CME

Remote symptomatic epilepsy

Does seizure severity increase mortality?

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Abstract—*Objective:* To investigate the excess mortality due to remote symptomatic epilepsy, taking account of frequency and type of seizures. *Methods:* The authors compared mortality in persons with (n = 8,156) and without (n = 72,526) history of epilepsy in a 1988 to 1999 California population of persons with mild developmental disabilities. Subjects had traumatic brain injury, cerebral palsy, Down syndrome, autism, or no identifiable condition. There were 506,204 person-years of data, with 1,523 deaths. Excess death rates and standardized mortality ratios were computed for the persons in the study with epilepsy, relative to those in the study without epilepsy. Controlled comparisons were made using logistic regression on person-years. *Results:* Compared to subjects with no epilepsy, the excess mortality was six (deaths per 1,000 persons per year) for persons with a recent (<12 months) history of status epilepticus, five for a recent history of generalized tonic-clonic seizure, three for a recent history of nonconvulsive seizures, and less than one for a history of epilepsy but no recent events. Proportion in remission and excess mortality showed no change over the 12-year study period. *Conclusions:* Persistent seizures are associated with increased mortality in remote symptomatic epilepsy. Mortality is highest among individuals with status epilepticus or generalized convulsions.

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It is well established that persons with epilepsy are subject to greater mortality than the general population. This has been documented both by research studies[1-6] and the actuarial experience of life insurance companies.[7-9,pp.756–759] What is less clear, however, is how much the mortality is increased, and how the excess depends on frequency and type of epilepsy. Further, there is only limited information available on how the comparisons depend on age and sex, whether the excess mortality has declined in recent years as new treatments have become available, and how much of the excess mortality reflects the epilepsy itself rather than the underlying condition that causes it.

A limitation in many studies is the lack of a controlled comparison: mortality in patients with epilepsy, some of whom have conditions such as cerebral palsy or traumatic brain injury, is frequently compared to that of the general population. In such cases it may not be possible to separate the effect of epilepsy from that due to the underlying condition. One exception is the study of German soldiers with head injuries from World War I, which found long-term excess mortality among those with epilepsy but not in those without epilepsy.[10] It may be that epilepsy in that study was to some extent a marker for other serious conditions. A more controlled comparison, however, based on a large population of children with severe cerebral palsy, also reported appreciably higher mortality associated with epilepsy.[11]

A second limitation in many studies is that changes in frequency and type of epilepsy are not tracked over the long term. Instead, the majority of studies follow groups of patients whose initial frequency or type of epilepsy is known, and compare their survival experience with other groups or with the general population. From such studies it is difficult to infer how the mortality risk depends on the patient's current type and frequency of epilepsy.

An alternative to this cohort approach is the analysis of person-years. In this method the unit of study is a short time interval, such as a year, rather than an individual subject. Associated with each year is an outcome variable, such as death or a particular cause of death, and explanatory variables such as the subject's sex, current age, type and severity of epilepsy, and the calendar year. This approach, which has been frequently used in the Framing-

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ham Heart Study,[12] overcomes many of the above-noted difficulties.[13]

In this article we analyze mortality within a large California population of persons with developmental disabilities. Subjects had only minimal motor dysfunction and at worst moderate mental retardation. In this group, 10% have a history of epilepsy. Our study was designed to answer the following questions:

1. After etiology and other factors are taken into account, what is the excess mortality associated with epilepsy?
2. How does the excess mortality depend on type of epilepsy and time since last episode?
3. How does the excess mortality depend on the patient's sex and age?
4. Has there been a change in mortality risk over the years of the study (1988 through 1999)?

