Survival of patients with multiple sclerosis in Denmark:

A nationwide, long-term epidemiologic survey

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Article abstract—We estimated survival probability and excess death rates for patients with MS on the basis of data from the Danish Multiple Sclerosis Registry, which includes virtually all patients diagnosed with MS in Denmark (population, five million) since 1948. We reviewed and reclassified all case records according to standardized diagnostic criteria. By linkage to the Danish Central Population Registry, we lost to follow-up only 25 patients who had emigrated. The median survival time from onset of the disease was 28 years in men (compared with 40 years in the matched general male population) and 33 years in women (versus 46 years). The median survival time from diagnosis was 22 years in men (versus 37 years) and 28 years in women (versus 42 years). The excess death rate between onset and follow-up (observed deaths per 1,000 person-years minus the expected number of deaths in a matched general population) was 14.3 in men, which was significantly higher than in women (12.0). Excess mortality increased with age at onset of MS in people of each sex. The 10-year excess death rate has decreased significantly in recent decades. Excess mortality was highest in cases with cerebellar symptoms at onset.

NEUROLOGY 1994;44:1901-1907

Since multiple sclerosis is a relatively infrequent disease and most patients survive for several decades, a large population must be followed for many years in order to determine survival after onset, especially excess mortality and differential survival probability in subgroups of patients. In most of the prospective studies published to date, the numbers of patients have been restricted. Use of the Danish Multiple Sclerosis Registry provides (1) the largest patient series studied so far, (2) inclusion of all cases diagnosed within one country over 39 years, and (3) long-term follow-up. Access to other registers also provided complete registration of deaths and age-, sex-, and time-matched survival data for the general population for calculating excess mortality.

Methods. *Sources of data.* A nationwide epidemiologic survey of MS in Denmark (current population, 5.2 million) has been conducted since 1948, following Hyllested's[1] original prevalence study and subsequent establishment of the Danish Multiple Sclerosis Registry in which virtually all people diagnosed with MS in Denmark have been registered. The completeness and validity of the registry were estimated to be about 90%.[2] The crude annual incidence rate of MS in Denmark is 4.7 per 100,000 population.[3]

The Danish Central Population Registry provides information on vital status for all Danish citizens. A unique personal identification code (a 10-digit code including the date of birth) makes it possible to trace any Danish citizen, irrespective of residence; we thus achieved complete follow-up of all MS patients, deceased or alive. A cross-check with the National Registry of Causes of Death, which includes all deaths that have occurred since January 1, 1943, provided information on deaths before the establishment of the Central Population Registry on April 1, 1968. As all deaths after that date were traced in by both registers, information on deaths was considered to be valid.

Case ascertainment. All 22 neurologic departments in Denmark and the two rehabilitation centers of the Danish Multiple Sclerosis Society currently send hospital discharge notices to the Danish Multiple Sclerosis Registry concerning all patients suspected or known to have MS. Additional sources of notification included (1) the National Patient Registry, in which all hospital admissions since 1977 are registered by personal identification code, date, and diagnosis at discharge (ICD8) and a code for hospital and department; (2) the National Registry of Causes of Death, in which all deaths in Denmark since 1943 are registered by direct and underlying cause of death according to the death certificate, name, date of birth, and date of death; (3) up to 1977, the National Disablement Insurance Court; and (4) practicing specialists.

Two of us (N.K-H. and K.H.) reviewed the discharge notices and available clinical information on all patients notified to the Danish Multiple Sclerosis Registry; supplementary clinical information, death certificates, and autopsy reports were requested when necessary, and all

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The Danish Multiple Sclerosis Registry is subsidized by the Danish Multiple Sclerosis Association.

Received June 10, 1993. Accepted in final form March 18, 1994.

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cases were reclassified according to diagnostic criteria based on those of Allison and Millar,[4] as reported by McAlpine et al,[5] further modified to include laboratory and paraclinical data (see reference 2, page 371). In cases with a doubtful diagnosis and no hospital contact for several years, we asked general practitioners about the patients' disability and symptoms and signs of MS. Calendar year of onset was assessed retrospectively on the basis of case reports and clinical information.

Inclusion criteria. Patients included in the survival study had to have (1) been notified to the Danish Multiple Sclerosis Registry before January 1, 1987; (2) had initial symptoms within the period January 1, 1948 to December 31, 1986 (time of follow-up); and (3) been classified as clinically definite, probable, or possible MS according to the diagnostic criteria.

