Trends in survival and cause of death in Danish patients with multiple sclerosis

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Summary
The Danish Multiple Sclerosis Registry contains information about all Danish patients in whom multiple sclerosis has been diagnosed since 1948. The purpose of this study was to analyse trends in survival and causes of death of these patients and to compare them with those of the general population. The study comprised all patients with onset in the period 1949–1996. All case records were validated and classified according to standardized diagnostic criteria. Data on emigration and death were obtained by record linkage to official registers. The end of follow-up was 1 January 2000 for emigration and death, and 1 January 1999 for cause-specific deaths. Standardized mortality ratios and excess death rates were calculated for various causes of death and periods after multiple sclerosis onset, and time trends in survival probability were analysed by Cox regression. The study comprised 9881 patients, of whom 4254 had died before end of follow-up. The median survival time from onset was ~10 years shorter for multiple sclerosis patients than for the age-matched general population, and multiple sclerosis was associated with an almost threefold increase in the risk for death. According to death certificates, more than half (56.4%) of the patients had died from multiple sclerosis. They also had excess mortality rates from other diseases, except cancer, and from accidents and suicide. The probability for survival improved significantly during the observation period. Thus, the 10-year excess mortality was almost halved in comparison with that in the middle of the 1900s.

Keywords: multiple sclerosis; epidemiology; survival; cause of death; Denmark

Abbreviations: CI = confidence interval; EDR = excess death rate; ICD = International Classification of Diseases; SMR = standardized mortality ratio


Introduction
Several studies have shown that multiple sclerosis is associated with an elevated risk for death. Thus, the survival of multiple sclerosis patients has been studied in a number of populations over the past 20 years (Phadke, 1987; Riise et al., 1988; Poser et al., 1989; Weinshenker et al., 1989; Wynn et al., 1990; Miller et al., 1992; Sadovnick et al., 1992; Runmarker and Andersen, 1993; Brønnum-Hansen et al., 1994; Midgard et al., 1995; Kantarci et al., 1998; Cottrell et al., 1999; Koch-Henriksen and Brønnum-Hansen, 1999; Kremenchutsky et al., 1999; Wallin et al., 2000; Sumelahti et al., 2002). The median survival time after onset varies from 28 years for Danish males (Brønnum-Hansen et al., 1994) to 43 years for United States white females (Wallin et al., 2000) and ~45 years among Finns (Sumelahti et al., 2002). Few population-based studies have included comparisons of the death rates of multiple sclerosis patients with those of the general population. Those that have are somewhat heterogeneous as regards study objectives, design and the subjects investigated, and only a few comprised patient samples large enough for analyses of secular trends in survival.

The causes of death of multiple sclerosis patients have been the subject of a number of studies (Malmgren et al., 1983; Larsen et al., 1985; Phadke, 1987; Sadovnick et al., 1991; Stenager et al., 1992; Midgard et al., 1995; Koch-Henriksen et al., 1998; Pekmezovic et al., 2002; Sumelahti et al., 2002), but most distinguished deaths only as multiple sclerosis-related or not, and none were comprehensive enough to show changes in the distribution of causes of death over time.

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The Danish Multiple Sclerosis Registry is a complete record of all Danish multiple sclerosis patients over half a century and contains sufficient data to show trends in survival and cause-specific mortality. As population death rates have changed over the past 50 years, the trends in excess mortality of multiple sclerosis patients must be evaluated by relating death rates to baseline rates reflecting the mortality of the general population. In this article, we report estimates of survival probabilities, excess mortality and cause of death for Danish multiple sclerosis patients, and compare them with those of the general population. In particular, secular trends in survival and cause-specific mortality are evaluated.

**Material and methods**

The Danish Multiple Sclerosis Registry was established on the basis of a prevalence survey conducted in 1956 (Hyllested, 1956), with the objectives of monitoring the incidence of multiple sclerosis and forming the basis of studies of multiple sclerosis epidemiology. The register includes information about patients in Denmark who had onset between 1949 and 1996 and who were notified before 1997. Virtually all Danish residents in whom multiple sclerosis was diagnosed by a neurologist or in a department of neurology are registered; these cases were subsequently reviewed and classified, according to the criteria of Allison and Millar (1954) for those with onset before 1994 and according to the criteria of Poser et al. (1983) for those with onset after 1 January 1994. Details of data collection and the validity of the register have been given previously (Koch-Henriksen et al., 2001). The patients included in the present study were recorded in the register before 1 January 1997, had initial symptoms over the period 1949–1996 and were classified as having clinically definite, probable or possible multiple sclerosis according to the diagnostic criteria.

