12 months, not GTC (though a prior history of GTC seizures is possible)
4. GTC seizure(s) in the last 12 months

Table 2. Comparison of Mortality Rates for Persons in the Study who had a History of Epilepsy but no Recent Events

| Attained Age (years) | Exposure Patient-Years E | Number of Deaths | | Mortality Ratio 100 d/d' | Mean Annual Mortality Rate per 1000 Patient-Years | | |
|----------------------|--------------------------|------------------|--------------|--------------------------|---|-------------|---------------|
| | | Observed d | Expected* d' | | Observed q | Expected q' | Excess q - q' |
| 5-14 | 1918 | 0 | 1.2 | 0% | 0.0 | 0.6 | -0.6 |
| 15-24 | 3957 | 5 | 6.1 | 82% | 1.3 | 1.5 | -0.3 |
| 25-34 | 4030 | 9 | 9.7 | 93% | 2.2 | 2.4 | -0.2 |
| 35-44 | 2724 | 16 | 9.9 | 162% | 5.9 | 3.6 | 2.3 |
| 45-65 | 1570 | 16 | 14.6 | 109% | 10.2 | 9.3 | 0.9 |
| 5-65 | 14199 | 46 | 41.4 | 111% | 3.2 | 2.9 | 0.3 |

* Basis of expected deaths: Quinquennial mortality rates for person-years in the study population with no history of epilepsy.

Table 3. Comparison of Mortality Rates for Persons in the Study who had Recent Seizures (<12 Months) but no Recent GTC Seizure

| Attained Age (years) | Exposure Patient-Years E | Number of Deaths | | Mortality Ratio 100 d/d' | Mean Annual Mortality Rate per 1000 Patient-Years | | |
|----------------------|--------------------------|------------------|--------------|--------------------------|---|-------------|---------------|
| | | Observed d | Expected* d' | | Observed q | Expected q' | Excess q - q' |
| 5-14 | 4023 | 10 | 2.6 | 385% | 2.5 | 0.6 | 1.8 |
| 15-24 | 4653 | 18 | 7.0 | 256% | 3.9 | 1.5 | 2.4 |
| 25-34 | 3306 | 26 | 7.9 | 331% | 7.9 | 2.4 | 5.5 |
| 35-44 | 1945 | 16 | 7.2 | 223% | 8.2 | 3.7 | 4.5 |
| 45-65 | 878 | 7 | 7.8 | 89% | 8.0 | 8.9 | -0.9 |
| 5-65 | 14804 | 77 | 32.5 | 237% | 5.2 | 2.2 | 3.0 |

* Basis of expected deaths: Quinquennial mortality rates for person-years in the study population with no history of epilepsy.

RESULTS

Tables 2 through 5 compare mortality rates for persons with no history of epilepsy (severity scale level 1) with those of persons at severity levels 2-4, and of persons with recent status epilepticus events. Expected numbers of deaths (q') were computed separately for each combination of quinquennial age group and severity as the product of the exposure time in the group and the mortality rates for person-years without a history of epilepsy. Table 6 provides information on the baseline mortality rates of the study population with no history of epilepsy as they compare with

rates of persons in the California general population from 1988-1999.¹⁹

Excess death rates (EDRs) increased with increasing level of the severity scale. Mortality rates for persons with a history of epilepsy but no recent events did not differ significantly from those of persons with no history of epilepsy (Table 2). Overall excess death rates compared to persons in the study population with no history of epilepsy were: 3 deaths per 1000 person years for persons with recent seizure activity but no recent GTC events (Table 3); 5.3 deaths per 1000 for persons with recent GTC events (Table 4);

Table 4. Comparison of Mortality Rates for Persons in the Study who had Recent GTC Seizures

| Attained Age (years) | Exposure Patient-Years E | Number of Deaths | | Mortality Ratio 100 d/d' | Mean Annual Mortality Rate per 1000 Patient-years | | |
|----------------------|--------------------------|------------------|--------------|--------------------------|---|-------------|---------------|
| | | Observed d | Expected* d' | | Observed q | Expected q' | Excess q - q' |
| 5-14 | 2931 | 8 | 1.9 | 420% | 2.7 | 0.6 | 2.1 |
| 15-24 | 4663 | 30 | 7.1 | 423% | 6.4 | 1.5 | 4.9 |
| 25-34 | 5194 | 52 | 12.4 | 419% | 10.0 | 2.4 | 7.6 |
| 35-44 | 3386 | 30 | 12.2 | 245% | 8.9 | 3.6 | 5.3 |
| 45-65 | 1629 | 23 | 15.1 | 152% | 14.1 | 9.3 | 4.8 |
| 5-65 | 17804 | 143 | 48.8 | 293% | 8.0 | 2.7 | 5.3 |

* Basis of expected deaths: Quinquennial mortality rates for person-years in the study population with no history of epilepsy.