Patients. A total of 8,721 patients with suspected or established MS were ascertained from the Multiple Sclerosis Registry. Of those, 6,727 patients (3,846 women and 2,881 men; female-to-male ratio, 1.33:1) complied with the diagnostic criteria and were included; 5,594 were classified as clinically definite or probable MS (83.2%) and 1,133 as possible MS (16.8%). Twenty-five of the patients who had emigrated before follow-up were counted as alive and at risk from onset until the date of emigration, which was provided by the national registers or the Central Population Registry. Most of the patients had been included in a previous incidence survey.[3]

Nine patients, known to have died from the Central Population Registry, could not be retrieved in the Registry of Causes of Death, probably owing to an inaccurate birth date on the death certificate. One patient who died in September 1968 could not be found in the Central Population Registry, which was not fully operational in the first few months after its establishment in April 1968.

Statistical analysis. We constructed life tables, with onset of MS as zero time and death as the end-point, in which patients were classified according to the year in which follow-up, emigration, or death was last reported, resulting in counts of "withdrawn" at time of follow-up or emigration and "death" at the time of death.

The survival rates of the Danish population of the same age in the calendar year of onset of MS cases were calculated from public population vital statistics (Danmarks Statistik) for people of each sex and used to estimate expected number of deaths and to calculate the standardized mortality ratio and excess death rates (observed minus expected number of deaths per 1,000 person-years of observation). The standardized mortality ratio is unsuitable for comparing groups with very different baseline death rates; the excess death rate is a measure of the increase in the number of deaths due to the disease over that expected and is suitable for comparisons between groups of patients. Exact 95% confidence limits of excess death rates and standardized mortality ratios were calculated assuming deaths to be Poisson variables.[6] The effect of the initial symptom on survival was estimated using proportional hazards regression models[7] that included age at onset, initial symptoms, and period of onset for men and women separately.

We used the statistical program packages SAS,[8] BMDP,[9] and EGRET[10] for the analysis. To include matched population mortality statistics in the actuarial analyses, we also employed a computer program developed at the Danish Institute for Clinical Epidemiology.

Results. A total of 2,300 of the 6,727 MS patients had died before the end of follow-up in 1986, whereas the expected number of deaths in the matched general population was only 709. The total standardized mortality ratio from onset was therefore 3.25 (95% confidence interval, 3.11 to 3.38), and the excess death rate from onset was 13.0 per 1,000 person-years of observation (table 1). The median survival time from onset for MS patients was 30 years.

Sex. Both female MS patients and women in the population had better survival rates than men (figure 1). The median survival time was 28 years in men (matched male population, 40 years) and 33 years in women (matched female population, 46 years), and the excess death rate was significantly lower in women (12.0/1,000 person-years; 95% confidence interval, 11.1 to 13.0) than in men (14.3; 13.1 to 15.6).

Excess mortality was low in people of each sex in the first 5 years after onset and was even lower for men than for women; however, in subsequent periods after onset, it rose markedly, and after 10 years of onset it was significantly higher in men than in women (table 2). A Poisson regression model shows that the effects of sex and period after onset and their interaction are highly significant.

Age at onset. Generally, the excess death rate increased with increasing age at onset, from 8.6 for age at onset <20 years to 19.1 for age at onset ≥50 years (table 1). Use of the standard mortality ratio showed a decreasing ratio with increasing age, simply because population mortality increases with age.

Interaction between sex and age at onset. The difference in prognosis for men and women was most evident for low age at onset. Thus, the excess death rate among patients in whom MS began before the age of 20 years was 7.4 in women and 10.8 in men; for onset at ≥50 years, the excess death rate was 21.4 in women and only 15.8 in men (table 1), emphasizing that the increase in excess death rate with increasing age at onset is clearest for women. The interaction between age at onset and sex is highly significant ($p < 0.001$).

Calendar-year effect. It might be expected that survival improved during the study period owing to better care and nursing of MS patients. To compare patients with recent and earlier onset, we estimated 10-year survival for cohorts of patients with onset 1948 to 1952, 1953 to 1958, 1959 to 1964, 1965 to 1970, and 1971 to 1976, to give a total of 5,547 patients. Patients for whom there was a more than 10-year delay between onset and diagnosis were omitted from the analysis, leaving 4,726 patients, of whom 534 had died within 10 years of onset.

