Suicide among patients with amyotrophic lateral sclerosis

Fang Fang,1 Unnur Valdimarsdóttir,1,2 Carl Johan Fürst,3 Christina Hultman,1,4 Katja Fall,1 Pär Sparén1 and Weimin Ye1

1Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, 2Centre of Public Health Sciences, University of Iceland, Reykjavik, Iceland, 3Stockholms Sjukhem Palliative Care Unit, Stockholm and 4Department of Neuroscience, Psychiatry, Ulleraker, Uppsala University, Uppsala, Sweden

Correspondence to: Fang Fang, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, 171 77 Stockholm, Sweden
E-mail: fang.fang@ki.se

Studies on the suicide risk among patients with amyotrophic lateral sclerosis (ALS) in countries without legalized euthanasia or assisted suicide are important additions to data on the wish to die of these patients. We conducted a population-based cohort study in Sweden between 1965 and 2004, which comprised of 6642 patients with incident ALS identified from the Swedish Inpatient Register. We calculated the standardized mortality ratios (SMRs) of suicide among the patients using the suicide rates of the general Swedish population as a reference. In total, 21 patients committed suicide during follow-up, compared to the predicted 3.6 suicides. Thus, we noted an almost 6-fold increased risk for suicide among ALS patients [SMR 5.8, 95% confidence interval (CI) 3.6–8.8]. Patients who committed suicide were, on average, around 7 years younger at the time of their first period of hospitalization than patients who did not commit suicide. The highest relative risk for suicide was observed within the first year after the patient’s first period of hospitalization (SMR 11.2, 95% CI 5.8–19.6). After that, the relative risks decreased with time after hospitalization (P-value for trend = 0.006), but remained elevated 3 years later. The relative risks of suicide among ALS patients did not show a clear trend over time in contrast to the decreasing trend of relative risks for suicide among patients with cancer during the same period. Patients with ALS are at excess risk of suicide in Sweden and the relative risk is higher during the earlier stage of the disease.

Keywords: amyotrophic lateral sclerosis; suicide; cohort study; relative risk

Abbreviations: ALS = amyotrophic lateral sclerosis; SMR = standardized mortality ratio; CI = confidence interval; ICD = International Classification of Diseases


Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating disease characterized by progressive loss of motor neurons, leading to weakness of the bulbar, limb, thoracic and abdominal muscles. Successive loss of function usually takes 3–5 years from the first onset of symptoms (Rowland and Schneider, 2001). The only effective drug for ALS, Riluzole, may at best prolong survival for up to 6 months (Bensimon et al., 1994; Lacomblez et al., 1996). Disease severity, treatment ineffectiveness and increasing dependence on caregivers give rise to thoughts to terminate life (e.g. euthanasia and physician-assisted suicide) among patients, especially those at an advanced stage (Ganzini et al., 1998; Veldink et al., 2002; Reagan et al., 2003; Albert et al., 2005).

In countries like Sweden, where neither euthanasia nor physician-assisted suicide is regulated, suicide may be the ultimum refugium for ALS patients. Thus studying the risk of actual death from suicide will provide further data on the wish to die of ALS patients in these countries. The low incidence of both ALS and suicide makes such studies rarely feasible. The availability of several Swedish nationwide health care registers offers us a unique possibility to explore the actual risk of suicide among ALS patients with reasonable statistical powers. We conducted a large population-based cohort study comprising all patients diagnosed with ALS and registered in the Swedish Inpatient Register between 1965 and 2004, to investigate whether ALS patients are at excessive risk of suicide compared to the
general population, and if so, when the excessive risk appears (i.e. at the earlier stages of the disease or only in the latest stage).