Table 5. Comparison of Mortality Rates for Persons in the Study who had Recent (<12 Months) Status Epilepticus

| Attained Age (years) | Exposure Patient-Years E | Number of Deaths | | Mortality Ratio 100 d/d' | Mean Annual Mortality Rate per 1000 Patient-Years | | |
|----------------------|--------------------------|------------------|--------------|--------------------------|---|-------------|---------------|
| | | Observed d | Expected* d' | | Observed q | Expected q' | Excess q - q' |
| 5-17 | 1108 | 6 | 1.0 | 612% | 5.4 | 0.9 | 4.5 |
| 18-65 | 2090 | 22 | 6.6 | 335% | 10.5 | 3.1 | 7.4 |
| 5-65 | 3198 | 28 | 7.5 | 371% | 8.8 | 2.3 | 6.4 |

* Basis of expected deaths: Quinquennial mortality rates for person-years in the study population with no history of epilepsy.

Table 6. Baseline Mortality Rates for Persons in the Study who had no History of Epilepsy Compared With the California General Population

| Attained Age (years) | Exposure Patient-Years E | Number of Deaths | | Mortality Ratio 100 d/d' | Mean Annual Mortality Rate per 1000 Patient-Years | | |
|----------------------|--------------------------|------------------|--------------|--------------------------|---|-------------|---------------|
| | | Observed d | Expected* d' | | Observed q | Expected q' | Excess q - q' |
| 5-14 | 94036 | 60 | 19.1 | 314% | 0.6 | 0.2 | 0.4 |
| 15-24 | 121765 | 187 | 122.8 | 152% | 1.5 | 1.0 | 0.5 |
| 25-34 | 118443 | 283 | 152.4 | 186% | 2.4 | 1.3 | 1.1 |
| 35-44 | 78210 | 284 | 172.2 | 165% | 3.6 | 2.2 | 1.4 |
| 45-65 | 46942 | 443 | 268.9 | 165% | 9.4 | 5.7 | 3.7 |
| 5-65 | 459396 | 1257 | 735.4 | 171% | 2.7 | 1.6 | 1.1 |

* Basis of expected deaths: California annual mortality rates, 1988-1999.

and 6.4 deaths per 1000 for persons with recent status epilepticus events (Table 5).

DISCUSSION

The authors found that both type and frequency of seizures affect mortality risk associated with remote symptomatic epilepsy. Compared to persons in the study population with no history of epilepsy, the excess mortality is minimal if there have been no recent episodes. The highest death rates were observed in individuals with a recent history of GTC events or of status epilepticus. It is not surprising that the severity or frequency of seizures affects mortality risk, but estimates of EDRs or SMRs stratified by severity of epilepsy seem not to have been reported previously.

Persons with epilepsy have frequently been reported to have a mortality risk 2 to 3 times greater than the general population.^{2,5,8,10,20} This study demonstrated that the risk relative to the control group declines with advancing age (Tables 3–5). For example, the relative risk for persons with recent GTC episodes ranged from 4.2 at ages 5–34 to 1.5 at ages 45–65.

The reported results are short term. The information in Tables 3–5 may be used to construct life tables for individuals with remote symptomatic epilepsy, but assumptions would have to be made regarding the future frequency and type of seizures.

Idiopathic epilepsy, ie, epilepsy not known to be a sequela of an identified medical condition, may be of particular significance in insurance medicine. The results reported here may not generalize to persons with idiopathic epilepsy, as most subjects in this study had at least some cognitive deficits and some had minor impairment of motor function. Nevertheless, the reported EDRs are based on a comparison of similar persons with and without epilepsy, and may thus serve as measures of the effect on mortality rates of epilepsy per se.

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