Data on emigration and death were obtained by record linkage to the Danish Civil Registration System established in 1968 and the Cause of Death Registry comprising data on all deaths since 1943 (Juel and Helweg-Larsen, 1999). The end of follow-up was 1 January 2000 for emigration and death, and 1 January 1999 for cause-specific mortality. Data on deaths and causes of death in the Danish population, distributed by sex, age and calendar year, were derived from the same official registers. The expected numbers of deaths (total and cause-specific) in the general population were estimated for each sex by multiplying the age- and time-specific person-years of observation by the similar age- and time-specific population death rate. Standardized mortality ratios (SMRs) and excess death rates (EDRs) were estimated and 95% confidence intervals (CIs) were established assuming that the numbers of deaths followed a Poisson distribution. The SMR is the quotient of the observed to the expected numbers of deaths, and the EDR is the observed minus the expected number of deaths per 1000 person-years. The SMR is suitable for comparing mortality rates among multiple sclerosis patients with those of the general population, whereas the EDR is a measure of the number of deaths due to the disease in excess of the expected number.

Time trends in 10-year survival probability were analysed by Cox regression, in which changes in mortality rates in the general population were taken into account by including the expected number of deaths as an ‘offset’ factor in the model. The SAS software package was used (SAS Institute, 1999).

**Results**

The register comprises 9881 patients (3954 males and 5927 females) with onset between 1949 and 1996, corresponding by systematic follow-up to 207,862 person-years. The mean age at onset was 34.7 years for men and 34.1 years for women, and increased by 2.3 years between 1949–1958 and 1979–1988. The diagnosis was classified as clinically definite or probable for 8344 patients (84.4%) and as possible for 1537 patients (15.6%).

**Overall survival**

A total of 4254 patients (1980 males and 2274 females) had died before 1 January 2000, whereas the expected number of deaths, in the matched general population, was 1471 (746 males and 725 females). Thus, SMR was 2.89 (95% CI: 2.81–2.98) for the whole group, 2.66 (95% CI: 2.54–2.78) for men and 3.2 (95% CI: 2.90–3.51) for women.

Table 1

<table>
<thead>
<tr>
<th>Years after onset</th>
<th>EDR (95% CI)</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>1.0 (–0.6–3.4)</td>
<td>2.3 (0.8–4.2)</td>
<td>1.8 (0.7–3.2)</td>
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<tr>
<td>1–5</td>
<td>1.9 (0.9–3.2)</td>
<td>4.1 (3.2–5.2)</td>
<td>3.2 (2.5–4.0)</td>
<td></td>
</tr>
<tr>
<td>5–10</td>
<td>9.7 (8.0–11.5)</td>
<td>7.7 (6.5–9.0)</td>
<td>8.5 (7.5–9.5)</td>
<td></td>
</tr>
<tr>
<td>10–15</td>
<td>18.1 (15.6–20.8)</td>
<td>12.2 (10.5–14.0)</td>
<td>14.6 (13.1–16.1)</td>
<td></td>
</tr>
<tr>
<td>15–20</td>
<td>19.9 (16.8–23.3)</td>
<td>15.7 (13.6–18.1)</td>
<td>17.4 (15.6–19.3)</td>
<td></td>
</tr>
<tr>
<td>20–50</td>
<td>28.2 (25.1–31.5)</td>
<td>22.3 (20.3–24.5)</td>
<td>24.6 (22.8–26.3)</td>
<td></td>
</tr>
<tr>
<td>0–50</td>
<td>15.0 (14.0–16.1)</td>
<td>12.3 (11.6–13.1)</td>
<td>13.4 (12.8–14.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Observed minus expected number of deaths per 1000 person-years. 95% confidence interval in parenthesis.
and 3.14 (95% CI: 3.01–3.27) for women. Table 1 shows the EDRs for various periods after the initial symptoms. Survival during the first 5 years after onset appeared to be better for men than for women, but the EDRs rose more rapidly among men than among women in subsequent periods. SMRs are not presented because, on the one hand, SMRs tend to decline with increasing follow-up as the expected number of deaths (denominator) increases with age and, on the other hand, the observed number of deaths (numerator) increases with length of follow-up, i.e. duration of disease. Thus, comparisons of SMRs for various periods after onset are misleading.

The median survival time from onset was 28 years for men and 33 years for women, compared with 38 years and 45 years for the matched male and female general population, respectively (Fig. 1). The survival probability 10 years after onset was 91% for men and 92% for women, whereas these percentages were 96% for men and 98% for women in the general population. Twenty-five years after onset, the survival probability was 57% for men (80% for the general male population) and 67% for women (88% for the general female population); 40 years after onset, 24% of the men and 37% of the women were still alive (43% and 62% in the general male and female population, respectively).