Methods

Health care system in Sweden

The Swedish health care system is divided into 27 financially and administratively independent areas. With rare exceptions, in-hospital medical services are public and organized by each county council. Charges for medical services are kept low enough to permit all citizens equal access and so in practice, in-hospital care registration is population-based and referable to the county where the patient lives. The Swedish Inpatient Register was established by the National Board of Health and Welfare in 1964–65 and its coverage has increased from 60% of the entire country in 1969, to 85% in 1983 and 100% in 1987. Each record in the register corresponds to one hospital admission and contains information on the patient’s national registration number (a unique identifier assigned to all Swedish residents), dates of admission and discharge, as well as all discharge diagnoses (The Swedish Hospital Discharge Register, 2005).

Study design

Through the Inpatient Register, we identified in total 6813 unique individuals who had been discharged from an in-hospital episode with ALS either as the main diagnosis or a secondary diagnosis at the time of discharge, between 1965 and 2004. The identification of an ALS diagnosis was made using the International Classification of Diseases 7th version (ICD-7) code 356.10, ICD-8 code 348.00, ICD-9 code 335C and ICD-10 code G12.2 for events occurring during 1965–68, 1969–86, 1987–96 and 1997–2004, respectively. The first identified hospitalization was defined as the ‘index hospitalization’. We first excluded 70 subjects (1.0%) who had inconsistent information discovered in register linkages as well as 101 subjects (1.5%) who died on the date of index hospitalization. Patients younger than 70 years had inconsistent information discovered in register linkages as well as 101 subjects (1.5%) who died on the date of index hospitalization. Patients were followed from the index hospitalization for as 101 subjects (1.5%) who died on the date of index hospitalization. We first excluded 70 subjects (1.0%) who had inconsistent information discovered in register linkages as well as 101 subjects (1.5%) who died on the date of index hospitalization. Patients were followed from the index hospitalization for whichever occurred first. Cross linkage to the Causes of Death Register identified all deaths from suicides among these patients during follow-up. Suicides were identified using ICD-7 codes E971-E979 and E9639, ICD-8 and 9 codes E950-E959, and ICD-10 codes X60-X84 and Y870.

Statistical analysis

In order to estimate the relative risk of suicide among patients with ALS, we calculated the standardized mortality ratio (SMR) of suicide, which is the ratio of the observed number of suicides among the ALS patients to the expected number of suicides among these patients. The number of expected events was calculated in the same way as described in the ALS cohort.

Results

The characteristics of the ALS cohort are presented in Table 1. In total, the cohort generated 12 995 person-years of observation with a mean follow-up duration of 2.0 years. During follow-up, we observed 21 cases of suicide including 14 men and 7 women. The mean age at index hospitalization for ALS was 67.6 years in the entire cohort, while the corresponding figure was 60.5 years among patients who committed suicide during follow-up. The cancer cohort included 1 251 200 primary malignant cancer patients and a total of 2 710 suicides (1 866 men and 844 women) were identified from the 7 082 874 person-years accrued during follow-up.

In Table 2, we present the SMRs of suicide among patients with ALS by various stratifications. ALS patients were about six times more likely to commit suicide compared to the age-, gender- and calendar period-matched individuals in the general population (SMR 5.8, 95% CI 3.6–8.8). The relative risk seemed to be higher among women than among men although the difference was not statistically significant (P-value for homogeneity = 0.14, adjusted for age at index hospitalization, time since index hospitalization and calendar period of follow-up). Although there was no overall trend of relative risks by age at index hospitalization (P-value for trend = 0.13, adjusted for gender, time since index hospitalization and calendar period), patients younger than 70 years tended to have a higher relative risk of suicide compared to
Table 1: Cohort of patients with amyotrophic lateral sclerosis in Sweden between 1965 and 2004

