Status Epilepticus Without an Underlying Cause and Risk of Death

A Population-Based Study

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Objective: To determine the independent effect of status epilepticus (SE) on risk of death.

Design: Retrospective cohort study. The increased risk of death after SE has been largely ascribed to the underlying medical condition. It is unknown whether SE itself affects risk of death. We address this question by studying idiopathic/cryptogenic SE.

Setting: Population-based study.

Participants: We identified all incident idiopathic/cryptogenic unprovoked seizures in the population of Rochester, Minnesota, from January 1, 1955, through December 31, 1984, and observed them until death, loss to follow-up, or the end of the study.

Main Outcome Measures: We compared the risk of death in those with a brief unprovoked seizure (<30 minutes) with risk of death in those with an unprovoked seizure of 30 minutes or longer (SE), using Kaplan-Meier and Cox proportional hazards regression. The standardized mortality ratio was also determined.

Results: We ascertained 291 people with a first brief unprovoked seizure and 16 with SE. There were 27 deaths among people with seizure and 5 deaths (all aged >65 years) among people with SE. Compared with people with seizure, the adjusted relative risk for death in those with SE was 2.4 (95% confidence interval [CI], 0.9-6.3) over 10 years. It was increased 5-fold (relative risk, 5.1; 95% CI, 1.6-15.7) among those older than 65 years and 6-fold among those with SE who later developed epilepsy (relative risk, 6.3; 95% CI, 1.5-26.0). Compared with the general population, the standardized mortality ratio was 2.6 (95% CI, 0.8-5.3) for SE and 1.2 (95% CI, 0.8-1.6) for a first seizure of short duration.

Conclusion: Idiopathic/cryptogenic SE was associated with an increased risk of death among elderly persons and those who later developed epilepsy.

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Status Epilepticus (SE) is a common medical condition associated with high morbidity and mortality rates.1,2 The seriousness of the underlying medical conditions associated with most cases of SE makes it impossible to determine the independent impact of prolonged seizure on mortality. Demonstration of an independent contribution of SE on mortality may further support the need for aggressive treatment to reduce the duration of prolonged seizures3 but can only be studied in subjects with idiopathic/cryptogenic SE in whom the confounding effect of other causes is absent.

We hypothesized that idiopathic/cryptogenic SE is associated with an increased long-term mortality over and above that associated with unprovoked seizure. We tested our hypothesis by comparing mortality of subjects with incident idiopathic/cryptogenic SE as a first seizure (SE group) with an incident cohort of subjects with first idiopathic/cryptogenic unprovoked seizure that was not SE (seizure group) and with that expected in the general population.

METHODS

We reviewed the medical records of residents of Rochester, Minnesota, with a first diagnosis of febrile seizure, acute symptomatic seizure, single unprovoked seizure, or incident epilepsy from January 1, 1955, through December 31, 1984, to identify those with SE.4 As in previous studies, SE was defined as a seizure or a series of seizures without an intervening period of lucidity lasting more than 30 minutes. In the unprovoked seizure group, cause was assigned according to the criteria of Hauser.5 The present report deals only with cases of first idiopathic/cryptogenic unprovoked seizure, defined as a seizure occurring...
Epilepsy is defined as recurrent unprovoked seizures. Sex-standardized mortality ratio. Specific death rate for Minnesota, by computing the age- and sex-adjusted mortality rate. The statistical difference between the seizure and SE groups were explored with the \( t \) test for continuous variables, the \( \chi^2 \) test for categorical variables, and the Fisher exact test when cell frequencies were less than 5. Kaplan-Meier methods were used to estimate mortality through 10 years, comparing those with SE with those with a briefer unprovoked seizure. The statistical difference was tested by the log-rank test. Relative risk was determined through a Cox proportional hazards model for mortality through 10 years following SE. The proportionality assumption was checked using standard procedures. Adjusted estimates of the relative risk were obtained after the introduction of age and sex as covariates in the model. The same procedures were used to compare subjects in whom SE or unprovoked seizure occurred as an isolated event with subjects who experienced a second unprovoked seizure. Analyses also evaluated the effect of SE on mortality in people younger than 65 years and in those 65 years and older.

The observed deaths in the seizure and SE groups were compared with that expected at 10 years following the index event (seizure or SE) based on the age-, sex-, and time period-specific death rate for Minnesota, by computing the age- and sex-standardized mortality ratio.

**RESULTS**

We ascertained 291 subjects (155 males and 136 females) in the first idiopathic/cryptogenic seizure group and 16 (11 males and 5 females) in the first idiopathic/cryptogenic SE group. The mean age was 28.3 years (SD, 29.5 years) in the seizure group and 46.9 years (SD, 33.0 years) in the SE group (\( t \) test=2.9, \( P < .004 \)).