Methods. *Subjects.* Our base population consisted of the 190,154 persons with developmental disability who received services from the State of California between January 1988 and December 1999. Services included medical treatment, occupational or physical therapy, and board and care. Eligibility for the California system is defined as "a disability which originates before an individual attains age 18, continues, or can be expected to continue, indefinitely, and constitutes a substantial disability for that individual."[14] All persons receiving services are evaluated approximately annually with a structured interview called the Client Development Evaluation Report (CDER).[15] This instrument contains over 200 psychological, medical, functional, behavioral, and cognitive items. The reliability of the functional items has been assessed previously and judged satisfactory.[16-20] For the CDER, details on seizure type and frequency are determined retrospectively from a patient's caregivers. In a comparison of these details with 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.[20] Inter-rater reliabilities[21] of the motoric variables described in the current study exceeded 0.85.

In order to assess the effect on mortality risk of epilepsy per se, we included only high functioning subjects. Individuals who were unable to walk well alone at least 20 feet and balance well, who were unable to climb stairs without support, or who were severely or profoundly mentally retarded were excluded. Persons with degenerative conditions were also excluded.

The resulting 80,682 subjects were identified as having traumatic brain injury (2%), cerebral palsy (5%), autism (12%), or chromosomal anomaly (10%, mostly Down syndrome). The majority (71%) of the subjects had none of these conditions, and were coded as other. Within this latter group, the majority had mild or moderate mental retardation without any known medical condition. Only 107 subjects appeared to have idiopathic epilepsy—i.e., were in the California system only because of their epilepsy. This number was too small to warrant separate consideration, and we therefore excluded these subjects from the study.

The study period was the 12-year interval 1988 through 1999. The beginning of the period "at risk" for a given subject was the date of the first CDER evaluation or January 1, 1988, whichever came later. The end of a subject's period at risk was the earliest of 1) the date of death, 2) the end of the study period (December 31, 1999), or 3) 3 years after the date of the subject's last CDER. This last condition was included to minimize the potential bias due to subjects who may have left California. Deaths of such persons would not be in our records, but because of condition 3 these subjects would also not be counted as being at risk for more than a fairly short period.

Sources of clinical information. Epilepsy was identified from three items on the CDER: type of seizure (coded as eight types, from "partial with elementary symptomatology" to "generalized tonic-clonic [grand mal]," here abbreviated as GTC), seizure frequency (eight levels, from "history of seizures, none in two years" to "more than one per day"), and "status epilepticus in the past year." We excluded 4,936 person-years with an indication of at least one type of epilepsy but no indication of seizure frequency, leaving 46,807 person-years and 266 deaths with at least a history of epilepsy and a definite indication of seizure frequency.

Mortality information was obtained from annual computer tapes from the California Department of Health Services,[22] and matched against the subjects on the basis of name, date of birth, and social security number when available.

Severity of epilepsy. After analyzing mortality by type and frequency of seizures (by logistic regression), we adopted the following severity scale:

1. No history of epilepsy
2. History of epilepsy (any seizure type), but no recent events (within the last 12 months)
3. Recent seizures, not GTC (although a previous history of GTC is possible)
4. Recent GTC seizure(s)

"Status epilepticus in the last 12 months," regardless of seizure type, was analyzed as a separate entity.

As noted above, the term recent seizures refers to seizures occurring within the last 12 months. We chose this as a cutpoint for our severity scale after preliminary analyses in which we considered finer categories of frequency: 1) history of seizures, none in 2 years; 2) history of seizures, none in 1 year; 3) 1 to 6 per year; 4) 7 to 11 per year; 5) 1 per month; 6) 1 per week; 7) 1 per day; and 8) more than 1 per day. We used logistic regression to investigate the pattern of mortality for GTC seizures and other types of seizures based on these frequencies. Seizures at least once per year were associated with significantly higher mortality rates than "history of seizures, none in a year or more." However, no clear pattern emerged for the frequency categories 3 through 8; i.e., one to six seizures per year, or more frequent.