**Trends in survival**

The survival probability improved significantly during the observation period. Figure 2 shows, as an example, the 10-year survival probability for multiple sclerosis patients aged 35 years at onset by period of initial symptoms in 1949–1958, 1959–1968, 1969–1978 and 1979–1988. In order to make the four periods comparable, the estimates were made only for multiple sclerosis patients for whom the maximum lag between onset and registration was 8 years, comprising 75% of all patients with onset between 1949 and 1988. Seven hundred patients had died within 10 years after initial symptoms. Ten-year survival probability for 35-year-old Danes varied only modestly between the four periods (from 97.8% to 97.6% for men and from 98.1% to 98.6% for women). The significantly improved survival ($P < 0.0001$ for men; $P = 0.001$ for women) during the long observation period does not reflect the general decline in mortality in Denmark since the 1950s, because the estimates were adjusted to calendar-year-specific population death rates. In all periods, the excess mortality was statistically significant.

**Cause-specific mortality**

Multiple sclerosis was indicated on 82% of the death certificates as the underlying or contributing cause of death. For 56.4%, multiple sclerosis was quoted on the death certificate as the underlying cause of death, $15.5\%$ died from cardiovascular diseases, $10.1\%$ died from cancer, $13.5\%$ died from other diseases and $4.5\%$ died from accidents or suicide (Table 2). The mortality rate due to cardiovascular disease was statistically significantly higher than in the matched general population (Table 3), whereas the rates for cancer were lower among multiple sclerosis patients than in the general population. More multiple sclerosis patients died from infectious or respiratory diseases than in the general population, and the death rates for accidents or suicide were significantly higher than expected.

For male multiple sclerosis patients, the marked improvement in 10-year survival was related to all major disease groups except cancer, whereas for female patients, no improvement was seen in the mortality rates from cardiovascular diseases or cancer (Table 4). No significant changes in excess mortality from accidents and suicide were seen. As only 23 patients died from infectious and respiratory diseases within 10 years after the initial symptoms, trends in mortality
from these causes could not be detected. The high SMR for other diseases simply reflects the fact that 450 (84%) of the 538 patients who died from other diseases died from multiple sclerosis. The remaining 16% died from infectious and respiratory diseases (4%), and 37 other different causes.

Discussion

We followed up unselected multiple sclerosis patients from the year of onset over a sufficient time and in sufficiently large numbers to obtain accurate statistics on trends in survival and cause-specific mortality during half a century. The study included patients classified in the Danish Multiple Sclerosis Registry as having clinically definite, probable or possible multiple sclerosis. The consequence of including the possible cases (15.6%) has been discussed previously (Koch-Henriksen and Brønnum-Hansen, 1999). The advantage of having complete data on the total population is at the expense of fewer details on each individual. For instance, the Register does not include systematically collected longitudinal data on disability; consequently, we were unable to present unbiased estimates of the progression of disease. Neither does the
Register include information on whether type of multiple sclerosis was relapsing–remitting or progressive for patients with onset before 1994. Unascertained cases concern individuals who are alive with no definite diagnosis plus a small, but unknown, number of patients with latent multiple sclerosis who died from non–multiple sclerosis-related causes before the diagnosis of multiple sclerosis could be established. When the estimated number of unascertained cases was included, the overall EDR fell from 13 to 12 per 1000 person-years (Brûnnum-Hansen et al., 1994). As most of the undiagnosed cases had a recent onset, we included only patients with a maximum of 8 years' time lag in the trend analysis. One probable effect of this restriction was to exclude the more benign cases; consequently, the 10-year survival probability might have been slightly underestimated. The improvement in survival might have been overestimated if a similar risk for bias arises when the time lag between initial symptoms and notification is shortened due to earlier establishment of a diagnosis with improved diagnostic techniques such as MRI. Alternatively, better knowledge of multiple sclerosis and other diseases with related symptoms might lead to a more careful diagnosis, which would lengthen the time lag between initial symptoms and diagnosis. Nevertheless, comparison of the distribution of time lags in recent notification periods did not indicate a change. We conclude that the length of survival has improved, which we believe to be due to improved rehabilitation and treatment, which in turn have a protective effect on survival.

The relative distribution of causes of death might be biased as the distribution of causes of death among patients with multiple sclerosis might differ from the distribution in the general population. The proportion of deaths due to cardiovascular disease, cancer, and accidents and suicide might be overrepresented, and the proportion of deaths due to infectious and respiratory diseases and other diseases might be underrepresented. However, no knowledge of the underlying cause of death is available in the current study, and the proportion of deaths due to infectious and respiratory diseases and other diseases might be underrepresented in the current study.

