ORIGINAL ARTICLE

Disability and Survival of Multiple Sclerosis in Saskatoon, Saskatchewan

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ABSTRACT: ***Background:*** A population-based prevalent group of 150 clinical definite patients ascertained on 1 January 1977, in Saskatoon, Saskatchewan, was followed for 30 years. ***Objectives:*** To outline the clinical characteristics, determine the levels of disability at 15, 25, 35, 40, and 45 years after onset, to estimate the survival after onset and life expectancy. ***Methods:*** Clinical records were maintained, and the cohort reviewed each decade for 30 years. The disability levels according to the Kurtzke Extended Disability Status Scale were recorded and survival times were estimated. SPSS and Kaplan-Meier methods were used for analysis. ***Results:*** On prevalence day, 1 January 1977, there were 48(32%) men and 102(68%) women, with an average age of onset of 32.2±10 years and 28.4±8.6 years. The average duration of disease was 15.7 years. On 1 January 2007, 39(26%) patients were living, 105(70%) deceased, and 6(4%) were missing The disability levels recorded in 1977 and 2007, at 15 and 45 years after onset, were mild (EDSS≤2.5), 33.3% and 8.0%; moderate (EDSS3-5.5), 17.3% and 2.7%; severe (EDSS6-7.5), 6.6% and 4.7%; maximum (EDSS8-9.5), 22.7% and 10.7%. The median survival time after onset was 33 (95% CI: 27.3-38.6) years for men and 38 (95% CI: 34.1-41.9) years for women. The median duration of life was 68.9 years for men and 69.5 years for women, and a decreased life expectancy of 7.7 and 12.8 years. ***Conclusions:*** Multiple sclerosis is a progressive neurological disorder and long-term survival is associated with moderate to severe disability and decreased life expectancy.

RÉSUMÉ: Invalidité et survie dans la sclérose en plaques à Saskatoon en Saskatchewan. ***Contexte :*** Un groupe de 150 patients atteints de sclérose en plaques (SP) certaine, identifiés le premier janvier 1977 à Saskatoon en Saskatchewan, a été suivi pendant 30 ans. ***Objectifs :*** Le but de l'étude était de définir les caractéristiques cliniques, de déterminer les niveaux d'invalidité 15, 25, 35, 40 et 45 ans après le début de la maladie, d'estimer la survie après le début de la maladie et l'espérance de vie. ***Méthodes :*** Les dossiers cliniques ont été mis à jour et la cohorte a été révisée à chaque décennie pendant 30 ans. Les niveaux d'invalidité selon la Kurtzke Extended Disability Status Scale (EDSS) ont été notés et le temps de survie a été estimé. Les données ont été analysées par SPSS et analyse de Kaplan-Meier. ***Résultats :*** Le premier janvier 1977, le jour où la prévalence a été déterminée, la cohorte était constituée de 48 hommes (32%) et de 102 femmes (68%) dont l'âge de début moyen était de 32,2 ± 10 ans et 28,4 ± 8,6 ans respectivement. La durée moyenne de la maladie était de 15,7 ans. Le premier janvier 2007, 39 patients (26%) étaient toujours vivants, 105 (70%) étaient décédés et 6 (4%) avaient été perdus de vue. Les niveaux d'invalidité notés en 1977 et en 2007, soit 15 et 45 ans après le début de la maladie, étaient légers (EDSS ≤ 2,5) chez 33,3% et 8,0%; modérés (EDSS 3 à 5,5), chez 17,3% et 2,7%; sévères (EDSS 6 à 7,5) chez 6,6% et 4,7%; maximaux (EDSS 8 à 9,5) chez 22,7% et 10,7% respectivement. La survie médiane après le début de la maladie était de 33 ans (IC à 95% de 27,3 à 38,6) chez les hommes et de 38 ans (IC à 95% de 34,1 à 41,9) chez les femmes. La durée médiane de vie était de 68,9 ans chez les hommes et de 69,5 ans chez les femmes et l'espérance de vie était diminuée de 7,7 et 12,8 ans respectivement. ***Conclusions :*** La SP est une maladie neurologique progressive et la survie à long terme est associée à une invalidité de modérée à sévère et à une espérance de vie réduite.