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3740</td>
<td>2902</td>
<td>6642</td>
</tr>
<tr>
<td>Total No. of person-years</td>
<td>8222</td>
<td>4773</td>
<td>12995</td>
</tr>
<tr>
<td>Mean follow-up (years, SD)</td>
<td>2.2 (4.3)</td>
<td>1.6 (3.2)</td>
<td>2.0 (3.9)</td>
</tr>
<tr>
<td>Mean age at hospitalization (years, SD)</td>
<td>66.7 (12.4)</td>
<td>68.8 (11.5)</td>
<td>67.6 (12.1)</td>
</tr>
<tr>
<td>No. of suicides</td>
<td>14</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Mean age at suicide (years, SD)</td>
<td>62.7 (13.3)</td>
<td>62.5 (79)</td>
<td>62.6 (11.6)</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabitated</td>
<td>2692 (72.0)</td>
<td>1654 (57.0)</td>
<td>4346 (65.4)</td>
</tr>
<tr>
<td>Single/divorced/widowed</td>
<td>1033 (27.6)</td>
<td>1232 (42.4)</td>
<td>2265 (34.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (0.4)</td>
<td>16 (0.6)</td>
<td>31 (0.5)</td>
</tr>
<tr>
<td>Highest attained educational level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or more (≥9 years)</td>
<td>1020 (43.0)</td>
<td>713 (36.3)</td>
<td>1733 (399)</td>
</tr>
<tr>
<td>Primary school (≤9 years)</td>
<td>1279 (53.8)</td>
<td>1188 (60.5)</td>
<td>2467 (56.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>76 (3.2)</td>
<td>63 (3.2)</td>
<td>139 (3.2)</td>
</tr>
</tbody>
</table>

*Marital status was identified from the Censuses 1960, 1970, 1980 and 1990; data recorded most recently to the index hospitalization were used.

Based on 4339 patients identified since 1985 when the Education Register was initiated; highest attained educational level was identified from the most recent year to the index hospitalization.

Patients at 70 years or older (SMR 7.2, 95% CI 4.2–11.5 versus SMR 3.2, 95% CI 0.9–8.1; P-value for homogeneity = 0.05, adjusted for gender, time since index hospitalization and calendar period). The relative risk was highest during the first year after the index hospitalization (SMR 11.2, 95% CI 5.8–19.6) and decreased over time since index hospitalization (P-value for trend = 0.006, adjusted for gender, age at index hospitalization and calendar period).

Marital status (P-value for homogeneity = 0.13) or educational level (P-value for homogeneity = 0.31) did not seem to further influence the relative risk of suicide when adjusted for gender, age at index hospitalization, time since index hospitalization and calendar period.

To allay potential concern of reversal causality (i.e., patients were hospitalized for initial suicidal attempts per se instead of ALS), we checked the discrepancy between the discharge date and the suicide date for the suicide cases. One out of 21 cases happened actually on the same day as the patient was discharged. Excluding this patient from the analysis only mitigated slightly the relative risk estimate (SMR 5.5, 95% CI 3.4–8.5).

The crude suicide rate in the general Swedish population has decreased continuously since the 1970s (Fig. 1). Compared to the general population, we did not observe any clear trend in the relative risks of suicide among ALS patients when classifying calendar periods either into 10-year groups (P-value for trend = 0.99) or 5-year groups (P-value for trend = 0.78), adjusted for gender and age at index hospitalization (Fig. 2). In contrast, the relative risks of suicide among patients with malignant cancer did decrease consecutively during this period (P-value for trend <0.0001) (Fig. 2).
Discussion

We observed an approximately 6-fold relative risk of suicide among patients with ALS compared to the general population in Sweden between 1965 and 2004. The relative risk was highest during the first year after the first hospitalization for ALS and was still elevated 3 years later. The excessive risks did not seem to decrease over the four decades in our study. These data are, to our knowledge, the first to confirm the apprehension that ALS patients are at a highly increased risk of death from suicide.