Statistical methods. The unit of study was a person-year rather than a person. We included all person-years for subjects in the age range of 5 to 65 years. Each person-year was linked to a binary outcome variable ("died in that year?") and explanatory variables including age, sex, severity of epilepsy, etiologic group (i.e., traumatic brain injury, cerebral palsy), and calendar year for analysis of secular trend (a trend of increasing or decreasing mortality rates over the years). In all there were 506,204 person-years of data, with 1,523 deaths. Of the person-years, 41% were derived from female subjects and 59% from male subjects. Twenty percent were associated with persons age 5 to 14; 70%, age 15 to 44; and 10%, age 45 to 65.

For each 5-year age group from 5 to 65 we computed mortality rates for persons in the study population with no history of epilepsy. These rates were then applied to the age- and sex-specific exposure times for persons in the study with at least a history of epilepsy. This yielded an expected number of deaths. The ratio of observed to expected number of deaths is a standardized mortality ratio (SMR).[23] We also calculated excess death rates (EDR), which are the differences between the observed and expected rates. Confidence intervals for the SMR and EDR were derived from the corresponding confidence intervals for the mean of a Poisson variable in the standard manner.[9,pp.59] For purposes of comparison, the above procedure was repeated using single-year mortality rates for the California general population as expected rates. These rates were obtained using the California mortality tapes and data on population over the time period 1988 to 1999.[22,24]

For comparisons adjusted for the effects of covariates (age, sex, calendar year, etiologic group, type and frequency of seizure) we used logistic regression on the person-years, with death as the outcome variable. This approach, sometimes referred to as pooled repeated observations, has been widely used in studies of this kind.[12,13]

We used two approaches to investigate a possible secular trend. First, if antiepileptic drugs and other treatments have improved over the study period and penetrated the California system, one expected consequence would be an increased proportion in remission. We therefore divided the study period into three 4-year periods and examined the proportion of subjects in each who had a history of epilepsy but had no seizure within the last 12 months. Second, in the logistic modeling we considered indicator variables for the three calendar periods and interactions of these terms with the levels of our epilepsy severity scale.

Table 1 *Person-years, classified by etiology and by type and frequency of epilepsy*

Person-years and epilepsy status	All, n = 80,682	TBI, n = 1,539	Cerebral palsy, n = 3,742	Autism, n = 9,281	Chromosomal anomalies, n = 8,438	Other, n = 57,682
Total number of person-years	506,204	8,497	24,828	46,061	49,759	377,058
No history of epilepsy	91	72	82	96	93	91
History of epilepsy, none in a year or more	3	8	7	2	2	3
Seizures in last year, not GTC	3	9	5	1	2	3
GTC seizures in last year	4	11	6	1	2	4
Total	100	100	100	100	100	100
Status epilepticus in last year	0.6	1.6	1.2	0.3	0.4	0.7

Values are percentages.

TBI = traumatic brain injury; GTC = generalized tonic-clonic seizures.

Results. The resulting population included 80,682 persons, of whom 8,156 had a history of epilepsy. The prevalence of epilepsy (10%) was therefore at least 10 times higher than in the general population.[25] A total of 1,523 subjects died during the 12-year study period, 266 of whom had a history of epilepsy.

In 82% of the epilepsy person-years, only a single type of seizure was recorded. In 16%, two types were indicated. The remaining 2% corresponded to three or more types of seizure. The most common seizure types were complex partial (19%), generalized absence (23%), and GTC (59%). These percentages overlap; overall, 87% of the person-years indicating epilepsy were associated with at least one of these three types of seizure. In 0.6% of the person-years the subject had had status epilepticus during the previous 12 months; 59% of these person-years also included GTC event(s). In our study population, epilepsy was most common in subjects with traumatic brain injury (28%) and cerebral palsy (18%), and least common in autism (table 1).

Among persons with a history of epilepsy, recent seizures were most common in the youngest age group (ages 5 to 15), with 45% having had one or more seizures in the last 12 months. This percentage declined steadily with age; only 23% of individuals over 34 years of age had had a seizure during the last 12 months. Interestingly, among persons with recent seizures the proportion with GTC events was considerably lower in the youngest age group (42%) than in the oldest group (64%). Overall, recent GTC events were more common in adults than in children, the proportions being 3.7% for adults and 2.9% for children.