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There are few population-based prevalent cohort studies that have assessed the long-term accumulation of disability or the progression of disease over 25 years after onset in multiple sclerosis (MS). About 50% of patients remain independently ambulatory 15 years after onset, and 75% develop progressive disease by 25 years after onset.[1-6] The progression of disability of MS over a life-time is uncertain. There are limited publications on incident or prevalence cohorts focusing on long-term disability outcomes after 30 years from the onset of the disease.[7,8]

Several incidence cohort studies by life-table analysis, estimate a 75% survival of MS 25 years after the onset.[9,10] Some longitudinal studies greater than 30 to 40 years have estimated the median duration or 50% survival after onset average 35 years. Life expectancy is reported decreased by seven to ten

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years and significantly reduced compared to a normal population.[11-15]

The objectives of this longitudinal natural history study were to determine the disability status, estimate the probability of survival after onset, and to calculate life expectancy, of a population based prevalence cohort of multiple sclerosis patients after 30 years surveillance. This paper extends on previous data on the prognosis of MS, to encompass nearly the entire course of the disease covering approximately forty-five years after onset of the disease.[16]

Methods

The original cohort of 150 clinical definite multiple sclerosis patients ascertained in a population-based prevalence study, in Saskatoon Saskatchewan, on 1 January 1977, was the basis of this study.[17] The development of a registry in 1969, the search of medical records and methods of ascertainment were detailed in previous reports.[18] From the opening of the University Hospital in 1954 up to 1 Jan 1977, 344/913 cases of MS were listed as having Saskatoon city addresses. One hundred and thirty-nine were categorized as having probable (clinical definite), 29 possible and 17 suspect MS. Sixty four had moved from Saskatoon, 56 had died and 39 were later classified as not having MS.

From the two other city hospitals, only two probable and three suspect cases were found. Follow-up was continued until 1980 to identify any missed cases and nine probable and two possible were found for which the diagnosis was made before 1 Jan 1977. Another 12 cases of probable and 5 possible according to the history were not included in the study because the diagnosis was made after 1 Jan 1977. All cases from 1962 to 1976 were accounted for and included in the study. The above search determined the 150 definite cases living on the prevalence date.

Follow–up reviews were carried out at ten year intervals to 1st January 2007, to determine the current level of disability, update on family history, the number living patients and dates of death. Two five year periods were conducted in the final decade. The longitudinal follow-up consisted of clinical reviews, and telephone calls to caregivers at home and staff in institutions where persons were unable to attend. The information from all 39 living patients was obtained in December 2006.

All original epidemiological questionnaires, and clinical records, have been maintained, and the data computerized. This database included demographic information on gender, date of birth, ethnic origin, date of onset, age at onset, date of diagnosis, onset symptoms, course of the disease, duration of disease after onset, date of death, and duration of life. The age of onset groups were 1 (1-19), 2 (20-29), 3 (30-39), and 4 (>40years). The symptoms were categorized into visual, sensory, motor, brainstem, cerebellar, cerebral, bowel and bladder and others.

The disability levels were summarized into mild (EDSS≤2.5), moderate (EDSS3-5.5), severe (6-7.5), maximum (8-9.5) and deceased (EDSS10). The course of MS was assigned as primary progressive, relapsing-remitting, and secondary progressive at prevalence date.

The diagnostic classification, modified from Allison and Miller,[19] and the clinical criteria adapted from Schumacher et al[20] the for clinical definite cases were used for the diagnosis. The clinical diagnosis was confirmed by neurologists according to the medical records.

Statistical Analysis

The descriptive analysis was performed using SPSS Version 16.0. The disability outcomes initially were measured according to the original ten point Disability Status Scale,[21] and changed to the 20 point Extended Disability Status Scale,[22] (EDSS) for the last three decades. It is a method of measuring neurological impairment in MS and is basically a mobility disability scale. The impairment has a combination of grades from 0-6 in the Functional systems as described in the symptoms of onset categories in the methods above. The EDSS is divided into 20 steps. The survival of MS patients was estimated by the Kaplan-Meier product-limit estimation and the equality of survival distribution by the Log-rank (Mantel-Cox) test.[23] The joint relationship of covariates to the mortality of MS were analyzed using the Cox proportional hazards analysis. The analyses yields estimates of risk factor effects adjusted simultaneously for the effects of all other risk factors in the model. In the present study, five covariates were considered in the Cox proportional analyses: gender, onset symptoms, age of onset group, birth cohort, and course of disease. The survival time from the onset of MS was used as the time variable, and the age of onset group 1-19 years was used as reference.

