

Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry

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Abstract

Objectives—To determine the underlying causes of death in a large population based register series of patients with multiple sclerosis.

Methods—The Danish Multiple Sclerosis Registry, which contains virtually all diagnosed cases of multiple sclerosis in Denmark who were alive in 1949 plus cases with onset of multiple sclerosis in the period 1949–93, who have been diagnosed and notified by 1 January 1994, was linked with the Danish Registry of Causes of Death, in which ICD codes for causes of death from the death certificate are stored for all Danish citizens.

Results—6068 register cases of multiple sclerosis, who had died in the period 1951–93, were included. Multiple sclerosis was noted on the death certificate as the underlying cause of death in 55.4%; cardiac or vascular diseases in 17.6%; cancers in 8.6%; respiratory or infectious diseases in 5.1%; other natural causes in 9.5%; accident or suicide in 3.8%. The distribution varied with age at death. Standardised mortality ratios (SMRs) were computed on the basis of the 8142 incident cases, who had onset of multiple sclerosis within the period 1951–93; the SMRs for causes of death other than multiple sclerosis were highest for infectious or pulmonary diseases: 2.46 (95% confidence interval (95% CI) 2.04–2.94); suicide: 1.62 (95% CI 1.29–2.01); cardiac or vascular diseases: 1.34 (95% CI 1.22–1.48); accidents 1.34 (95% CI 1.02–1.71); and significantly lower than unity for cancers: 0.79 (95% CI 0.70–0.90), lower for men than for women.

Conclusions—More than half of the patients with multiple sclerosis die from multiple sclerosis or complications of the disease. Among other causes, patients with multiple sclerosis have an increased risk of dying from heart or vascular diseases but a reduced risk of dying from cancer. An increased risk of death from suicide and accidents can be indirectly attributed to multiple sclerosis. The diminished risk of dying from cancer may be a result of incomplete ascertainment of cancers in disabled patients with multiple sclerosis.

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Keywords: multiple sclerosis complications; multiple sclerosis mortality; cause of death; death certificates; registries statistics and numerical data

The excess mortality in multiple sclerosis is high and the life expectancy is shorter than for the background population.¹ However, multiple sclerosis is not itself a lethal disease and deaths in patients with multiple sclerosis are attributed to complications as well as to other diseases or conditions that may occur through life or in the aging person. Knowledge about the cause of death in multiple sclerosis is important for understanding the natural history of the disease and the need for terminal care and treatment.

Cause of death in multiple sclerosis has previously been surveyed in a patient series comprising 438 deceased cases with the purpose of assessing the validity of epidemiological data based on death certificates,² in a survival study based on cases from a prevalence study comprising 216 deceased cases,³ and in 145 deceased clinic patients.⁴

Although death certificates do not in all cases give precise clinical information,⁵ they are the only available sources of determining the cause of death in large unselected patient series.

We examined the cause of death in deceased patients with multiple sclerosis, identified through the Danish Multiple Sclerosis Registry, by means of the death certificates. The study was funded by the Danish Multiple Sclerosis Society.

Material and methods

DATA SOURCES

This study was based on the nationwide Danish Multiple Sclerosis Registry and the National Registry of Causes of Death. The Multiple Sclerosis Registry was established based on *Hyllested's* 1949 prevalence survey⁶ and has since collected information on virtually all new cases of multiple sclerosis in Denmark with an eventual completeness estimated at more than 90% of diagnosed cases.⁷ All notified cases have been reviewed and classified according to the diagnostic criteria given in *McAlpine et al*⁸ and only data on patients complying with these criteria were transferred to the study database. The National Registry of Causes of Death has since 1943 classified and coded the diagnoses on all Danish death certificates according to the international classification of diseases (ICD) 6–7 (1951–68) and ICD 8 (1969–93). By cross linking the two registers, the ICD

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Table 1 Underlying causes of death grouped into six major categories (ICD codes)

| | ICD 6-7 (1951-68) | ICD 8 (1969-93) |
|---|-----------------------|------------------|
| Cardiac or vascular diseases | 330-334, 400-468 | 390-458 |
| Cancers | 140-205 | 140-209 |
| Accidents or suicide | E800-E999 | E800-E999 |
| Respiratory tract diseases and infections | 001-138, 241, 470-527 | 000-136, 460-519 |
| Multiple sclerosis | 345 | 340 |
| Miscellaneous | All other | All other |