The strengths of our study include the population-based cohort design and the virtually complete follow-up. As a reminder of the challenges of studying rare exposure (ALS) and outcome (suicide), only 21 suicides occurred in the cohort despite the large sample size and long follow-up. The small number of outcomes made certain estimates less precise. Second, information on potential effect modifiers such as site of disease onset (spinal or bulbar) was not obtainable through the registers and thus not available for further investigation. Using only hospitalization data as the resource in identifying ALS cases could be another concern. But in our previous study, when pooling cases identified both from the Inpatient Register and the Causes of Death Register, we found that the Inpatient Register caught >88% of all the potential ALS cases between 1987 and 2005 in Sweden, assuming that cases identified from the Causes of Death Register were real ALS cases (Fang et al., 2008). Additionally, the ‘index hospitalization’ as defined in the current study may not be perfectly accurate as the point of first diagnosis since hospitalization for ALS is not specifically related to diagnosis in Sweden. Thus, we might have overestimated the relative risk of suicide by shortening the real follow-up time, i.e., from the real first diagnosis to suicide. But we believe this concern could be allayed for two reasons: first, the mean follow-up in our study was 2.0 years and it is similar to the average survival time of 1–3 years for ALS patients as reported previously (del Aguila et al., 2003); and second, we did a sensitivity analysis by artificially increasing the mean follow-up duration to 3.0 years and, although the relative risk of suicide decreased slightly as expected, it remained statistically significant (SMR 3.9, 95% CI 2.4–5.9). Thus, we believe that the first hospitalization is a valid proxy for ALS incidence in Sweden.

The magnitude of the relative risk of suicide among patients with ALS as reported in our study was higher than that of multiple sclerosis [SMR 2.3 in Sweden (Fredrikson et al., 2003) and SMR 1.83 in Denmark (Stenager et al., 1992)], Parkinson’s disease [modest increase in Sweden (Stensman and Sundqvist-Stensman, 1988) and no increase in Denmark (Stenager et al., 1994)] and most malignant cancers [relative risks <2 for all cancer in both Sweden and Denmark (Bjorkenstam et al., 2005; Yousaf et al., 2005)]. As shown in our data, patients who committed suicide were diagnosed at a relatively younger age (around 60 years) compared to those who did not commit suicide (around 68 years). The potential loss of years to live, self-independence and other aspects might cause greater distress among the younger patients.

Following the first year after first hospitalization, when the relative risk for suicide was >11 times of that in the background population, the suicide risk decreased over time from first hospitalization, in a fashion similar to that of patients diagnosed with malignant cancers (Hem et al., 2004; Yousaf et al., 2005) and other neurological disorders (Bronnum-Hansen et al., 2005; Karvonen et al., 2007). Although most recent studies have focused on psychological suffering and thoughts about euthanasia or physician-assisted suicide in more advanced stages of ALS (Ganzini et al., 1998; Veldink et al., 2002; Reagan et al., 2003; Albert et al., 2005), we had expected a higher risk of suicide during the earlier phases of the disease, hypothesizing first that a severe emotional burden might have debuted when waiting for the diagnosis confirmation, and second that patients had to be physically capable to perform suicide.

After peaking in the 1970s, the absolute suicide rates in the general population of Sweden had been decreasing significantly. The relative risk of suicide among patients with various malignant cancers compared to the general population had also decreased continuously during the study period, indicating that the absolute rate of suicide among cancer patients had been decreasing even more compared to the general population, likely as a consequence of successively improved appreciation of the psychosocial needs of patients with cancer (Hem et al., 2004). But the relative risks of suicide among patients with ALS, on the other hand, did not show a similar decreasing trend over time despite the improvements in supportive and palliative care in Sweden over recent decades (Furst, 2000).

The prevalence of suicidal thoughts and attempts among patients with ALS is inevitably higher than the observed mortality from suicide in our study. Therefore, the observed excess risk likely reflects only a small part of the psychological suffering experienced by these patients.
Future studies are thus warranted to figure out specific risk indicators and effect modifiers of the suicidal outcome among the ALS patients, especially among the younger patients in Sweden. Our findings also illustrate the importance and need of an increasing awareness of the psychological distress experienced by patients diagnosed with ALS among the professional caregivers, not only in the end-of-life stage but rather from the earliest stage of the disease, preferably from the diagnostic phase when various interventions are available.

References