Ten-year survival appears to have improved since 1948 (figure 2), and more clearly for men than for women. The difference in survival between the sexes thus disappears for patients with onset within the period 1971 to 1976. This improvement in the survival of MS patients with time is not due only to lower mortality in the general population

Table 1. Standardized mortality ratios and excess death rates from onset and from time of diagnosis of MS

Age at onset (yr)	Sex	No. of observed deaths	No. of expected deaths	Person-years	Standardized mortality ratio	95% Confidence interval	Excess death rate	95% Confidence interval
<20	Men	47	6.6	3,741	7.07	5.20-9.41	10.8	7.5-14.9
	Women	54	7.1	6,370	7.59	5.70-9.91	7.4	5.3-9.9
	All	101	13.7	10,111	7.34	6.00-8.96	8.6	6.8-10.8
20-29	Men	274	53.4	16,481	5.13	4.54-5.78	13.4	11.5-15.5
	Women	259	51.5	24,068	5.02	4.43-5.68	8.6	7.3-10.0
	All	533	104.9	40,549	5.08	4.66-5.53	10.6	9.5-11.7
30-39	Men	370	116.4	17,702	3.18	2.86-3.52	14.3	12.3-16.6
	Women	411	102.5	23,472	4.01	3.63-4.42	13.1	11.5-14.9
	All	781	218.9	41,174	3.57	3.32-3.83	13.7	12.3-15.0
40-49	Men	338	150.7	11,318	2.24	2.01-2.50	16.6	13.5-19.9
	Women	329	109.7	13,599	3.00	2.68-3.34	16.1	13.6-18.9
	All	667	260.4	24,917	2.56	2.37-2.76	16.3	14.3-18.4
≥50	Men	101	63.7	2,355	1.59	1.29-1.93	15.8	7.9-25.1
	Women	117	47.0	3,268	2.49	2.06-2.98	21.4	15.2-28.5
	All	218	110.7	5,623	1.97	1.72-2.25	19.1	14.1-24.6
All ages, from onset	Men	1,130	390.8	51,596	2.89	2.73-3.07	14.3	13.1-15.6
	Women	1,170	317.8	70,777	3.68	3.47-3.90	12.0	11.1-13.0
	All	2,300	708.6	122,373	3.25	3.11-3.38	13.0	12.2-13.8
All ages, from diagnosis	Men	1,123	346.2	39,159	3.24	3.06-3.44	19.8	18.2-21.6
	Women	1,164	278.8	52,920	4.17	3.94-4.42	16.7	15.5-18.0
	All	2,287	625.1	92,079	3.66	3.51-3.81	18.0	17.0-19.1