The relationship between length of survival and age at onset and the prognostic significance of initial symptoms has been reported previously (Brûnnum-Hansen et al., 1994). Koch-Henriksen and Brûnnum-Hansen, 1999). EDR rose with increasing age at onset; EDR was lowest for optic neuritis as presenting symptom and highest for cerebellar symptoms. The time lag between initial symptoms and notification is shorter for patients with no history of multiple sclerosis and no other more obvious symptoms as presenting symptom and highest for cerebellar symptoms. No evidence of an effect of new medical treatments was detected in this study. For instance, interferon-β treatment, introduced in Denmark in 1996, could not have affected our results.

<table>
<thead>
<tr>
<th>Underlying cause of death</th>
<th>SMR (95% CI)</th>
<th>EDR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Women</td>
<td>All</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.22 (1.10–1.36)</td>
<td>1.47 (1.31–1.65)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.72 (0.61–0.85)</td>
<td>0.95 (0.84–1.07)</td>
</tr>
<tr>
<td>Other diseases</td>
<td>8.20 (7.76–8.66)</td>
<td>9.74 (9.26–10.2)</td>
</tr>
<tr>
<td>Infectious and respiratory diseases</td>
<td>2.13 (1.74–2.58)</td>
<td>1.86 (1.49–2.30)</td>
</tr>
<tr>
<td>Other diseases excluding multiple sclerosis</td>
<td>1.70 (1.51–1.92)</td>
<td>1.83 (1.62–2.06)</td>
</tr>
<tr>
<td>Accidents and suicide</td>
<td>1.46 (1.20–1.76)</td>
<td>1.37 (1.08–1.71)</td>
</tr>
<tr>
<td>Total</td>
<td>2.66 (2.54–2.78)</td>
<td>3.14 (3.01–3.27)</td>
</tr>
</tbody>
</table>

End of follow-up, 1 January 1999. *Quotient of observed to expected numbers of deaths. †Observed minus expected number of deaths per 1000 person-years. 95% confidence interval in parenthesis.
The extent to which multiple sclerosis is specified as the underlying cause of death on death certificates varies considerably. A study based on 2329 prevalent cases followed over 10 years until 1980 in two counties in the USA found multiple sclerosis was given as the underlying cause of 53% of the deaths, while 19% of the death certificates did not mention multiple sclerosis (Malmgren et al., 1983). Between 1970 and 1980, 62% of 1055 prevalent cases in the Grampian region of Scotland died from multiple sclerosis-related causes (Phadke, 1987). In a Canadian study, 47% of 119 deaths were related to multiple sclerosis (Sadovnick et al., 1991). A longitudinal study in the counties of Møre and Romsdal, Norway, comprising 251 patients with a mean follow-up time of 18 years, found that 70 had died, of whom 77% had multiple sclerosis as the underlying or contributing cause of death (Midgard et al., 1995). This was somewhat lower than the 83.3% found in Hordaland, western Norway (Larsen et al., 1985). Seventy percent of the 219 deaths among Finnish multiple sclerosis patients were due to multiple sclerosis or were multiple sclerosis-related, but, contrary to the results of our study and the majority of other studies, excess mortality from cancer and fewer cardiovascular deaths than expected were found (Sumelahti et al., 2002). Multiple sclerosis was the underlying cause of death of 90% of 79 patients out of 823 registered between 1985 and 1996 in the Belgrade region of Serbia (Pekmezovic et al., 2002). The mean follow-up time in our study was 21 years and we found that 82% of death certificates had multiple sclerosis as the underlying or contributing cause of death. The specification of an underlying cause of death on a death certificate is not a scientific process; furthermore, because studies differ in design, type of patients included and length of follow-up, international comparisons of the relative distribution of causes of death should be made cautiously. When incident cases are studied, the pattern of causes of death depends on the follow-up period, reflecting the ageing of the patients. Thus, relatively more suicides and fewer cancer deaths are expected over a short than a long follow-up. Suicide is more frequent during the first few years after diagnosis (Stenager et al., 1992).

This study shows that, on average, Danes with multiple sclerosis can expect to live ~10 years less than the age-matched general Danish population; nevertheless, the gap in remaining life years has narrowed significantly since the
1950s. In comparison with the general population, multiple sclerosis patients had a higher risk for death from all causes except cancer. The improved survival was due to reductions in death rates from all major disease groups, except from cancer and cardiovascular diseases for women and from accidents and suicide for both men and women, for which the excess death remained almost unchanged.

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References