In the remainder of the study we worked with the epilepsy severity scale described in Methods. Table 2 shows the numbers of person-years of exposure and the crude death rate by severity level. Also shown are the SMR and EDR relative to the study subjects with no epilepsy. For subjects with a history of epilepsy but no events in the previous year, the SMR of 1.1 was not significantly different from 1.0, indicating mortality in this group was comparable to mortality of persons with no history of epilepsy. Similarly, the EDR of 0.3 per 1,000 was small and not significant. Among those with recent seizures that were not GTC, the EDR of 3.0 per 1,000 was larger and highly significant. The EDR for persons with recent GTC seizures was 5.3 per 1,000, and the EDR for those with recent status epilepticus was 6.4 per 1,000, both significant. We found no significant age or sex differences in SMR or EDR. Compared to the California general population the persons in the study with no history of epilepsy had an SMR of 1.7 and an EDR of 1.1 deaths per 1,000 person-years (not shown).

Because our dataset did not include information on specific antiepileptic drugs used, we cannot comment directly on their effect. However, if there have been improvements in antiepileptic drugs or other treatments over the study period then one possible marker would be the proportion of persons with epilepsy in remission. The proportion of subjects in remission, defined as having a history of epilepsy but no events in the last 12 months, was constant (at 29 to 31%) across the three 4-year periods. Further, the logistic regression modeling did not indicate any decline in the relative risk for epilepsy over the three 4-year intervals of the 12-year study period. These two findings do not support the hypothesis that changes in treatments and drugs have resulted in better control of seizures over the study period, based on the seizure history obtained in the annual review.

Discussion. For persons in our study population with a history of remote symptomatic epilepsy we found that both type and frequency of seizures affect mortality. The excess mortality is minimal if there have been no recent episodes, suggesting that the mortality risk is largely confined to persons with ongoing seizures. The highest death rates were ob-

Table 2 *Mortality rates, based on 506,204 person-years from 80,682 subjects age 5–65 and 1,523 deaths*

Epilepsy status	Exposure, person-years	Crude death rate per 1,000 person-years	SMR*	EDR†
No history of epilepsy	459,396	2.7	1.0 (reference)	0.0 (reference)
History of epilepsy, no seizures in a year or more	14,199	3.2	1.1 (0.8, 1.5)	0.3 (−0.5, 1.4)
Seizures in last year, no GTC event	14,804	5.2	2.4 (1.9, 3.0)	3.0 (1.9, 4.3)
GTC event in last year	17,804	8.0	2.9 (2.4, 3.4)	5.3 (3.9, 6.6)
Status epilepticus in the last year	3,198	8.8	3.7 (2.5, 5.4)	6.4 (3.5, 10.3)

95% CI are in parentheses.

* Standardized mortality ratio, relative to persons in the study with no history of epilepsy.

† Excess death rate, per 1,000 person-years, relative to persons in the study with no history of epilepsy.

served in individuals with a recent history of GTC events or of status epilepticus.

This mortality "gradient" is hardly surprising, but estimates of excess mortality stratified according to severity of epilepsy seem not to have been reported previously. The actuarial text of Brackenridge and Elder[9,pp.759] suggests that frequency of seizures is of more value as a predictor of death than the seizure type, essentially because the type of seizure often changes with age. Frequency may also change over time, however, and the pattern of change in type and frequency of seizures over the long term appears not to have been studied. We hope to report on this issue shortly.

We observed that developmentally delayed children with a history of epilepsy are more likely to have recent seizures than are older persons, and that the proportion of those whose recent seizures are GTC is highest among the older subjects. Our findings are consistent with the observation that the majority of patients with childhood-onset epilepsy eventually achieve remission.[26] Our findings also suggest that in individuals with persistent epilepsy, the severity of seizures may increase with age. However, the cross-sectional analyses reported here are not sufficient to establish such results; longitudinal analysis would be required. We hope to report on this subsequently.