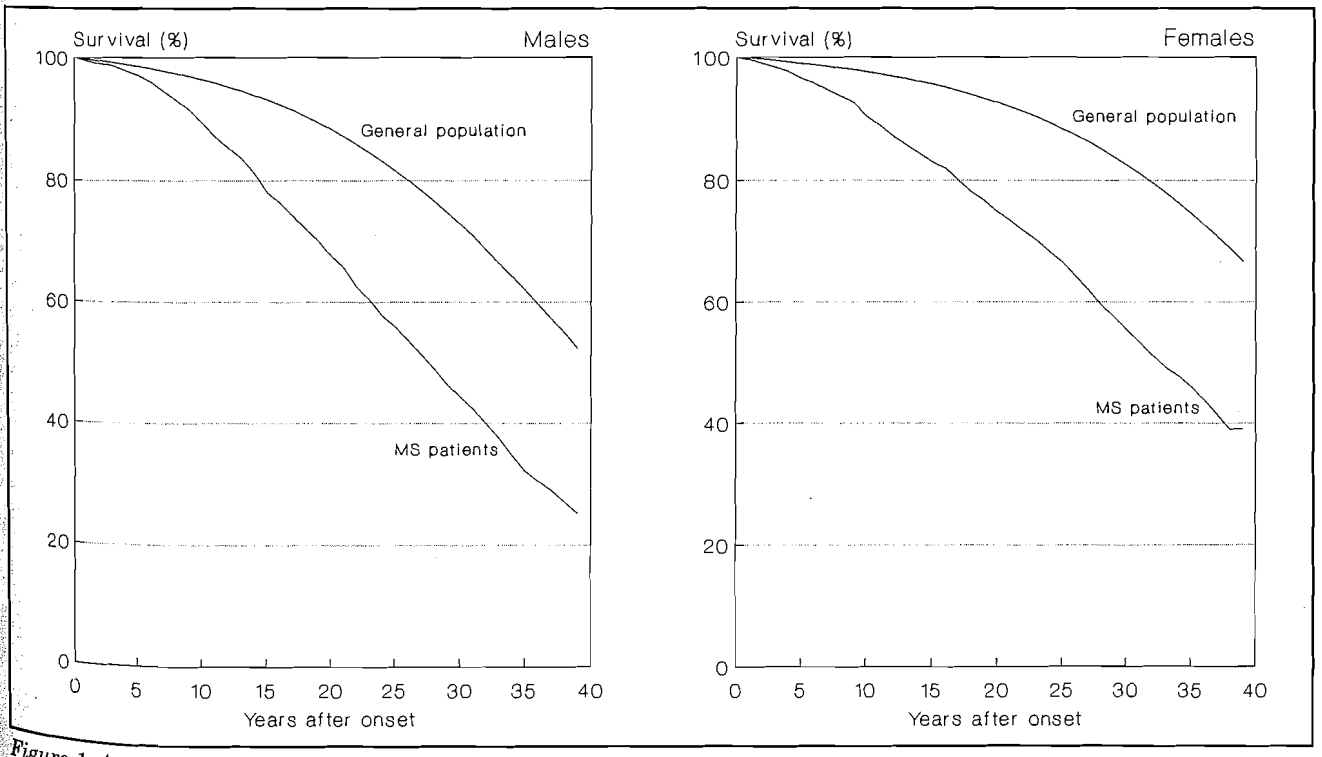

Figure 1. Actuarial survival probability of Danish MS patients and of the general population.

since a comparison of the cohort with onset in 1948 to 1952 with that with onset in 1971 to 1976 shows a significant decrease in the 10-year excess death rate per 1,000 per year (table 3).

Initial symptom. The prognostic value of the initial symptom for survival was evaluated by a pro-

Table 2. Variation in excess death rate with period after onset of MS

Sex	Time since onset (yr) 0-5 Excess death rate	0-5 95% Confidence interval	5-10 Excess death rate	5-10 95% Confidence interval	10 to end of follow-up Excess death rate	10 to end of follow-up 95% Confidence interval
Men	2.8	1.6-4.2	12.2	10.0-14.6	21.7	19.5-24.0
Women	4.8	3.6-6.0	10.1	8.4-11.9	16.6	15.1-18.3
Both sexes	3.9	3.1-4.8	11.0	9.6-12.4	18.7	17.4-20.1