By life tables analysis, using the cohort approach, in five year intervals, an abridged life expectancy table was constructed using standard methods.[24,25] The Canadian population period tables 2002, by age and sex, were used for comparison of life expectancy.[26] The results of the median survival for the cohort was compared to other prevalent and incidence longitudinal studies that estimated survival.

Results

The original cohort of 150 clinical definite cases included 48 (32%) men and 102 (68%) women, whose average of onset was 32.2±SD10.1 and 28.4±SD8.4 years. The median age of onset for men was 30.5 years and 28.4 years for women.

The mean age of the men was 48.4±12 years and 44.4±13.3 years for the women. The mean duration of disease was 15.5±9.5 years for the men and 15.9±10.3 years for the women. The mean time to diagnosis was 4.8(±6.0) years for the men and 3.9(±4.6) for the women. There were 23(15.3%) primary progressive, 75 (50%) relapsing-remitting and 52(34.7%) secondary progressive cases. (Table 1).

After 30 years follow-up, 29/102(28.4%) women were living, 67/102(65.6%) were deceased, and 6/102(5.9%) missing. For the men 10/48(20.8%) were living and 38/48(79.2%) were deceased. The clinical course of the cases are included in Table 2.

The age of onset of the surviving men was 27.9±7.9 years and 25.3±6.9 years for the women. Four men and eight women survivors were EDSS≤2.5, one man and three women were EDSS3-5.5, and five men and 18 women were EDSS6-9.5.

The mean duration of disease of the living women was 40.3±7.1 years, and 32.9±12.9 years for the deceased. The mean duration of disease of the living men was 41.0± 4.0 years and for the deceased 30.8±10.9 years. The mean age of the living women was 65.8±9.6 years and 68.2±8.2 years for the men.

Table 1: Baseline clinical features of the prevalent cohort of multiple sclerosis on prevalence day 1 Jan 1977. Means in years ± standard deviations

	Men n 48	Women n 102	Total n 150
Age	48.4 (12.0)	44.4 (13.3)	45.7 (13.2)
Age at onset	32.2 (10.1)	28.4 (8.4)	29.7 (9.2)
Time to diagnosis	3.9 (4.6)	4.8 (6.0)	4.5 (5.6)
Duration of disease	15.5 (9.5)	15.9 (10.3)	15.7 (10.0)
Course of disease * Number and percent			
Relapsing-Remitting	23 (47.9%)	53 (52.0%)	75 (50%)
Secondary Progressive	17 (35.4%)	34 (33.3%)	52 (34.6%)
Primary Progressive	8 (16.7%)	15 (14.7%)	23 (15.4%)

* Pearson Chi-Square p=0.89

Table 2: Clinical features of multiple sclerosis after 30 years follow-up. Means and ±standard deviations. Course of disease by number and percent.

	Women		Men	
	Living	Deceased	Living	Deceased
	29 (28.4%)	67 (65.6%)	10 (20.8%)	38 (79.2%)
Age of onset	25.3 (±6.9)	30.3 (±8.5)	27.9 (7.9)	33.3 (10.4)
Disease duration	40.3 (±7.1)	32.9 (±12.9)	41.0 (4.0)	30.8 (10.9)
Life duration	65.8 (±9.6)	63.9 (±13.7)	68.2 (8.2)	62.4 (14.0)
Course of MS *				
Relapsing-remitting	11 (37.9)	10 (14.9)	5 (50.0)	9 (23.7)
Secondary progressive	18 (62.1)	42 (62.7)	5 (50.0)	21 (55.3)
Primary progressive	0	15 (22.4)	0	8 (21.0)

* Pearson Chi-square p=0.83

The clinical features of the six missing women lost to follow-up are summarized in Table 3.

Disability

Fifteen years after onset 76/150(50.6%) persons were ambulatory without aids (<EDSS6), and 74/150(49.3%) had severe to maximum disability(≥EDSS6-9.5) (Table 4). After 25 years from onset the ambulatory cases decreased to 40(29.1%) the more severe and maximum disabled 56(40.9%) and there were 41(29.9%) deaths. With the numbers of mild disability decreased in each decade there is a corresponding increase in numbers with the severe disability At 30 years follow-up (mean of 45 years after onset), the group with disability EDSS≤2.5 had decreased to 12(8.0%) including 4 men and 8 women. There were 23(15.4%) severely disabled and 105(70.0%) had deceased. There was no significant difference in distribution of first onset symptoms and course of disease between the genders at prevalence date in this final group after 30 years.