At 10 years after the index seizure, there were 5 deaths (31.2%) among the SE group and 27 deaths (9.3%) among the seizure group. Kaplan-Meier survival analysis comparing the survival of the 2 groups showed an estimated cumulative mortality of 32.3% in the SE group and 11.8% in the seizure group (log-rank test=9.3, \( P < .002 \)). In the Cox proportional hazards model, SE was associated with a 4-fold risk of dying during follow-up when compared with seizure (Table 1). After adjusting for age and sex, SE remained associated with a higher risk of death that was no longer statistically significant.

To eliminate the possibility that the risk of death is further increased in association with repeated unprovoked seizures or their correlates (electroencephalographic findings and familial history of unprovoked seizure), we conducted a stratified analysis, classifying subjects based on whether they had a second unprovoked seizure. In the 184 subjects who did not develop epilepsy, the cumulative risk of death at 10 years was 20.0% for the SE group and 13.7% for the seizure group (log-rank test=0.5, \( P = .50 \)). In the 123 subjects with subsequent epilepsy, the cumulative risk of death at 10 years was 60.0% for the SE group and 9.6% for the seizure group (log-rank test=28.7, \( P < .01 \)). After adjusting for age and sex, the presence of SE was associated with an increased risk of death among subjects who developed epilepsy.

There was no increase in risk in those who did not have additional unprovoked seizures (Table 1). We also examined whether having SE following a first brief seizure as opposed to having SE as one of the following seizures had an effect on mortality. The cumulative risk of death by 10 years was 32.3% in those who had SE as the first idiopathic/cryptogenic unprovoked seizure (n=16), 7.7% in those who had SE but not as the first unprovoked seizure (n=13), and 12.1% in those who did not have SE (n=278) (log-rank test=9.4, \( P < .009 \)).

The incidence of idiopathic/cryptogenic SE increases in elderly persons, and all 5 deaths occurred in this age group. We therefore conducted an analysis among the idiopathic/cryptogenic seizure subjects (n=28) who were 65 years and older. Among the elderly subjects, the cumulative incidence of death at 10 years was 71.4% for the SE group and 41.9% for the seizure group (log-rank test=5.0, \( P < .02 \)). In a Cox proportional hazards model, after adjusting for age and sex, there was a significantly higher risk of dying for SE compared with shorter seizures among those older than 65 years.

The mortality at 10 years for subjects who experienced SE was increased 2.6-fold compared with the age- and sex-matched general population (Table 2), but was not statistically significant. The standardized mortality ratio was not different from that of the general population for the group with shorter seizures. The mortality among patients with SE 65 years and older was higher than the mortality in the age- and sex-matched general population (standardized mortality ratio, 3.18; 95% confidence interval, 1.01-6.60). Among elderly persons, the mortality of subjects experiencing a seizure of short duration was not different from that of the general population (standardized mortality ratio, 0.73; 95% confidence interval, 0.39-1.18).

The distribution of causes of death was not different in subjects with and without SE (\( P = .20 \)). Causes of death in the SE group included cardiovascular disease in 1, cerebrovascular disease in 2, pneumonia in 1, and other in 1. Causes of death in subjects without SE included neoplasm in 1 (3.7%), cardiovascular disease in 7 (25.9%), cerebrovascular disease in 2 (7.4%), pneumonia in 2 (7.4%), and other in 15 (55.6%).
In this study, subjects with idiopathic/cryptogenic SE as their first unprovoked seizure had a nonsignificant 2.4-fold increased risk of death compared with subjects who had briefer unprovoked seizures at 10 years. There was also a 2.6-fold increased risk of death when compared with the general population. Previous studies of mortality following SE had several limitations, including a short follow-up (<1 year) and the inclusion of cases with multiple causes. This is, to our knowledge, the first study to show an independent association between SE without an underlying cause and reduced life expectancy, although it is restricted to subjects who later developed epilepsy and to elderly subjects. The excess mortality identified in studies10-12 of newly diagnosed cases of idiopathic/cryptogenic epilepsy among elderly persons may be largely attributed to that associated with incident SE.