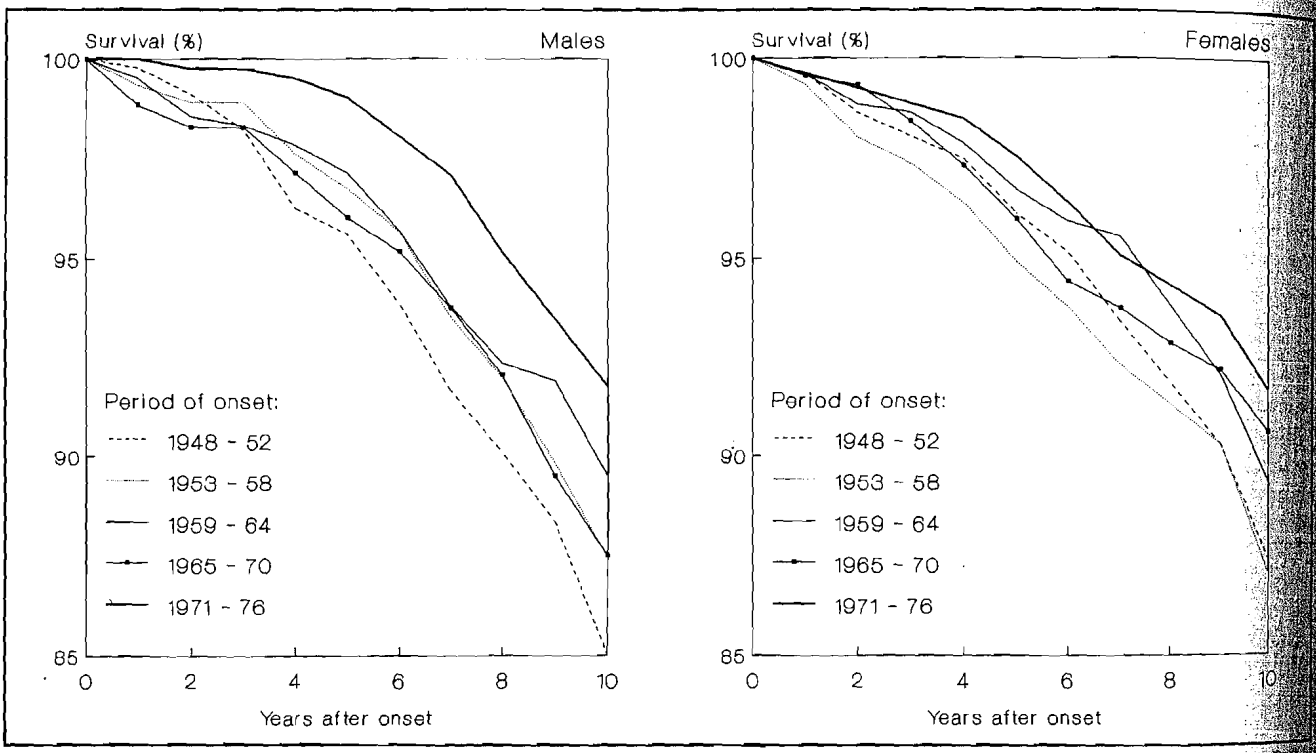

Figure 2. Ten-year survival in five cohorts of Danish patients with MS ascertained within 10 years of onset.

Table 3. Time trends of 10-year standardized mortality ratios and excess death rates from MS per 1,000 per year

Sex	Period of onset	No. of observed deaths	No. of expected deaths	Person-years	Standardized mortality ratio	95% Confidence interval	Excess death rate	95% Confidence interval
Men	1948-1952	69	15.0	4,304.2	4.60	3.58-5.82	12.5	9.0-16.8
	1953-1958	58	15.2	4,419.0	3.81	2.90-4.93	9.7	6.5-13.5
	1959-1964	44	14.9	4,018.7	2.94	2.14-3.95	7.2	4.2-11.0
	1965-1970	44	12.5	3,353.4	3.52	2.56-4.73	9.4	5.8-13.9
	1971-1976	34	16.0	4,039.0	2.13	1.47-2.98	4.5	1.9-7.8
	1948-1976	249	73.6	20,134.5	3.38	2.98-3.83	8.7	7.2-10.3
Women	1948-1952	65	11.8	4,925.6	5.51	4.25-7.02	10.8	7.8-14.4
	1953-1958	79	12.7	5,778.7	6.22	4.93-7.75	11.5	8.6-14.8
	1959-1964	55	12.0	4,982.4	4.59	3.46-5.97	8.6	5.9-12.0
	1965-1970	42	10.5	4,297.1	3.98	2.87-5.39	7.3	4.6-10.8
	1971-1976	44	13.6	5,128.4	3.24	2.36-4.35	5.9	3.6-8.9
	1948-1976	285	60.6	25,112.2	4.70	4.17-5.28	8.9	7.7-10.3

Only patients ascertained within 10 years of onset were included in the analysis.

Table 4. Prognostic value of initial symptom analyzed by a proportional hazards regression model

Initial symptom	Men Hazards ratio	Men 95% Confidence interval	Women Hazards ratio	Women 95% Confidence interval
Cerebellar	1.00	—	1.00	—
Optic neuritis	0.79	0.64-0.97	0.58	0.47-0.71
Diplopia	0.74	0.57-0.96	0.72	0.55-0.96
Pyramidal	0.77	0.64-0.93	0.65	0.54-0.78
Sensory	0.65	0.54-0.78	0.71	0.60-0.85

Estimated hazards ratios adjusted to the hazard of cerebellar onset. Model adjusted for age and year of onset.

portional hazard regression model,[7] with separate analyses for men and women. The effects of age and period of onset were included.

Only 4,833 of the 5,547 patients with onset in 1948 to 1976 were included in the analysis, because some categories of first symptoms used in the database up to 1964 could not be recoded according to the improved classification used after that time. Hence, most of the cases excluded from this analysis had onset before 1965.

Of the 4,833 patients, 965 (20%) had optic neuritis as the presenting symptom, 379 (8%) had diplopia, 1,183 (24%) had upper motor neuron symptoms, 769 (16%) had cerebellar symptoms, and 1,537 (32%) had sensory symptoms.