Survival

The percentage survival of patients by age and sex after onset were compared to the Canadian population in 2002. The median survival after onset for men was 33 (95% CI: 27.3-38.6) years and 38 (95% CI: 34.1-41.9) years for the women. The log-rank test (Mantel-Cox) for equality of survival for different levels of gender shows no significant difference (p=0.08) (Figure 1).

In the Cox proportional analysis, for the effect of factors on survival, the relapsing and remitting (RR) course was used as reference and the estimated hazard ratios (HR) for patients with secondary progressive (SP) and primary progressive (PP) was

Table 3: Features of the missing women

Cases n 6	Birth year	Onset year	Age onset years	Onset symptom	Course disease	Year censored	Duration disease years	EDSS
1	1937	1961	24	Sensory	RR	1993	32	1.0
2	1929	1958	27	Sensory	RR	1996	38	0
3	1926	1955	29	Sensory	RR	1997	22	1.0
4	1956	1974	18	Motor	RR	1997	3	1.0
5	1954	1969	15	Brainstem	SP	1980	11	7.0
6	1931	1945	16	Motor	RR	1997	30	3.0

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Table 4: Disability outcomes of MS after 30 years follow-up. EDSS frequencies and cumulative percent

Mean years after onset	Mild 0-2.5	Moderate 3.5.5	Severe 6-7.5	Maximum 8-9.5	Deceased 10
15	50 (33.3)	26 (17.3)	40 (26.6)	34 (22.7)	0
25	31 (22.6)	9 (6.5)	29 (21.2)	27 (19.7)	41 (29.9)
35	21 (14.0)	4 (2.7)	13 (8.7)	31 (20.6)	76 (50.7)
40	13 (8.7)	6 (4.0)	8 (5.3)	24 (16.0)	92 (61.3)
45*	12 (8.0)	4 (2.7)	7 (4.7)	16 (10.7)	105 (70.0)