This may be the first study of mortality in epilepsy with internal controls; that is, we compared the mortality of persons with epilepsy to that of individuals with similar disabilities and underlying conditions who do not have seizures, rather than to the general population. As a result we may be closer to measuring the effect of epilepsy itself, rather than the combined effect of epilepsy and the underlying conditions that may have caused the seizures. This may explain why the EDR of the current study are less than have been reported elsewhere. For example, data from a large recent Dutch study[1] lead to an overall EDR of approximately 7 per 1,000 per year, which is higher than the EDR reported here even for persons with recent status epilepticus. This higher EDR may reflect cerebral palsy or other conditions directly linked to increased mortality.

From a methodologic point of view, the use of a person-years analysis[12,13] has advantages over the more common cohort approach. Technically, the person-year method is equivalent to a cohort analysis with time-varying covariates, and can be considered a computationally convenient approach to implementing such an analysis.[13] Rather than focusing on the subject's status at the time of entry into the study, the researcher can disentangle the effects of the subject's current age, seizure status, and calendar year. Researchers may wish to consider this design in future studies of epilepsy mortality.

Our study is subject to a number of important limitations. First, our population is comprised entirely of individuals with remote symptomatic epilepsy and minimal cognitive and motor disabilities, and therefore is not generalizable to all individuals with epilepsy. Second, although the CDER information on seizure type and frequency has been validated, it is possible that a proportion of individuals with complex partial seizures were misclassified as having "generalized absence" given the unusually high frequency of this seizure type in our group of patients with remote symptomatic epilepsy. However, GTC seizures and status epilepticus are less likely to be misdiagnosed. Third, early mortality from incident cases of seizure or epilepsy would be missed in our evaluation of prevalent cases. Studies have suggested that the highest mortality from epilepsy occurs in the first year after diagnosis,[27] and that there is little if any increase in mortality after the first 5 years.[28] From our cross-sectional analysis we cannot comment on mortality shortly after onset or the change in mortality over time in an individual. Finally, the results given here are essentially short term, and cannot be used to estimate the effect of epilepsy on an individual's life expectancy without making assumptions about the frequency and type of seizure throughout the life span.

However, our study has some important strengths by comparison to previous reports of epilepsy mortality. We report one of the largest population-based studies of mortality among individuals with remote symptomatic epilepsy, with 46,807 person-years of data. Studies of epilepsy mortality in children are particularly sparse,[29,30] whereas 20% of our person-year data derive from children under age 15. Further, our data permit us to link mortality risk to the subject's current frequency and type of seizures. Finally, the value of the internal comparison population has been noted previously.

How much the increased mortality among individuals with remote symptomatic epilepsy can be attributed to the seizures themselves rather than to the underlying medical conditions continues to be debated.[1,28] Some clinical studies have suggested that mortality rates among individuals with idiopathic epilepsy may not be significantly elevated above that of the general population.[31-33] Extensive actuarial data from life insurance companies, however, document a substantially increased mortality in persons with idiopathic epilepsy and no other relevant medical problems (tables 12-28 in reference [28]).[9,pp.756] The "internal" comparisons made here suggest that in high functioning individuals with remote symptomatic epilepsy, the epilepsy per se is associated with an increased mortality rate.

This study does not include information regarding cause of death. A number of investigators have found an elevated SMR for deaths from a wide range of conditions including malignancy, stroke, and cardiovascular disease among individuals with epilepsy.[3,27,34] It is not clear whether deaths related to seizures themselves are common[1,32] or relatively rare.[3] Also unknown is the frequency of avoidable mortality, or deaths that could be prevented in some way through better seizure treatment or improved

services.[29,33] We hope to report separately on causes of death in our population of individuals with remote symptomatic epilepsy.

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