The shortest survival time was for patients with cerebellar symptoms at onset, and any other onset symptom had statistically significantly lower hazard ratios (table 4). In men, sensory symptoms were predictive of the longest life expectancy, but survival did not differ significantly from that following optic neuritis, diplopia, or upper motor neuron symptoms. In women, there was a tendency for a better prognosis following optic neuritis as the initial symptom. Extension of the model indicated that the effects of presenting symptom and age at onset do not interact statistically significantly (men, $p = 0.37$; women, $p = 0.49$).

Survival after diagnosis. Table 1 (bottom) shows the absolute numbers, the standardized mortality ratios, and the excess death rates from time of diagnosis. Not surprisingly, excess mortality is considerably higher when time of diagnosis is used as the starting point. The median survival time after diagnosis was 22 years in men (versus 37 years in the matched male general population) and 28 years in women (versus 42 years); for the two sexes combined, the median survival time after diagnosis was 25 years. The large difference between the sexes is probably due partly to the fact that men had a shorter interval between onset and diagnosis.

Discussion. Studies on the survival of MS patients have differed widely with regard to study design, patient type (prevalent, incident, or mixed), methods of ascertainment, and sample size. Few studies have involved prospective analyses of incident cases[11-14]; others are based on cases identified through prevalence surveys.[15,16] The study of Poser et al[17] involved a small, population-based, prevalent patient sample and a larger, probably somewhat selected, incident patient sample. The only prospective analyses of survival in population-based cohorts of MS cases are that from the Mayo Clinic,[12] which covered eight decades but included only 206 incident cases, and that from Norway,[14] which comprised 542 incident cases.

Our prospective study involved follow-up of the largest unselected cohort of MS patients published to date, with complete follow-up of virtually all patients with a diagnosis of MS in one country over the course of four decades. Thus, only minor sources of bias are present, which would affect the results to a modest and estimable degree. The starting point of the survival analyses is the time of onset, but the Danish Multiple Sclerosis Registry ascertains patients after diagnosis, which may be separated from the onset by several years. The summary probability of being ascertained by the Registry was 53% within 5 years of onset and 73% within 10 years of onset; for 7% of the patients, more than 20 years had lapsed between onset and ascertainment. Most MS patients not ascertained at follow-up would be alive; the exceptions would be a small but unknown number of latent MS cases who died from competing causes, eg, cancer or accidents, before a diagnosis of MS was established. We did not distinguish between death from natural causes and death from suicide, as there were only 50 to 60 suicides in the cohort.[18] To evaluate the bias due to delayed diagnosis, we calculated and added the hypothetical number of MS patients not ascertained at follow-up to the number of patients known to be alive at that time. We estimated that 1,578 patients, representing 9,619 person-years of observation, had not yet received a diagnosis or been ascertained at the time of follow-up (the total number of person-years observed in the survey was 122,373). Using this correction, the overall excess death rate was only slightly reduced, from 13.0 to 11.9 per 1,000.

The crude survival estimates in this study are of the same magnitude as those in a number of other survival studies (table 5).[12-17,19,20] The differences may be due to small sample sizes and different sampling methods in some of those studies. The 80-year Mayo Clinic survey of Wynn et al[12] indicated somewhat better survival but was based on only 43 deaths. In addition, they used the diagnostic criteria outlined in the Workshop on the Diagnosis of Multiple Sclerosis,[21] which does not include possible cases. In a recent study from Sahlgren's Hospital, Gothenburg, Sweden,[22] life-table analysis indicated a 25-year survival of about 81%, but the authors did not specify whether patients who died from other causes were withdrawn at death. In the cohort study of US army veterans by Kurtzke et