Missing 6 Cases

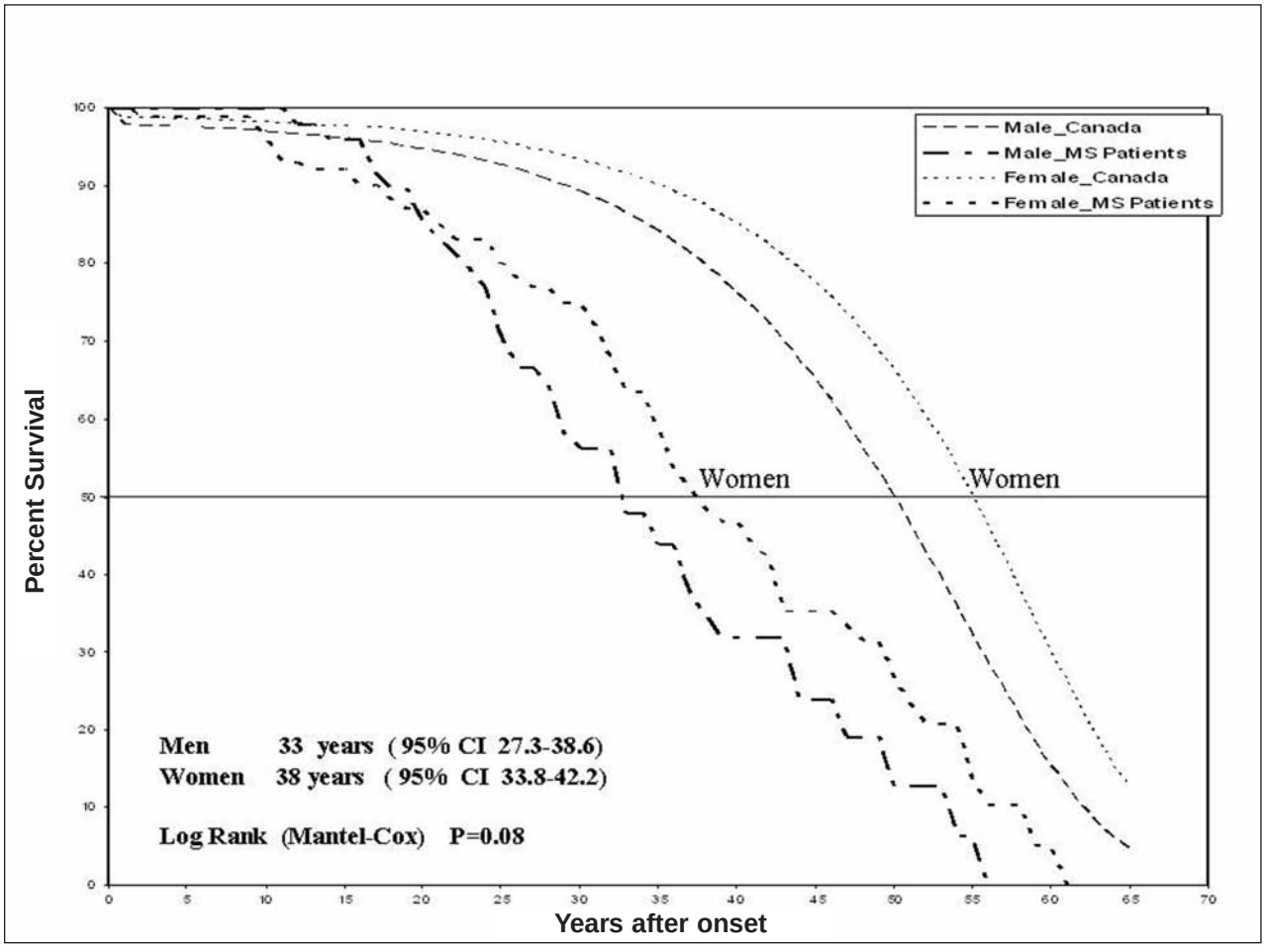

Figure 1: *Survivorship in multiple sclerosis. Percentage survival by years after onset, by age and sex compared to expected population.*

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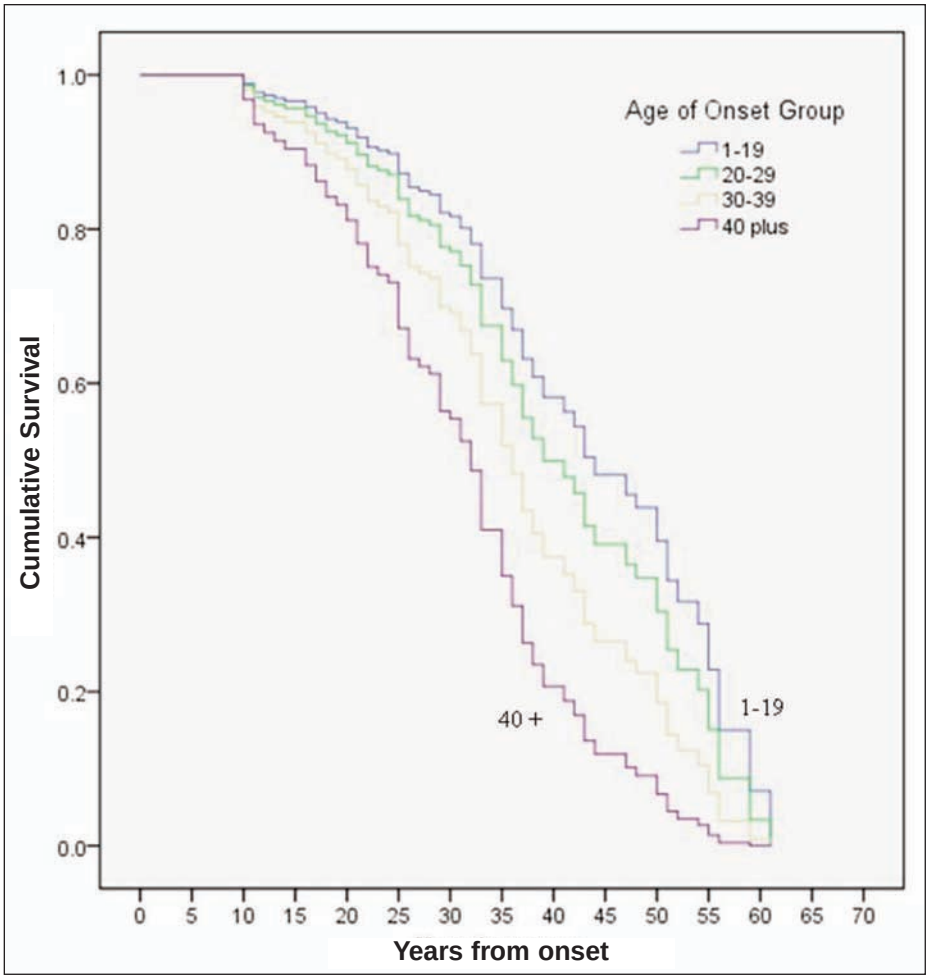