Table 2 Deceased patients with multiple sclerosis by cause of death and age of death

| Cause of death | Age at death | | | All n (%) |
|--------------------------------------|---------------|----------------|--------------|--------------|
| | 0-39 n (%) | 40-59 n (%) | ≥60 n (%) | |
| Cardiac and vascular diseases | 15 (2.9) | 240 (9.1) | 816 (28.1) | 1071 (17.6) |
| Cancer | 10 (1.9) | 184 (7.0) | 330 (11.4) | 524 (8.6) |
| Respiratory* and infectious diseases | 23 (4.4) | 110 (4.4) | 175 (6.0) | 308 (5.1) |
| Multiple sclerosis | 398 (76.4) | 1723 (65.3) | 1239 (42.6) | 3360 (55.4) |
| Other natural causes | 36 (6.9) | 255 (9.7) | 284 (9.8) | 575 (9.5) |
| Accidents or suicide | 39 (7.5) | 128 (4.8) | 63 (2.2) | 230 (3.8) |
| Total | 521 (100) | 2640 (100) | 2907 (100) | 6068 (100) |

*Except pulmonary cancer.

Table 3 Distribution on underlying cause of death in deceased cases who had a postmortem and who did not

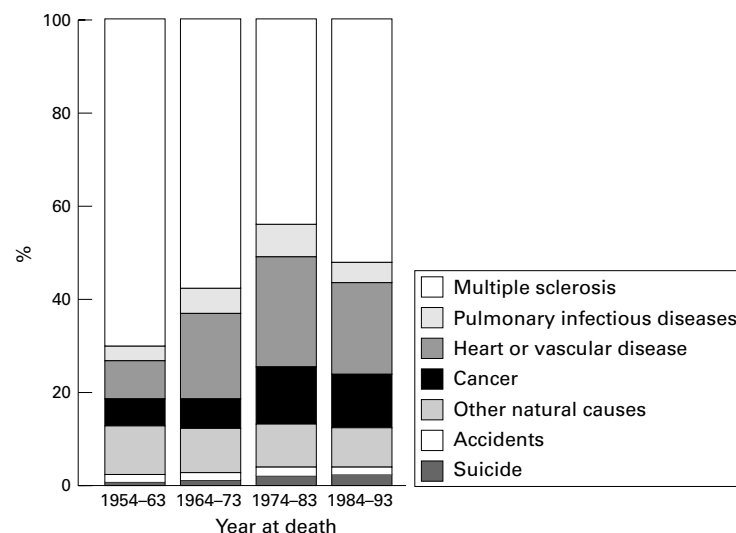
| Cause of death | No postmortem n (%) | Postmortem n (%) |
|---|------------------------|---------------------|
| Cardiac or vascular diseases | 952 (17.7) | 119 (17.6) |
| Cancers | 466 (8.6) | 58 (8.6) |
| Accidents or suicide | 184 (3.4) | 32 (4.7) |
| Respiratory tract diseases and infections | 272 (5.0) | 36 (5.3) |
| Multiple sclerosis | 3000 (55.6) | 360 (53.3) |
| Miscellaneous | 518 (9.6) | 71 (10.5) |

codes for the causes of death for diseased patients were transferred to the Multiple Sclerosis Registry (approved by the Danish Registry Inspection).

INCLUSION OF PATIENTS

The total case series

In the descriptive part of the study we included all patients, who were prevalent in 1949 or had onset of multiple sclerosis in the period 1949-93 and had died within the period 1951-93, amounting to 6141. In 73 cases the cause of death was unknown, leaving 6068 cases for the total case series, 2790 men and 3278 women.



Distribution of underlying causes of death by time 1954-93.

The incident case series

In the cohort based part of the study, in which standardised mortality ratios (SMRs) were computed, we included the 8142 patients (3326 men and 4816 women) with onset within the period 1951-93. Of those 2803 had died in the interval (1330 men and 1473 women). In just 16 of the deceased cases, the cause of death was unknown.

CLASSIFICATION OF UNDERLYING CAUSES OF DEATH

The underlying causes of death were distributed over more than 310 different ICD diagnoses, and 136 of these occurred only once. Thus it was necessary to lump the diagnoses into explicit groups: (1) cardiac or vascular diseases; (2) cancers; (3) infections and respiratory tract diseases (except cancer); (4) accidents and suicide; (5) multiple sclerosis; (6) miscellaneous. Table 1 shows the ICDs for the groups.