Subjects older than 65 years with SE experience a higher risk of death than subjects older than 65 years with a briefer seizure. A prolonged seizure might be more dangerous among elderly persons because any damage induced by SE might be more extensive in the aging brain. An alternative explanation may be that some elderly subjects may have underlying vascular or neurodegenerative disease without clinical manifestations and, therefore, are incorrectly classified as having idiopathic/cryptogenic SE.7 To our knowledge, there are no published data on the risk of epilepsy among subjects with silent stroke or cognitive decline to support or refute this hypothesis, which postulates that there is an interaction between subclinical pathological features and SE, and not SE itself, that determines the increased mortality. The major determinant of seizures and epilepsy among elderly persons is vascular lesions.13,14 Silent strokes are common among elderly persons, and their incidence is high even in individuals without a previous clinical episode.13 Subclinical vascular lesions may potentially increase the risk of death, because SE after clinical stroke has been associated with a higher risk of death at 3 years compared with subjects with clinical stroke without SE.16 Several hypotheses may explain why mortality is increased in subjects with a first idiopathic/cryptogenic SE who develop epilepsy during follow-up. Status epilepticus may induce neuronal damage in vulnerable areas of the central nervous system, leading to a permanent dysregulation of neurovegetative activities. Alternatively, SE may be a clinical marker of severity of idiopathic/cryptogenic epilepsy when it occurs as the first unprovoked seizure. An additional hypothesis relates to the basic underlying mechanism of SE: SE is effectively the result of a failure of inhibitory mechanisms. Factors responsible for this failure may also have a synergistic effect with age, affecting mortality.

The main limitation of the present study was the small sample size; we had only 16 patients with idiopathic SE. Nevertheless, we were able to show

Table 1. Data Comparing the Risk of Death Among First Idiopathic/Cryptogenic Unprovoked Seizure That Was and Was Not SE

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>Crude Risk (95% Confidence Interval)</th>
<th>Adjusted a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>307</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>First unprovoked seizure without SE</td>
<td>291</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>First unprovoked seizure with SE</td>
<td>16</td>
<td>3.9 (1.5-10.3)</td>
<td>2.4 (0.9-6.3)</td>
</tr>
<tr>
<td>Patients without epilepsy</td>
<td>184</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>First unprovoked seizure without SE</td>
<td>173</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>First unprovoked seizure with SE</td>
<td>11</td>
<td>1.7 (0.4-7.5)</td>
<td>1.1 (0.2-5.0)</td>
</tr>
<tr>
<td>Patients with epilepsy</td>
<td>123</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>First unprovoked seizure without SE</td>
<td>118</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>First unprovoked seizure with SE</td>
<td>5</td>
<td>14.8 (4.0-55.0)</td>
<td>6.3 (1.5-26.0)</td>
</tr>
<tr>
<td>Patients &gt; 65 y</td>
<td>45</td>
<td>NA NA</td>
<td>NA NA</td>
</tr>
<tr>
<td>First unprovoked seizure without SE</td>
<td>38</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>First unprovoked seizure with SE</td>
<td>7</td>
<td>3.1 (1.1-8.7)</td>
<td>5.1 (1.6-15.7)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, data not applicable; SE, status epilepticus.
aAdjusted for age and sex.

Table 2. Data at 10 Years for First Idiopathic/Cryptogenic Unprovoked Seizure That Was and Was Not SE

<table>
<thead>
<tr>
<th>Type of Seizure</th>
<th>No. of Patients</th>
<th>Deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First unprovoked seizure with SE</td>
<td>16</td>
<td>5</td>
<td>2.6 (0.8-5.3)</td>
</tr>
<tr>
<td>First unprovoked seizure without SE</td>
<td>291</td>
<td>27</td>
<td>1.2 (0.8-1.6)</td>
</tr>
<tr>
<td>All first unprovoked seizures</td>
<td>307</td>
<td>32</td>
<td>1.3 (0.9-1.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SE, status epilepticus; SMR, standardized mortality ratio.
a significant effect on mortality in elderly persons and in those who subsequently developed epilepsy. Our results need to be confirmed in a larger multicenter study. The second limitation is that by current standards, few patients in this series received adequate antiseizure therapy at the time of SE. Current therapy may have modified the prognosis, but evidence in this direction is lacking. Third, we were unable to address mortality in subjects with seizure durations between 5 and 30 minutes. Status epilepticus as a diagnostic entity is seldom coded in medical records, and absolute duration of a seizure is also seldom recorded. The timing of seizures in this study was determined through review of all records available: ambulance and emergency department records, nurse’s notes, and the clinical record. A retrospective study could not reliably distinguish between a seizure of less than 5 minutes and a brief seizure of greater duration. This group should also be considered in future prospective studies.

These data are clinically relevant because they may indicate that the high mortality associated with SE in elderly persons may not be because of the underlying cause of SE, but because of SE itself. However, before a more aggressive treatment of SE may be considered among elderly persons, it is necessary to examine the potential for increased susceptibility to the effect of treatment among these patients, who may have several comorbidities. This is a relevant problem because of the increased incidence of SE among older subjects, who represent the fastest-growing group of the US population.17

In conclusion, idiopathic SE is associated with an increased but low risk of death after 10 years when compared with a seizure of short duration. The risk of death is restricted to elderly subjects and to those who subsequently develop epilepsy. Future larger studies should focus on the role of SE as the first unprovoked seizure, because this seems to be the most important factor for long-term prognosis.

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REFERENCES