Figure 2: *Survivorship in multiple sclerosis by age groups. Percentage survival in years after onset of MS by comparing age of onset groups. Cox proportional hazard (p=0.003).*

2.2 and 2.6. The median survival for RR, SP and PP was 43 years (95% CI: 39.9-46.2), 33 years (95%CI: 29.0-36.9) and 31 years (95% CI: 27.4-34.6) p=0001. Compared to MS patients with onset at 20 years and younger, the HR for age of onset groups 20-29, 30-39, and 40 and older years was 1.3, 1.8, and 2.9. The median time of survival for the four age groups after onset of disease was 43 years (95% CI 28.9-57.1), 42 years (95% CI 35.3-48.7), 35 years (95% CI 31.3-38.7), and 26 years (95% CI 18.2-33.8) p=003. (Figure 2). This analysis provides strong evidence for a relation between age of onset and the course of disease on survival. The percentage difference of the surviving cases, (female 28.4% and men 20.4%) was analysed. The median survival for women under age 29 was 43 years (95% CI 35.2-48.8) and 33 years (95% CI 24.7-41.3) for the men(p=0.02). The longer life expectancy of women also may contribute to the gender percent differences in this group of survivors.

The population was mainly of British descent and from continental Europe, and race may be an etiological factor. The gender, first onset symptoms, and year of birth cohort, diabetes, hypertension, smoking, other neurological disorders, infectious diseases including measles were not contributory to the survival outcomes in this model. The causes of death have not been determined for the whole group in this analysis.

The Life table by actuarial analysis by five year intervals estimates a median survival of 68.95 (95% CI: 65.4-72.6) years for men and 69.5 (95% CI: 65.5-72.6) for women. The Canadian life expectancy for men is 76.7 years and 82.3 years for women with a significant difference of 7.7 years less for men and 12.8 years for women.

The abridged life expectancy table constructed in ten year intervals, by age and sex, as years remaining after onset, estimates life expectancy of MS patients compared to the Canadian normal population (Table 5).

Discussion

Disability: This long-term study over 30 years has determined the disability outcomes and survival of a population-based prevalent cohort of clinical definite MS patients in Saskatoon. The baseline analysis occurred on prevalence date at 15 years after onset of the disease. The course of the disease and

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Table 5: Life Expectancy in multiple sclerosis

Age	Canada Women	MS Women	Canada Men	MS Men
30	52.85	39.93	48.17	38.59
40	43.13	26.80	38.64	25.19
50	33.67	16.94	29.41	15.20
60	24.72	10.28	20.84	8.22
65	20.52	7.76	16.98	5.92
70	16.57	5.72	13.46	4.12
75	12.92	3.77	10.33	2.61
80	9.67	2.40	7.67	1.44
85	6.96	1.50	5.50	.22
90	4.94	.50	3.87	-

Life table analysis by age and sex, expressed as the average number of years of life remaining at the beginning of the age interval compared to the general population

disability was determined on the prevalence date, and the disability levels were recorded each ten years for three decades. The original cohort of untreated MS patients is a representative group that fulfills the five strategies proposed by Weinshenker et al, to improve the validity of a natural history study.[27] The main strength of this work is the population-based cohort, and the longitudinal evaluation by one primary investigator and loss of only six cases. The limitations of this work include the small number of subjects, and mild cases may be under reported by not seeking medical attention at local facilities. Probable and possible cases were not included. The results however do compare with other small cohort studies in terms of disability and survival at 15 and 25 years after onset.