STANDARDISED MORTALITY RATIOS

To compare the underlying causes of death in patients with multiple sclerosis with the background population, we calculated SMRs—that is, the observed number of multiple sclerosis decedents who have died from the specific cause divided by the expected number calculated from population mortality statistics. This part of the analyses was confined to the cohort of patients who had onset of multiple sclerosis in the period 1951-93.

Results

DISTRIBUTION OF UNDERLYING CAUSES OF DEATH (THE TOTAL PATIENT SERIES)

The excess death rate of multiple sclerosis has declined since 1950.¹ Consequently, the average age at death has increased from about 51 years in 1950 to about 60 years in 1993, which may affect the causes of death. Of the 6068 patients from the total series 3360 (55.4%) died from multiple sclerosis; 524 (8.6%) died from cancer (among whom only eight died from primary malignant neoplasm of the brain); 1071 (17.6%) died from cardiac or vascular disease; 308 (5.1%) died from infectious or respiratory tract disease (excluding pulmonary cancer); 575 (9.5%) died from other natural causes; 230 (3.8%) died from accidents or suicide. Table 2 shows the figures, broken down by age at death, and the figure shows the proportions of causes of death by the period in which death occurred, broken down in four 10-year intervals.

Of the 6068 patients, 676 had undergone postmortem examination. Comparing these cases with those without postmortem showed no difference between the two groups as to underlying cause of death (table 3). Postmortem was more common in young than in older patients: 15.2% of cases dying before the age of 40 years had a postmortem as opposed to 13.2% for patients dying in the interval 40-59 and 8.5% of those dying at the age of 60 or older.

The figure shows an increase in percentage of cancers, and accidents/suicide. The percentage

of heart and vascular diseases, respiratory tract diseases, and infections increased in the first part of the interval, thereafter it decreased. Conversely, the percentage of multiple sclerosis, when noted as the underlying cause of death, declined from the first to the third decade, after which it increased a little. Multiple sclerosis as an underlying cause of death indicates that these patients have died from complications of multiple sclerosis and not from independently competing causes. Throughout the entire period, the average age of death was 58.4 years and the mean duration of multiple sclerosis from onset was 24.5 years.

As could be expected, the mean age at death differed significantly among the different causes of death: the patients who died at the youngest age were those who died from suicide (48.5 years) followed by patients dying from "MS" (54.9 years) and accidents (56 years). On the other end of the scale were patients who died from cancer (63.3 years) and from cardiac or vascular disease (66.9 years). Patients who died from respiratory tract diseases or infections were on average 60.2 years old.

There was no link between multiple sclerosis and autoimmune diseases. The diagnosis of rheumatoid arthritis was noted on only eight death certificates, and diabetes mellitus occurred in only 177 cases.

STANDARDISED MORTALITY RATIOS

Table 4 shows the SMRs for common causes of death with 95% confidence intervals (95% CIs). An interval not encompassing unity indicates a significant deviation from population mortality figures.

The SMR for respiratory tract disease was high, reflecting that most of these cases may be related to multiple sclerosis.

Death from cardiac or vascular disease was significantly more common in both male and female patients with multiple sclerosis than in the population although the SMR was just 1.34.

Deaths from suicide were also more common in patients with multiple sclerosis, and the SMR was higher than for cardiac and vascular diseases. We found in this survey that the SMR from suicide was 1.62, which is a little less than previously published.⁹

The SMR for all cancers was only 0.79, which was significantly lower than unity. In particular, the SMR for lung cancer was low (0.54), but there was a striking sex difference: males 0.45; females 0.69, and in females it did not differ significantly from the female population. SMR for breast cancer in women was 1.17.

Table 4 Standardised mortality ratios (95% CIs) by sex and diagnoses

| Cause of death | Males | Females | All |
|--------------------------------------|------------------|------------------|------------------|
| Cardiac and vascular diseases | 1.22 (1.07–1.38) | 1.55 (1.34–1.79) | 1.34 (1.22–1.48) |
| Cancers | 0.71 (0.57–0.86) | 0.86 (0.73–1.00) | 0.79 (0.70–0.90) |
| Respiratory* and infectious diseases | 2.46 (1.90–3.14) | 2.46 (1.86–3.20) | 2.46 (2.04–2.94) |
| Accidents† (1953–93) | 1.32 (0.93–1.82) | 1.36 (0.87–2.03) | 1.34 (1.02–1.71) |
| Suicide† (1953–93) | 1.70 (1.26–2.26) | 1.53 (1.07–2.11) | 1.62 (1.29–2.01) |
| All causes of death | 2.73 (2.59–2.88) | 3.39 (3.21–3.56) | 3.04 (2.93–3.15) |

*Except pulmonary cancer.