Table 5. Previous studies on survival of patients with MS

Authors	Publication year	Geographic area	Sample type	Cases/ Deaths	Survival parameter	Findings	Present study	Comments
Leibowitz et al[19]	1969	Israel	Prevalent	266/52	Mean survival time	17.4 yr	17.3 yr	Bias due to selection by death
Kurtzke et al[13]	1970	USA	Incident	527/(not specified)	25-year survival probability	68.8% ± 5.3%	68.4% ± 3.8%	Men with onset at ages 20-29 years
Phadke[15]	1987	Scotland	Prevalent	1,055/216	Mean survival time	24.5 yr	17.3 yr	Bias by selection by death
Riise et al[14]	1988	Norway	Population-based incident	598/136	Median survival time after diagnosis	27 yr	25 yr	
Poser et al (i)[17]	1989	Germany	Population-based mixed prevalent-incident	224/28	Median survival time	35-42 yr	30 yr	Epidemiologic series
Poser et al (ii)[17]	1989	Germany	Incident	1,429/170	Median survival time	30 yr	30 yr	Revised hospital series
Wynn et al[12]	1990	Minnesota	Population-based incident	206/43	25-year survival probability	76% ± 4.5%	62% ± 1.4%	
Sadovnick et al[16]	1992	Canada	Incident	2,348/115	Standardized mortality ratio	2.00	3.25	
Miller et al[20]	1992	New Zealand	Prevalent	107/36	25-year survival probability	60%	62%	

al,[13] the 20-year survival rate was 76% and the 25-year survival rate 69%. The corresponding figures for men in our survey were 68% and 56%; however, when the analysis is restricted to men with onset at age 20 to 29, which would be a better comparison with the army cases, our results are similar to those of Kurtzke et al: 77% and 69%.

In agreement with other surveys,[14,15,17,19,23] we found a better prognosis for young age at onset and a worse prognosis for cerebellar symptoms at onset.[14,15,23]

Few other studies have estimated changes in survival with time. The Norwegian study of Riise et al[14] also concluded that survival is improved for patients with more recent onset of MS. The long-term survey of Wynn et al[12] in Olmsted County found no increase in survival with time; however, the number of patients was too small for definite conclusions to be reached.

In this large unselected series of MS patients, obtained from a survey of incidence in 1948 to 1986 and compared with a matched general population, the median survival time was estimated at 30 years. The excess death rate was low in the first 5 years after onset but then increased markedly. The rate was significantly higher in men than in women, in patients who were older at onset, and in patients with cerebellar symptoms at onset. The 10-year excess death rate declined significantly throughout the study period.

Acknowledgments

The authors wish to thank Bodil Andersen of the Danish Multiple Sclerosis Registry for keeping the case files, Lise Stenager Eriksen of the Danish Institute for Clinical Epidemiology (DICE) for maintaining the database, and Mette Madsen, DICE, for helpful advice and suggestions.

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Morning reduction of cerebral vasomotor reactivity

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Article abstract—We measured cerebral vasomotor reactivity during normoventilation, hyperventilation (hypocapnia), and breathing of 6% CO_2 (hypercapnia) in 20 normal subjects during the hours of 6 to 8 AM, 1 to 3 PM, and 7 to 9 PM. Cerebral vasomotor reactivity was calculated, using transcranial Doppler, as percent change in the mean blood flow velocity of the middle cerebral artery per mm Hg change in end-tidal CO_2 during hypocapnia and hypercapnia. Vasomotor reactivity during hypercapnia was lower in the morning (1.72 ± 0.66 %/mm Hg) than in the afternoon (2.34 ± 0.74 %/mm Hg, $p < 0.01$) and evening (2.31 ± 0.56 %/mm Hg, $p < 0.001$). Vasomotor reactivity during hypocapnia did not vary significantly during the three periods (2.34 ± 0.59 %/mm Hg in the morning, 2.43 ± 0.51 %/mm Hg in the afternoon, and 2.26 ± 0.52 %/mm Hg in the evening). This reduced morning response to hypercapnia suggests diminished vasodilator reserve during this period, and may be related to the increased stroke risk during the morning hours.

NEUROLOGY 1994;44:1907-1909

There is an increased frequency of ischemic stroke during the morning,[1] attributed in part to reduced fibrinolytic activity,[2] increased platelet aggregability,[3] and increased vascular tone[4] during this period of the day. We evaluated potential circadian variation in the vasoconstrictor and vasodilator responses of cerebral vessels in normal subjects by measuring cerebral vasomotor reactivity (ie, middle cerebral artery mean blood flow velocity [MCA-BFV] following changes in P_{CO_2}) at three different time intervals in 24 hours, and report herein a reduction in the vasodilator response in the morning.

Methods. We studied 20 normal subjects (10 men and 10 women). None of the participants had a history of stroke, TIA, or other cerebrovascular or cardiovascular disorder. None of the subjects had hypertension or dia-

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Supported by Los Angeles County-University of Southern California Medical Center Health Research Association. Computational assistance was provided by NIH MO1 RR-43.

Received August 27, 1993. Accepted in final form April 5, 1994.

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