There are only about five prevalent cohorts that have determined the accumulation of disability over 25 and 30 years.[1-5] The average duration of disease of 15.7 years after onset compares with several studies with similar follow-up. In the Turkish sample of 1259 patients, after 15 years duration, the disability reached was 33% ≤EDSS 3, similar to this study.[28]

In the New Zealand natural history prevalence cohort including 107 probable and suspect cases, from 1968-1983, after adjusting for MS-related deaths, the number estimated after 15-20 years with mild disease was 33%, and this decreased to 15% after 25 years.[2]

In the Iceland cohort study of 372 cases, after 30 years from onset, 52% remained mild (≤EDSS2.5), 21% were moderate (EDSS4-6.5) and 27% (≥EDSS7) were severely disabled.[15]

In the London-Middlesex county natural history study 50% of the patients remained independent-ambulatory after 15 years similar to this study. Twenty-five years after onset 82/273 (29.9%) were <EDSS6 and 128/273(46. 9%) were ≥EDSS6 and 62/273(22.5%) were deceased and 75% of patients had progressed.[4]

This result compares very closely to the data presented here in that 25 years after onset, 40(29.1%) of patients were <EDSS6, 56(40.9%) were ≥EDSS6-9.5 and 41(29.9%) were deceased (Table 4). About 75% had progressed as estimated by the numbers with moderate to severe and maximum disability. In the 30 year follow-up only 16/150(10.7%) remain ambulatory (≤ EDSS5.5).

There is lack of consensus on the criteria for a benign or mild clinical form of MS.[29,30] There is question whether there is truly a benign form.[31] In the Sayao et al select group of benign patients with ≤EDSS3 at ten years, 52% of MS continued a benign course after 20 years.[32] In the Gothenburg cohort 37-50 year follow-up study, the proportion of benign patients defined at 30 and 40 years after onset were 26% and 21%.[33] The methodologies differ greatly but between the Gothenburg study and this cohort study both provide evidence that the disease progresses. In this Saskatoon cohort the group with ≤EDSS2.5 was 33% at 15 years after onset and experienced a continuous decline to 8% over the next 30 years. The data presented here confirms that the benign term is misleading[34] since the disease eventually progressed to severe disability over many years.

Survival

The survival of MS by actuarial analysis has been reported in about eight longitudinal natural history cohorts, after 30 years onset of the disease.[1-8] In the Poser et al, 1989 epidemiological group of 224 cases, the median survival was 35-42 years.[2] Miller et al 1968-1993, from a small group of 107 cases, reported a 58% survival after 30 years,[3] Riise et al 1989, reported a median survival after diagnosis of 27 years.[12] Benedikz et al, in a 50 year follow-up in Iceland, estimated a 50% survival after 30 years.[8] Sumelahti et al, in a 1964-1993 cohort reported a 53% survival after 40 years.[14] Bronnum-Hansen et al estimate the median survival time from onset of 33 years for the women and 28 years for the men and a decreased life expectancy of around ten years compared to their general population,[7]

The United States Veterans cohort series 1956-1996 by Wallin et al in a prevalent cohort of 2489 veterans, 2089 had deceased over 40 years.[1] The actuarial analysis estimated the median survival from onset at 43 years for women and 34 years for men. The 50 year survival from onset was estimated at 20%, similar to the estimate in the study presented here.

These longitudinal studies estimate a median survival rate averaging 35 years after onset that compares very closely to the to the survival estimates in this study. The observed number and percentage of deaths is recorded in each decade (Table 3).

Confavreux et al,[35,36] in the large French series states that a reasonable estimate from onset to death is 31 years. This represents a five to ten years reduction in life expectancy compared to a normal population. In the Danish study,[7] survival was around ten years less and in the Finland series[14] life expectancy was estimated to be 6-13 years less.

The life expectancy table reported by Sadovnick et al,[37] based on 115 deaths identified in 2348 patients, expressed as years remaining in ten year intervals, is similar to the life expectancy calculations in this study (Table 5).

This study has determined that life expectancy is significantly reduced as compared to the Canadian general population by 7.7 years in the men and 12.8 years in the women in this prevalent group. There is a general consensus on the median survival of MS of 35 years after the onset of the disease.

This study provides new longitudinal information over three decades on the observed disability outcomes, in a community based prevalence group of MS patients representing a mean of 45 years after onset not previously done in other studies. The cohort numbers are small and are a representative community group with disability levels and course of disease at the time of ascertainment similar to other studies.[35,36] The numbers of mild cases decreased significantly over time. Multiple sclerosis becomes a progressive disorder and long-term survival is associated with moderate to very severe disability.

The median survival after onset compares with other major longitudinal studies. Survival is significantly affected by the older age of onset and by the primary and secondary courses of the disease. Life expectancy is significantly decreased as compared to the Canadian general population. With the arrival of the disease modifying therapies in the past decade, the prospects of any future natural history studies is limited. This natural history study denotes an unfavorable prognosis for victims of multiple sclerosis.

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