†Accidents and suicides could not be separated before 1953.

Discussion

Diagnoses on death certificates are not the results of a scientific process with formal and uniform diagnostic criteria and strict requirements for documentation of the cause of death. Only 676 of the 6068 deceased cases in this study had undergone postmortem but the distribution of underlying causes of death in the postmortem cases did not differ much from that of the cases without a postmortem (table 3). Assessment of cause of death is in most cases the result of a practical medical judgement, sometimes done by a house doctor with a good knowledge of the patient, in other cases by a visiting physician or a young registrar on night duty, forced to make his or her decision without knowing the patient. Multiple sclerosis was only indicated on 78% of the death certificates either as immediate, underlying, or contributory cause of death. A low frequency of multiple sclerosis on the death certificates was also found in other studies,^{2 5 10 11} and underscores this diagnostic imprecision. Hence, death certificates prove unreliable as a source of estimates of mortality rates of multiple sclerosis. The particular low frequencies of multiple sclerosis on the death certificates in this study and in a Norwegian survey¹¹ may be attributed to a high completeness of ascertainment of benign cases, in which the multiple sclerosis diagnosis is not obvious at death and may be overshadowed by an independent cause of death. Incomplete reporting of the diagnosis on the death certificate was also seen in Parkinson's disease.¹² The imprecision of diagnoses on the death certificate was also underscored by the fluctuation of proportions of causes of death with time (figure), which may not entirely be attributed to change in disease pattern with time.

We found an increased occurrence of cardiac and vascular disease as the underlying cause of death, which is not directly explicable but may be ascribed to a lower level of physical activity in patients with multiple sclerosis. In a Canadian study,⁴ however, the proportion of cases dying from myocardial infarction or stroke was exactly the same as in an age matched population, but the number of patients in that study was very small.

Respiratory diseases and infections as an underlying cause of death are in many instances related to multiple sclerosis, and many terminally ill patients succumb to pulmonary infection; the high SMR is easily understood in this way.

The lowered risk of cancer as the underlying cause of death found in this study, is in agreement with the study of Sadovnick *et al.*⁴ In a study implementing the Norwegian Cancer Registry, Midgård *et al.*¹³ in a smaller sample also found an overall reduced risk of cancer although the reduction did not reach significance. The reduced risk might be explained by a diminished exposure to carcinogenic agents or by a more alert immune system in patients with multiple sclerosis. However, it did not apply to all types of cancer: the SMR for breast cancer was near unity (Midgård *et al.*¹³ found an increased risk), and in lung cancer there was a

striking sex difference opposite to the usual male preponderance.

However, a simpler explanation for the apparently lower risk of cancer in patients with multiple sclerosis may be that cancers in some patients with advanced multiple sclerosis remain undetected. In favour of that view a post-mortem series of 120 cases of multiple sclerosis¹⁴ showed that the frequency of cancer did not deviate from what was expected.

The significantly increased SMR for accidents may be attributed to falls in disabled patients, as most casualties occurred in the old age group. The true risk of death from falls may be even higher, as a presumed lower risk of dying from other accidents—for example, traffic accidents—tends to reduce the all over SMR for accidents in patients with multiple sclerosis. An increased SMR for accidents was also seen in another disabling neurological disease: Parkinsons disease.¹² The absolute number of deaths from accidents was, however, small.

The increased risk of suicides in patients with multiple sclerosis is well known.^{4,9} Suicides are just the culmination of severe psychological problems, which are often associated with multiple sclerosis. It stresses the need for psychological care of patients with multiple sclerosis.

The results of this study confirm that more than half of patients with multiple sclerosis die from multiple sclerosis or complications of the disease. As the life expectancy after onset is only reduced by 10–15 years, and about half of the patients survive 30 years or more from onset, patients with multiple sclerosis are subjected to the risks of many other diseases. Con-

sequently, many patients with multiple sclerosis die from conditions without a direct relation to the disease. Treatable conditions may be overlooked in the disabled patient with multiple sclerosis, and may, if left untreated, cause the patient unnecessary discomfort, pain, or even death.

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